Frailty in chronic diseases: prevalence and implications for clinical management

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Summary

Background:

A growing number of people worldwide live with frailty. Frailty describes an age-related state of reduced physiological reserve, characterised by increased vulnerability to decompensation in response to physiological stress. People living with frailty are at increased risk of adverse health outcomes including mortality and hospital admission. There is often uncertainty over clinical management of long-term conditions in the presence of frailty. This includes uncertainty over how frailty should be identified, how frailty influences the balance of risks and benefits arising from specific diagnostic and therapeutic choices, and over the applicability of trial evidence when trials rarely measure or report frailty. Three conditions in which frailty is common, and in which these uncertainties manifest, are type 2 diabetes, rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD).

Aims:

This thesis addresses the following aims in each of these exemplar conditions:

- assess the prevalence of frailty
- quantify the relationship between frailty and adverse clinical outcomes
- identify and measure frailty within randomised controlled trials for each condition.

Methods:

Three approaches were used for each condition: systematic review of observational studies, analysis of observational data, and analysis of individual participant data from industry-sponsored randomised controlled trials. Systematic reviews included observational studies of adults with the condition of interest (each reviewed separately), using any frailty measure, in any setting, and assessing either frailty prevalence or the relationship between frailty and

clinical outcomes relevant to the exemplar condition. Observational analyses used UK Biobank (all conditions) and the Scottish Early Rheumatoid Arthritis (SERA) cohort (rheumatoid arthritis only) and assessed frailty using the frailty phenotype and the frailty index. Analyses quantified the relationships between frailty and mortality and hospital admission (all conditions); major adverse cardiovascular events (MACE), falls and hypoglycaemia (type 2 diabetes); rheumatoid arthritis disease activity; and COPD exacerbations. Finally, a frailty index was constructed using individual participant data from industry-sponsored drug trials for type 2 diabetes, rheumatoid arthritis and COPD, the prevalence of frailty examined, and the relationship between frailty and Serious Adverse Events assessed.

Results:

Research question 1: Frailty prevalence

In each exemplar condition, a wide range of frailty measures were used in observational studies within the published literature (20 measures used in 118 studies of frailty in diabetes, 11 measures in 17 studies of frailty in rheumatoid arthritis, and 11 measures in 56 studies of frailty in COPD). For all conditions, the frailty phenotype was the most commonly used (69/118 diabetes studies, 5/17 rheumatoid arthritis studies, and 32/53 COPD studies). In all conditions, prevalence varied considerably by frailty measure (generally lower using the frailty phenotype compared to other measures), age (higher prevalence in studies with greater mean age) and setting (higher in residential care and inpatient settings, lower in community-based studies). However, even among community-based studies using similar frailty measures, prevalence estimates were highly heterogenous. For all three conditions, frailty was present in people under 65-years in all studies in which this was assessed.

Research question 2: Frailty and clinical outcomes

Among participants aged between 40 and 70, frailty was associated with a range of subsequent adverse health outcomes.

In type 2 diabetes frailty was associated with an increased risk of mortality, MACE, and hospital admission with fall or fracture or with hypoglycaemia after adjustment for sociodemographic factors. These findings were similar for the frailty phenotype and frailty index. At any given level of frailty, the absolute risk of each of these outcomes was greater for older participants. The association between higher HbA1c and mortality was stronger in people with frailty compared with pre-frail or robust participants according to the frailty phenotype.

In rheumatoid arthritis frailty was associated with mortality and hospital admission using both the frailty phenotype and frailty index after adjustment for sociodemographic factors and disease activity. In SERA, a higher frailty index was also associated with higher disease activity. However, in the two years following initial diagnosis and with initiation of disease-modifying antirheumatic therapy, the mean frailty index of SERA participants reduced indicating an improvement in frailty at the group level.

Both the frailty phenotype and frailty index were associated with increased risk of mortality, hospital admission, MACE, and COPD exacerbations in people with COPD. In each case, the magnitude of the association was similar before and after adjusting for the severity of airflow limitation (measured using forced expiratory volume in 1 second [FEV1]).

Research question 3: Frailty in clinical trials

Out of 39 trials for which individual participant data were obtained, 19 trials (7 type 2 diabetes, 8 rheumatoid arthritis, 4 COPD) provided sufficient data to construct a 40-item frailty index. Based on a cut-off of 0.24, frailty was common in trials for each condition (range 7-21% in type 2 diabetes trials, range 33-73% in rheumatoid arthritis trials and range 15-22% in COPD trials). The mean frailty index was highest in rheumatoid arthritis trials, followed by COPD then type 2 diabetes. The 99th centile of the frailty index in all trials was lower than is seen in most general populations-based estimates. For all three conditions, frailty was associated with increased risk of Serious Adverse Events during trial follow-up (incidence rate ratios per 0.1-point increase in frailty index were 1.46 (95%

confidence interval 1.21–1.75), 1.45 (1.13–1.87), and 1.99 (1.43–2.76) for type 2 diabetes, rheumatoid arthritis, and COPD, respectively).

Conclusion:

Frailty is common in each of the exemplar conditions, including in people aged under 65-years in whom it is far less frequently studied. Frailty in younger people is also associated with a range of clinically significant adverse health outcomes in each condition. However, the absolute risks associated with frailty are considerably lower among younger people. This, along with the observation that frailty can improve within individuals, highlights the need to individualise clinical decisions around the implications of frailty, taking into account factors such as age and clinical context, as the implications of frailty may differ depending on age as well as the nature and severity of underlying long-term conditions. Frailty is also identifiable within clinical trials, a field where frailty is rarely reported. This shows that it is feasible to report frailty for most trials. Doing so could help inform shared clinical decision making for people living with frailty.

Acknowledgement

I would like to sincerely thank my supervisors Professor Frances Mair, Professor David McAllister and Professor Jim Lewsey for their guidance and support throughout all stages of this project. From the early stages of preparing the fellowship application, guiding me through the interview process, to the last three years of completing the work of the thesis itself, you have been wise and supportive in equal measure. Thanks also to Michelle McKelvie and Karen Penman for their support in organising meetings, conference registration, travel and many more things in between.

I am also grateful to all those who have collaborated, advised and assisted with the various aspects of this work: Dr Bhautesh Jani, Dr Barbara Nicholl, Dr Elaine Butterly, Dr Neave Corcoran, Professor Stefan Siebert, Fraser Morton, Dr Holly Morrison, Professor Jennifer Quint, Isabella Faure, Xuetong Guo, Eveline McGhee. This work would not have been possible without your help.

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Finally, a huge thanks are due to my family who have supported me throughout this project. My wife Cheryl for putting up with the long hours and for the huge role she played in facilitating my working from home. To my children Charlotte and Oliver for their patience with me juggling time with them and time spent writing this thesis, and for being such a joyful and welcome distraction. Finally, to my parents for their support in this and in all stages leading up to it. I am hugely grateful to all of you.

Author's Declaration

The work presented here was completed during a Clinical Research Training Fellowship funded by the Medical Research Council. I declare that I am the primary author of this thesis and was responsible for the conceptualisation, design and conduct of all analyses presented here, under the supervision and with the guidance of my supervisors. A number of colleagues collaborated on various aspects of the work presented, and their contributions are acknowledged below.

This thesis is presented in journal format, whereby results chapters which are published or submitted for publication are presented in their published or submitted form. In the case of each of these papers I was the primary author, wrote to first draft of each manuscript, and revised each manuscript based on feedback from co-authors. Co-authors are listed in each of the relevant chapters and their specific contributions are detailed below.

Systematic reviews

I acted as first reviewer for all stages of the review process (screening, quality assessment, data extraction and synthesis) for the systematic reviews presented in chapter 4, chapter 6, and chapter 8. The following colleagues performed duplicate screening, quality assessment and data extraction: Isabella Fauré, Dr Neave Corcoran and Dr Elaine Butterly (type 2 diabetes systematic review, chapter 4); Dr Holly Morrison (rheumatoid arthritis systematic review, chapter 6); and Xuetong Guo and Eveline McGhee (COPD systematic review, chapter 8). I performed all analyses of extracted data. The above-listed colleagues, along with Professor Jim Lewsey, Professor David McAllister, and Professor Frances Mair, provided feedback on drafts of the systematic reviews.

Analyses of cohort and trial data

I planned the analyses presented here with support from supervisors Professor Jim Lewsey, Professor David McAllister, and Professor Frances Mair as well as Dr Bhautesh Jani and Dr Barbara Nicholl for UK Biobank analyses. Colleagues with expertise in each of the exemplar long-term conditions also provided advice

which informed the planning of these analysis (Dr Elaine Butterly, Professor Stefan Siebert and Professor Jennifer Quint). Fraser Morton provided code for the identification of long-term conditions within the SERA dataset. Those listed above provided feedback on drafts of the manuscripts prior to submission for publication (presented in chapter 5, chapter 7, chapter 9 and chapter 10).

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List of publications

Publications arising from this thesis

1. Hanlon, P., Fauré, I., Corcoran, N., Butterly, E., Lewsey, J., McAllister, D.A. and Mair, F.S., 2020. Identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: a systematic review protocol. BMJ open, 10(9), p.e037476.

2. Hanlon, P., Fauré, I., Corcoran, N., Butterly, E., Lewsey, J., McAllister, D. and Mair, F.S., 2020. Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis. The Lancet Healthy Longevity, 1(3), pp.e106-e116.

3. Hanlon, P., Jani, B.D., Butterly, E., Nicholl, B., Lewsey, J., McAllister, D.A. and Mair, F.S., 2021. An analysis of frailty and multimorbidity in 20,566 UK Biobank participants with type 2 diabetes. Communications Medicine, 1(1), pp.1-9.

4. Hanlon, P., Morrison, H., Morton, F., Jani, B.D., Siebert, S., Lewsey, J., McAllister, D. and Mair, F.S., 2021. Frailty in people with rheumatoid arthritis: a systematic review of observational studies. Wellcome Open Research, 6(244), p.244.

5. Hanlon, P., Morton, F., Siebert, S., Jani, B.D., Nicholl, B.I., Lewsey, J., McAllister, D. and Mair, F.S., 2022. Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalisation and mortality: a longitudinal analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank. RMD open, 8(1), p.e002111.

6. Hanlon P, Guo X, McGee E, Lewsey J, McAllister D, Mair, FS. Systematic review and meta-analysis of prevalence, trajectories, and clinical outcomes for frailty in COPD. Primary Care Respiratory Medicine (in press). Doi: 10.1038/s41533-022-00324-5

7. Hanlon P, Lewsey J, Quint J, Jani BD, Nicholl B, McAllister DA, Mair FS. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. BMJ Open Resp Res 2022;1–9. doi: bmjresp-2022-001314

8. Hanlon, P., Butterly, E., Lewsey, J., Siebert, S., Mair, F.S. and McAllister, D.A., 2020. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. BMC medicine, 18(1), pp.1-12.

Publications related to but not directly included in this thesis

1. Hanlon, P., Hannigan, L., Rodriguez-Perez, J., Fischbacher, C., Welton, N.J., Dias, S., Mair, F.S., Guthrie, B., Wild, S. and McAllister, D.A., 2019. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. BMC medicine, 17(1), pp.1-12.

2. Hanlon, P., Jani, B.D., Nicholl, B., Lewsey, J., McAllister, D.A. and Mair, F.S., 2022. Associations between multimorbidity and adverse health outcomes in UK Biobank and the SAIL Databank: A comparison of longitudinal cohort studies. PLoS medicine, 19(3), p.e1003931.

3. Hanlon, P., Blane, D.N., Macdonald, S., Mair, F.S. and O'Donnell, C.A., 2021. Our response to rising frailty in younger people must address prevention burden. The Lancet Healthy Longevity, 2(5), p.e245.

4. Hanlon, P., Corcoran, N., Rughani, G., Shah, A.S., Mair, F.S., Guthrie, B., Renton, J.P. and McAllister, D.A., 2021. Observed and expected serious adverse event rates in randomised clinical trials for hypertension: an observational study comparing trials that do and do not focus on older people. The Lancet Healthy Longevity, 2(7), pp.e398-e406.

Conference presentations arising from this thesis

1. Frailty in trials: an analysis of individual participant data from trials of pharmacological interventions. North American Primary Care Research

Group Annual Meeting 2020 (Winner: North American Primary Care Research Group/ Australasian Association for Academic Primary Care reciprocal prize)

2. Quantifying the prevalence of frailty in drug trials and the relationship with serious adverse events. British Geriatrics Society Autumn meeting 2020 (President's round presentation)

3. A Systematic Review of the Prevalence and Implications of Frailty in Diabetes Mellitus. British Geriatrics Society Autumn meeting 2020

4. Frailty and multimorbidity in type 2 diabetes: A UK Biobank analysis. British Geriatrics Society Spring meeting 2021

5. What are the implications of frailty and multimorbidity in middle-aged and older people with type 2 diabetes? Society for Academic Primary Care Annual Scientific Meeting 2021

6. Multimorbidity and adverse outcomes in UK Biobank: are findings biased by lack of representativeness? Society for Academic Primary Care Annual Scientific Meeting 2021

7. Identifying frailty in industry-sponsored drug trials. Australasian Association for Academic Primary Care Annual Conference 2021

8. Frailty and multimorbidity in middle-aged people with type 2 diabetes. Australasian Association for Academic Primary Care Annual Conference 2021

9. Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalization and mortality: an analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank. Australasian Association for Academic Primary Care Annual Conference 2021

10. Frailty and multimorbidity in middle aged adults with Type 2 diabetes: A UK Biobank analysis. North American Primary Care Research Group

Annual Meeting 2021 (Winner: North American Primary Care Research Group/Dutch College of General Practice reciprocal prize)

11. Multimorbidity in a selected cohort compared to a representative sample: Does selection bias influence outcomes? North American Primary Care Research Group Annual Meeting 2021

12. Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalization and mortality: an analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank. Scottish Society for Rheumatology annual meeting 2022

13. Analysis of frailty in rheumatoid arthritis and its relationship with disease activity, hospitalization and mortality: findings from the Scottish Early Rheumatoid Arthritis cohort and UK Biobank. British Society for Rheumatology annual meeting 2022

14. Frailty prevalence, trajectories and clinical implications in people with COPD: A systematic review. British Geriatrics Society Spring meeting 2022

15. What is the prevalence and clinical implications of frailty in middle-aged people with COPD? Society for Academic Primary Care annual scientific meeting 2022

16. What is the prevalence, trajectory, and clinical implications of frailty in people with COPD? A systematic review. Society for Academic Primary Care annual scientific meeting 2022

List of Accompanying Material

Abbreviations

ACG: Adjusted clinical groups

ACR: American College of Rheumatology

AIC: Akaike Information Criteria

ATS: American Thoracic Society

CGA: Comprehensive Geriatric Assessment

COPD: Chronic Obstructive Pulmonary Disease

DAS-28: Disease Activity Score in 28 joints

DMARD: Disease modifying antirheumatic drug

eFI: Electronic Frailty Index

ELSA: English Longitudinal Study of Aging

EQ-5D: EuroQol 5-dimention quality of life questionnaire

ERS: European Respiratory Society

EULAR: European Alliance of Associations for Rheumatology

FEV1: Forced expiratory volume in 1 second

FI: Frailty index

FiND: Frailty in Non-Disabled

FRAIL scale: Fatigue, Resistance, Ambulation, Illness and Loss of Weight scale

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HAQ-DI: Health Assessment Questionnaire – Disability Index

HbA1c: Glycated haemoglobin

ICD-10: International Classification of Diseases 10th revision

IWQOL: Impact of Weight on Quality of Life

LTC: Long-term condition

MACE: Major Adverse Cardiovascular Event

mPPT: Modified physical performance battery

NICE: National Institute for Health and Care Excellence

RA: Rheumatoid arthritis

Sd: Standard deviation

SERA : Scottish Early Rheumatoid Arthritis cohort

SES: Socioeconomic status

SF-36: Short form 36 quality of life questionnaire

SGRQ: St George Respiratory Questionnaire

SHARE: Survey for Health, Aging and Retirement in Europe

T2DM: Type 2 diabetes mellitus

VES: Vulnerable Elders Survey

Chapter 1 Thesis Overview

1.1 Chapter summary

This chapter provides a general overview of the rationale, aims and content of the thesis. It will first introduce the concept of frailty, and its relevance to the management of chronic disease using three exemplar long-term conditions. It will then set out the overall objectives of the thesis and the specific aims that will be addressed. These will then be broken down into individual research questions and presented alongside a brief description of the data sources used to answer each question. Finally, a summary of chapters will be presented, including how each chapter relates to the aims and research questions.

1.2 Frailty

1.2.1 Definition of frailty

Frailty is a state characterised by a reduction in physiological reserve.[1] This confers a greater risk of decompensation in response to physiological stress, with impaired or delayed resolution of homeostasis.[2] In practical terms, people living with frailty often experience greater adverse consequences (such as hospital admission, loss of independence, or mortality) in response to potentially minor physiological stressors (for example intercurrent infection, or side effects from medication).[3]

While the conceptual definition of frailty (reduced physiological reserve and impaired resolution of homeostasis) is well established,[3] there is no single universally accepted operational definition of frailty.[4] Two contrasting models of frailty have dominated the field of frailty research for the past 20 years: the frailty phenotype and the frailty index.[5,6] The frailty phenotype defines frailty as a specific biological syndrome with characteristic features.[5] The frailty index, in contrast, quantifies frailty as the sum of multiple age-related deficits, with the number of deficits (rather than any specific feature) characterising the degree of frailty.[6] The frailty phenotype and frailty index were both first described in 2001 and, while they still dominate the field of frailty research, many alternative measures to identify frailty have been developed in the intervening period.[4] While these measures all define frailty differently, and identify different populations, there are core features that are common to all definitions of frailty.

First, frailty is associated with age.[3,7] However, frailty is not universal even at extremes of age, nor does there appear to be a clear lower limit to the development of frailty. While most early studies of frailty focused exclusively on people aged over 65, it is increasingly recognised that frailty is identifiable, and is associated with adverse clinical outcomes, in ‘middle-aged’ people as well as those aged over 65.[8,9]

Second, frailty is a dynamic state,[10] and the degree of frailty within an individual may fluctuate over time. There is growing interest in factors and interventions

which might influence the course of frailty, prevent its development, or slow its progression over time.

Lastly, frailty is multifactorial, with multiple causes and implications.[1,2] Physical processes of aging and chronic illness contribute to the development of frailty, but so too do psychological and social factors. Frailty may therefore impact the clinical management of chronic illness in a variety of ways, including increasing the likelihood of specific adverse outcomes, altering the potential risks and benefits of treatments, and influencing the capacity of patients to meet the demands of living with a long-term condition.[3,11]

1.2.2 Management of chronic disease

Aging population demographics,[7] widening health inequalities,[12] and rising levels of multimorbidity (the presence of two or more long-term conditions)[13] all contribute to the rising prevalence and clinical importance of frailty. The relationships between each of these factors and frailty is introduced in detail in chapter 2. The result is an increasing need for approaches to care which reflect this complexity.[11] However, the clinical management of long-term conditions is often driven by disease-specific clinical guidelines. While some clinical guidelines have begun to acknowledge the importance of frailty in the management of long-term conditions, they generally lack clear recommendations around how the management of specific conditions should be tailored to people living with frailty.[3,14]

1.2.3 Challenges of frailty in the management of chronic disease

Frailty presents challenges for the effective management of long-term conditions on several levels:

- *How to identify frailty:*

  There is currently no universally accepted ‘gold-standard’ method to define frailty. It is therefore not clear how clinicians should best identify people living with frailty.

- *Relationship between frailty and clinical outcomes:*

For many long-term conditions, the relationship between frailty and disease-specific clinical outcomes has not been well described. This presents clinical challenges in identifying management priorities or judging prognosis.

- *What treatments are effective or appropriate:*

  There are concerns that people living with frailty are often excluded from clinical trials, however frailty is not directly measured or quantified in most trials. Therefore, the representativeness of trial populations, and the applicability of trial evidence in the context of frailty, is not clear.

This thesis will explore the implications of frailty for the clinical management of long-term conditions at each of these three levels. It will consider three exemplar conditions: type 2 diabetes mellitus, rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD). These were selected as frailty is recognised to be common in each condition.[15-17] Furthermore, frailty may be identifiable in some younger people (aged under 65 years) with these conditions.[9] Finally, for each of these conditions, frailty has been suggested to have clinically significant implications for management.[18-21] However, questions remain over how frailty should best be addressed within clinical guidelines.[18,20] For each condition, the implications of frailty will be considered across a range of ages, not just people over 65 years. This reflects the growing recognition of the importance of frailty across the life-course.

1.3 Objectives

The overall aim of this thesis is to understand the clinical implications of frailty within the context of specific long-term conditions. Specifically, it aims to explore how an understanding of frailty might influence clinical management for the three exemplar long-term conditions described above: type 2 diabetes, rheumatoid arthritis, and COPD. The main objectives are:

1. To explore the prevalence of frailty in each condition and the association between frailty and clinical outcomes relevant to each of the three conditions.

2. To assess the prevalence of frailty within randomised controlled trials for each condition and explore the implications of frailty within a trial setting.

1.4 Research questions

The research questions that will be addressed in the chapters that follow are:

1. What is the prevalence of frailty in each of the three long-term conditions.

2. In each of the three long-term conditions, what is the relationship between frailty and clinical outcomes. This includes generic outcomes (such as mortality and hospital admission) as well as disease-specific clinical outcomes (such as glycaemic control in type 2 diabetes, or disease activity in rheumatoid arthritis).

3. Can frailty be identified in trials of pharmacological agents for each condition, and if so:

    a. How common is frailty within randomised controlled trials.

    b. What is the relationship between frailty and Serious Adverse Events within a trial setting.

1.5 Data sources and methodological approach

The following data sources and methodological approaches have been used in this thesis to answer the research questions outlined above.

1.5.1 Research questions 1 and 2 – prevalence and clinical outcomes

For each exemplar condition, frailty prevalence and the association with clinical outcomes is assessed by a systematic review of published observational studies, and by analysis of the UK Biobank research cohort.

The systematic reviews allow a broad approach considering the wide range of frailty definitions within the published literature.

UK Biobank is a large (n=502,640), population-based cohort of people aged between 40 and 70 at the time of baseline recruitment. This therefore allows analysis of the implications of frailty at a relatively younger age than most of the existing literature. Both dominant frailty definitions, the frailty phenotype and the frailty index, have previously been adapted and applied to baseline UK Biobank data.[9,22] Analyses of UK Biobank therefore allow analysis of these two definitions within the same population.

For rheumatoid arthritis, in addition to UK Biobank, prevalence and implications of frailty are analysed using the Scottish Early Rheumatoid Arthritis (SERA) cohort. SERA is an inception cohort comprising people recruited at the point of initial diagnosis of rheumatoid arthritis (n=1073 in total, of which 899 have confirmed rheumatoid arthritis).[23] It therefore allows analysis of frailty at an early point in the disease process, as well as assessment of rheumatoid arthritis-specific measures (such as disease activity) and serial follow-up following initial diagnosis.

1.5.2 Research question 3: prevalence and implications of frailty in drug trials

Research question 3 is addressed through analysis of individual-participant data from industry-sponsored randomised controlled trials of pharmacological

interventions for each of the three exemplar conditions. This analysis includes trials for each of the three conditions available via two repositories for sharing individual-level trial data: the Yale Open Data Access repository and Clinical Study Data Request. Data from these trials have been made available to enable secondary analysis by third party researchers. Using baseline data, frailty is estimated using the frailty index approach to examine the degree of frailty among trial participants. This allows assessment of the prevalence of frailty in trial populations as well as the relationship between frailty and Serious Adverse Events during trial follow-up.

1.6 Outline of chapters

The chapters presented in this thesis are summarised below. This thesis is presented in journal format, whereby the results are presented in the form in which they are submitted or published in peer-reviewed journals. The literature review, methods, and discussion chapters provide context and interpretation of the thesis.

Chapter 2: Literature review. Frailty and its importance in chronic disease

This chapter provides an overview of the concept of frailty and how it has developed over the preceding 20 years. Particular attention is given to how frailty is identified and quantified, the relationship between frailty and clinical outcomes, and the challenges of translating this understanding into clinical practice.

Chapter 3: Methods overview

A summary of the methods and data sources is presented in this chapter. This includes the approaches used to assess frailty and how these have been applied to the available data sources. The strengths and limitations of the data sources used are discussed.

Chapter 4: Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis

This chapter presents a systematic review addressing research questions 1 and 2 (prevalence of frailty and association with clinical outcomes) focusing on diabetes. It will contrast the range of methods used to identify frailty within the current literature and explore the relationship between frailty and clinical outcomes in diabetes.

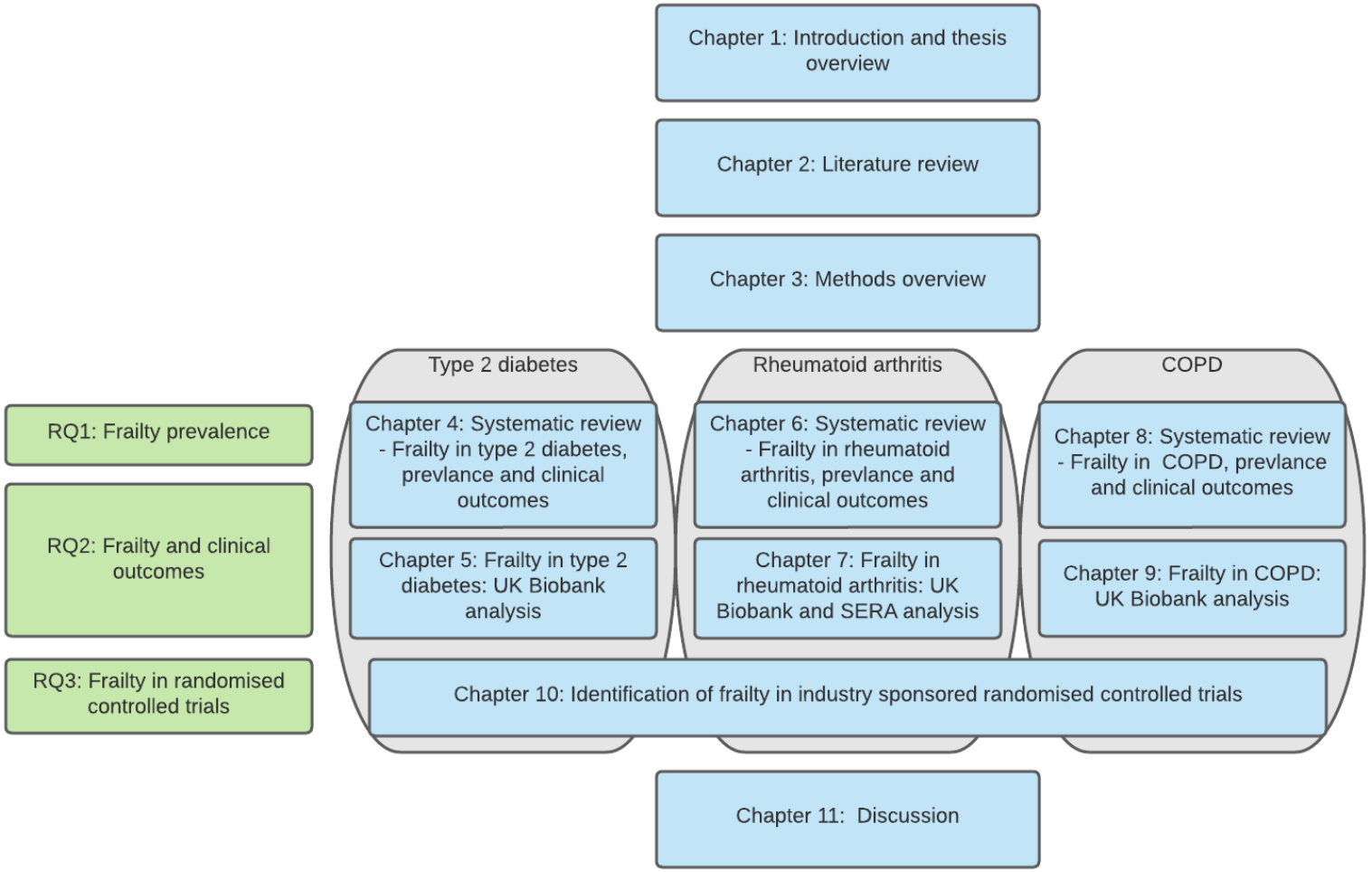

Figure 1-1: Outline of thesis

Chapter 5: An analysis of frailty and multimorbidity in 20,566 UK Biobank participants with type 2 diabetes

An analysis of the prevalence of frailty, and its association with clinical outcomes, in middle- and older-aged people with type 2 diabetes in UK Biobank. This addresses research questions 1 and 2, with a focus on the relationship with glycaemic control and diabetes-specific clinical outcomes.

Chapter 6: Frailty in people with rheumatoid arthritis: A systematic review of observational studies

Chapter 6 presents a systematic review of observational studies of frailty in rheumatoid arthritis. It will summarise current literature on frailty measures used in rheumatoid arthritis, frailty prevalence, and relationship between frailty and disease activity and clinical outcomes.

Chapter 7: Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalisation and mortality: a longitudinal analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank

This chapter explores the prevalence and clinical implications of frailty (research questions 1 and 2) in the context of rheumatoid arthritis. It focusses on the relationship between frailty and disease activity in rheumatoid arthritis as well as outcomes such as mortality and hospitalisation.

Chapter 8: Frailty in COPD: A systematic review and study level meta-analysis of prevalence, trajectories, and relationship with clinical outcomes

This systematic review explores research questions 1 and 2, prevalence and association with clinical outcomes, in the context of COPD. It outlines the relationship between frailty and severity of COPD as well as outcomes such as COPD exacerbations, hospitalisation and mortality.

Chapter 9: Frailty in COPD: An analysis of prevalence and clinical impact using UK Biobank

This chapter presents analyses of UK Biobank quantifying the relationship between frailty and the severity of COPD, as well as the relationship between frailty and clinical outcomes including mortality, hospitalisation, major adverse cardiovascular events, and COPD exacerbations (research questions 1 and 2).

Chapter 10: Identifying frailty in trials: An analysis of individual participant data from trials of novel pharmacological interventions

This chapter presents analyses using individual participant data from randomised controlled trial of drugs for each of the three exemplar conditions. It explores the prevalence of frailty within drug trials, the association with serious adverse events, and implications for assessing treatment efficacy (research question 3).

Chapter 11: Discussion

This final chapter considers the findings of the thesis in the context of the current literature. Strengths and limitations of the work are presented, along with potential implications for clinical practice and future research.

Chapter 2 Frailty and its importance in chronic disease (literature review)

2.1 Chapter summary

The previous chapter outlined the objectives for the thesis, namely, to describe the prevalence and clinical implications of frailty in three exemplar long term conditions (type 2 diabetes, rheumatoid arthritis, and COPD). This chapter summarises the current literature on frailty and its importance in the clinical management of chronic disease more generally, providing context for these objectives.

The chapter will initially introduce the definition of frailty and how this has developed in recent decades. It will then detail how frailty has been measured and quantified and will introduce the two main measures of frailty which will be used throughout this thesis: the frailty phenotype and the frailty index. It will go on to describe the public health context (in terms of aging population demographics) as well as clinical challenges presented by frailty at the individual level. Having established how frailty is defined and measured, it will explore the relationship between frailty and two distinct but related concepts: multimorbidity (the presence of two or more long-term conditions) and social vulnerability (a broad concept comprising socioeconomic status, social support and social engagement).[24,25] Finally, this chapter will highlight some specific gaps in the literature and how these relate to the aims of the thesis.

Frailty in each of the exemplar conditions will be introduced briefly, however detailed review of the literature on frailty in type 2 diabetes, rheumatoid arthritis and COPD will be presented in subsequent chapters (see thesis outline in Figure 1-1: Outline of thesis, with a general overview presented in the present chapter, and condition-specific systematic reviews in chapters 4, 6 and 8, respectively).

2.2 Frailty definition

Frailty describes a state of increased vulnerability to decompensation and adverse health outcomes in response to physiological stress.[3,26] The concept of

frailty has evolved within the scientific literature over the past 20 years, with ongoing debate about its precise definition and scope. Despite this, several core features have emerged as central to the concept of frailty:[3,27]

- **Vulnerability**: Frailty, by definition, describes a greater risk of adverse health outcomes when people living with frailty encounter physiological stress (e.g., an infection or a drug side-effect).[26,27] In practical terms, frailty is associated with greater risk of mortality,[28,29] unplanned hospital admission,[30] falls,[31] and loss of independence. This relationship with adverse health outcomes has been observed across a range of operational definitions of frailty. While these differ in their underlying theory and biological models, they share a common conceptual basis of identifying a state of increased physiological vulnerability.[26,27,32]

- **Multidimensional**: Frailty has a wide range of causes or determinants, and is expressed as vulnerability or dysfunction across multiple domains.[1,2] Frailty is associated with age but, importantly, is not simply an expression of normal aging.[26] The concept of frailty implies dysfunction or vulnerability across multiple organ systems.[1,2] Theories around the pathways leading to this dysfunction, and the nature of the physiological processes and deficits involved, vary depending on the model of frailty studied. Additionally, some models of frailty explicitly include additional dimensions, such as cognitive impairment or social vulnerability,[33,34] which are seen as distinct in other models of frailty. However, common to all definitions is that frailty is a multifaceted state that is multiply determined.

- **Dynamic**: Frailty is not a fixed state.[10] Regardless of how it is specified, frailty is recognised to be an acquired state which develops over time. Frailty also fluctuates, and an individual's degree of frailty may improve as well as deteriorate.[10] The extent to which this dynamism has been observed and studied varies between different models of frailty. However, the dynamic nature of frailty is consistently observed across definitions.

These characteristics were highlighted in a systematic review published in 2017 entitled *The essence of frailty: a systematic review and qualitative synthesis on frailty concepts and definitions* which synthesised commonalities from 78 publications.[27] This understanding of frailty as a dynamic and multiply-determined state, characterised by vulnerability to adverse health outcomes, is also echoed by several recent reviews of the frailty literature.[1-3]

There are many frailty measures used in the scientific literature and in clinical practice. Some of the most common are highlighted in Table 2-1 and described in greater detail below. Despite the lack of a universally agreed definition, two operational measures of frailty have dominated the scientific literature on the topic: the frailty phenotype and the frailty index.[1,3,5,6,26,35] The frailty phenotype defines frailty as a biological syndrome identifiable through five specific characteristics (described below).[5] The frailty index, in contrast, is based on a 'cumulative deficit' model of frailty whereby frailty reflects the number of age-related health deficits identifiable within an individual.[6,35] In the frailty index, frailty is defined by the total number of deficits present, rather than any specific deficit.[36] Both definitions were first described in 2001 and have been the basis for the development of the frailty literature which has emerged in the intervening two decades.

Table 2-1: Summary of frailty measures: This table highlights some of the most frequently cited measures of frailty and their criteria for identifying frailty. This is not an exhaustive list. Text adapted from Hanlon et al 2020[37].

Frailty measure	Description
Earliest measures	
Frailty phenotype	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity). 1-2 criteria: Pre-frail. ≥3 criteria: Frail.
Frailty index	Count of health-related deficits (≥30, type and number of chosen deficits may vary between studies). Total present divided by number of possible deficits. Range 0-1. Sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24)).
Multi-component scales	
Groningen Frailty Indicator	15 items across 4 domains (physical, cognitive, social and psychological). Range 0-15. ≥4 indicates frailty.
Tilburg Frailty Indicator	15 questions across 3 domains (physical, psychological and social) Responses combined into unweighted sum. Range 0-15. ≥5 indicates frailty.

Edmonton Frail Scale	9 components: cognition, general health, functional independence, social support, medication, nutrition, mood, continence and functional performance. Score 0-17. Mild (7-8), moderate (9-10) and severe frailty (≥11).
Clinical tools	
Clinical Frailty Scale	Clinical tool based on functional status. Ranges 1 (very fit) to 9 (terminally ill) with some variation depending on iteration of the scale.
FRAIL scale	5 components (weight loss, fatigue, weakness, ambulation, illness/comorbidity). 1-2 criteria: Pre-frail. ≥3 criteria: Frail.
Scales based on electronic health records	
Electronic Frailty Index	Count of deficits identified from electronic medical records (primary care Read codes), based on the Frailty index approach. In practice categorised as robust (<0.12), mild (0.12-0.24), moderate (0.24-0.36) and severe frailty (≥0.36).
Hospital Frailty Risk Score	Risk stratification tool developed for hospital in-patients based on ICD-10 codes.

2.2.1 Frailty phenotype

The frailty phenotype was described in a seminal work by Fried and colleagues: *"Frailty in older adults: Evidence of a phenotype"*, published in 2001.[5] Frailty is based on five criteria: low hand-grip strength, slow walking pace, unintentional weight loss, self-reported exhaustion, and low physical activity. The presence of three of more of these criteria identifies an individual as frail. One or two criteria indicate pre-frailty. Frailty is therefore conceptualised as a specific clinical syndrome, identified by a combination of specific features, based on an underlying biological model of physiological dysregulation. The original description was based on secondary analysis of the Cardiovascular Health Study in the USA and has been replicated widely (often with some modification). The theoretical models underlying the frailty phenotype, along with modifications to its original criteria, are described in detail in chapter 3.2 Measurement of frailty.

2.2.2 Frailty index

Also in 2001, Rockwood and Mitnitski published *"Accumulation of deficits as a proxy measure for ageing"*, from which the frailty index model has been developed.[6,35] The frailty index is based on the clinical observation that people

who have a greater number of age-related health deficits tend to experience greater vulnerability to adverse health outcomes and hence frailty. Frailty, according to the frailty index, is identified based on the accumulation of age-related deficits. Unlike the frailty phenotype, there is no pre-specified list of deficits that must make up a frailty index. Rather, deficits are selected based on available data providing they fulfil the following criteria:[36]

- Increase in prevalence with age
- Are associated with poor health
- Span a range of organ systems
- Are neither too rare (e.g. <1% prevalence) nor ubiquitous (e.g. >80% prevalence) in the target population

At least 30 deficits are recommended to estimate a frailty index, and typically include long-term health conditions (e.g. diabetes or coronary artery disease), symptoms (e.g. pain, breathlessness, fatigue), functional limitations (e.g. difficulty washing or dressing), and laboratory values (e.g. anaemia or reduced renal function).[36] The frailty index is calculated as the proportion of deficits present, divided by the total number of possible deficits. This gives a value between 0 and 1, greater values indicating a greater degree of frailty.

The frailty index has been replicated widely and is associated with a range of adverse health outcomes.[1] There is also a standard approach developed to apply the frailty index, which is discussed in greater depth in chapter 3.2.2.[36] Applied in this way, despite variation in the specific deficits included, the frailty index has been found to have consistent properties across datasets in terms of the overall distribution, accumulation of deficits with age, and association with adverse health outcomes.

2.2.3 Comparing the frailty phenotype and frailty index

While the frailty phenotype and the frailty index share the nomenclature of frailty, they differ in both conceptual and practical terms.

At a practical level, individuals identified as 'frail' by the frailty phenotype and the frailty index only partially overlap.[38,39] Furthermore, the frailty phenotype is explicitly categorical (i.e. frailty is identified once a specific threshold of three criteria is crossed) whereas the frailty index expresses a continuum (although cut points are often used to denote 'mild', 'moderate' or 'severe' frailty).

The frailty phenotype and frailty index share some important characteristics, causing some to argue that the differences between the two definitions have been overstated.[1] Both reflect dysfunction across multiple domains and biological systems.[2,40] Furthermore, neither definition has a single antecedent at the individual level: frailty, regardless of definition, is 'multiply determined'.[1,2] Both the frailty phenotype and frailty index have been successfully applied to population cohorts,[41,42] where they have been observed to be dynamic (i.e. frailty status may fluctuate over time)[43] and consistently demonstrate associations with adverse health outcomes.[28,29] Both constructs consistently identify people at a greater risk of death at the population level.[44] Furthermore, both show predictive validity for mortality beyond that of age alone, suggesting that both the frailty phenotype and the frailty index can model the observable phenomenon that not all people age at the same rate, and that degree of risk and vulnerability is variable at any given age.[1-3,9] Both the frailty phenotype and the frailty index, therefore, describe dynamic and multidimensional states of increased vulnerability to adverse health outcomes. To this extent, at least, it can be argued that both definitions successfully capture 'frailty'.

Throughout this thesis, where possible, both the frailty phenotype and frailty index will be used to enable comparison of findings using these different definitions. A more in-depth discussion of the theoretical models underpinning each, and the technical aspects of their specification, is presented in the methods section (Chapter 3.2: Measurement of frailty).

2.2.4 Other frailty measures

While the frailty phenotype and frailty index have been the most widely used and most frequently cited frailty measures, a multitude of others have also been developed over the past 20 years.[4] These have included alternative models of frailty some of which explicitly draw on cognitive or social deficits in addition to

physical or function measures; tools developed primarily for use in clinical practice; and models of frailty based on electronic health records. An exhaustive discussion of each of these measures is beyond the scope of this literature review chapter, and specific details of frailty measures used for each of the exemplar long-term conditions are given in systematic review chapters 4, 6 and 8, respectively. The text that follows lays out the rationale for some of the influential models and contextualises their use.

Among the many alternative frailty measures which have been used in research, three of the most commonly studied include the Groningen Frailty Indicator,[45] Tilburg Frailty Indicator,[46] and the Edmonton Frail Scale.[47] While the content of these scales varies, each is based on an individual clinical assessment with 'tick-box' identification of deficits across several domains. Unlike the frailty index, the domains to be scored in each of these measures are fixed and pre-specified. The scored component of the Tilburg Frailty Indicator comprises 15 questions across physical, psychological and social domains.[46] The Groningen Frailty Indicator also comprises 15 items across similar domains, but also includes assessment of cognition.[45] The Edmonton Frail Scale is broader still, spanning cognition, general health, functional independence, social support, medication use, nutrition, mood, continence, and self-reported performance.[47] Some have argued that the explicit inclusion of these additional domains (e.g. social context or cognitive function) within frailty assessment is an important step forward from a 'physical' model of frailty.[48] Others argue that the conflation of cognitive or social vulnerability with physical frailty obscures the differences between the two.[1,2] For example, the clinical implications and appropriate response for someone who is relatively physically robust but cognitively impaired may differ from someone for whom the inverse is true. In general, proponents of a physical model of frailty do not deny the central importance of assessing cognition and social vulnerability in people living with frailty, but rather see these as related but distinct concepts. However, there is currently no universal consensus over the scope of the term frailty in this regard.

Measures designed more specifically for clinical practice include the Clinical Frailty Scale[49] (developed by Rockwood who also pioneered the frailty index) and the FRAIL (Fatigue, Resistance, Ambulation, Illness, and weight Loss) scale.[50,51]

The Clinical Frailty Scale is a tool based on clinical judgement and was developed based on principles of comprehensive geriatric assessment including domains of function, comorbidity and cognition.[49] Individuals are graded from 1 (very fit) to 9 (terminally ill). The Clinical Frailty Scale has been used in a wide variety of settings, including hospital inpatients and community healthcare, as a method of screening for frailty and of identifying people at risk of adverse outcomes.[52] The FRAIL scale is conceptually closely linked to the frailty phenotype model and employs the same cut-offs (3 or more criteria indicating frailty, 1-2 pre-frailty). It has also been demonstrated to predict mortality,[53] but has been less widely adopted.

Several studies have assessed the agreement between a range of frailty measures within the same cohort.[39,54,55] Findings have generally shown agreement to be low at the individual level, with different scores demonstrating varying levels of frailty within the same individual.[39,55] Estimates of frailty prevalence are highly measure-dependent.[55] Feasibility of assessment (assessed by proportion of missing data within the same dataset) and accuracy of mortality prediction are also highly variable. Agreement appears to be highest between measures drawing on a cumulative deficit model of frailty,[55] although multidimensional models of frailty appear to give frailty estimates that are closest to the 'mean frailty level' across multiple measures. The current literature therefore demonstrates that different frailty measures identify variable levels of frailty within the individual, differ in their complexity, feasibility of measurement, and their theoretical basis. However, all appear to be predictive of higher mortality risk.[4,28,29,52,53] No study has demonstrated a single, 'optimal' frailty measure.

More recently, several groups have developed measures of frailty based purely on electronic medical records. These include the electronic frailty index (eFI) based on the cumulative deficit frailty index model and applied to primary care data in the UK (using the Read code system).[56] The eFI is currently used routinely across primary care in England to stratify the population aged over 65 years by frailty risk (discussed below under 'Frailty and health policy'). Others have sought to apply the eFI approach to other healthcare systems including in the USA, where this has been demonstrated to be a feasible approach to

identifying older adults at greater risk of adverse outcomes.[57] Another measure, the Hospital Frailty Risk Score, has also been developed in the UK aiming to use International Classification of Diseases (ICD)-10 codes from inpatient hospital episodes to identify people at high risk of frailty and to predict adverse outcomes.[58]

Both the eFI and the Hospital Frailty Risk Score have been externally validated to predict mortality.[59] However, they are either largely (eFI) or exclusively (Hospital Frailty Risk Score) based on the presence of specific long-term conditions rather than broader physiological measures. It is therefore not clear to what extent 'frailty' as identified by these measures equates to frailty as understood at the level of individual patients within clinical practice. This is reflected in guidance from NHS England that the eFI should not be used to determine the frailty status of individuals, but rather to stratify practice populations and identify people for individualised assessment of frailty status.[60] This caution has been borne out in subsequent work comparing the eFI to 'research standard' frailty index, in which the eFI mapped to frailty index at the group level but not the individual level.[61] The hospital frailty risk score was compared to the frailty phenotype and the frailty index in its original validation paper, and showed only partial overlap with the frailty phenotype, clinical frailty scale, and frailty index.[58] A recent comparison of the eFI with the Hospital Frailty Risk score showed that the two scales had weak correlation, indicating that the respective scores identify different levels of frailty within the same individual.[62] At the group level, higher scores on either scale were associated with greater risk of mortality. As such, while scales using electronic medical records may have utility in identifying people at higher clinical risk with greater efficiency, there is currently no gold-standard measure for this purpose.

2.3 Frailty and adverse clinical outcomes

Frailty has been widely and consistently shown to be associated with a range of adverse clinical outcomes. The original validation of both the frailty phenotype and the frailty index were based on their relationship with all-cause mortality. The frailty phenotype has subsequently been shown to be associated with mortality across multiple studies, often with some modification of the original criteria. One meta-analysis estimated a pooled hazard ratio of 2.00 (95%

confidence interval 1.73-2.32) across 11 studies.[29] The relationship between the frailty index and mortality has been replicated including in cohorts from USA, Canada, Europe and China.[28,36,44,63-78] Each of these studies demonstrated a greater risk of mortality with higher frailty index values, with a meta-analysis published in 2018 estimating a pooled hazard ratio per 0.01-point increase in the frailty index of 1.04 (95% confidence interval 1.03-1.04).[28] For both definitions, there is some evidence to suggest that effect sizes for mortality are higher for men than for women.[28,29] Frailty is also associated with mortality across a wide spectrum of age using both the frailty phenotype and the frailty index.[9,79] Other frailty definitions have also shown associations with mortality.[4,52,53] Frailty, defined through various definitions, has been associated with increased risk of all-cause hospitalisation,[5,30,80-89] incident coronary heart disease,[90] incident stroke,[91] and cardiovascular mortality.[91,92] Frailty is also a predictor of falls in both hospitalised and community-dwelling individuals.[31,93] In summary, frailty has been associated with increased risk of a wide range of adverse health outcomes in general population cohorts. The literature on the relationship between frailty and adverse outcomes in each of the exemplar long-term conditions for this thesis will be explored in detail in subsequent chapters.

2.4 Societal and public health context of frailty

2.4.1 Population demographics

Most countries across the world are experiencing a growth in the proportion of older people within their populations. This demographic shift is being driven, in part, by increased life expectancy and greater longevity, coupled by decreasing birth rates in many countries. As a result, the most rapid increases in population globally are in the over-65 age group.[94] The United Nations estimate that between the years 2019 and 2050 the proportion of the world's population aged over 65 will rise from 9% to 16%.[94] As age is a key determinant of frailty, the prevalence of frailty is also likely to increase in the coming decades.

Alongside population ageing, there has been an increase in prevalence of many non-communicable diseases.[95] Behavioural risk factors such as smoking, obesity, alcohol excess and physical inactivity, as well as wider social determinants such as poverty and adverse childhood experiences, are closely linked to the

development of non-communicable disease.[24,96-98] Each of these factors are also associated with the development of frailty.[99-104]

While aging populations, rising prevalence of non-communicable diseases, and the presence of individual and population-level risk factors may contextualise the rising prevalence of frailty, frailty is not solely determined by any one of these factors. For example, while frailty prevalence increases with age, frailty is not a ubiquitous state even among the 'oldest-old'.[75,105] Similarly, while frailty is more common among people with multimorbidity, living in high socioeconomic deprivation, or with multiple behavioural risk factors, many people in these states are not characterised as frail.[9,12] Frailty is multiply determined, with a range of contributing causes. Variation in these population-level factors, as well as differences in the way frailty is measured, leads to wide differences between estimates of frailty prevalence.[106,107] Despite this variation, frailty is consistently observed to be more common in older people, those living with multiple long-term conditions,[13] and in areas of high socioeconomic deprivation.[108-110]

2.4.2 Global and regional prevalence of frailty

Frailty is common and rising in prevalence, however the global prevalence of frailty is not clear. Prevalence estimates are dependent on the frailty definition used.[7,107,111] Furthermore, most studies of frailty have been conducted in high income countries. A recent systematic review, with database searches up to April 2020, synthesised population-based studies of frailty prevalence using any validated frailty measure.[7] The authors restricted their inclusion criteria to studies judged to include representative population-based samples and identified 253 frailty prevalence estimates from 62 different countries. They reported a pooled frailty prevalence of 12% among adults over 50 years old using the frailty phenotype, and a higher prevalence of 24% using the frailty index. Pooled prevalence was higher in women than men (15% and 11%, respectively, using the frailty phenotype). Estimates of frailty prevalence using the frailty phenotype were also higher in Africa (22% based on 5 data sets) and the Americas (17% based on 60 data sets) compared to Europe (8% based on 60 data sets) and Asia (11% based on 47 data sets). These findings highlight the variation in frailty estimates by region, as well as the relative lack of prevalence estimates from lower income countries.

Within the UK, perhaps the most reliable estimates of frailty prevalence come from the English Longitudinal Study of Ageing (ELSA). ELSA is a cohort study comprising 2-yearly waves of data collection from adults aged 50 years and older in England.[112] Comparison with national census data has shown ELSA to be broadly representative of the English population in terms of sociodemographic characteristics.[112] Furthermore, the ELSA survey provides cross-sectional and longitudinal weights which can be used to adjust for differential non-response and to calibrate the sample to the age-sex structure of the UK population based on the 2001 census. In ELSA, the overall weighted prevalence of frailty in those over 50 years old using the frailty phenotype was 14% (12% in men and 16% in women). Prevalence rose steeply with age, from 6.5% in people aged 60-69, to 65% in people aged 90 years and older.[105] Other representative cohorts, albeit with narrower age spectrums, have shown similar prevalence estimates using the frailty phenotype and have replicated the higher prevalence seen in women.[87,113]

Frailty in the UK has been repeatedly demonstrated to have a marked social gradient.[9,12] Studies from ELSA have shown that both neighbourhood-level and individual level socioeconomic deprivation is associated with a higher frailty prevalence.[108,114] These findings have been replicated in further cohorts including the Hertfordshire Cohort study,[113] the Whitehall II study,[12] and UK Biobank.[9] Lower socioeconomic status, as well as individual-level factors such as obesity, smoking and sedentary behaviour, are also associated with more rapid progression of frailty.[114] As such, while frailty prevalence in the UK and elsewhere may be estimated on a national level, this prevalence is likely to vary considerably between areas and communities based on socioeconomic status.

2.4.3 Frailty and healthcare costs

Frailty, as discussed above, is associated with a range of adverse clinical outcomes including falls, hospital admission, need for long-term care, and mortality.[28,30,31,53,115] This has the potential to result in considerable healthcare and social care costs associated with frailty. Until recently, however, there have been few studies exploring the economic impact of frailty. Some small, single-centre studies explored the hospitalisation-related cost associated with frailty (such as the FRADEA study from Spain, in which people with frailty had on average double the healthcare costs of people without frailty).[116] Others studies

in more specific healthcare contexts (such as post-acute rehabilitation care) demonstrated a higher baseline frailty index was associated with greater healthcare costs.[117] More recently, attempts have been made to estimate the costs of frailty at a national level. Using the eFI, Han and colleagues estimated the annual primary care consultation rates, hospital admission rates, and annual inpatient days stratified by frailty status.[118] Annual estimated healthcare costs were higher for greater degrees of frailty (estimated at £561 per year for mild frailty, £1,209 per year for moderate frailty, and £2,108 per year for severe frailty based on cost data from 2013/2014). The authors estimated, based on national prevalence estimates, that this translated to £6 billion per year in healthcare costs associated with frailty. Further UK-based studies, drawing upon two nationally representative cohort studies (the ELSA and the CARE75+ study), estimated social care costs associated with frailty identified using the frailty index. This study estimated an average of £2,962 per person per year of social care expenditure for people aged over 75 years living with frailty, compared to £330 per year for people without frailty.[119] This study also estimated the cost saving that could be achieved for every 1% of people without frailty who were prevented from transitioning to a frail state. This saving was estimated at £4.4 million per year. Studies from Germany and the USA have also similarly shown greater degree of frailty to be associated with greater estimated healthcare costs.[120,121] In summary, the well-established associations between frailty and adverse health outcomes translate into a significant economic burden for healthcare systems. Costs associated with frailty also span both health and social care, with considerable expenditure at the national level. Delaying or reversing frailty, in addition to responding adequately and appropriately to its adverse health consequences, may therefore have the potential to reduce the costs associated with frailty.

2.4.4 Frailty and health policy

Responding to the challenge of frailty has become an important aspect of health policy. This is in response to the range of issues described above including the clinical impact of frailty on adverse health outcomes, demographic shifts leading to higher frailty prevalence, and mounting financial and logistical pressures on health and social care systems to respond to the needs of people living with frailty.[122] In some health systems, such as the NHS in England, this has led to

policy changes setting explicit targets around frailty.[60] In other contexts, health policy has developed around the need to respond to the rising complexity of care delivery in an ageing society, implicitly drawing on the concept of frailty.[123]

NHS England was the first healthcare system globally to introduce the systematic identification of frailty in people aged 65 years and over. This was introduced in 2017 with changes to the General Medical Services contract which governs the delivery of primary care in England.[124] General practices were required to identify and manage all people aged over 65 years living with moderate or severe frailty. The electronic Frailty Index (eFI) was recommended as the appropriate tool to stratify practice populations and facilitate the identification of frailty. eFI scores are categorised as either robust or mild, moderate or severe frailty, however these scores alone are not intended to identify frailty at the individual level, rather to identify groups of people within a practice population with likely moderate or severe frailty, for whom an individualised assessment can take place. General practices in England, as part of their core contract, are instructed to carry out annual reviews of medications and falls in people with severe frailty and to consider additional interventions and anticipatory care planning. This requirement for general practices to identify and manage frailty forms a key component of the NHS England Long-term Plan; a document that lays out the strategic response of the NHS to emerging challenges over the next 10 years.[125] This document also recommends the proactive management of people living with moderate frailty to identify additional health problems and offer targeted support.

Many other countries are shaping health policy around the challenges of ageing populations and increasing clinical complexity. Frailty is a key, if sometimes implicit, aspect of these policies. The “Choosing Wisely” campaign, which began in the USA in 2012 and has now spread to over 20 countries, has been influential in attempting to change policy.[126] The campaign has sought to promote discussion between clinicians and patients around unnecessary or harmful interventions or procedures. Since its inception, changes have begun to emerge within clinical guidelines and recommendations, clinician appraisal, incentivisation. A key campaign shaping Scotland’s health policy in recent years has been “Realistic Medicine”.[127] Realistic medicine includes an emphasis on

shared decision making between patients and healthcare professions, understanding of risk, and addressing over- and under-intervention in healthcare. A common aspect to each of these is the need to understand clinical risk, promote dialogue over appropriate clinical decisions, and individualise treatments. Frailty is a key concept in translating these principles into clinical practice.

Given that frailty expresses variation in risk at an individual level, an understanding of frailty may help inform the sort of discussions and shared decisions that initiatives such as Choosing Wisely and Realistic Medicine seek to promote. Frailty may help guide judgements around prognosis as well as the tolerability or likelihood of harm caused by interventions. To fulfil this aim, however, it is necessary to understand the implications of frailty in specific clinical contexts (e.g. in specific long-term conditions or for people undergoing specific interventions). This underpins the rationale for examining frailty in the context of specific exemplar long-term conditions, as in this thesis.

2.5 Factors associated with frailty

2.5.1 Age

Frailty, however defined, is a state closely related to age. Frailty is uncommon (but not absent) in people aged under 65 years of age, in whom it is closely related to socioeconomic deprivation and the presence of multiple long-term conditions.[9] Prevalence increases with increasing age and has been shown to rise more steeply above the age of 70.[128] Importantly, however, frailty is not a necessary or intrinsic part of the aging process: many people reach advanced chronological age without developing frailty.[26,105]

Frailty in younger people (under 60 years) was the topic of a recent rapid review.[8] This identified 85 studies with evidence of frailty measure validity in people under 60 years. No frailty measure was identified that had been exclusively developed or validated for younger people. However, in studies with populations both older and younger than 60, several frailty measures including the frailty phenotype and frailty index predicted adverse outcomes such as mortality and hospital admission in younger as well as older people. The authors

highlighted that no studies provided evidence of the clinical impact of measuring frailty in younger populations, nor had previous studies explored the validity of frailty across the possible spectrum of younger ages. This review highlights, therefore, that frailty can be identified in younger populations using a range of measures, and that people identified as frail appear to experience greater risk of hospitalisation and death. However, the clinical implications of identifying frailty in this age group are less clear.

A recent study based on data from the United States between 1999 and 2018 assessed the degree of frailty, based on the frailty index, among people aged 20 and older.[79] In men of all ages, and in women above the age of 35, the mean frailty index was higher in more recent cohorts, indicating that frailty is rising at a population level including among younger age-groups. The authors conclude that the proportion of people in middle- as well as older-age living with frailty is continuing to rise in the United States. Similar trends of increasing population frailty over time have been demonstrated in the United Kingdom[129] and in other cohort from the United states,[130,131] although these studies were limited to adults aged over 65 years.

These previous studies show that frailty is less common, but present, in younger people. However, the clinical implications of frailty in younger people are currently less clear. This thesis will therefore place some emphasis on the impact of frailty at younger ages.

2.5.2 Sex

Frailty is more common in women than men, as demonstrated in multiple studies using a range of frailty measures.[107,132,133] Women are consistently demonstrated to experience higher levels of frailty than men of a similar age. Paradoxically, however, women also tend to live longer than men despite having greater levels of frailty: a phenomenon sometimes termed the “sex-frailty paradox”.[134] Some have speculated that this may indicate that women tend to have a greater physiological reserve than men, meaning they can accumulate a greater number of deficits (under a frailty index model) without acquiring the same propensity to physiological decompensation and thus reducing their mortality risk. This is supported by observations that the upper limit of the frailty index distribution

(above which survival is rare) is higher for women than for men.[135] It has been speculated this phenomenon may reflect differences in how biological sex impacts various physiological systems (including chronic inflammation or hormonal regulation). Conversely gender differences in behavioural risk factors such as smoking and alcohol (which tend to be higher in men) may also influence the lethality of frailty when it is expressed.

2.5.3 Ethnicity

Frailty prevalence varies by geographical location and has been observed to differ between ethnic groups in some countries. However, little work has been carried out to examine if and how the clinical or biological features of frailty differ between ethnic groups.[106] Higher frailty prevalence at a given age in low- or middle-income compared to high-income countries could be due to a variety of factors including social and economic inequalities or access to healthcare, and the role for ethnicity here is far from clear.[136] Within high-income countries both indigenous minority ethnic groups and migrants from minority ethnic groups exhibit higher degrees of frailty, at a younger age, than the white majority populations of the countries in which this has been assessed.[137-142] However, this relationship is likely, at least in part, to be driven by socioeconomic factors and structural inequalities.[140,142] Therefore, while frailty does appear to vary by ethnicity the nature and determinants of these differences have not yet been clearly elucidated.

2.5.4 Socioeconomic status

Much of the early research on frailty focused on the biological basis of the development of physiological vulnerability, with less emphasis on how the social determinants of health may influence frailty status. Both individual and area-level measures of socioeconomic deprivation are associated with greater frailty prevalence, however the overall contribution of these inequalities to the development of frailty is not clear.[108] Socioeconomic deprivation is also associated with more rapid progression of frailty and with the development of frailty earlier in life.[9,12,143-145]

Behavioural factors have been linked to the development of frailty. Smoking, for example, has been associated with both the development and progression of frailty.[145] Low physical activity and obesity are also linked to frailty development.[146-148] Some dietary factors such as inadequate protein intake or low vitamin D have also been linked to frailty, however the causal mechanisms behind these relationships are not clear.[149] Factors such as smoking, low physical activity, and poor diet and strongly linked to socioeconomic status, and tend to co-occur with greater frequency in people living in the most socioeconomically deprived areas.[150] These behaviours are also driven by complex mechanisms across multiple levels from 'upstream' structural factors, through social normalisation of unhealthy behaviour, through to individual-level exposures.[151]

Early life-factors appear to drive some of the inequalities in frailty status. Fewer years spent in education,[152] adverse childhood experiences,[97,153] and lower paid occupations in early life[12,154] all appear to be associated with greater frailty in later life. Socioeconomic inequalities in older age may also give rise to circumstances under which frailty may be more lethal. For example, frailty increases susceptibility to hypothermia, dysregulated blood pressure, and immunosuppression in response to cold conditions.[155,156] It is likely, therefore, that a combination of frailty and social inequalities may explain some existing trends in excess winter mortality.

2.6 Frailty and related constructs

Frailty is a complex and multi-faceted state. There is inevitably, therefore, overlap between frailty and other related constructs that characterise health status of individuals. Two such constructs which are particularly relevant to the work presented in this thesis are multimorbidity and social vulnerability.[24,25]

The diversity of measures used to define frailty also means that the extent to which frailty overlaps with these constructs may vary. This section introduces the concepts of multimorbidity and social vulnerability, in turn, and explores their commonality and points of departure from the concept of frailty.

2.6.1 Frailty and multimorbidity

Multimorbidity describes the co-existence of two or more long-term conditions within an individual. Multimorbidity shares many important features with frailty.[70] For example, multimorbidity becomes more common as people age,[24] as many long-term conditions become more prevalent with age and individuals tends to accumulate long-term conditions throughout the lifespan. However, ageing itself is less intrinsic to the definition of multimorbidity: younger people may have multiple long-term conditions which are themselves not related to age.

Multimorbidity, like frailty, is also strongly associated with adverse health outcomes such as mortality and hospital admission.[157-159] However, while this association with adverse health outcomes may be a consequence of multimorbidity, it is not a defining feature.

Assessing the overlap between frailty and multimorbidity is challenging. Like frailty, multimorbidity is quantified in a range of different ways.[160] This lack of consistency makes comparison between multimorbidity studies challenging. A systematic review and meta-analysis published in 2019 sought to assess the overlap between frailty and multimorbidity.[13] This review included 48 observational studies, 45 of which were cross-sectional, assessing the relationship between frailty and multimorbidity. Most (33 out of 48) studies used the frailty phenotype to define frailty. Multimorbidity was quantified in a range of different ways including counts of long-term conditions (14 studies, with the number of conditions included in the count ranging from 4 to 28) and weighted scores such as the Charlson Comorbidity Index (12 studies). The authors performed meta-analyses and provided pooled estimates of the prevalence of frailty among people with multimorbidity (16%, 95% confidence interval 12%-21%) and of the prevalence of multimorbidity among people living with frailty (72%, 95% confidence interval 63%-81%). Heterogeneity in each of these estimates was high which likely reflects differences in the study populations and the way that frailty and multimorbidity were each quantified. For example, frailty prevalence ranged from 0% to 76% in the included studies, which may reflect significant differences in the underlying populations and the way frailty was characterised. Similarly, multimorbidity prevalence ranged from 2% to 70% in the included

studies. This degree of heterogeneity calls into question the utility of a single pooled estimate of the overlap between frailty and multimorbidity, as studies that measure these constructs in different ways are likely to produce very different estimates. However, the findings indicate three important points. First, frailty and multimorbidity are distinct constructs and many people with multimorbidity do not meet the criteria for frailty. Second, frailty and multimorbidity are closely associated, with frailty being more common among people with multiple long-term conditions. Third, variation in the way multimorbidity is measured can be a barrier to making generalisable inferences about multimorbidity. This is a similar challenge to frailty which, as discussed above, is measured in a variety of ways.

This close relationship between frailty and multimorbidity has begun to translate into clinical guidelines. For example, the National Institute for Health and Care Excellent (NICE) guideline for the management of multimorbidity, published in 2016, recommends that clinicians consider assessing frailty in people with multiple long-term conditions.[161] It also makes the following recommendations when reviewing medications in people with multimorbidity:

- "Take into account the possibility of lower overall benefit of continuing treatments that aim to offer prognostic benefit, particularly in people with limited life expectancy or frailty."[162]

- "Discuss with people who have multimorbidity and limited life expectancy or frailty whether they wish to continue treatments recommended in guidance on single health conditions which may offer limited overall benefit."[162]

These recommendations highlight two important aspects to how frailty may inform clinical management. First, as a prognostic indicator. If people with frailty have limited life expectancy, this may influence judgements around how appropriate a given medication or treatment may be. Second, guidelines are typically focused on single conditions and stated benefits may not hold for people living with frailty. However, life expectancy among people living with frailty may vary depending on how frailty is defined as well as other factors such as age.[9,28,29,53] Furthermore, frailty may change within individuals and for some

may improve. Also, the applicability of disease-specific recommendations for people living with frailty may vary by condition and would require understanding of the impact of frailty in specific long-term conditions. This thesis will explore these aspects of frailty for three long-term conditions.

2.6.2 Frailty and social vulnerability

There is ongoing debate over the extent to which the term frailty describes a primarily physical state or if it should explicitly include broader social vulnerability. Vulnerability to adverse health outcomes, a key hallmark of frailty, is not solely determined by physical characteristics. Psychological and social factors are well understood to influence health and, crucially, the experience of poor health. Some have argued that a narrow 'physical' definition of frailty fails to account for wider social and psychological factors.[163,164] Others see frailty as solely describing physiological vulnerability, which may then interact with other determinants to lead to adverse outcomes.[2]

The extent to which the frailty concept includes social vulnerability depends, in part, on the operational definition used to define frailty.[4,164] The frailty phenotype is an explicitly physical definition of frailty, based on an underlying biological model of physiological decline across multiple systems.[2,5] The frailty index, on the other hand, has the potential to include a wider range of deficits which may capture broader psychological or social vulnerability.[1,165] For example depression, anxiety and loneliness are frequently included as deficits within a frailty index, however this is not universally true across all applications of the frailty index. Other functional measures, such as difficulty washing, dressing, or shopping, may be influenced by the degree of support available to an individual (thus potentially influencing the measurement of a frailty index). Other models, for example the Groningen frailty indicator or the Edmonton Frail Scale are more explicit in their conceptualisation of the social aspects of frailty, and contain specific domains dedicated to social vulnerability.[45,47]

While there is clearly some overlap between frailty and social vulnerability, and some frailty definitions explicitly include elements of social vulnerability, most investigators draw a distinction between the two concepts. For example, the developers of the frailty phenotype model clearly define this as a physical state,

to be considered alongside different conceptualisations of social vulnerability.[2,5] Similarly, a series of studies led by Melissa Andrew working alongside Rockwood and Mitnitski (the developers of the frailty index) have sought to develop and refine the concept of social vulnerability as distinct from frailty.[25,166,167] This group used a methodological approach similar to the frailty index itself, identifying a range of 'social' deficits (including measures of social support, socioeconomic status, leisure activities, and satisfaction with various aspects of life) that are summed to produce a social vulnerability index. The social vulnerability index, so constructed, is moderately correlated with the frailty index, increases with age, and is associated with increased risk of mortality after adjustment for age, sex and degree of frailty index.[25,168,169] In such a framework, frailty defines physiological vulnerability, which is one aspect of an individual's overall risk of adverse outcomes.

When considered as distinct entities, frailty and social vulnerability appear to have a complex and bi-directional relationship. Frailty is associated with higher prevalence of loneliness and social isolation regardless of whether the frailty model includes purely physical variables or explicitly includes a social dimension to the frailty definition.[170] Several longitudinal studies have demonstrated that social isolation (quantified based on the number and frequency of social contacts) and loneliness (the subjective experience of feeling alone) are associated with a higher probability of developing physical frailty over time and of transitioning towards a greater degree of frailty.[171-176] Conversely, similarly designed analyses have also shown that baseline frailty is associated with greater declines in social functioning and with the development of social isolation compared to people not living with frailty.[177] Finally, the combination of physical frailty with loneliness or social isolation carries a greater risk of mortality than physical frailty alone.[178] These studies suggest there may be merit in separating physical frailty from social vulnerability when analysing risk factors or trajectories of each construct, or associations with adverse outcomes. They also highlight, however, that frailty and social vulnerability are inextricably linked and that understanding the implications of one construct will require careful consideration of the other.

The term “social frailty” has been used within the literature to describe vulnerability conferred by social (as opposed to physical) factors, often associated with aging. However, there have been few attempts to precisely define social frailty, and there is little consensus over its usage and conceptualisation.[33] This is one of a number of uses of the term ‘frailty’ to have emerged in the literature describing vulnerability in specific domains. Others include “cognitive frailty” (describing a vulnerability to adverse outcomes indicated by poor cognitive reserve)[34] and “oral frailty” (describing a range of age-associated declines in oral health).[179] There is controversy, however, over the use of the term frailty to describe these vulnerabilities in specific domains, particularly as they are distinct from the original conceptualisation of frailty as a vulnerability to physiological decompensation, with delayed resolution of homeostasis, in response to physiological stress.[3,26,180] Critics of the extension of the term frailty to these other specific domains argue that the clinical identification of (physical) frailty should lead to a broad assessment including social circumstances, cognition, oral health etc.[181] However, the presence of poor health or vulnerability in any one of these domains does not automatically indicate that frailty is present.[180] While acknowledging that debate around these issues is ongoing, this thesis will focus on a physical definition of frailty, distinct from social vulnerability. Social vulnerability, while clearly important, will be considered as a conceptually distinct entity.

2.7 Summary of literature review

This literature review demonstrates some core aspects of frailty:

- Frailty is a state of increased vulnerability to physiological decompensation and to adverse health outcomes.

- Frailty is rising in prevalence and is associated with a significant burden both at the level of individuals, communities, health-care systems and societies.

- Frailty is associated with older age but can also be identified in younger people (e.g. below 65 years) in whom it is similarly associated with

adverse health outcomes. The clinical significance of frailty in younger people has not been explored in depth.

- There is no universally accepted method for how frailty should be best defined and measured. The two models which have dominated the frailty literature are the frailty phenotype and the frailty index. These are distinct constructs.

- Frailty is associated with various long-term conditions as well as with multimorbidity. Some clinical guidelines advise caution in applying treatment recommendations to people living with frailty. However, these recommendations are based upon assumptions of limited life-expectancy and of less applicability of disease-specific clinical evidence to people living with frailty.

The extent to which these assumptions (limited life expectancy, and reduced potential to benefit from disease specific treatments) apply to younger people living with frailty is not clear. Neither is it clear if these same assumptions hold across a range of different long-term conditions. This thesis will therefore explore the implications of frailty across three exemplar long-term conditions: type 2 diabetes, rheumatoid arthritis and COPD. Particular attention will be given to the implications of frailty for younger ages, the relationship between frailty and disease-specific clinical outcomes, and the potential applicability of disease-specific clinical evidence for people living with frailty.

2.8 Current knowledge gaps addressed in this thesis

As laid out in the literature review above, frailty is common, variably measured, consistently associated with adverse health outcomes, and is widely held to have important implications for the management of chronic disease. However, important gaps remain in our understanding of how frailty should influence clinical management. These include the clinical implications of frailty within the context of specific long-term conditions and how frailty is identified at younger ages (such as below 65 years).

2.8.1 Implications of frailty in specific long-term conditions

There is currently a tension between clinical evidence developed to inform the management of specific long-term conditions and the emerging evidence and research agenda for managing the concept of frailty. The former has developed in the context of increasing specialisation in both healthcare delivery and health research. This disease-specific paradigm has been criticised for resulting in clinical evidence and guidelines which are excessively 'single-disease focused' and fails to reflect the complexity experienced by people living with frailty or multiple long-term conditions and the resulting challenges to clinical management.[14]

Frailty research, in contrast, has tended to focus less on specific diseases in favour of a holistic or systems level approach that seeks to respond to or modify the ageing process itself.[182] Some have argued that the common non-communicable diseases – such as cardiovascular disease, diabetes, chronic respiratory disease and cancers – may be best conceptualised as expressions of abnormal ageing: the result of cumulative damage arising from complex interaction between genes and environment throughout the life course.[1,40,183] Despite advances in gerontology, attempts to 'treat ageing' according to this paradigm have yet to translate into routine clinical practice.

Between these extremes, however, lies a recognition of the need for an understanding of frailty to inform our management of chronic diseases.[3,11] This is particularly true in the context of multimorbidity and social vulnerability, where the impact of frailty is most clearly observed. The extent to which clinicians and researchers focusing on specific conditions have embraced and explored the concept of frailty is variable. This thesis will take three exemplar conditions (type 2 diabetes, rheumatoid arthritis and COPD) to explore the implications of frailty in the context of each condition. The literature on frailty in each of these conditions is summarised in chapters 4, 6 and 8, respectively.

2.8.2 Frailty in younger age-groups

As highlighted in the section above on multimorbidity, clinical guideline recommendations for the management of people living with frailty are often

based on an assumption of limited life-expectancy or reduced potential to benefit from disease specific treatment. However, these assumptions may not hold for relatively younger people living with frailty. The recent rapid review on frailty in younger people also emphasised that although frailty may be associated with risk of adverse outcomes in younger people, the clinical implications have not been widely explored.[8]

2.8.3 Applicability of clinical trial evidence to people living with frailty

There is uncertainty as to the optimal approach to managing specific long-term conditions in people living with frailty. This is highlighted in the section above on multimorbidity, with clinical guidelines (such as the NICE multimorbidity guideline) urging caution in the application of single-disease guidelines in the context of frailty. This is partly driven by concerns that people living with frailty may be excluded from randomised controlled trials, which form the basis for guideline recommendations.[184] As such, treatment recommendations based on unrepresentative trials may not be applicable to people living with frailty.[185,186] However, frailty is rarely measured in randomised controlled trials. As such, the true prevalence of frailty in trial populations, and the extent to which people living with frailty are excluded from trials, is not clear.

2.9 Aims of thesis

In view of the gaps highlighted above, this thesis will address the following aims (re-stated from chapter 1):

1. To explore the prevalence of frailty in each of the three exemplar long-term conditions (type 2 diabetes, rheumatoid arthritis, and COPD) and the association between frailty and clinical outcomes relevant to each of the three conditions.

2. To assess the prevalence of frailty within randomised controlled trials for each of these conditions and explore the implications of frailty within a trial setting.

Chapter 3 Methods: Frailty measurement, description of datasets, and methodological approach

3.1 Chapter summary

This chapter provides an overview of the methods used in this thesis. The analyses and results of this thesis are presented in *journal format*, in the form of published or submitted papers (chapters 4 to 10). As such, detailed description of the specific analyses is presented in the manuscript text of each of the results chapters. This methods chapter will provide a broad overview focusing on two specific issues:

- The theoretical basis for the frailty phenotype and frailty index, the two main frailty definitions used throughout this thesis

- Data sources used for the analyses presented in this thesis

First, this chapter will outline the frailty phenotype and the frailty index – providing detail around their quantification, theoretical underpinning, and relative strengths and weaknesses. Second, the data sources used in each of the analyses are outlined (specifically UK Biobank, the Scottish Early Rheumatoid Arthritis cohort, and individual participant data from industry-sponsored drug trials) with reference to each of the research questions. The methods used to identify frailty in each of these datasets will be explained here (in greater detail than in the subsequent results chapters) along with the strengths and weaknesses of each data source.

This thesis also includes three systematic reviews of observational studies (one for each exemplar condition, presented in chapters 4, 6 and 8). The methods for these reviews are not included in this methods chapter, as these followed standard systematic review methods (guided by the Preferred Reporting in Systematic Reviews and Meta-analyses [PRISMA] statement) and are described in full in the text of chapters 4, 6 and 8, respectively.

3.2 Measurement of frailty

As was introduced in chapters 1 and 2, the two commonest measures of frailty within the epidemiological and clinical literature are the frailty phenotype and the frailty index. Both were first described in 2001 and have been widely used and adapted since. The analyses of observational data presented in this thesis, using UK Biobank, make use of both. Therefore, this section delineates the theoretical basis for each definition, describes how their operationalisation for analyses, and discusses the relative strengths and limitations of each.

Many other frailty measures exist, as discussed in chapter 2. While these will not be directly quantified within the datasets analysed in this thesis (as the necessary variables are not available) the systematic reviews assessing prevalence of frailty and associations with adverse outcomes (chapters 4, 6 and 8) will consider a broad range of potential definitions and draw contrasts between different frailty measures.

3.2.1 Frailty phenotype

3.2.1.1 Development of the frailty phenotype

The frailty phenotype was described by Fried et al in 2001 using data from the Cardiovascular Health Study in the USA.[5] It is based on five characteristics: unintentional weight loss, low hand-grip strength, slow walking pace, self-reported exhaustion, and low physical activity.

3.2.1.2 Biological basis for the frailty phenotype

The frailty phenotype is based on a specific biological model of physiological dysregulation. The underlying theoretical model conceptualises the biology of health and homeostasis as a *complex dynamic system*. Put simply, a complex dynamic system is one in which the system as a whole is greater than the additive sum of its parts. Frailty, under such a system, results from dysfunction across multiple interacting systems. The vulnerability to decompensation that defines frailty results from dysregulation of the interaction between these interconnected systems rather than from any single deficit. Under this model,

the five characteristics of the frailty phenotype are the organism-level manifestations of dysfunction across multiple, interacting, physiological systems.

Physical frailty, defined by the frailty phenotype, tends to reflect dysfunction in the three main systems. These include the musculoskeletal system (including sarcopenia – the age-related decline in skeletal muscle function), metabolic systems (particularly glucose metabolism) and the stress-response system (including elements of the autonomic nervous system, the innate immune system, and the hypothalamic-pituitary-adrenal axis). Fried and colleagues lay out several features of dysfunction in these systems, supported by clinical and pre-clinical evidence, to support the frailty phenotype model:[2]

- Dysfunction in multiple systems is evident in individuals exhibiting features of frailty

- The ability of these systems (musculoskeletal, metabolic, autonomic, immune etc.) to respond to stress is impaired in the context of frailty

- The organism-level response to physiological stress relies on complex interactions between these systems, with frailty reflecting dysregulation in these interactions with subsequent feedback loops leading to further dysregulation

- Cumulative dysfunction in these multiple systems is not linear, but appears to exhibit threshold affects

- When thresholds for dysregulation are reached this can lead to profound changes in physiology with impaired ability to respond to stressful stimuli, resulting in decompensation and adverse outcomes

Since its proposal as a model for frailty 20 years ago, several lines of evidence have developed supporting these assumptions. Longitudinal analysis of biomarkers from multiple datasets demonstrate that decline in multiple interacting systems tends to occur in parallel.[187] Phenotypic frailty has been independently associated with altered glucose metabolism and insulin resistance,[188-191] mitochondrial dysfunction within skeletal muscle,[192,193] and

markers of chronic inflammation.[194,195] Dysregulation in each of these systems also exhibit feedback to the others.[196,197] There is also a relationship between the number of physiological systems showing evidence of dysregulation and the prevalence of phenotypic frailty. This relationship is non-linear,[198,199] supporting the hypothesis that there are thresholds above which the risk of physiological decompensation rises more rapidly.

What remains controversial is whether there are one or more shared biological drivers for the dysregulation observed in the context of phenotypic frailty. The prevalence of the frailty phenotype in populations and its identification in specific individuals appears to be highly sensitive to how the individual components are defined and coded,[200] such as difference in how low grip strength or slow walking pace are defined, or how missing data are handled. Therefore, while there appears to be biological evidence to support the frailty phenotype model, it cannot be assumed that these precise processes are underlying the expression of the frailty phenotype in all its applications.

3.2.1.3 Application of the frailty phenotype in this thesis

The use of the frailty phenotype in this thesis is limited to analyses of UK Biobank and systematic reviews of observational studies. Other data sources (such as trial data or the SERA dataset) lack key variables required to assess the frailty phenotype.

3.2.1.4 Strengths and limitation of the frailty phenotype

Strengths:

- The frailty phenotype has been widely implemented in a range of contexts and datasets and has consistently shown associations with higher mortality risk and hospitalisation.

- As described above, the frailty phenotype in underpinned by a specific biological model with a growing body of pre-clinical and clinical evidence supporting its validity.

- The designation of frailty is unambiguous (i.e. frailty is present if three of more criteria are met), however some argue this is an oversimplification.

Limitations:

- A categorical measure of frailty does not allow nuanced description of the degree of frailty. Risk among people identified as 'frail' may not be homogeneous.

- One main criticism of the frailty phenotype is that it relies on a relatively narrow set of criteria. Specifically, the frailty phenotype does not include any measures of cognitive function or sensory impairment. Also, it relies solely on physical measures and does not incorporate any psychosocial constructs that are important in predicting adverse outcomes.

- The frailty phenotype is also sensitive to changes in the way the individual components are specified.[200] This is important in the context of this thesis, as the definitions of the individual components had to be adapted to baseline variables collected in UK Biobank. These adaptations are discussed in detail below. This limits the direct comparability of findings from this adapted version of the frailty phenotype to the wider frailty literature.

3.2.2 Frailty index

3.2.2.1 Development of the frailty index

As discussed in chapter 2, Rockwood and Mitnitski conceptualised the frailty index approach in 2001.[6] The frailty index is based on a 'cumulative deficit' model of frailty. This states that, as people age, health 'deficits' accumulate. The more deficits are present within an individual, the greater their degree of frailty. In this context, deficits can be long-term conditions, symptoms, functional limitations, or physiological abnormalities (e.g. laboratory studies such as anaemia or physical measurements such as blood pressure or grip strength).[36] The frailty index is calculated as the arithmetic sum of all deficits present in an individual, divided by the total number of possible deficits, giving a value between 0 and 1. Higher values indicate greater frailty.

The frailty index approach does not rely on a pre-specified list of deficits which must be measured. Rather, deficits must meet specific criteria to be included in the frailty index.[36] The frailty index can therefore be applied to any dataset with a sufficient number of variables that meet these criteria (typically at least 30, discussed below).

To be included in a frailty index, a variable must:

- Increase in prevalence with age.
- Be associated with poor health status.
- Be neither ubiquitous in the target population (i.e. >80%), nor too rare (i.e. <1% prevalence).

These criteria are laid out in a publication by Searle et al in 2008 which described a standard approach for constructing a frailty index. This argues that the minimum number of deficits which should be included in a frailty index is 30, below which the performance of the frailty index is less predictable and reproducible.[1,36,165]

3.2.2.2 Biological basis for the frailty index

The frailty index, unlike the frailty phenotype, does not define frailty as a specific syndrome. Rather, the frailty index is a more general measure of an individual's degree of vulnerability or state of age-related poor health. Frailty, under this model, is proportional to the total number of age-related health deficits present within an individual. These deficits are intended to reflect damage that has accumulated over the life-course. Deficits are thought to arise through a variety of mechanisms and reflect complex interactions between genetic susceptibility, environmental exposures, and biological process of regeneration and repair.[1] This results in changes at the sub-cellular level that go on to affect cellular processes, which in turn impact tissues and physiological systems, dysregulation of which is expressed in the clinical manifestations of frailty. Under this model, the symptoms, functional limitations, laboratory deficits, and long-term health conditions which are measured as part of the

frailty index are understood as the organism-level expression of accumulated damage across multiple levels (from sub-cellular up to organism-level).

Several strands of evidence support this conceptualisation of frailty as the accumulation of deficits across multiple systems and processes. First, deficits can be observed to accumulate throughout the life-course. Twin-studies suggest a substantial proportion of frailty (25-45%) is attributable to genetics.[201,202] Birth cohort studies have demonstrated associations between variation in childhood growth and in early-life inflammation and the development of frailty in older age.[10,203] Socioeconomic circumstances in childhood also substantially influence subsequent frailty.[204-206] The prevalence of observable deficits also accumulates across the life-span from adolescence up until older age.[67,79] Secondly, frailty assessed clinically at the level of the organism is associated with markers of accumulated damage at the cellular level. Higher frailty index values correlate closely with sub-cellular measures of damage or dysregulation including shortened telomere length and changes in DNA methylation.[207-209] Finally, animal models of frailty, based on the frailty index, demonstrate that molecular- and cellular-level modifications manifest as organ-level dysfunction (for example, measured through differences in cardiac contractility).[210] These molecular-level models of frailty in mice,[210] which manifest in observable deficits across multiple organ systems, explain much of the heterogeneity in physiological function between mice of different ages, just as the frailty index in humans is proposed to do. In summary, deficits can be observed to accumulate across the life-course and age-attributable deficits in molecular and cellular processes appear to manifest as deficits at the level of physiological systems.

The frailty index has several consistently observable properties when applied to population-based studies. This is despite variation in the specific deficits included within each frailty index. First, the rate of accumulation of deficits appears relatively constant, doubling approximately every 15 years.[128,211,212] As a result, individuals with fewer early-life deficits tend to accumulate fewer deficits, and the absolute rate of deficit accumulation increases with age. Secondly, frailty indices consistently have a right skewed distribution which becomes more symmetrically distributed as age increases.[213] However, the mean value of the frailty index does appear to differ depending on how the index is

constructed (for example being higher with self-reported compared to directly measured deficits, and potentially higher when based on electronic health records compared to research cohort data).[214,215] Thirdly, frailty indices are generally robust to the removal of individual deficits (usually assessed through jack-knife sampling techniques whereby the association with an outcome (e.g. mortality) is assessed repeatedly, removing a different deficit from the index in turn) suggesting that it is the index rather than any specific deficit that is important for outcome prediction.[216] Finally, the frailty index is consistently shown to have an upper limit, typically around 0.7, above which survival is rare. This upper limit is seen consistently across the age spectrum.[217]

3.2.2.3 Application of the frailty index in this thesis

In all datasets analysed in this thesis, the frailty index approach is used. For some (e.g. UK Biobank) a frailty index had already been constructed according to the standard approach described by Searle et al. In others (e.g. individual participant data from randomised controlled trials or the SERA cohort) appropriate deficits were identified using the criteria described here as the frailty index had never previously been calculated. In each case, the identification of appropriate deficits and construction of the frailty index is described in this chapter under the description of the respective datasets.

3.2.2.4 Strengths and limitations of the frailty index

Strengths:

- A key strength of the frailty index is its flexibility. The frailty index can be applied to different datasets and adapted to the variables available (indeed this has been the approach followed in most research utilizing the frailty index). This has allowed the frailty index to be applied to a range of contexts (community, hospital inpatient, residential care) as well as being adapted to alternative data sources (e.g. electronic health records or laboratory values).

- The properties of the frailty index (e.g. distribution, upper limit, and association with mortality) have been consistently demonstrated across multiple different iterations.

- Several studies have suggested that the frailty index is more predictive of mortality than the frailty phenotype.[218]

- The frailty index expresses a spectrum of severity of frailty, rather than relying on specific thresholds.

- Cognitive and psychological deficits, as well as sensory impairment and social functioning, can be included within a frailty index. The absence of these dimensions of frailty has been a criticism of the alternative, frailty phenotype, measure.

- The frailty index has been adapted to animal models facilitating pre-clinical research which has complimented clinical and epidemiological observations.

Limitations:

- Different iterations of the frailty index may differ in the extent to which they include deficits from specific domains (e.g. cognitive function, sensory deficits, psychological deficits, or social indicators). While this does not appear to substantially impact the utility of the frailty index to predict mortality, it is not clear if this variation in the application of the frailty index influences relationships with other outcomes.

- The frailty index is also potentially time consuming to administer and calculate, which may limit translation to clinical practice.

- The frailty index is closely related to multimorbidity, and some have argued that it blurs the boundaries between these two concepts. However, the section above (explaining the biological theory underlying the frailty index) illustrates how the two are conceptually different. The frailty index is based on the concept of cumulative damage, rather than explicitly requiring multiple diagnosable conditions. While accumulation of deficits may well result in multimorbidity, frailty may also manifest along with sub-clinical disease and functional impairment. However, where a frailty index relies heavily on the presence of diagnosed long-

term conditions (e.g. when based on electronic medical records) this distinction becomes less clear.

3.2.3 Summary of frailty measurement

In summary, analyses in this thesis will utilise the two measures of frailty which are dominant within the epidemiological literature: the frailty index (for all datasets) and the frailty phenotype (for UK Biobank only). Both definitions have been widely validated and have been consistently shown to be predictive of adverse health outcomes. They are, however, based on different theoretical models of frailty. When applied to the same population, those identified as living with frailty by the frailty index and frailty phenotype only partially overlap despite both predicting adverse outcomes. These measures should be seen as complimentary to each other, rather than equivalent measures.

3.3 Overview of data sources and methods

3.3.1 UK Biobank

UK Biobank is a population based longitudinal cohort study. Data from UK Biobank were used to address research questions 1 and 2: the prevalence of frailty in people with each of the three exemplar conditions, and the association between frailty and adverse clinical outcomes relevant to these conditions (e.g. mortality and hospitalisation in all conditions, hypoglycaemia in type 2 diabetes, and acute exacerbations in COPD).

UK Biobank was chosen for several reasons. First, its large sample size meant it was possible to focus on participants with a specific index condition (e.g. type 2 diabetes, rheumatoid arthritis, or COPD) and still have a relatively large number of participants compared to many studies of frailty in the context of specific conditions. Statistical power to detect associations is therefore greater than would be the case in most other datasets. Second, UK Biobank collected data on a wide range of variables (including physical measurements) during the baseline assessment, which facilitates the assessment of frailty. Third, UK Biobank participants were aged between 40 and 70 at baseline. This therefore offers an opportunity to study the implications of frailty in ‘middle-age’ as well as older

people. As highlighted in chapter 2, the implications of frailty in younger ages are currently not well understood.

This section first describes the participants and recruitment procedures of UK Biobank, the baseline assessment, and data linkage. It then describes the methods used to quantify frailty in UK Biobank, both using the frailty index and an adaptation of the frailty phenotype definition. Finally, the strengths and limitations of UK Biobank are discussed, as they pertain to the analyses presented in this thesis. Specific analyses focusing on each of the three exemplar long-term conditions are described in chapters 5, 7 and 9 (for type 2 diabetes, rheumatoid arthritis, and COPD, respectively).

3.3.1.1 Participants and recruitment

From 2006 to 2010, UK Biobank recruited adults aged 40-70 years to participate in a longitudinal cohort study. Participants were eligible if they lived within 20 miles of one of 22 assessment centres throughout England, Scotland and Wales. Postal invitations were sent to people potentially eligible to participate. The response rate was 5.5%,[219] notably lower than many cohorts or surveys.[220] It has been speculated that this low response rate is in part because potential applicants who were undecided were not re-contacted.[220,221] Just over 500,000 people completed the baseline assessment.[222] Repeat assessments were carried out 3-5 years later on a small subset (around 18,000) of the original participants.

Although large, UK Biobank is not a random sample and is not representative of the wider UK population. Notably, a smaller proportion of UK Biobank participants are from minority ethnic populations or from areas of high socioeconomic deprivation than the wider UK population.[223] Furthermore, UK Biobank participants are less likely to be obese, to smoke, or to drink alcohol daily, compared to the UK population.[223] There is therefore evidence of 'healthy volunteer bias'. The full implications of this bias are the subject of some debate,[220,224-226] and are discussed further in the limitations section below, and in the discussion sections on the chapters describing UK Biobank analyses.

3.3.1.2 Baseline assessment

Participants attended a baseline assessment centre where they completed a touchscreen questionnaire which collected data on a range of demographic, health and lifestyle factors. They then completed a nurse interview, which included self-reported details of all long-term conditions as well as all regular medications. Finally, participants underwent several physical measurements (including hand-grip strength and (non-post bronchodilator) spirometry) and provided blood samples for analysis.

3.3.1.3 Assessment of outcomes

Participants also gave consent for data linkage including to national mortality registers and healthcare data. At the time of writing, linked data from national mortality registers, cancer registers, and inpatient hospital episodes are available for all UK Biobank participants. Primary care data is currently available for a smaller subset of participants (n=230,062). This restriction is due to data only being available from certain primary care data providers rather than any individual-level factors.

Associations between baseline frailty status and adverse health outcomes were generally assessed using linked mortality and hospitalisation data, with International Classification of Disease version 10 (ICD-10) codes used to identify specific causes of death or hospital admission. Outcomes were selected to be relevant to each of the exemplar conditions, and are presented in detail in chapters 5, 7, and 9.

3.3.1.4 Frailty phenotype in UK Biobank

UK Biobank baseline assessment includes variables that may be combined to estimate an adapted version of the frailty phenotype (e.g. measured hand grip strength or self-reported exhaustion). Prior to starting the work presented in this thesis, I published an analysis adapting UK Biobank baseline data to the frailty phenotype criteria.[9] This adaptation of the frailty phenotype is used in the analyses presented in this thesis.

Variables used to identify the five frailty phenotype characteristics differed from those used in the original description of the frailty phenotype by Fried and colleagues.[5] The specification of each of the components used in UK Biobank is shown in Table 3.1, alongside the original frailty phenotype definition. Most notably, weight loss in the original frailty phenotype description was specifically 'unintentional weight loss', whereas in UK Biobank weight loss was not qualified as intentional or unintentional. In addition, walking speed was measured directly in the original frailty phenotype, but was self-reported in UK Biobank.

Table 3.1 - Adaptation of frailty phenotype for UK Biobank

Domain	**Cardiovascular Health Study (Fried and colleagues) criteria**	**UK Biobank adaptation**
Weight loss	Self-reported: "In the last year, have you lost more than 10 pounds unintentionally?" (response: yes=1, no=0)	Self-reported: "Compared with one year ago, has your weight changed?" (response: yes, lost weight=1, other=0)*
Exhaustion	Self-reported (Centre for Epidemiologic Studies depression scale, two questions): "How often in the last week (a) did you feel that everything was an effort, or (b) could you not get going?" (response: moderate amount of the time [3–4 days] or most of the time=1, other=0)	Self-reported: "Over the past two weeks, how often have you felt tired or had little energy?" (response: more than half the days or nearly every day=1, other=0)*
Low physical activity	Self-reported: Minnesota Leisure Time Activity Questionnaire (18 items). Kcal of activity per week estimated, and the lowest 20% were identified as meeting frail criteria	Self-reported: UK Biobank physical activity questionnaire. We classified the responses into: none (no physical activity in the last 4 weeks), low (light DIY activity [e.g., pruning, watering the lawn] only in the past 4 weeks), medium (heavy DIY activity [e.g., weeding, lawn mowing, carpentry and digging], walking for pleasure, or other exercises in the past 4 weeks), and high (strenuous sports in the past 4 weeks) (response: none or light activity with a frequency of once per week or less=1, medium or heavy activity, or light activity more than once per week=0)**
Slow walking pace	Measured time to walk 15 feet	Self-reported: "How would you describe your usual walking pace?" (response: slow=1, other=0)

Low grip strength	Measured grip strength, adjusted for sex and body-mass index (lowest 20% of cohort identified as meeting frail criteria)	Measured grip strength (sex and body-mass index adjusted cut-offs taken from Fried and colleagues)

Table adapted from Hanlon and colleagues 2018 (with permission)[9]
Criteria were adapted from Fried and colleagues and a comparison is shown with those used in the Biobank study.
*Approximation based on available variables in UK Biobank assessment centre data.
**Definition used in SHARE adaptation of the frailty phenotype.[227]

Adaptation of the original frailty phenotype definitions to fit available data is not unusual, and many subsequent analyses of the frailty phenotype have used adapted definitions.[200] While this practice is common, it is important to note that adaptations are likely to impact the prevalence of frailty. One systematic review of studies reporting the frailty phenotype demonstrated that only 24 out of 264 studies used the exact specification of the original frailty phenotype.[200] The authors then used data from the Survey of Health, Aging and Retirement in Europe to reproduce 262 different adaptations of the frailty phenotype. They found that frailty prevalence varied from 12.7% to 28.2% depending on the adaptation used. Agreement with the original description of the frailty phenotype varied, as did the relationship with 5-year mortality. Therefore, although adaptation of the frailty phenotype criteria is common, it is likely that this adaptation will impact estimates of frailty prevalence and associations with outcomes.

In previous analyses assessing the adaptation of the frailty phenotype for UK Biobank, the relationship with each of the five frailty criteria with all-cause mortality was assessed separately.[9] Each criterion was independently associated with all-cause mortality in all age groups, apart from in women aged <45 years in whom the 95% confidence intervals for weight loss, low physical activity, and low grip strength included the null value. Nonetheless, in all age and sex strata, higher numbers of criteria present were associated with increased mortality risk, and in men of all ages, and women above the age of 45, both frailty and pre-frailty were associated with all-cause mortality after adjustment for age, sex, socioeconomic status, smoking, alcohol, and number of self-reported long-term conditions. Therefore, although the UK Biobank adaptation is not strictly equivalent to the original frailty phenotype description, the adapted variables

do, both individually and when combined, show associations with all-cause mortality that would be expected of a frailty measure.

3.3.1.5 Frailty index in UK Biobank

The general approach to creating a frailty index has already been applied to UK Biobank. This used the method described by Searle and colleagues to identify deficits meeting the criteria for inclusion in a frailty index.[36] The development of this UK Biobank frailty index was described by Williams and colleagues and includes 49 deficits taken from self-reported UK Biobank baseline measures.[22] These are reproduced in Table 3.2 below.

Table 3.2 - Frailty index deficits used in UK Biobank

Deficit	Categorisation
Glaucoma	Categorised 0/1
Cataracts	Categorised 0/1
Hearing difficulty	Categorised 0/1
Migraine	Categorised 0/1
Dental problems	Categorised 0/1 for none vs. any
Self-rated health	0 – excellent; 0.25 – good; 0.5 - fair, 1 - poor
Fatigue: frequency of tiredness / lethargy in last two weeks	0, 0.25, 0.5, 1, respectively
Sleep: experience of sleeplessness/insomnia	Categorised 0, 0.5, 1, respectively
Depressed feelings: frequency in last two weeks	0 – not at all, 0.5 – several days, 0.75 -- more than half, 1 – nearly every day
Self-described nervous personality	Categorised 0/1
Severe anxiety/ panic attacks	Categorised 0/1
Common to feel loneliness	Categorised 0/1
Sense of misery (ever/never)	Categorised 0/1
Infirmity: long-standing illness or disability	Categorised 0/1
Falls in last year	0 - no fall, 0.5 - one fall, 1 - more than one fall
Fractures/broken bones in last five years	Categorised 0/1
Diabetes	Categorised 0/1
Myocardial infarction	Categorised 0/1
Angina	Categorised 0/1
Stroke	Categorised 0/1
High blood pressure	Categorised 0/1
Hypothyroidism	Categorised 0/1
Deep-vein thrombosis	Categorised 0/1
High cholesterol	Categorised 0/1
Breathing: wheeze in last year	Categorised 0/1
Pneumonia	Categorised 0/1

Chronic bronchitis/emphysema	Categorised 0/1
Asthma	Categorised 0/1
Rheumatoid arthritis	Categorised 0/1
Osteoarthritis	Categorised 0/1
Gout	Categorised 0/1
Osteoporosis	Categorised 0/1
Hay fever, allergic rhinitis or eczema	Categorised 0/1
Psoriasis	Categorised 0/1
Any cancer diagnosis	Categorised 0/1
Multiple cancers diagnosed (number reported)	Categorised 0/1
Chest pain	Categorised 0/1
Head and/or neck pain	Categorised 0/1
Back pain	Categorised 0/1
Stomach/abdominal pain	Categorised 0/1
Hip pain	Categorised 0/1
Knee pain	Categorised 0/1
Whole-body pain	Categorised 0/1
Facial pain	Categorised 0/1
Sciatica	Categorised 0/1
Gastric reflux	Categorised 0/1
Hiatus hernia	Categorised 0/1
Gall stones	Categorised 0/1
Diverticulitis	Categorised 0/1

The UK Biobank frailty index showed the expected relationship with age, sex, and all-cause mortality when applied to the cohort as a whole.[22] The hazard ratio per 0.1-point increase in the frailty index was 1.65 (95% confidence interval 1.62-1.68) with stronger associations in younger compared to older participants and in men compared to women.[22] Analyses of the frailty index in UK Biobank in this thesis will use this same list of 49 deficits.

3.3.1.6 Ethical approval and data management

The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). All participants gave informed consent for participation in UK Biobank. Access to UK Biobank data for the analyses presented in this thesis was granted under project 14151 and was subject to a material transfer agreement with UK Biobank.

3.3.1.7 Strengths and limitations of UK Biobank

Strengths:

- UK Biobank has a large sample size, which increases the precision with which associations between exposures and outcomes can be estimated.

- A wide range of variables were collected at baseline. This allows comparison of two different frailty measures (frailty index and frailty phenotype) as well as assessment of a wide range of demographic and lifestyle measures that may be used to adjust for potential confounding.

- The inclusion of people younger than 65 years, with assessment of variables from which frailty can be estimated, is unusual. This provides opportunities for new insights into an under-researched area.

- Data have been linked to a range of sources including national-level mortality and hospitalisation records. This allows assessment of a range of outcomes with minimal loss to follow-up.

Weaknesses

- UK Biobank is not a representative sample, with evidence of 'healthy volunteer bias'.[223] Selection bias in observational studies may lead to collider bias,[228,229] which in turn may lead to biased associations between exposure and outcomes.

- The mortality and hospitalisation rate in UK Biobank is lower than the population as a whole.[223] Therefore, absolute event rates estimated from UK Biobank are likely to be conservative.

- As discussed above, the frailty phenotype criteria used in UK Biobank have been adapted from the original description. Such adaptations impact on the prevalence and predictive ability of the frailty phenotype.[200] This limitation is as a result of the variables collected at baseline, and it is

therefore not possible to formally test the impact of these adaptations on estimates using the frailty phenotype.

3.3.2 Scottish Early Rheumatoid Arthritis (SERA) cohort

For rheumatoid arthritis, data from the Scottish Early Rheumatoid Arthritis (SERA) cohort were used to analyse the prevalence of frailty and the association with clinical outcomes.[23] SERA is an inception cohort of people with rheumatoid arthritis or undifferentiated arthritis, recruited at the point of initial diagnosis. SERA was designed to facilitate longitudinal analysis of rheumatoid arthritis phenotypes, disease-related outcomes, and linkage to routine healthcare data. This section describes the SERA cohort, baseline assessment, the methods used to identify frailty, and the assessment of outcomes.

3.3.2.1 Participants and recruitment

SERA participants were recruited from rheumatology units across Scotland. The aim was to recruit patients with newly diagnosed rheumatoid arthritis or undifferentiated arthritis. For the purposes of this thesis, analyses will focus on those with confirmed rheumatoid arthritis. Patients were eligible for recruitment if they had at least one swollen joint which was not explained by an alternative diagnosis (e.g. psoriatic arthritis). Carriers of blood borne viruses were also excluded. Although patients were recruited at the point of initial assessment by rheumatology services, duration of symptoms or swelling was not an exclusion criterion. Thus, patients with longstanding, undiagnosed joint swelling would be eligible for recruitment. Also, patient who had had treatment such as Disease Modifying Anti-Rheumatic Drugs (DMARDs) or steroids commenced prior to diagnosis (e.g. by their general practitioner) were also eligible for recruitment providing this treatment had been commenced in the previous 6 months. Screening and baseline assessments for SERA were carried out by research nurses, while all clinical care and treatment decisions remain the responsibility of their local rheumatology service.

To date, 1073 patient have been recruited to SERA and have data available for analyses. Of these, 899 meet the American College of Rheumatology/European

League against Rheumatism (ACR/EULAR) criteria for rheumatoid arthritis at baseline and are included in the analyses presented in chapter 7.

3.3.2.2 Baseline assessment, diagnostic classification and follow-up

The initial SERA assessment was performed by research nurses. The standard operating procedure for data collection at each visit is described in the supplementary appendices of the cohort description by Dale and colleagues.[23] The baseline data collection included demographic and lifestyle information including age, gender, smoking status and alcohol consumption. Socioeconomic status was assessed using the Scottish Index of Multiple Deprivation (SIMD; an area-based measure of socioeconomic status). Baseline assessment also includes documentation of medical history (based on self-report, collected by the study nurse), regular medication, and symptom duration.

Follow-up assessments are carried out at 6 monthly intervals for the first two years following diagnosis, and annually thereafter. Standardised assessments and questionnaires are administered at baseline and at each subsequent follow-up assessment.

Baseline diagnosis (rheumatoid arthritis or undifferentiated arthritis) was classified according to the 2010 ACR/EULAR criteria.[230] These criteria are primarily a research tool intended to allow consistency in the definition of rheumatoid arthritis between studies. The ACR/EULAR criteria comprise numerical scores for number of swollen joints, duration of symptoms, serological markers (rheumatoid factor and anti-citrullinated peptide antibody), and acute phase reactants (C-reactive protein or erythrocyte sedimentation rate).[230] The 2010 revision was produced to facilitate classification of rheumatoid arthritis early in the disease process compared to the previous 1987 iteration.[231] A systematic review, published two years after the revised criteria and comprising 17 published articles and 17 meeting abstracts, assessed the sensitivity and specificity of the 2010 ACR/EULAR criteria.[232] This review demonstrated a pooled sensitivity of 82% and specificity of 61% for the 2010 ACR/EULAR criteria using a range of different reference standards (expert opinion, initiation of methotrexate, or initiation of any DMARD). The sensitivity was similar (between 80% and 88%) between these different reference standards. This sensitivity is

higher than the previous 1987 criteria, however the specificity of the 2010 criteria is lower. Therefore, rheumatoid arthritis in SERA in defined according to a validated measure which is sensitive for detecting early disease, but which may lack specificity for rheumatoid arthritis defined by other criteria such as expect opinion or requirement for DMARD therapy.

Functional status was assessed in SERA using the Health Assessment Questionnaire – Disability Index (HAQ-DI).[233] HAQ-DI is a tool based on self-report to assess functional status for performing activities of daily living in the context of musculoskeletal disorders. The HAQ-DI comprises eight domains (dressing, arising, eating, walking, hygiene, reach, grip and activities). Each domain is assessed by either two or three questions, with each question scored between 0 (no disability) to 3 (severe disability or unable to perform). It has been demonstrated to be sensitive to clinically meaningful changes in function in people with rheumatoid arthritis.[234] The HAQ-DI is used in two ways in this thesis. First, the global score is used as a measure of overall functional status in SERA participants (as used in observational studies and trials of rheumatoid arthritis).[235] Secondly, selected elements from the HAQ-DI will be used to identify specific functional deficits that will form part of the frailty index. The selection of specific elements to include in the frailty index was based on the criteria described by Searle and colleagues in their description of the standard approach for constructing a frailty index,[36] as described below.

3.3.2.3 Frailty index in SERA

Frailty in SERA was assessed using the frailty index approach. The theoretical basis for the 'cumulative deficit' model, on which the frailty index is based, is described in detail in section 3.2.2. The standard process for compiling a frailty index is described earlier in this chapter, in section 3.2.2. According to this procedure, 42 deficits were identified which met the criteria for inclusion in a frailty index (increasing prevalence with age, biological plausibility (association with adverse health status), and neither ubiquitous nor too rare). Deficits in SERA comprised long-term conditions (identified from self-reported baseline assessment of medical history), symptoms (such as pain or anxiety, identified from the EuroQol EQ-5D questionnaire), functional limitations (such as difficulty washing or dressing, identified from the Health Assessment Questionnaire –

Disability index (HAQ-DI) questionnaire) and laboratory deficits (such as anaemia or impaired renal function, identified from baseline blood tests). The full list of deficits that were included, the source from which they were identified, and the scores assigned to respective values, are shown in Table 3.3. The deficit score was summed and divided by the total number of non-missing deficits for that individual (as is standard for calculating the frailty index) to obtain a value between 0 and 1.[36]

Table 3.3 - Frailty index deficits used in SERA

Deficit	Source	Coding
Alcohol problems	Medical history	Present = 1, absent = 0
Anxiety	Medical history	Present = 1, absent = 0
Asthma	Medical history	Present = 1, absent = 0
Atrial fibrillation	Medical history	Present = 1, absent = 0
Bronchiectasis	Medical history	Present = 1, absent = 0
Cancer	Medical history	Present = 1, absent = 0
Coronary heart disease	Medical history	Present = 1, absent = 0
Chronic kidney disease	Medical history	Present = 1, absent = 0
Chronic liver disease	Medical history	Present = 1, absent = 0
COPD	Medical history	Present = 1, absent = 0
Depression	Medical history	Present = 1, absent = 0
Diabetes	Medical history	Present = 1, absent = 0
Diverticular disease	Medical history	Present = 1, absent = 0
Dyspepsia	Medical history	Present = 1, absent = 0
Epilepsy	Medical history	Present = 1, absent = 0
Glaucoma	Medical history	Present = 1, absent = 0
Heart failure	Medical history	Present = 1, absent = 0
Hypertension	Medical history	Present = 1, absent = 0
Osteoporosis	Medical history	Present = 1, absent = 0
Chronic pain	Medical history	Present = 1, absent = 0
Parkinson’s disease	Medical history	Present = 1, absent = 0
Pernicious anaemia	Medical history	Present = 1, absent = 0
Peripheral vascular disease	Medical history	Present = 1, absent = 0
Schizophrenia	Medical history	Present = 1, absent = 0
Stroke or TIA	Medical history	Present = 1, absent = 0
Thyroid disease	Medical history	Present = 1, absent = 0
Difficulty getting out of bed	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with household chores	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty climbing stairs	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0

Difficulty with shopping (groceries)	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficult standing	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with toilet	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited mobility	EQ5D-1	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with self-care	EQ5D-2	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited in usual activities	EQ5D-3	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety	EQ5D-5	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoglobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Platelets	baseline laboratory measures	<150 = 1, >150 = 0

To be a valid frailty index, the selected variables must meet the criteria described by Searle and colleagues in their standard procedure for assessing the frailty index (described in detail in section 3.2.2).[36] These criteria were confirmed for each of the included variables using existing literature and published population norms for the questionnaires from which deficits were identified.[24,157,236-242] Symptoms and functional limitations from the HAQ-DI and EQ-5D were selected to span a range of organ systems and functional domains. The correlation between these functional limitations was also assessed. While assessment of correlation between variables is not part of the standard procedure for a frailty index, this practice has been employed in subsequent studies operationalising the frailty index, such as the electronic frailty index used in routine healthcare data.[56] Where variables were moderately correlated (>0.3), only one variable was included in the frailty index. This decision was taken to avoid over-estimating the impact of functional limitations related to a similar process (for example joint inflammation or pain).

3.3.2.4 Assessment of outcomes

Clinical outcomes were assessed using two sources of data, standardised measures collecting during serial follow-up (assessed as described above) and linkage to routine healthcare data.

All SERA participants consented to data linkage to routinely collected healthcare data. This includes national mortality records, inpatient healthcare data through linkage to Scottish Morbidity Record (SMR01) and national prescribing registers.

3.3.2.5 Ethical approval and data management

The protocol and procedures for the SERA cohort study have been approved by the West and Scotland Research Ethics Committee (approval reference 10/S0704/20). All participants provided written, informed consent to the use of their data, including linked healthcare data, for approved research purposes. Access to SERA data is granted by a Scientific Steering Committee as well as patient representatives and governed by the SERA Access Policy.[23] Linkage to routine healthcare data was granted by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (application 1819-0176). The analyses presented in this thesis were approved by the SERA Access Committee on 29th April 2020 (project number 2020042901).

3.3.2.6 Strengths and limitations of SERA

Strengths

- Rheumatoid arthritis is defined in SERA according to validated, internationally recognised diagnostic criteria.

- SERA collects longitudinal data on measures of disease activity as well as functional measures and quality of life. This allowed longitudinal analysis of both frailty (through repeated measures of functional status) and rheumatoid arthritis disease activity.

- Linkage to routine healthcare data facilitates robust assessment of outcomes such as mortality and unscheduled hospital admission. Loss to

follow-up for these outcomes is minimal as data are linked to national registers.

Limitations

- The SERA baseline assessment was not specifically designed to measure frailty.

- It is not possible to assess alternative measures of frailty, such as the frailty phenotype, as SERA does not collect the necessary data (e.g. hand grip strength or weight loss).

3.3.3 Individual participant data from randomised controlled trials

Research question 3, the prevalence and implications of frailty in the context of randomised controlled trials (RCTs, hereafter trials), was addressed using individual participant data (IPD) from industry-sponsored trials of pharmacological agents for each of the three exemplar long-term conditions. IPD was required as trials rarely measure or report frailty, even trials focusing on older populations. Despite this, trials do collect data on a wide range of variables including medical history, concomitant medications, functional limitations, and laboratory measurements. Therefore, by obtaining IPD from trials participants, frailty could be measured using the standard approach to constructing a frailty index (as described in section 3.2.2).

3.3.3.1 Identification of RCTs

Trials were identified in a two-stage process. First, relevant trials were identified from clinicaltrials.gov. Next, from this set of eligible trials, trials for which IPD were available were identified from two repositories: the Yale Open Data Access (YODA) project, and Clinical Study Data Request (CSDR).

Clinicaltrial.gov is a registry of clinical trials which is maintained by the United States National Library of Medicine and is the largest registry of clinical trials in the world.[243] Registration of trials with clinicaltrials.gov is required for drugs to be licensed by the United States Food and Drug Administration. Therefore, although the database is maintained in the United States of America, trials

registered with clinicaltrials.gov are international. The denominator set of trials (from which trials with available IPD were selected) was identified by applying the inclusion criteria below to the clinicaltrials.gov database. This part of the process was performed prior to the start of the work presented in this thesis, as part of a wider programme of work analysing multimorbidity within clinical trials (Appendix 1).[244]

Trials were eligible if they:

- Concerned a pharmacological therapy for one of the exemplar long-term conditions (type 2 diabetes, rheumatoid arthritis or COPD).
- Recruited and randomised at least 300 participants.
- Had either a maximum age ≥60 years or no maximum age.
- Were phase 3 or phase 4 randomised controlled trials.
- Started after 1st January 1990.

After identifying potentially eligible trials registered with clinicaltrials.gov, YODA and CSDR repositories were searched to identify any trials for which IPD could be obtained through application to the data holders. Both of these platforms facilitate the analysis of industry-sponsored RCT data by third party researchers. YODA carries data from trials by Janssen Research and Development L.L.C. CSDR, at the time this analysis was conducted, facilitated access to trials sponsored by GlaxoSmithKline, Lilly, Boehringer-Ingelheim, Roche, Takeda and Sanofi. These trials are not a random sample of trials for the exemplar conditions as not all sponsors share IPD from trials, and those that do share data do not make all trials available. This process therefore identified a sample of trials for the exemplar conditions meeting the inclusion criteria, however, these trials are not necessarily representative of all trials for these conditions.

3.3.3.2 Individual participant data

Both YODA and CSDR allow access to trial IPD, subject to a material transfer agreement. Access is facilitated through a secure, remote platform. All data

processing and analyses must be performed within this secure environment. Only non-disclosive summary data can be exported from these secure environments, subject to approval by the data holders.

Within these secure environments, IPD for screening, baseline and follow-up assessments are available, as well as trial outcome data and details of adverse events. However, some data are redacted to ensure that data are not disclosive. This redaction process varies by sponsor and by trial, and therefore limits the availability of some variables.

3.3.3.3 Identifying deficits for a frailty index

As with UK Biobank and SERA, a frailty index was constructed from the trial IPD using the standard approach described by Searle and colleagues.[36] This involved identifying sufficient deficits (at least 30) which met the criteria for inclusion in the frailty index (association with age, poor health, and being neither too rare nor too common, as described in detail above). Information on long-term conditions meeting these criteria were sought from medical history data and prescribing data. Functional limitations and symptoms were identified from patient reported outcome measures (health-related quality of life and disease severity scores) and laboratory deficits were identified from baseline assessment. The full list of included deficits is shown in Table 3.4, Table 3.5 and Table 3.6. The text that follows describes the process for identifying and defining these deficits.

Long term conditions

Identifying long-term conditions from baseline trial data was challenging because of inconsistent coding and redaction of data in many trials. Before the data had been obtained, plans had been to use medical history to identify long-term conditions. However, after accessing the trial data, it became clear that for many trials medical history data within the trial IPD had either not been collected in sufficient detail (for example, only coding the presence or absence of ‘cardiovascular disease’ without further detail) or had been redacted by the trial sponsor to preserve patient anonymity prior to releasing IPD for third party analysis.

In contrast to medical history data, concomitant medications were reported in all available trials without redaction. Furthermore, medications were consistently coded using the World Health Organisation Anatomic Therapeutic Classification (WHO-ATC). Therefore, concomitant medications were used to identify likely comorbidities.

Only medications which were reported to have been started prior to trial baseline were used to define comorbidities. While concomitant medications have been previously used to identify comorbidities in epidemiological studies, no standard approach exists to define comorbidities using medication alone. Therefore, in consultation with a steering committee for a separate project analysing multimorbidity in trial IPD, definitions were developed based on WHO-ATC codes.[244] Some misclassification of comorbidities is inevitable, as medications typically have more than one indication, and some conditions may not be managed using medication. The approach developed is therefore a balance between sensitivity and specificity.

Decisions around definitions were taken to maximise specificity where possible. For example, aspirin was excluded from the group of drugs used to identify cardiovascular disease as aspirin is commonly used for primary prevention. Anti-acid medications (WHO-ATC codes A02A or A02B) were used to identify people with acid-related disorders, but not if participants also reported taking nonsteroidal anti-inflammatory drugs or antithrombotic medication (as in this case it is possible that the anti-acid medications were being used prophylactically rather than to treat an underlying condition). This approach was taken to define comorbidities (or identify broad categories of comorbidities).

The advantage of this approach was that definitions would be applied consistently to each trial, using data which were coded according to an established ontology. However, using medications in this way has important limitations. Some common and important long-term conditions, such as chronic kidney disease, could not be identified using medication. Other conditions (such as asthma and COPD) had to be grouped together in broad categories as these could not be distinguished by medication use alone. Finally, some medications could not be used in our definitions as their use in clinical practice is too heterogenous to allow assessment of the likely underlying diagnosis (for

example, amitriptyline was not used to define any comorbidities as although classed as an antidepressant in the WHO-ATC, it is commonly used to treat chronic pain or insomnia in clinical practice).[245]

The medication-defined comorbidities included in the frailty index for each of the trials is shown in Table 3.4, Table 3.5 and Table 3.6 for type 2 diabetes, rheumatoid arthritis and COPD, respectively. A full protocol for the identification of comorbidities in trial data using concomitant medication is detailed in the supplementary appendix of Hanlon et al 2019 (manuscript in appendix 1).

Symptoms and functional limitations

Symptoms and functional limitations were identified from standardised questionnaires used as part of trial baseline assessments. These questionnaires varied depending on the index condition of the trial (e.g. St George's Respiratory Questionnaire in COPD, HAQ-DI in rheumatoid arthritis). There was also some variation in questionnaires within conditions (for example quality of life was assessed using EQ-5D in some trials, and short-form 36 (SF-36) in others). Where possible, equivalent questions were identified across quality of life questionnaires.

Deficits were selected so that the same definitions could be applied for trials of the same index condition. There was some variation, however, between conditions.

For type 2 diabetes trials, functional limitations and symptoms were identified using EQ-5D or SF-36 (limited to questions common to both questionnaires) and the Impact of Weight on Quality of Life (IWQOL) questionnaire. IWQOL includes variables on more specific functional limitations (e.g. difficulty dressing or shortness of breath on mild exertion). It should be noted, however, that these questions are framed within an assessment of the impact of body weight and may therefore lack sensitivity for people who experience similar functional limitations but for other reasons (e.g. joint pain or muscle weakness).

For rheumatoid arthritis trials, deficits were identified from HAQ-DI and EQ-5D using the same definitions and cut-offs as for the SERA dataset described above.

Where trials used SF-36 rather than EQ-5D, equivalent questions for pain, anxiety, mobility, self-care and difficulty with usual activities were used.

For COPD trials, the only questionnaire that was consistently used across all available trials was the St George Respiratory Questionnaire (SGRQ). SGRQ assess a wide range of deficits (for example, difficulty dressing, difficulty shopping, feeling easily exhausted, feeling of panic). However, like the IWQOL in type 2 diabetes, these questions are being asked within the context of the underlying condition. Therefore, there is potential that functional limitations that participants felt were unrelated to the COPD may not be fully reported as part of the questionnaire.

Deficits were selected for inclusion in the frailty index where they were confirmed on independent literature review to fulfil the standard criteria for frailty index deficits (association with age, poor health status, and neither too rare nor too common).[237-242,246,247] In addition, as for SERA, the correlation between each of the possible deficits was calculated and where two or more variables were moderately correlated only one variable was selected for inclusion. Where correlation was present (>0.3), deficits were selected to maximise the number of organ systems or functional domains represented within the final set of deficits.

Laboratory values and physical measurements

Baseline data from laboratory assessment was used to identify additional deficits.

Final selection of deficits

From the processes described above, for each of the respective index conditions, 40 deficits were identified for inclusion in the frailty index. These are shown for each condition in Table 3.4, Table 3.5 and Table 3.6, respectively.

Table 3.4 - Frailty index deficits for trials of type 2 diabetes

Diabetes trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboembolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Arthritis and arthralgia	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthropathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional disorders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0
Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parkinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty picking up objects	IWQOL1	Present = 1, absent = 0
Difficulty getting up from chairs	IWQOL3	Present = 1, absent = 0
Trouble with stairs	IWQOL4	Present = 1, absent = 0
Difficulty dressing	IWQOL5	Present = 1, absent = 0
Difficulty with mobility	IWQOL6	Present = 1, absent = 0
Short of breath on mild exertion	IWQOL8	Present = 1, absent = 0
Self-rated health	EQ5D/SF36-1	((Total out of 100)-100)/100
Limited mobility/difficulty walking several blocks	EQ5D-1/SF36-10	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with self-care	EQ5D-2/SF36-12	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0

Limited in usual activities	EQ5D-3/SF25-32	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4/SF36-21	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety or Down in dumps	EQ5D-5/SF36-25	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoglobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0
Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Cholesterol	baseline laboratory measures	>6.2 mmol/L = 1, <6.2 = 0
Systolic blood pressure	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

Table 3.5 - Frailty index deficits for trials of rheumatoid arthritis

Rheumatoid arthritis trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboembolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthropathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional disorders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0
Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parkinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty getting out of bed	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with household chores	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty climbing stairs	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with shopping (groceries)	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficult standing	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with toilet	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0

Self-rated health	EQ5D/SF36-1	((Total out of 100)-100)/100
Limited mobility	EQ5D-1/SF36-10	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with self-care	EQ5D-2/SF36-12	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited in usual activities	EQ5D-3/SF25-32	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4/SF36-21	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety	EQ5D-5/SF36-25	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoglobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0
Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Glucose	baseline laboratory measures	>11 mmol/L = 1, >7 = 0.5, <7 = 0
Cholesterol	baseline laboratory measures	>6.2 mmol/L = 1, <6.2 = 0
Systolic blood pressure	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

Table 3.6 - Frailty index deficits for trials of COPD

COPD trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboembolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Arthritis and arthralgia	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthropathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional disorders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0
Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parkinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty with Stairs	SGRQ	Present = 1, absent = 0
Difficulty with Dressing	SGRQ	Present = 1, absent = 0
Difficulty with Housework	SGRQ	Present = 1, absent = 0
Difficulty with Shopping	SGRQ	Present = 1, absent = 0
Difficulty with Sports	SGRQ	Present = 1, absent = 0
Bath/shower long time	SGRQ	Present = 1, absent = 0
Everything too much effort	SGRQ	Present = 1, absent = 0
Feel that exercise not safe for me	SGRQ	Present = 1, absent = 0
Feel frail because of chest	SGRQ	Present = 1, absent = 0
Panic	SGRQ	Present = 1, absent = 0
Exhausted easily	SGRQ	Present = 1, absent = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoglobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)

Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0
Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Glucose	baseline laboratory measures	>11 mmol/L = 1, >7 = 0.5, <7 = 0
Systolic BP	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

3.3.3.4 Analysing Serious Adverse Events

A key feature of frailty is its association with adverse health outcomes. Therefore, to assess whether frailty identified in the trial setting has this expected association, Serious Adverse Events were assessed as an outcome. In a trial setting, Serious Adverse Events comprise any event which results in death, results in or prolongs hospitalisation, is life-threatening, causes lasting impairment or disability, or causes a birth defect.[248] In practice, most Serious Adverse Events are accounted for by hospitalisations or deaths. Trial sponsors are required to record and report Serious Adverse Event regardless of their relationship to the trial treatment (i.e. all events meeting this definition are recorded).

3.3.3.5 Strengths and limitations of trial data

The trial data on which these analyses are based have several strengths and limitations:

Strengths:

- These are ‘standard’ phase 3 or 4 industry-sponsored drug trials. A separate analysis of the trials for which IPD were available, compared to all eligible trials registered with clinicaltrials.gov, showed that IPD trials were similar in terms of start date, study design, number of participants enrolled, and indication for the drug under evaluation (appendix 1).[244]

- Access to IPD allows analysis of frailty in trials which do not explicitly measure or report frailty, and therefore has potential to lead to new insights around the prevalence and implications of frailty in trials.

- Trials use standardised measures (e.g. quality of life questionnaires) and coding systems (WHO-ATC classification for concomitant medications) which allowed consistent definitions to be applied across multiple trials within the same index condition.

- Reporting of Serious Adverse Events is a regulatory requirement for drug licensing, which implies that these outcomes are likely to be recorded accurately and consistently.

Limitations

- Despite being broadly similar to the wider body of trials, IPD trials are not a random sample and may not be representative of trials as a whole.

- Furthermore, the necessary data to identify deficits for the frailty index may not be collected by all trials. This may lead to further selection bias in the sample of trials for which frailty could be assessed.

- Trials did not consistently record, or (as a result of algorithmic approaches designed to protect participant privacy) redacted, medical history data, meaning that concomitant medications had to be used to identify long-term conditions. This is likely to lead to some misclassification.

- Functional limitations often had to be identified using instruments specific to the index condition (e.g. HAQ-DI and SGRQ). The frailty index may therefore be more sensitive to functional limitations caused by the index condition in the trial compared with deficits caused by other conditions or pathological processes.

3.4 Chapter summary

This chapter set out the models of frailty which will be analysed in this thesis – the frailty phenotype and the frailty index – as well as detailing the data sources that will be used in the analyses presented in the subsequent results chapters. This provides a theoretical basis for the inclusion of each of these frailty models, as well as outlining their strengths and weaknesses. The specific analyses undertaken using each of these models, and in each of the respective datasets, are described in the chapters that follow.

Chapter 4 Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis

4.1 Chapter summary

This chapter presents a systematic review of observational studies addressing research question 1 (the prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in the context of diabetes.

The text and figures presented here are as published in Hanlon P, Fauré I, Corcoran N, Butterly E, Lewsey J, McAllister D, Mair FS. Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis. The Lancet Healthy Longevity. 2020 Dec 1;1(3):e106-16.

The published protocol for this review is in appendix 2, as published in Hanlon P, Fauré I, Corcoran N, Butterly E, Lewsey J, McAllister DA, Mair FS. Identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: a systematic review protocol. BMJ open. 2020 Sep 1;10(9):e037476.

4.2 Abstract

Background: Frailty, a state of increased vulnerability to adverse health outcomes, is important in diabetes management. We aimed to quantify the prevalence of frailty in people with diabetes, and to summarise the association between frailty and generic outcomes (e.g., mortality) and diabetes-specific outcomes (e.g., hypoglycaemia).

Methods: In this systematic review and study-level meta-analysis, we searched MEDLINE, Embase, and Web of Science for observational studies published between Jan 1, 2001 (the year of the original publication of the Fried frailty phenotype), to Nov 26, 2019. We included studies that assessed and quantified frailty in adults with diabetes, aged 18 years and older; and excluded conference abstracts, grey literature, and studies not published in English. Data from eligible studies were extracted using a piloted data extraction form. Our primary outcome was the prevalence of frailty in people with diabetes. Secondary outcomes were incidence of frailty and generic and diabetes-specific outcomes. Data were assessed by random-effects meta-analysis where possible and by narrative synthesis where populations were too heterogeneous to allow meta-analysis. This study is registered with PROSPERO, CRD42020163109.

Findings: Of the 3038 studies we identified, 118 studies using 20 different frailty measures were eligible for inclusion (n=1 375 373). The most commonly used measures of frailty were the frailty phenotype (69 [58%] of 118 studies), frailty index (16 [14%]), and FRAIL scale (10 [8%]). Studies were heterogenous in setting (88 studies were community-based, 18 were outpatient-based, ten were inpatient-based, and two were based in residential care facilities), demographics, and inclusion criteria; therefore, we could not do a meta-analysis for the primary outcome and instead summarised prevalence data using a narrative synthesis. Median community frailty prevalence using frailty phenotype was 13% (IQR 9–21). Frailty was consistently associated with mortality in 13 (93%) of 14 studies assessing this outcome (pooled hazard ratio 1·51 [95% CI 1·30–1·76]), with hospital admission in seven (100%) of seven, and with disability in five (100%) of five studies. Frailty was associated with hypoglycaemia events in one study, microvascular and macrovascular complications in nine (82%) of 11 studies assessing complications, lower quality of life in three (100%) of three

studies assessing quality of life, and cognitive impairment in three (100%) of three studies assessing cognitive impairment. 13 (11%) of 118 studies assessed glycated haemoglobin finding no consistent relationship with frailty.

Interpretation: The identification and assessment of frailty should become a routine aspect of diabetes care. The relationship between frailty and glycaemia, and the effect of frailty in specific groups (e.g., middle-aged [aged <65 years] people and people in low-income and lower-middle-income countries) needs to be better understood to enable diabetes guidelines to be tailored to individuals with frailty.

4.3 Research in context

4.3.1 Evidence before this study

We searched MEDLINE, Embase, and Web of Science from Jan 1, 2001, to Nov 26, 2019, for observational studies published in English that assessed frailty in diabetes (type 1, type 2, or unspecified) using the terms “diabetes” and associated terms and “frail”. We included studies using any frailty measure and done in any setting. We did not identify any existing systematic reviews that synthesise data on the prevalence of frailty in people with diabetes. One review (eight studies) showed increased risks of mortality and cardiovascular events in people with diabetes and frailty, but did not distinguish between different definitions of frailty, nor did it consider other clinical outcomes.

4.3.2 Added value of this study

This study shows that frailty is common in diabetes. However, the methods used to identify and define frailty are highly variable between studies. Within the same population, some definitions (e.g., frailty index) identify a higher proportion of people as frail than do others (e.g., frailty phenotype). Despite this variation in measurement, frailty is consistently associated with a range of adverse outcomes, including mortality, hospital admission, disability, and lower quality of life. Important evidence gaps remain. Frailty is present in middle-aged (aged <65 years) and older people (>65 years) with diabetes; however, variation in prognosis or association with outcomes at different ages has not been widely explored. Evidence from lower-income and lower-middle-income countries is scarce, which is an important gap because of the rising prevalence of diabetes, along with an increasing proportion of older people, in many countries. The absolute risk of mortality associated with frailty is highly variable between studies and frailty definitions. The relationship between glycated haemoglobin (HbA1c) and adverse outcomes in frail versus non-frail individuals has not been quantified in the literature, and only one study has assessed the relationship between frailty and hypoglycaemia. These are important research gaps, as clinical guidelines recommend different HbA1c targets in the context of frailty, and lower life expectancy forms part of the rationale for these targets.

4.3.3 Implications of all the available evidence

Identifying and assessing frailty should become a routine aspect of diabetes care, which will require frailty screening to become embedded within existing protocols and systems for managing diabetes. There is also a need for a more nuanced understanding of how frailty should be identified and characterised, including the implications of the choice of frailty measure. This is particularly important if clinicians are to identify people likely to benefit from guideline recommendations for managing diabetes in the context of frailty. As these guidelines focus on glycaemic targets, the scarcity of studies exploring the relationship between frailty, HbA1c, and clinical outcomes is an important research gap. Because frailty is also prevalent in middle-aged people with diabetes, there is a need to question and explore the clinical implications of frailty across a wider age range, as the basis for current guideline recommendations is based on observations from older populations.

4.4 Introduction

Clinicians and health-care systems worldwide are facing the challenges associated with ageing populations. Diabetes (type 1 and type 2) is prevalent in up to 30% of people older than 65 years.[249] Frailty is a key concept for health care, particularly as people age.[3] Frailty describes a dynamic state of increased vulnerability to adverse health outcomes resulting from loss of physiological reserve.[3] The prevalence of frailty increases with increasing age.[3] However, frailty is not universal among older people (aged >65 years), and can also be identified in younger people (aged <65 years), particularly in the context of long-term conditions, including diabetes.[9,250]

The importance of frailty is increasingly recognised in clinical guidelines for diabetes management.[19,251] Specifically, more relaxed glycated haemoglobin (HbA1c) targets are recommended among people who are older or living with frailty.[251] These recommendations are based on lower life expectancy and greater risks of hypoglycaemia in older individuals with frailty.[19] However, guidelines are not explicit about to whom these recommendations should be applied. Frailty is not a single homogeneous concept, and there is no single standard definition or measure.[3] Instead, multiple operational definitions of frailty exist.[32] Some are based on characteristics which are measured directly (frailty measures based on physical assessments such as grip strength and walking pace) or self-reported measures, and others on past medical records. Definitions also vary in their inclusion of cognitive status, social vulnerability, and functional disability.[252] Differences in the definition and identification of frailty can alter the clinical implications for management.[11]

There is, therefore, uncertainty as to how frailty should be identified, measured, and managed, including in the context of diabetes. Because of the complex and multifaceted nature of frailty, understanding its relationship with a broad range of outcomes is important to inform clinical decision making around care and treatment. This systematic review aims to: first, identify frailty measures that have been used to identify frailty in people with diabetes; second, quantify the prevalence of frailty in people with diabetes; and, third, summarise the association between frailty and generic outcomes (e.g.,

mortality), and diabetes-specific clinical outcomes (e.g., hypoglycaemia) in the context of diabetes.

4.5 Methods

4.5.1 Search strategy and selection criteria

We did a systematic review and study-level meta-analysis of observational studies assessing frailty in the context of diabetes. Methods were prespecified and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Criteria for inclusion are described in detail in the review protocol,[253] and were deliberately broad in terms of setting, frailty definition, and outcomes. We included studies done in any setting (community, outpatient, inpatient, and residential care). Criteria included observational studies, including cross-sectional and cohort studies, that included adults (≥18 years) with diabetes (any type or unspecified) and quantified frailty in participants with diabetes, using any frailty measure or definition to allow comparison between different methods of identifying frailty. Exclusion criteria were grey literature, conference abstracts and any studies not published in English.

We searched MEDLINE, Embase, and Web of Science databases between Jan 1, 2001 (which was the year of the original publication of the Fried frailty phenotype),[5] to Nov 26, 2019, using keywords and Medical Subject Headings. The search structure was “diabetes” and “frail” (full search strategy in appendix 3). We screened all titles and abstracts and assessed full texts of all relevant articles for eligibility. We supplemented electronic searches by hand-searching reference lists of relevant articles and forward-citation searching using Web of Science. All stages of screening, data extraction, and quality assessment were done independently by two authors (PH and IF, NC, or EB). Discrepancies were resolved by consensus and by a third author (NC or EB).

4.5.2 Data analysis

Data from eligible studies were extracted using a piloted data extraction form. Differences in data extraction between reviewers were resolved by consensus. We extracted data for study aims, study design, setting, population characteristics (eligibility, recruitment method, summary data for age and sex), diabetes type (type 1, type 2, unspecified), frailty measure (including whether

criteria were adapted from the original description of the frailty definition), prevalence of frailty in participants with diabetes, and the association between frailty and clinical outcomes. The risk of bias in the included studies was assessed using an adaptation of the Newcastle-Ottawa tool to make the questions about exposure specific to the assessment of frailty (e.g., use of a validated tool) (appendix 3).[254]

Our primary outcome was prevalence of frailty in people with diabetes. Secondary outcomes were incidence of frailty, generic healthcare associated outcomes (including mortality, hospitalisation, health-care utilisation, quality of life, disability, cognitive impairment, and depression), and diabetes-specific outcomes (glycaemic control, macrovascular and microvascular complications).

Estimates of the prevalence of frailty in diabetes are likely to vary depending on the characteristics of the underlying population (e.g., age, sex, and ethnicity), definition of diabetes, frailty definition used, adaptations to frailty criteria, and study setting. Because of these multiple sources of heterogeneity, we did a narrative synthesis of prevalence estimates incorporating these features. The quality of the included studies (judged by the quality assessment) was incorporated into the narrative synthesis presented in the text (e.g., highlighting where samples were unrepresentative and length of follow-up).

Due to the high likelihood of residual heterogeneity between populations and cohort inclusion criteria, we did not do a meta-analysis of these estimates.[255]

Studies reporting the relationship between frailty and clinical outcomes in diabetes were synthesised using a combination of narrative synthesis and random-effects meta-analysis. A meta-analysis was done only when there were at least two studies assessing the same outcome, using a comparable method of analysis (i.e., the same statistical approach was used [e.g., Cox proportional hazard model of time to event data for mortality]). Where these studies used the same measure of frailty, a summary estimate was calculated, and heterogeneity assessed using I^2 statistic. Where different frailty measures were used to assess the same outcome, studies were grouped by frailty measure and meta-analysed in subgroups (prespecified in the protocol).[253] Where outcomes or analytic approaches were too heterogeneous, a narrative synthesis was done and

data summarised using Harvest plots.[256] Harvest plots use bars to represent individual studies placed on a matrix to indicate whether the studies showed a positive, negative, or neutral association with the outcome in question, and allow synthesis of heterogeneous outcome data. Data processing and analysis was done using R (version 3.6.1). Meta-analyses were done using RevMan5.

This study is registered with PROSPERO, CRD42020163109.

4.5.3 Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4.6 Results

After screening 3038 records, we identified 118 (which included 106 cohorts and samples) that met our inclusion criteria (1 375 373 participants overall; Figure 4.1).[5,9,81,84,250,257-370] Details of each included study are summarised in appendix 3.

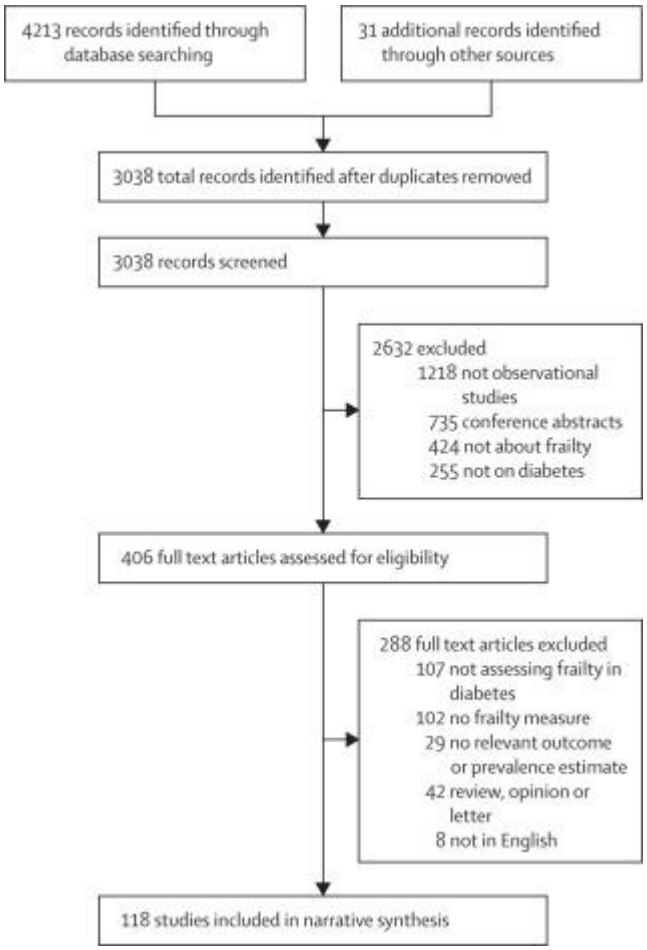

Figure 4.1: PRISMA diagram of study selection

Most studies were community-based population studies (88 [75%]), 18 (15%) were outpatient studies, ten (8%) were inpatient studies and two (2%) studies were based in residential care facilities. Studies were from a wide range of geographical locations (appendix 3). Most studies were from high-income (88 [75%] of 118 from 18 countries) or from upper-middle-income countries (27 [23%] from five countries), three studies (3%) were from three lower-middle-income countries and none were from low-income countries. 25 (21%) of 118 studies included people with type 2 diabetes specifically and in 93 (79%) studies the type of diabetes was unspecified. 30 (25%) of 118 studies specifically recruited

people with diabetes, while in the remaining 88 (75%) studies, people with diabetes were a subgroup of the study population. Eight (7%) studies assessed specific ethnic groups (one study with African Americans, six studies with three different cohorts of Mexican Americans, and one study with Aboriginal Australians). A wide variety of frailty measures (either validated or well described) were used in the included studies: 20 different measures in total (Table 4.1). The frailty phenotype was used in 69 (58%) studies; however, in 51 (74%) of these studies the definition of one or more of the five frailty criteria differed from the original description from the Cardiovascular Health Study.[5] The frailty index (16 [14%] studies) and FRAIL scale (10 [8%] studies) were also frequently used. The remaining 23 studies used other measures of frailty (Table 4.1).

In the 118 included studies, the median number of people with diabetes was 205 (IQR 104–570). Study populations were heterogeneous. Mean age ranged from 50·4 years to 88·0 years (median 72·8 [IQR 69·6–74·4]). Eight (9%) of 88 community-based studies analysed adults of any age. Of these 88 studies, 72 (82%) sampled people above a specified age cut-off (most commonly aged 60 [ten studies] or 65 years [39 studies]). Eight (9%) of 88 studies assessed specific age ranges, with three of these studies including middle-aged people (age ranges 37–73 years, 45–74 years, and 49–65 years). Most community-based studies were judged to be representative in terms of age and sex (determined by sampling methods, response rates and demographics of people included); however, very few reported differences between included participants and non-responders. 14 community-based studies focused on specific populations (i.e., four studies on men, two on women, and eight on specific ethnic groups). Whole population studies varied in their sampling method (household survey, postal invitation, stratified sampling, or routine data analysis) and in their exclusion criteria. For example, 81 (69%) of 118 excluded individuals who were institutionalised (e.g., living in residential care or nursing homes), people with restricted mobility (unable to attend an assessment), people with cognitive impairment, or people with specific disorders (e.g., neurological conditions such as Parkinson's disease or stroke, often when the study included assessments of mobility or functional status). As many of these factors have established associations with frailty, it is

likely that variation in these population characteristics will influence the estimated prevalence of frailty in the studies.

Table 4.1: Frailty measures in included studies

Frailty measure	Components	Range and categorisation	Included studies (n)	Outcomes reported in included studies
Frailty phenotype	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	69	Mortality (n=2), HbA1c (n=1), complications (n=1), cognitive impairment (n=2), disability (n=1), QOL (n=1).
Frailty index	Count of health-related deficits (≥30, type and number of chosen deficits may vary between studies). Total present divided by number of possible deficits	Range 0-1 Sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24)	16	Mortality (n=3), hospitalisation (n=1), HbA1c (n=1), complications (n=1), disability (n=1).
FRAIL scale	5 components (weight loss, fatigue, weakness, ambulation, illness/comorbidity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	10	Mortality (n=4), hospitalisation (n=4), ED visit (n=2), disability (n=2), complications (n=2), depression (n=1).
Clinical frailty scale	Clinical tool based on functional status.	Ranges 1 (very fit) to 9 (terminally ill). Some dichotomise as ≥5 = frail.	5	Mortality (n=2), HbA1c (n=2), complications (n=1)
Edmonton frailty scale	9 components: cognition, general health, functional independence, social support, medication, nutrition, mood, continence and functional performance.	Score 0-17. Mild (7-8), moderate (9-10) and severe frailty (≥11).	4	Complications (n=2), depression (n=1), QOL (n=1).
John Hopkins adjusted clinical groups	Weighted comorbidity score identified from electronic medical records	Presence of frailty identified by specific indicator conditions.	3	HbA1c (n=1), complications (n=1)
Kihon checklist	Self-administered checklist (components: activities of daily living, exercise, falling, nutrition, oral health, cognition, depression)	Range 0-25. Pre-frail (4-7), Frail (≥8).	3	None
Comprehensive geriatric assessment	Multidisciplinary assessment, typically led by a geriatrician, aiming to reach a holistic assessment of health and wellbeing.	Frailty identified by clinical judgement rather than pre-defined criteria	2	Hospitalisation (n=1), hypoglycaemia (n=1), complications (n=1), depression (n=1), cognitive impairment (n=1), QOL (n=1).
Electronic frailty index	Count of deficits identified from electronic medical records, based on the Frailty index approach.	Mild (0.12-0.24), moderate (0.24-0.36) and severe frailty (≥0.36)	2	HbA1c (n=1), complications (n=1).

Frailty risk class	List of 'indicator conditions' identified from electronic medical records.	Presence of frailty identified by specific indicator conditions.	2	Mortality (n=1).
Frailty risk score	Count of 16 frailty 'risk factors' (symptoms, behavioural factors, biomarkers, nutritional factors)	Range 0-16	1	Mortality (n=1), hospitalisation (n=1), HbA1c (n=1).
Frailty staging system	7 components (disability, mobility, cognition, vision, hearing, continence, social support).	Range 0-7. Mild (1) moderate (2-3) or severe frailty (≥4).	1	Mortality (n=1), cognitive impairment (n=1)
Frailty trait score	12 items across 7 components (nutrition, activity, nervous system, vascular system, weakness, endurance, and slowness).	Range 0-49	1	None
Gill index	Composite of chair stand and walking speed tests.	Moderate (unable to perform one element) or severe frailty (both elements)	1	None
Groningen frailty indicator	15 items across 4 domains (physical, cognitive, social and psychological).	Range 0-15 ≥4 indicates frailty	1	None
Modified physical performance test	9 item instrument assessing physical tasks.	Range 0-36. Moderate (22-29) and severe frailty (≤21).	1	Complications (n=1)
QFrailty	Algorithm based on electronic medical records combining mortality (QMortality score) and hospital admission (QAdmission score) risk.	Categorised as mild, moderate and severe frailty.	1	None
RAND-36 questionnaire	Physical function sub-scale of the RAND-36 questionnaire.	Range 0-100. Score <80 taken to indicate frailty.	1	Mortality (n=1), complications (n=1).
Study of Osteoporotic Fracture frailty indicator	3 components (weight loss, chair stand, exhaustion)	1 component: prefrail 2-3 components: frail	1	None
Vulnerable Elders Survey (VES-13)	Telephone questionnaire with 13 components (age, self-rated health, physical function and disability)	Score ≥4 = frail.	1	HbA1c (n=1), complications (n=1).
Footnote: Three studies used more than one frailty measure.				

The prevalence of frailty in people with diabetes is shown in Figure 4.2, with estimates from each study expressed as a proportion (with 95% CIs). Results are stratified by setting and frailty definition and ordered by mean age of the study population. Prevalence estimates varied widely. Median community frailty prevalence using frailty phenotype was 13% (IQR 9–21). Studies with a lower mean age tended to show lower frailty prevalence, particularly those studies without a lower age cut-off. However, prevalence was mixed even among populations with similar mean age and using the same frailty measure (particularly in community-based studies using the frailty phenotype). These differences in results might reflect a combination of differences in the underlying population, variation in exclusion criteria and in methods of recruitment affecting representativeness of the sample, and differences in how frailty components were specified.[200] Three (3%) of 118 studies used both the frailty index and frailty phenotype.[258,288,371] In each of these studies, the percentage of people identified as frail was higher using the frailty index (53%, 30%, and 32%) compared to using the frailty phenotype (23%, 26%, and 24%), highlighting the sensitivity of frailty prevalence to the measure used. Frailty prevalence was also notably high in some ethnic groups (e.g., African Americans and Aboriginal Australians) and lower in others (e.g., Mexican Americans).[250,295,304]

Diabetes was consistently associated with frailty prevalence after adjustment for age, sex, and other risk factors. Furthermore, diabetes was associated with a greater degree of frailty when assessed using the frailty index.

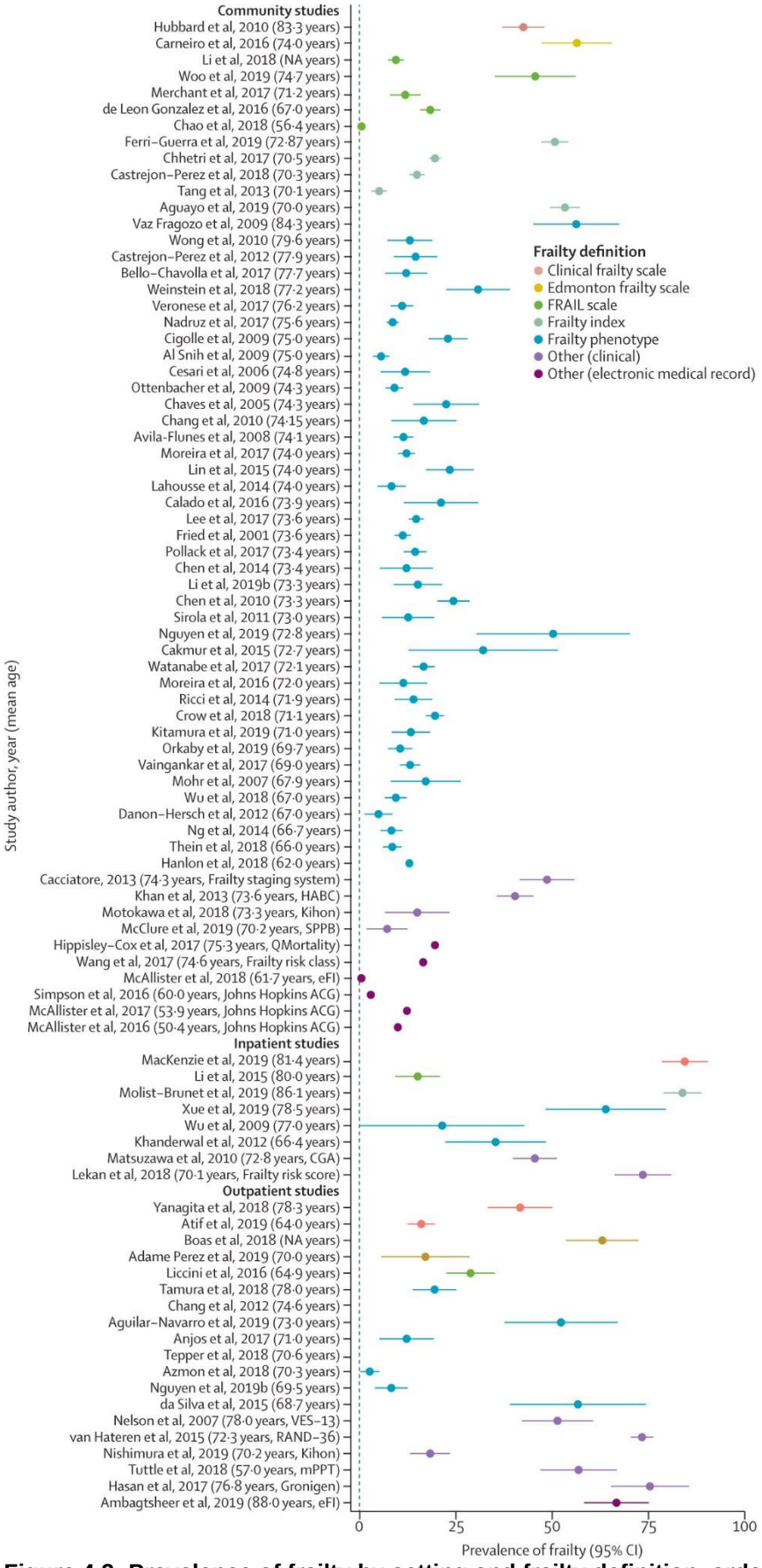

Figure 4.2: Prevalence of frailty by setting and frailty definition, ordered by mean age of study population. Full list of references of all the studies mentioned is included in the appendix 3. eFI=electronic frailty index. ACG=adjusted clinical groups. CGA=comprehensive geriatric assessment. VES-13=vulnerable elders survey RAND-36=research and Development Corporation. Kihon=Kihon checklist. mPPT-modified physical performance test. Groningen=Groningen frailty indicator.

Eight (9%) of 88 community-based studies assessed the incidence of frailty, all using the frailty phenotype, among people who did not meet criteria for frailty at baseline. In each of these studies, diabetes was included as one of a range of baseline factors associated with the development of frailty. Meta-analysis of these studies shows that diabetes was consistently associated with the development of frailty (pooled odds ratio 1·48 [95% CI 1·33–1·64]; Figure 4.3). Heterogeneity between study estimates was low (I^2=0%) despite variation in the length of follow-up and the variables in each model. The only study assessing the association between HbA1c and changes in frailty status showed that a higher HbA1c at baseline was associated with worsening frailty over a 10-year period measured using the frailty index. Three studies (3%) of 118 assessed transitions between frailty phenotype states and found that people with diabetes were less likely to improve from a frail to a pre-frail or robust state compared to people without diabetes.[297,342,372] Together, these data provide evidence that diabetes, and perhaps poor glycaemic control, are risk factors for the development and persistence of frailty.

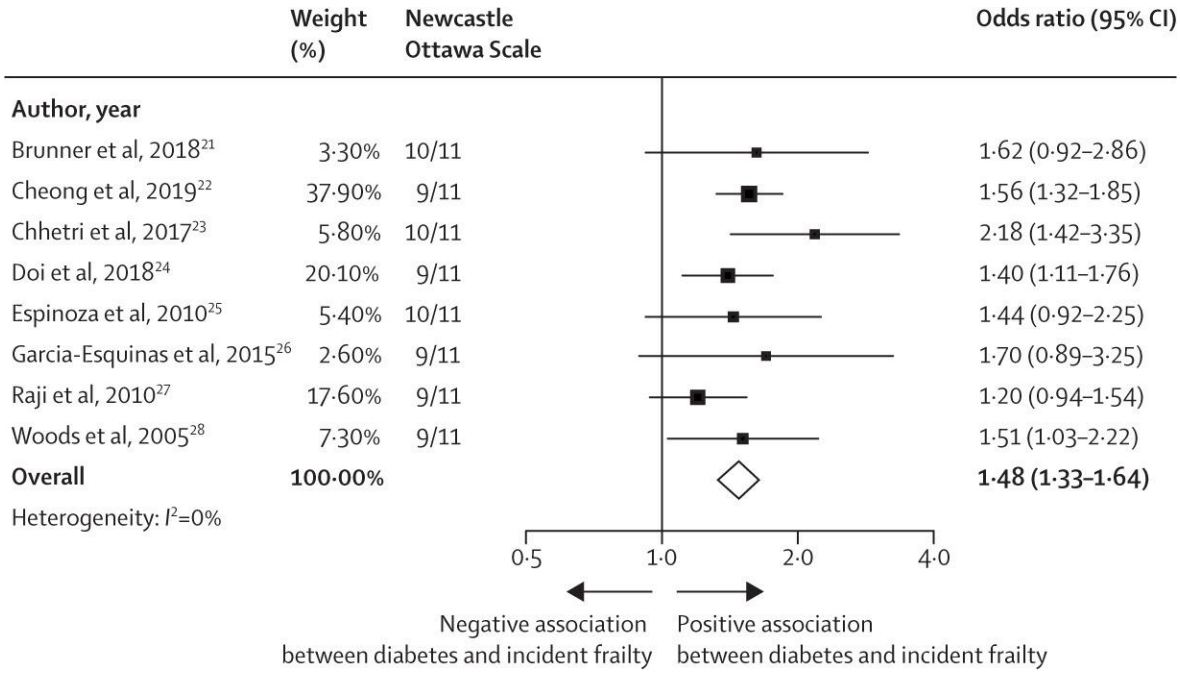

Figure 4.3: Random-effects meta-analysis of odds of incident frailty associated with diabetes

14 (12%) of 118 studies, using eight different frailty measures, assessed the relationship between frailty and all-cause mortality in people with diabetes. Eight of these used time-to-event analyses and were included in a meta-analysis,

with each frailty measure as a separate subgroup (Figure 4.4). Frailty was consistently associated with mortality (pooled hazard ratio 1·51 [95% CI 1·30–1·76]); however, the relative effect size varied considerably between studies using different frailty measures (I^2=88% showing high heterogeneity).

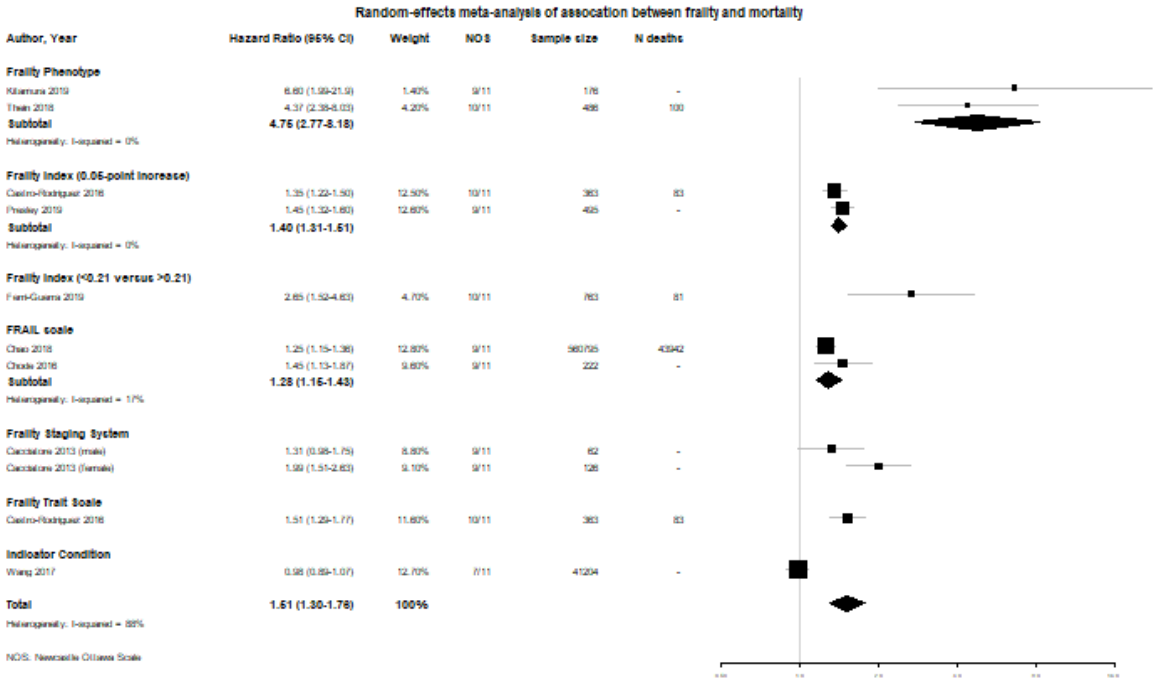

Figure 4.4: Random effects meta-analysis of association between frailty and mortality

Studies varied in length of follow-up, covariate adjustment, and method of mortality assessment, limiting comparison of the absolute mortality rates associated with frailty in diabetes. However, the absolute mortality rate associated with frailty clearly differed between studies. In one study,[321] hospitalised older patients with diabetes and frailty, according to the Clinical Frailty Scale, had a median life expectancy of 23 months. Mortality incidence in people with frailty was 60 per 1000 person-years in one study using the frailty phenotype in Japan (mean age 72 years),[308] and 161 per 1000 person-years in another study using the FRAIL scale in Taiwan (mean age 71 years).[281] Crude mortality rates in three different studies at 10-year follow-up were 50% using the frailty risk class,[270] 68% using the frailty phenotype,[352] and 96% using the frailty staging system.[359]

Frailty is therefore consistently associated with all-cause mortality in people with diabetes. However, the method used to assess frailty, along with the underlying population, can lead to wide variation in both the relative and absolute risk of mortality in people identified as frail.

Studies assessing frailty and health-care utilisation are summarised in Figure 4.5. Details on study methods and effect sizes are presented in the appendix 3. Frailty was consistently associated with increased risk of hospitalisation and with emergency department visits in people with diabetes.

Frailty was consistently associated with disability in five (4%) of 118 studies.[250,277,317,319,352] Three of these were cross-sectional, while two showed associations between frailty and incident disability over variable lengths of follow-up. Cross-sectional studies also showed associations between frailty and cognitive impairment (three studies), depression (two out of three studies), and lower quality of life (three studies).

The relationship between frailty and diabetes-specific characteristics are shown in Figure 4.5.

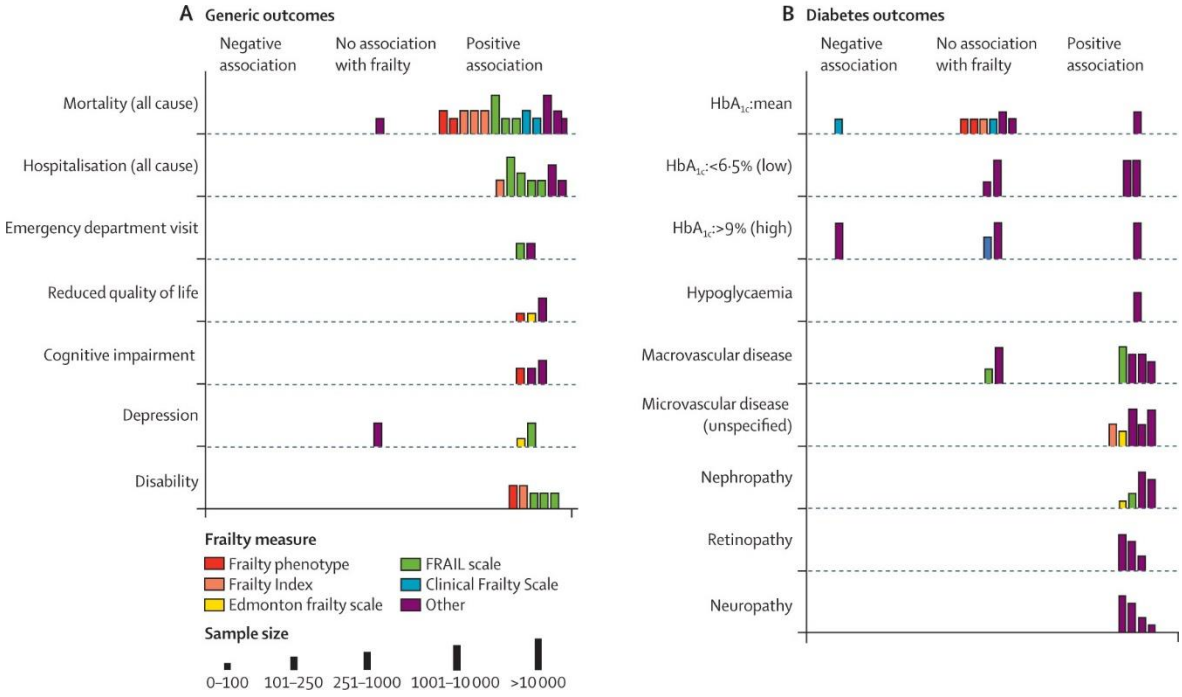

Figure 4.5: Harvest plot of association between frailty and generic (A) and diabetes-specific (B) clinical outcomes

Overall, there was little evidence of a relationship between frailty status and mean HbA1c. Two of four studies assessing low HbA1c and one of four studies assessing high HbA1c found that people with frailty were more likely to have particularly high or low HbA1c values.[323,325] Frailty was associated with microvascular and macrovascular complications. These studies were cross-sectional; none assessed changes in HbA1c over time or prospective relationships between frailty and the development of complications. Two studies (2%),[323,325] which identified frailty using electronic medical records, observed that people living with frailty who had overly tight glycaemic control (HbA1c <6·5%) tended to be prescribed hypoglycaemic agents and that these were rarely discontinued despite low HbA1c. No included studies assessed the relationship between HbA1c and clinical outcomes in people with frailty. One study assessed the relationship between frailty and hypoglycaemic episodes.[341] Frailty, identified by multidisciplinary comprehensive geriatric assessment, was associated with a higher incidence of hypoglycaemic episodes, as well as greater risk of hospitalisation with hypoglycaemia. No studies using either epidemiological or clinical measures to identify frailty examined hypoglycaemia as an outcome.

No studies assessed the relationship between frailty and glycaemic variability or the relationship between HbA1c and clinical outcomes in the context of frailty.

4.7 Discussion

This systematic review synthesised data from 118 studies from 18 high-income, five upper-middle-income, and three lower-middle-income countries that assessed the relationship between frailty and diabetes. Frailty was measured using a range of different scales, incorporating different constructs and developed for different purposes. However, across all measures used, frailty was prevalent in community and hospital-based settings and associated with various adverse clinical outcomes, including mortality, hospitalisation, lower quality of life and disability. In community settings, studies showed that frailty prevalence can be expected to lie between 10% and 25% in people with diabetes older than 60 years. Frailty was also present in people younger than 65 years, although this was only examined in six studies. Frailty also appears to be more common in some ethnic groups (e.g., Aboriginal Australians and African Americans) although this was only examined in eight studies. Diabetes was also associated with the development and progression of frailty. There were cross-sectional associations between frailty and microvascular and macrovascular complications but not higher mean HbA1c. This is notable as clinical guidelines recommend higher HbA1c targets in people with frailty.[19]

Clinicians managing diabetes will encounter frailty regardless of clinical setting. In clinical contexts, a nuanced approach that involves differentiating between levels of frailty and understanding individual patient needs and priorities within the context of frailty is likely to be important, rather than a one-size-fits-all approach to identifying frailty. The identification and assessment of frailty should become part of routine management of people with diabetes. The included studies show that frailty can also be present in younger people with diabetes, including people younger than 65 years. However, the prognostic implications of frailty in diabetes at younger ages have not been examined.

Our findings show that diabetes is a risk factor for the development and progression of frailty. Possible mechanisms include accelerated muscle loss and sarcopenia in diabetes,[373] along with neuropathic and inflammatory mechanisms,[374] and shared cardiovascular risk factors.[268] There is emerging evidence that nutritional and exercise-based interventions can limit the development of frailty in community settings.[375] However, diabetes was not

considered or analysed separately in these studies; therefore, people with diabetes would have been eligible for inclusion, but the findings relate to the population in general and not to diabetes specifically. Non-pharmacological management of diabetes might be synergistic with efforts to prevent the development of frailty. Measuring frailty at baseline and as an outcome in trials of diabetes interventions would be an important step in understanding if and how interventions might mitigate frailty.

The importance of frailty is recognised in several national and international diabetes guidelines.[19,251,376] Specifically, more relaxed HbA1c targets are recommended, and the risks of hypoglycaemia are highlighted.[251,376] An international position statement on frailty in diabetes recommended aiming for the tightest control that could be achieved, while minimising the risk of hypoglycaemia.[19] In mild-to-moderate frailty a target of 7·0–8·0% was recommended and in severe frailty 7·5–8·5% was considered more protective.[19] This review showed an association between frailty and HbA1c values that were either higher (i.e., >9·0%) or lower (i.e., <6·5%) than standard targets. Although higher values can be explained by higher targets, the association between frailty and low HbA1c values suggests that many patients with diabetes and frailty might be over-treated. People with frailty and excessively low HbA1c were prescribed hypoglycaemic drugs,[341] which tended not to be discontinued over time.[323] Continuing hypoglycaemic agents despite low HbA1c could put people with frailty at greater risk than if these agents were discontinued.

It is also notable that only one study in this review quantified the risk of hypoglycaemia in frailty,[341] suggesting that the association between current models of frailty and hypoglycaemia has largely been unquantified. The guideline recommendations are generally based on the high proportion of older people among those presenting with hypoglycaemic complications,[377,378] as well as data from trials such as ACCORD in which older patients (>80 years) had particularly high rates of hypoglycaemia when randomly assigned to the intervention groups.[379] Although this provides evidence of the greater risk of hypoglycaemia, particularly in older people, it is not clear if current measures of frailty accurately identify people at greatest risk of hypoglycaemia. Several of the included studies identified frailty in relatively young people with diabetes;

however, it is not clear if frailty is associated with similar risks of hypoglycaemia in younger populations. Because the choice of frailty measure, and the way it is implemented, has considerable influence over the population that is identified as frail,[200] it is not clear how best to identify people with diabetes and frailty who are most likely to benefit from these recommendations around HbA1c targets.

Greater consistency in how frailty is measured and reported would improve our understanding of the implications of frailty. However, as frailty is a complex and multifaceted state, broad agreement on a single definition is unlikely.[3,252] Translation to clinical practice is a key consideration in analysis of frailty because the most frequently used epidemiological measures (such as the Frailty Phenotype) are rarely incorporated into routine health care. The high prevalence and clinical importance of frailty in diabetes are clear, and there is therefore a need to advance our understanding of how frailty in diabetes should be managed. To do so will mean explicitly measuring frailty in diabetes trials and interventions. Such measurement is particularly important as recommendations for the management of diabetes in the context of frailty are based on studies in which frailty was not directly quantified. Because of the variation in how frailty is measured, there is a risk that recommendations will be applied inconsistently, and perhaps inappropriately, in clinical practice. Frailty-specific evidence in the context of diabetes is required to refine the management of people living with frailty.

Our review used a comprehensive search strategy supplemented by hand-searching of relevant literature. However, our search was limited to studies published in English and excluded grey literature and conference abstracts, which could result in language or publication bias. Because the included studies were observational in nature, the relationships between diabetes and frailty cannot be assumed to be causal. There was considerable heterogeneity between included studies, in terms of inclusion criteria and representativeness (introducing potential selection bias), frailty measures (validated vs adapted), adaptation of frailty criteria, and study settings. Although we explored the effect on frailty prevalence of some of these factors, we were limited by the reporting of these in the included studies and the variable level of detail

provided, particularly around non-response rates and completeness of follow-up data. It was therefore not possible to specify which factors drove the heterogeneity in prevalence estimates.

Frailty identification, assessment, and management should be part of routine diabetes care, which will require integration and embedding of frailty assessment tools into existing templates and protocols. Frailty is not a homogenous entity, and the prognosis and implications of frailty are likely to differ depending on the level of frailty and how it is defined, as well as by other factors such as age. Management must therefore be tailored to the individual. A nuanced and consistent understanding of frailty is needed to inform the evidence base. There is a need to examine the differential consequences of frailty in different sub-populations (such as younger people and people from different ethnic groups). Future research should also focus more on lower-income and middle-income countries, in which diabetes and ageing are growing public health concerns. Finally, despite guidelines calling for lower glycaemic targets in people with diabetes and frailty, HbA1c is below target in many people. Longitudinal assessments of the consequences of glycaemic control in the context of frailty are largely absent from literature. These gaps should be addressed to improve management of people living with diabetes and frailty.

Chapter 5 An analysis of frailty and multimorbidity in 20,566 UK Biobank participants with type 2 diabetes

5.1 Chapter summary

This chapter presents an analysis of the UK Biobank cohort addressing research question 1 (prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in people with type 2 diabetes.

In addition to frailty, two measures of multimorbidity are also presented (a count of long-term conditions and the Charlson comorbidity index). Multimorbidity was assessed alongside frailty in this study because clinical guidelines for type 2 diabetes often present recommendations for frailty and multimorbidity together, despite these being distinct concepts. This rationale is explained in more detail in the introduction below.

The text and figures presented here are as published in Hanlon P, Jani BD, Butterly E, Nicholl B, Lewsey J, McAllister DA, Mair FS. An analysis of frailty and multimorbidity in 20,566 UK Biobank participants with type 2 diabetes. Communications Medicine. 2021 Aug 27;1(1):1-9.

5.2 Abstract

Background: Frailty and multimorbidity are common in type 2 diabetes, including people <65 years. Guidelines recommend adjustment of treatment targets in people with frailty or multimorbidity. It is unclear how recommendations to adjust treatment targets in people with frailty or multimorbidity should be applied to different ages. We assess implications of frailty/multimorbidity in middle/older-aged people with type 2 diabetes.

Methods: We analysed UK Biobank participants (n=20,566) with type 2 diabetes aged 40-72 years comparing two frailty measures (Fried frailty phenotype and Rockwood frailty index) and two multimorbidity measures (Charlson Comorbidity index and a count of long-term conditions (LTCs)). Outcomes were mortality, Major Adverse Cardiovascular Event (MACE), hospitalisation with hypoglycaemia or fall/fracture.

Results: Here we show measure choice influences the population identified: 42% of participants are frail or multimorbid by at least one measure; 2.2% by all four measures. Each measure is associated with mortality, MACE, hypoglycaemia and falls. The absolute 5-year mortality risk is higher in older versus younger participants with a given level of frailty (e.g. 1.9%, and 9.9% in men aged 45 and 65, respectively, using frailty phenotype) or multimorbidity (e.g. 1.3%, and 7.8% in men with 4 LTCs aged 45 and 65, respectively). Using frailty phenotype, the relationship between higher HbA1c and mortality is stronger in participants with frailty compared with pre-frail or robust participants.

Conclusions: Assessment of frailty/multimorbidity should be embedded within routine management of middle-aged and older people with type 2 diabetes. Method of identification as well as features such as age impact baseline risk and should influence clinical decisions (e.g. glycaemic control).

5.3 Plain language summary

People living with type 2 diabetes often have multiple other long-term conditions (multimorbidity) or increased vulnerability to aging-related declines in health (frailty). These states are common in older people, however their prevalence and impact in people aged under 65 years is less clear. This study uses data from UK Biobank, a large group of people aged 40-72 years old, to study the impact of frailty and multimorbidity in relatively younger people with type 2 diabetes. We found that both frailty and multimorbidity were common in people with type 2 diabetes, even at relatively younger ages. People living with frailty or multimorbidity were at greater risk of mortality, heart attacks or strokes, falls or fractures, and of being hospitalised with low blood sugar. Assessing frailty and multimorbidity may help to identify people requiring individualised clinical management and assessment of risk.

5.4 Introduction

Type 2 diabetes mellitus is increasingly common, with prevalence rising with age.[249] Aging populations across the world present a growing challenge for the management of diabetes.[18] Type 2 diabetes is associated with states linked to the ageing process,[373,380] such as frailty and multimorbidity.[373,381] While the majority of people living with frailty are aged over 65 years (with prevalence rising steeply above this age), both frailty and multimorbidity are also often present in 'middle-aged' people with type 2 diabetes.[9,381] However, the clinical implications of these concepts in younger people are less well understood.

Frailty and multimorbidity are related but distinct concepts.[13] Neither has a universally accepted definition.[27,382] Frailty describes a dynamic state of increased vulnerability to decompensation in response to physiological stress, characterised by reduced physiological reserve.[3] The two most common definitions are the frailty phenotype[5] and the frailty index.[35] Multimorbidity refers to the presence of two or more long-term conditions (LTCs) within an individual.[382] Multimorbidity is often quantified using a count of conditions, sometimes weighted depending on nature or severity.[382] Counts vary, however, in the number and type of conditions included. In both frailty and multimorbidity, the choice of definition dictates which individuals are identified as frail or multimorbid, and the degree of overlap between definitions is variable.

Guidelines for type 2 diabetes are beginning to recognise the importance of identifying frailty in older people with type 2 diabetes, and tailoring management accordingly.[19,251] Specifically, targets for HbA1c should be relaxed in people with frailty or multimorbidty.[19] The rationale for less stringent targets in this context includes shorter life expectancy, as well as increased vulnerability to serious adverse effects of hypoglycaemia.[383]

However, guidelines do not offer tailored guidance as to what degree of multimorbidity may alter the balance of risks and benefits in favour of more relaxed glycaemic targets, or indeed what conditions should be included in an assessment of multimorbidity. Importantly, it is not clear if the

recommendations around glycaemic targets hold for younger people with type 2 diabetes who meet the definition of frailty or have multimorbidity.[9,381]

To address this evidence gap, this study aims, in UK Biobank participants aged 40-72 with type 2 diabetes, to: (i) describe the prevalence of both multimorbidity and frailty using a range of possible definitions; (ii) assess the overlap between each definition multimorbidity and of frailty; (iii) compare the association between multimorbidity/frailty and adverse outcomes; and (iv) quantify the association between glycaemia (HbA1c) and adverse outcomes in people with and without frailty/multimorbidity.

We show that both frailty and multimorbidity are common in middle-aged people with type 2 diabetes, although different measures of each construct identify different individuals. We also show that, regardless of measure used, frailty and multimorbidity are both associated with increased risk of mortality, major adverse cardiovascular events, falls or fractures, and hypoglycaemia. However, at a given level of frailty or multimorbidity, the absolute risk of each of these outcomes is higher among older people.

5.5 Methods

5.5.1 Study population

This is an analysis of UK Biobank participants with type 2 diabetes. Participants were recruited between 2006-2010 by postal invitation and attended one of 22 assessment centres in England, Scotland or Wales where they completed a touchscreen questionnaire, a nurse interview, had physical measurements, and provided blood samples. Participants also consented to data linkage to healthcare records including mortality and hospital episode statistics. Participants with type 2 diabetes were identified according to the validated algorithm developed by Eastwood et al.[384] The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). All participants gave informed consent for participation in UK Biobank. Permission to access and analyse UK Biobank data was approved under UK Biobank project 14151.

5.5.2 Measures: multimorbidity

For this analysis, we compared two measures of multimorbidity: the Charlson Comorbidity Index,[385] and a numerical count of long-term conditions.[24] For each score we removed diabetes, as type 2 diabetes is the index condition for the analysis. We chose the Charlson Comorbidity Index as it was recommended in a recent systematic review as the best tool to assess risk of mortality in younger populations.[386] We also included a numerical count of LTCs, as this is a commonly used alternative to a weighted score.[382,387] Conditions were identified from self-report or from ICD-10 codes from hospital admission prior to baseline.

The simple count was based on a list of 42 long-term conditions originally developed in a large epidemiological study in Scotland and subsequently adapted for UK Biobank. Conditions were identified based on either self-report or on ICD-10 codes from linked hospital episode statistics. Participants were considered to have a condition at baseline if they either reported the condition at the assessment centre nurse interview, or if they had a hospital admission prior to the assessment centre date with a relevant ICD-10 diagnostic code. The total number of conditions at baseline was summed to give an overall count.

Conditions included in the Carlson Comorbidity Index were similarly identified from self-report or from ICD-10 codes from hospital admission prior to baseline. ICD-10 codes were taken from a previously validated algorithm for administrative data. Each condition was then weighted (ranging 1 to 6) according to the algorithm and the weights summed to give a total score.

5.5.3 Measures: Frailty

We assessed two operational measures of frailty at baseline: the frailty phenotype[5] and the frailty index.[35] These have both been adapted for use in UK Biobank.[9,22]

The frailty phenotype was based on five criteria (low hand-grip strength, slow walking speed, weight loss, self-reported exhaustion, and low physical activity) and categorised as robust (0 criteria), pre-frail (1-2 criteria) and frail (≥3 criteria).[5,9] Definitions were adapted to UK Biobank baseline data from the original description where required. Weight loss was self-reported according to the question "Compared with one year ago, has your weight changed?" (yes, reduced = 0, other response = 0). Exhaustion was assessed using the question "Over the past two weeks, how often have you felt tired or had little energy?" (more than half the days or nearly every day=1, other=0). Slow walking pace was self-reported as "How would you describe your usual walking pace?" (slow=1, other=0). Physical activity was self-reported according to UK Biobank physical activity questionnaire. We classified the responses into: none (no physical activity in the last 4 weeks), low (light DIY activity [e.g., pruning, watering the lawn] only in the past 4 weeks), medium (heavy DIY activity [e.g., weeding, lawn mowing, carpentry and digging], walking for pleasure, or other exercises in the past 4 weeks), and high (strenuous sports in the past 4 weeks). Participants reporting none or light activity with a frequency of once per week or less were coded as 'low physical activity'. Grip strength was assessed using a Jamar J00105 hydraulic hand dynamometer. The highest valid reading was used to classify grip strength according to cut-offs described by Fried et al.[5]

The frailty index is an unweighted count of 'deficits' which (i) increase in prevalence with age; (ii) are associated with poor health; and (iii) are neither ubiquitous in the population nor too rare (i.e. <1% prevalence).[35,36] Deficits

include long-term conditions, symptoms, and functional limitations. We used the list of deficits developed by Williams et al for UK Biobank (excluding diabetes).[22] This is summarised in section 3.3.1.5. The frailty index is calculated by dividing the number of deficits present by the total number of possible deficits, giving a value between 0 and 1 (higher values indicating a greater degree of frailty). Where an individual had missing data for a deficit, this deficit was also excluded from the demoninator.[36]

5.5.4 Measures: Covariates

All covariates used in analyses were based on baseline assessment centre data. Age and sex were used as recorded. BMI was calculated based on measured weight and height. Smoking was categorised as never, previous, or current based on self-report. Frequency of self-reported alcohol intake was categorised as never/special occasions only; 1-3 times per month, 1-4 times per week, and daily or almost daily. Townsend scores were calculated from postcode areas based on previous census data to give an area-based measure of socioeconomic deprivation.[388] HbA1c was taken from baseline blood samples obtained by UK Biobank.

5.5.5 Outcomes

Outcomes were identified by linkage to national mortality records (Office for National Statistics) and Hospital Episode Statistics. Linkage was carried out by UK Biobank and made available to approved researchers. Median follow-up was 8 years. Outcomes were all-cause mortality, cardiovascular mortality (underlying cause of death ICD-10 code beginning with “I”), cancer mortality (ICD-10 code beginning with “C”), Major Adverse Cardiovascular Event (MACE; cardiovascular death, or hospitalisations coded as non-fatal myocardial infarction [I21] or stroke [I63-I64]), hospitalisation with hypoglycaemia (E16.0, E16.1, E16.2), and hospitalisation with fall or fracture (W0, W1, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T05).

5.5.6 Statistical analysis

We plotted the distribution of each frailty and multimorbidity measure descriptively. We then summarised the relationship between each measure and baseline characteristics by dividing each measure into four quartiles.

To assess the overlap between the four measures of frailty or multimorbidity we took all participants with scores above the 75th centile for each score (or the 'frail' category for the frailty phenotype). We then constructed a Venn diagram of the overlap between people above the 75th centile (or "frail" by frailty phenotype) for each measure.

To assess the relationship between each measure and clinical outcomes we used parametric survival models. We used Weibull models as this distribution was found to fit the data well for each measure and other covariates (assessed by plotting log time against log of the estimated cumulative hazard). Models were adjusted for age, sex, ethnicity, socioeconomic status, BMI, smoking and alcohol frequency. We modelled nonlinear effects of the frailty index, Charlson index, multimorbidity count and age using fractional polynomials. We also assessed interactions between each measure and age, and between age and sex, and included these in the model where they were significant (p-interaction <0.05). We modelled time to first event. Competing risks were accounted for by using cause-specific models (i.e. participants were censored at first occurrence of the outcome of interest, end of follow-up, or death, whichever occurred first. In models for MACE, falls or hypoglycaemia, deaths of other causes were coded as '0').

After fitting each model, we predicted the 5-year risk of incident outcome. Predictions were calculated separately for males and females, holding age, BMI and socioeconomic status at the sample mean, smoking status as 'previous' and alcohol frequency as 1-4 times per week (the most numerous category).

Finally, to assess the impact of HbA1c on all-cause mortality at different levels of frailty or multimorbidity, we fitted Weibull models including HbA1c along with the covariates described above. Non-linear relationships between HbA1c and mortality were modelled using fractional polynomials. We included any

significant interactions between HbA1c and frailty or multimorbidity. Predicted 5-year risk was calculated across all observed values of HbA1c, and at the 25th, 50th, 75th and 90th centiles of each frailty or multimorbidity definition (or at each category of the frailty phenotype). This allowed us to assess the relationship between HbA1c and mortality at different levels of multimorbidity or frailty.

All analyses were prespecified and reported according to the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) statement (www.strobe-statement.org). Analyses were performed using R version 3.6.1. All syntax for deriving variables and for generating analysis will be returned to UK Biobank for record and will be available upon application to UK Biobank.

5.6 Results

5.6.1 Baseline characteristics

20,566 UK Biobank participants were identified as having type 2 diabetes at baseline. The distribution of multimorbidity (defined by Charlson Comorbidity Index and by a count of 42 long-term conditions) and frailty (defined by the frailty index and by the frailty phenotype) is shown in Figure 5.1. Baseline characteristics are shown in appendix 4 and correlation between each of these measures in Figure 5.2.

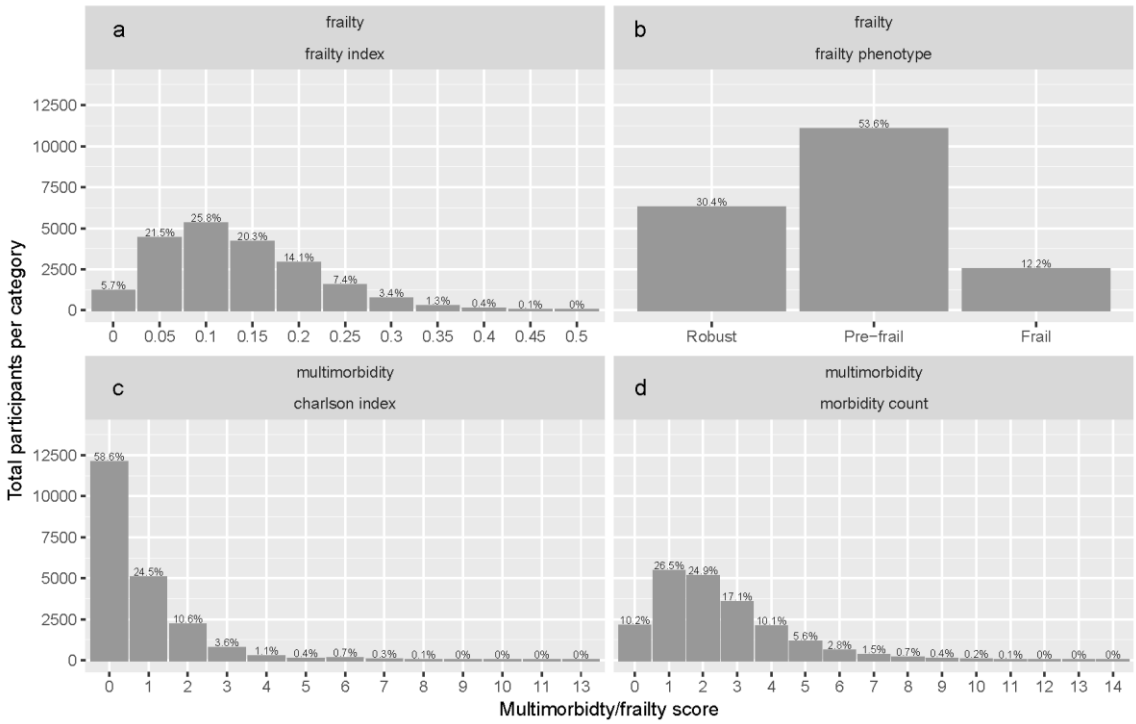

Figure 5.1 - Distribution of frailty or multimorbidity. This figure shows the distribution of each measure of frailty or multimorbidity (panel (a) frailty index, (b) frailty phenotype, (c) Charlson index, (d) long-term condition count). The height of the bar indicates the number of participants with percentages indicated above the bars.

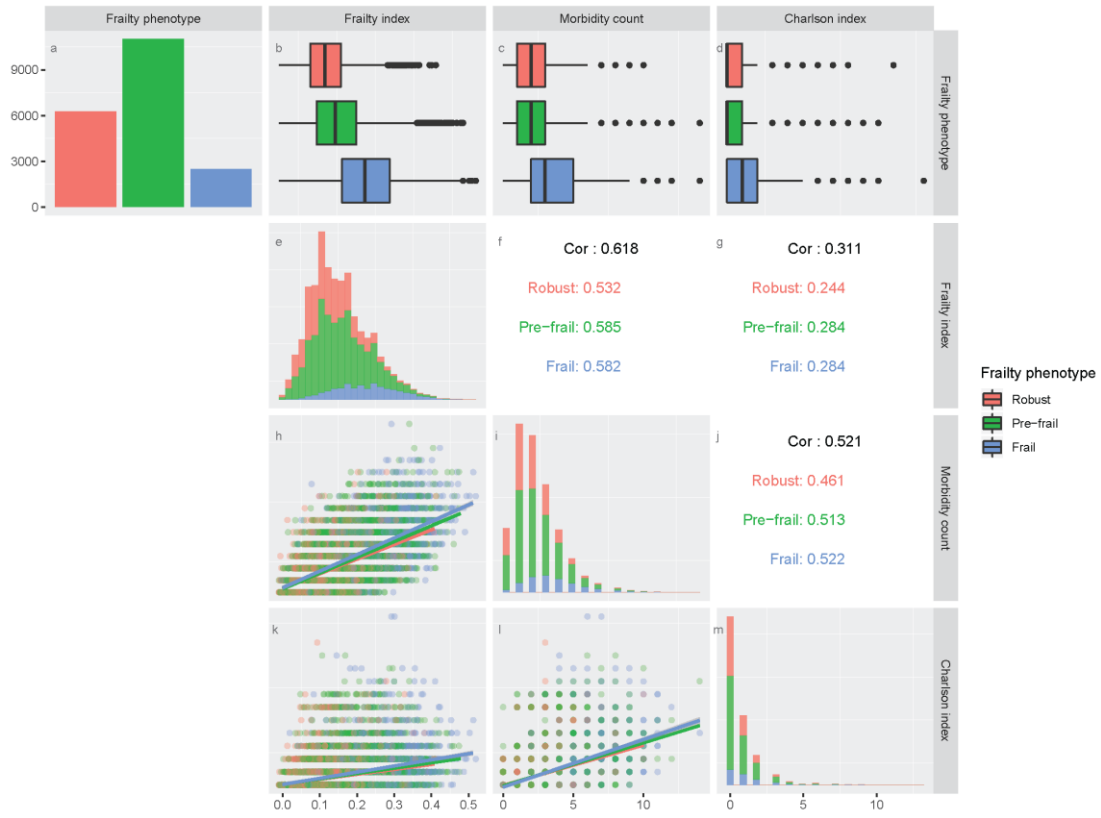

Figure 5.2 - Correlation between measures. This plot shows the distribution of each measure of frailty or multimorbidity, as well as the correlation between each of the measures. Panel a shows the distribution of the frailty phenotype. Panels e, i, and m show the distribution of the frailty index, long-term condition count, and Charlson index, respectively, with the corresponding frailty phenotype levels shown in colour. Box-plots in panels b, c, and d show the median, interquartile range, range, and outliers of the frailty index, long-term condition count, and Charlson index, respectively, stratified by levels of the frailty phenotype. Scatter plots in panels h, k and l show the correlation between the frailty index and the long term condition count (panel h, with correlation coefficients shown in panel f), the frailty index and the Charlson index (panel k, with correlation coefficients shown in panel g) and the long-term condition count and the Charlson index (panel l, with correlation coefficients shown in panel j). Correlation coefficients are shown for all participants (black text) and stratified by level of the frailty phenotype (coloured text).

Most participants with type 2 diabetes were aged over 60 years (12,755, 62%). Only 1,858 (9%) were aged under 50 years. The prevalence of frailty was broadly similar across age categories (e.g. frailty prevalence by frailty phenotype was 12.6% at age 40-50, 13.4% at age 50-60, and 11.5% at age 60-72; details in appendix 4). The relationship with age varied between the individual components of the frailty phenotype. Low grip strength and slow walking speed increased in prevalence with increasing age, however low physical activity, self-reported exhaustion, and self-reported weight loss were more common in younger participants. However, the prevalence of multimorbidity with either measure rose with age (e.g. using the Charlson Comorbidity Index 7.7% scored ≥2 at age 40-50, 11.6% aged 50-60, and 20.6% aged 60-72).

The relationship between frailty and ethnicity differed depending on the frailty definition: compared to White participants, frailty is more common among Black and Asian participants when using the frailty phenotype definition, but less common when using the frailty index definition. Multimorbidity was less common among Black or Asian participants, compared to White. Both frailty and multimorbidity were strongly associated with socioeconomic deprivation by all definitions. Frailty phenotype (but not frailty index) were associated with slightly higher HbA1c. Participants with multimorbidity (using LTC count or Charlson) had lower mean HbA1c. However, in all cases, the differences were small (<2mmol/mol) (appendix 4).

5.6.2 Overlap between definitions

There was relatively little overlap between the four measures of frailty or multimorbidity. Forty-two percent of participants were above the 75th percentile for at least one of the measures, but only 2.2% were identified by all 4 measures (Figure 5.3).

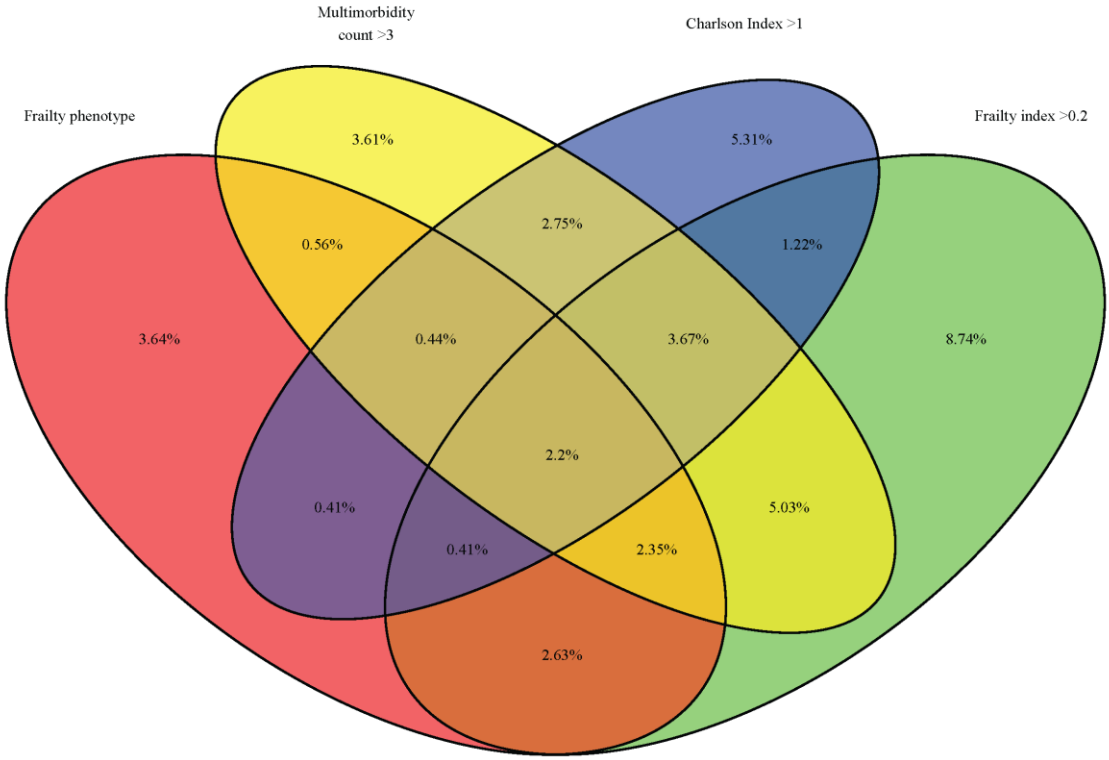

Figure 5.3 - Venn diagram of overlap between frailty and multimorbidity measures. This figure shows the overlap between each definition of frailty or multimorbidity. The percentage of participants identified by each combination of measures is shown by the percentages in each overlapping section. Note that 58% of participants were below the 75th centile for all definitions and are therefore not included in the Venn diagram.

5.6.3 Relationship between frailty or multimorbidity and outcomes

5.6.3.1 Mortality

Figure 5.4 shows the adjusted 5-year mortality at different levels of frailty/multimorbidity. Higher degrees of frailty or multimorbidity were associated with greater all-cause mortality using each measure. The absolute mortality risk was higher at the extremes of the multimorbidity count and Charlson Index than for the frailty phenotype or frailty index, however there were also fewer participants with values at these extremes. Males had a higher mortality risk than females.

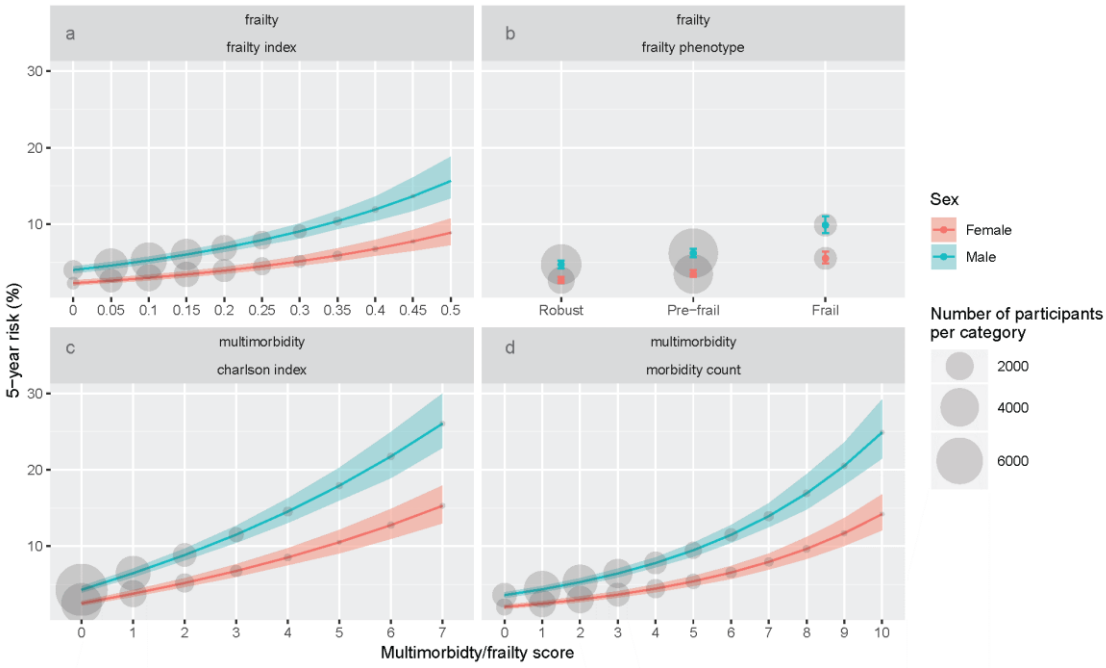

Figure 5.4 - Relationship between frailty or multimorbidity and all-cause mortality. This figure shows the predicted 5-year mortality rate for each measure of frailty or multimorbidity (panel (a) frailty index, (b) frailty phenotype, (c) Charlson index, (d) long-term condition count). Coloured lines or points indicate point estimates for predicted 5-year mortality. Men are shown in blue, and women in red. Shaded areas indicate 95% confidence intervals. Grey circles indicate the number of participants with each level of frailty or multimorbidity. Models are adjusted for age, sex, socioeconomic status, body mass index, smoking, and alcohol. Predicted 5-year mortality is based on age 60, socioeconomic status and body mass index held at the sample mean, previous smokers, and 1–4 times weekly alcohol intake.

Age was a significant predictor of mortality risk, independent of frailty or multimorbidity. For example, using the frailty phenotype, the 5-year mortality for frailty was 1.9%, 4.4%, and 9.9% in men aged, 45, 55, and 65, respectively. For a multimorbidity count of 4, predicted 5-year mortality was 1.3%, 3.7%, and 7.8% in med aged 45, 55, and 65, respectively. There was no statistically significant interaction between age and any measure. Therefore, although the increase in relative risk associated with frailty or multimorbidity is similar across all ages studied, the absolute risk of mortality associated with any level of frailty or multimorbidity is higher at older ages.

These patterns were similar for cardiovascular mortality and for cancer mortality (appendix 4).

In post-hoc analyses, we assessed the relationship between the frailty phenotype and mortality within strata of multimorbidity (0, 1, 2, and 3 or more long-term conditions). At each level of multimorbidity, frailty was associated with an

increased risk of mortality. Participants meeting the criteria for both frailty and multimorbidity had a greater risk of mortality than those meeting the criteria for frailty or multimorbidity alone.

5.6.3.2 MACE, falls and hypoglycaemia

The estimated 5-year risk of incident hospital episode related to MACE, fall/fracture, or hypoglycaemia, are shown in Figure 5.5. Each of these outcomes was associated with both frailty and multimorbidity. Female participants were at greater risk of falls/fractures. Males had higher risk of MACE and hypoglycaemic hospitalisation. As with mortality, the risk was highest at the extreme end of the distributions for the frailty index, multimorbidity count and Charlson Index. Age was also a significant predictor of each outcome, with higher absolute risks among older participants at a given level of frailty or multimorbidity (appendix 4).

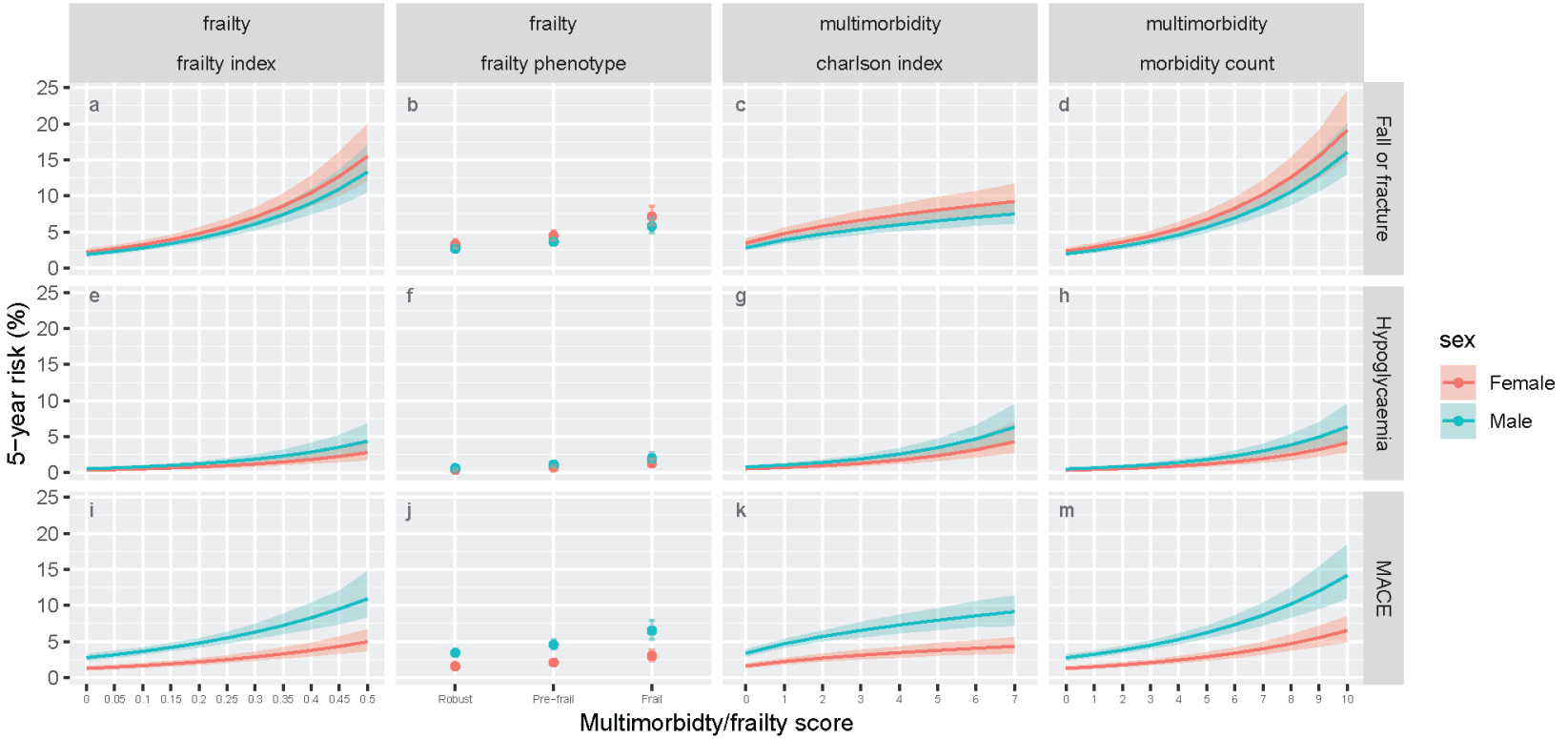

Figure 5.5 - Relationship between frailty or multimorbidity and MACE, hypoglycaemia, and falls. This figure shows the predicted 5-year rate of fall or fracture (panels a, b, c, and d showing the frailty index, frailty phenotype, Charlson index, and long-term condition count, respectively) hospitalisation with hypoglycaemia (panels e, f, g, and h showing the frailty index, frailty phenotype, Charlson index, and long-term condition count, respectively) and MACE (panels i, j, k and m showing the frailty index, frailty phenotype, Charlson index, and long-term condition count, respectively). Coloured lines or points indicate point estimates for predicted 5-year mortality. Men are shown in blue, and women in red. Shaded areas indicate 95% confidence intervals. Models are adjusted for age, sex, socioeconomic status, body mass index, smoking, and alcohol. Predicted 5-year risk is based on age 60, socioeconomic status and body mass index held at the sample mean, previous smokers, and 1–4 times weekly alcohol intake.

5.6.3.3 HbA1c and all-cause mortality

Figure 5.6 presents the relationship between HbA1c and all-cause mortality at different levels of frailty or multimorbidity. Results were stratified according to centiles (25th, 50th, 75th and 90th) of each measure, and categories of the frailty phenotype. The expected J-shaped relationship with mortality was observed throughout all levels apart from participants with frailty identified using the frailty phenotype, in whom the risk of mortality increased in a more linear fashion with increasing HbA1c. These analyses were repeated after stratifying by baseline use of drugs associated with hypoglycaemia (insulin and sulphonylureas). In participants who were frail according to the frailty phenotype, the steep rise in mortality risk with HbA1c was only observed in those not taking insulin or sulphonylureas at baseline. In participants taking these hypoglycaemic agents, the relationship between HbA1c and mortality was J-shaped for participants with frailty, as it was for pre-frail and robust participants (appendix 4).

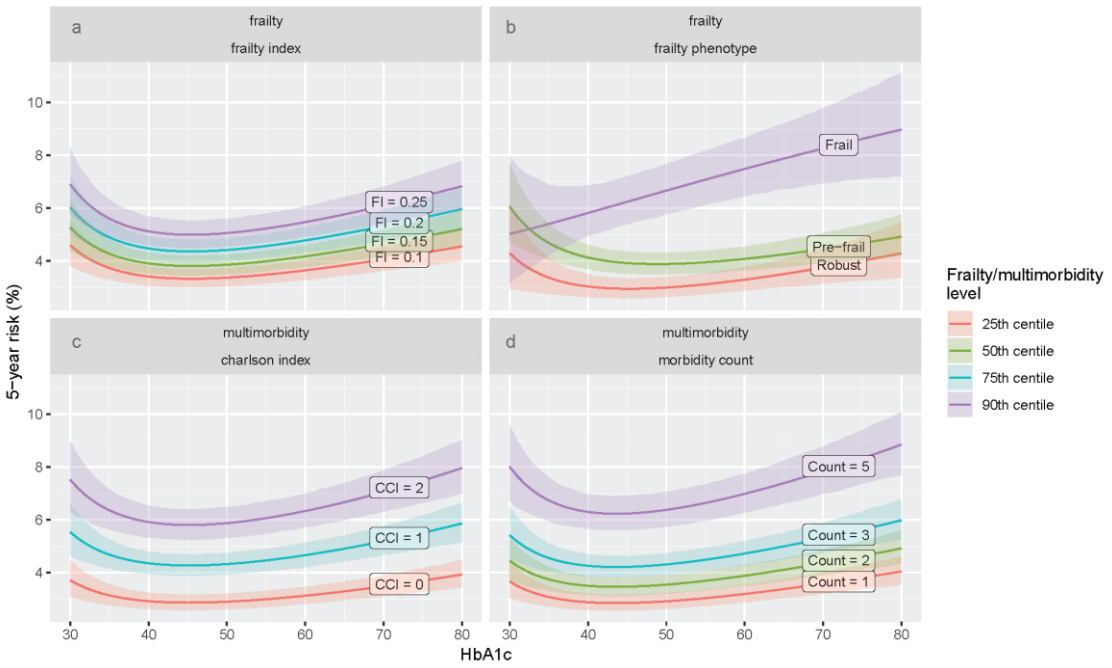

Figure 5.6 - HbA1c and all-cause mortality. This figure shows the relationship between HbA1c and predicted 5-year mortality at different levels of frailty or multimorbidity (panel (a) frailty index, (b) frailty phenotype, (c) Charlson index, (d) long-term condition count). Coloured lines or points indicate point estimates for predicted 5-year mortality. Colours indicate the level of frailty or multimorbidity according to centiles. Shaded areas indicate 95% confidence intervals. Models are adjusted for age, sex, socioeconomic status, body mass index, smoking, and alcohol. Predicted 5-year mortality is based on age 60, socioeconomic status, and body mass index held at the sample mean, previous smokers, and 1–4 times weekly. There was a significant interaction between the frailty phenotype and HbA1c. Interactions between frailty index, Charlson index, and LTC count were not significant.

5.7 Discussion

Both frailty and multimorbidity were common at all ages in this cohort of 20,566 people with type 2 diabetes aged 40-72 years. Both the frailty phenotype and frailty index, as well as both weighted and unweighted measures of multimorbidity, identified people at greater risk of mortality as well as MACE and hospital admission resulting from falls, fractures or hypoglycaemia. However, despite similarities in the risks associated with each measure, the participants who were identified as 'high risk' differed considerably between measures. Therefore, even in this relatively young population, frailty and multimorbidity identify people with type 2 diabetes at risk of a wide range of adverse outcomes, however relying on a single narrow construct may overlook others who may also be at higher risk.

Guidelines recommend higher glycaemic targets in people with frailty or substantial multimorbidity.[19] The higher mortality and risk of falls and hypoglycaemia that we observed in people with frailty or multimorbidity are consistent with the rationale for these higher targets: namely reduced life expectancy and greater risk of complications of hypoglycaemia.[383] However, our findings also demonstrate that the absolute risk of mortality in younger people with frailty or multimorbidity is considerably lower than in older people. Furthermore, the risk of all-cause mortality among people identified as 'frail' using the frailty phenotype was highest among people with higher baseline HbA1c. This suggests that the implications of frailty or multimorbidity for clinical decision making must rely on careful consideration of additional factors that influence baseline risk (including age) as well as individual patient preferences. This is important, as our findings suggest that frailty and multimorbidity are common among people with diabetes under the age of 65, however absolute risk of outcomes, and thus implications for clinical management, may differ at younger ages.

It is perhaps surprising that the prevalence of frailty, particularly using the frailty phenotype, did not increase with age. This was largely driven by higher prevalence of low physical activity, self-reported exhaustion, and self-reported weight loss among younger participants. This could reflect a lack of specificity for these constructs in identifying frailty when applied to younger people, in

whom characteristics such as exhaustion or weight loss may be biologically or phenotypically different from older people. It is important to note, also, that weight loss was not specified as unintentional in UK Biobank, limiting its specificity for indicating frailty. Finally, this relationship between frailty and age in this study could represent collider bias. For example, low physical activity may have a causal relationship with the manifestation of type 2 diabetes at younger ages, but also with the identification of frailty, thus influencing the relationship between frailty and age when conditioning on a diagnosis of type 2 diabetes.

The finding that frailty and multimorbidity are common among middle-aged and older people with type 2 diabetes is consistent with previous studies.[37,381] So too is the increased risk of mortality and cardiovascular events.[37,380] The finding that the populations identified by each measure did not fully overlap is consistent with previous literature and is not surprising, given that these are distinct constructs underpinned by different models of frailty or multimorbidity.[389] Our findings add to this literature by demonstrating that even in this relatively young population, each measure identifies individuals at increased risk of adverse outcomes. Therefore, a narrow focus on a single measure may overlook others who are also at risk. Individualised person-centred care is likely to be appropriate and beneficial regardless of measure and further research, ideally using randomised trials, is required to understand if and how our approach should differ by how frailty or multimorbidity manifests.

The small magnitude of difference in HbA1c with frailty or multimorbidity identified is consistent with existing literature, the majority of which have shown no association with HbA1c.[37,380] This is perhaps surprising given guidelines for lower targets. Our findings may reflect the relatively young age of this cohort. However others have observed hypoglycaemic medications are rarely discontinued in patients with frailty and low HbA1c, despite the risk of hypoglycaemia that this presents.[323,325]

The relationship between HbA1c and mortality in people classified as ‘frail’ using the frailty phenotype is surprising, as we had expected the risks associated with lower HbA1c to be higher in people with frailty. Further analyses stratified by baseline use of hypoglycaemic agents suggests that low HbA1c in the context

of insulin or sulphonylurea use (potentially reflecting over-treatment) is associated with increased mortality regardless of frailty status. Patients with low HbA1c may therefore benefit from deprescribing or dose reduction. The steeper rise in mortality with higher HbA1c and frailty was mostly driven by participants not taking these agents and may reflect greater risk of suboptimal glycaemic control in younger people living with frailty. This finding would need to be verified in other cohorts, and also explored further in older populations which represent the majority of people living with frailty.

Few studies have assessed the relationship between frailty and hypoglycaemia.[37] Several studies, mostly using the Charlson comorbidity index, have shown increased risk of hypoglycaemia associated with multimorbidity.[380] Evidence linking frailty with hypoglycaemia has been based on findings from trials such as ACCORD where patients over 80 years old had high rates of hypoglycaemia when randomised to the intervention arm,[390] as well as the fact that older people appear most likely to be hospitalised with hypoglycaemic complications.[377,378,391] In both cases frailty has been hypothesised to explain the underlying vulnerability. Our findings are concordant with this hypothesis and suggest that frailty may also confer some increased risk at younger ages.

Clinicians managing type 2 diabetes are likely to encounter high levels of frailty and multimorbidity, even among relatively young patient populations. Guideline recommendations for less stringent glycaemic targets in people with frailty are in part predicated on limited life-expectancy.[19,251,383] Our findings demonstrate that both frailty and age are important predictors of mortality risk, and while younger people with type 2 diabetes may meet the criteria for frailty, their absolute risk of mortality may be considerably less than an older person identified as frail. Furthermore, the choice of measure for frailty or multimorbidity substantially impacts which individuals are identified as ‘high risk’, with only partial overlap between definitions. These observations, consistent with previous literature, are important in this context and diabetes guidelines do not currently give recommendation for how frailty in younger people should influence management (and in whom the assumptions around life expectancy underpinning recommendation for older people are unlikely to hold) or how frailty and multimorbidity should be identified. Within populations

identified as frail or multimorbid there is considerable heterogeneity in personal characteristics as well as variation in risk of adverse outcomes. This highlights the importance of individualised decision making for patients, taking into account patients' age and the measure used to assess frailty and multimorbidity, rather than blanket recommendations for 'frailty' or 'multimorbidity'. So, while a recent systematic review has suggested the need to embed screening for frailty within routine diabetes reviews,[37] this work suggests that clinicians need to ensure care is tailored to the potential needs of people with frailty or multimorbidity taking account of a wide range of factors. While frailty and multimorbidity do indicate gradients of risk, it may be that these are not the optimal tools to assess the appropriate targets for treatment in middle-aged people.

The strengths of this study include its large sample size with linkage to mortality and hospital event data. We also used a range of definitions of frailty and multimorbidity, which is an advantage as comparisons between studies are often limited by differences in the definitions used. Our focus on younger people than most previous frailty studies is relatively novel, as the implications of frailty in younger ages is not well understood. However, our findings may not be entirely transferable to older people (>70 years), in whom frailty is both more prevalent and may have greater impact. UK Biobank was not specifically designed to assess frailty or aging, which limits our assessment of frailty. Specifically, some of the frailty phenotype components were adapted (e.g. weight loss was self-reported and not specifically unintentional) and the frailty index, while constructed according to standard guidelines, contains relatively few functional and sensory deficits.

Our analysis was limited by only having access to baseline measures of frailty and multimorbidity, as well as covariates such as HbA1c and body mass index. Both frailty and multimorbidity are dynamic states and change (often progressing) over time. We were not able to model the impact of any such change. Modelling of the impact of multimorbidity and frailty in diabetes could potential be improved by using serial measurements, over a longer follow-up, and with measurement of additional outcomes such as retinopathy and nephropathy. Several of the baseline variables were based on self-report,

however participants were supported by a study nurse in providing this information and for the multimorbidity measures we supplemented these definitions with linkage to previous hospital episodes. Finally, it is important to note that UK Biobank is not a nationally representative sample. Participants were more affluent, more likely to be white, and have fewer long-term health conditions than the national average. Our prevalence findings therefore cannot be generalised to the population as a whole and estimates of risk of adverse outcomes are likely to be conservative. Selection bias may also lead to collider bias, where conditioning on one criteria (UK Biobank inclusion) may bias estimates of the relationship between causally proximal variables (such as age and frailty).[228,392] This may explain the surprising finding that the prevalence of the frailty phenotype did not rise with age as expected.

In conclusion, our findings demonstrate that both frailty and multimorbidity are both common and clinically important in middle-aged as well as older people with type 2 diabetes, regardless of the definition used. The greater risk of mortality, cardiovascular events, and hypoglycaemia, in people living with frailty and multimorbidity means that it is important to actively detect both frailty and multimorbidity in people with type 2 diabetes, regardless of age. However, our findings also demonstrate that guidelines for managing frailty and multimorbidity in people with type 2 diabetes may not be directly applicable to younger people, in whom the absolute mortality risk remained low even among the most frail groups. While this work further supports the idea of embedding screening for both multimorbidity and frailty as part of routine diabetic reviews, it also reinforces the need to tailor risk stratification to individual patients. This should take account of patients' age, measure used to assess frailty or multimorbidity, and other risk factors, rather than adopting prescriptive targets and recommendations to everyone who might meet some criteria for frailty or multimorbidity.

Chapter 6 Frailty in people with rheumatoid arthritis – A systematic review of observational studies

6.1 Chapter summary

This chapter presents a systematic review of observational studies addressing research question 1 (the prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in the context of rheumatoid arthritis.

The text and figures presented here are as published in Hanlon P, Morrison H, Morton F, Jani BD, Siebert S, Lewsey J, McAllister D, Mair FS. Frailty in people with rheumatoid arthritis: a systematic review of observational studies. Wellcome Open Research. 2021 Sep 23;6(244):244.

6.2 Abstract

Background: Frailty, an age-related decline in physiological reserve, is an increasingly important concept in the management of chronic diseases. The implications of frailty in people with rheumatoid arthritis are not well understood. We undertook a systematic review to assess the prevalence of frailty in people with rheumatoid arthritis, and the relationship between frailty and disease activity or clinical outcomes.

Methods: We searched 4 electronic databases (January 2001 to April 2021) for observational studies assessing the prevalence of frailty (any measure) in adults (≥18 years) with rheumatoid arthritis or analysing the relationship between frailty and disease activity or clinical outcomes (e.g. quality of life, hospitalisation or mortality) in people with rheumatoid arthritis. Titles, abstracts and full texts were assessed independently by two reviewers. Study quality was assessed using an adapted Newcastle-Ottawa Scale. Screening, quality assessment and data extraction were performed independently by two reviewers. We used narrative synthesis.

Results: We identified 17 analyses, from 14 different sample populations. 15/17 were cross-sectional. These studies used 11 different measures of frailty. Frailty prevalence ranged from 10% (frailty phenotype) to 36% (comprehensive rheumatologic assessment of frailty) in general adult populations with rheumatoid arthritis. In younger populations (<60 or <65 years) prevalence ranged from 2.4% (frailty phenotype) to 19.9% (Kihon checklist) while in older populations (>60 or >65) prevalence ranged from 31.2% (Kihon checklist) to 55% (Geriatric 8 tool). Frailty was cross-sectionally associated with higher disease activity (10/10 studies), lower physical function (7/7 studies), and longer disease duration (2/5 studies), and prospectively with hospitalisation and osteoporotic fractures (1/1 study, 3.7 years follow-up).

Conclusion: Frailty is common in adults with rheumatoid arthritis, including those aged <65 years, and is associated with a range of adverse features. However, these is substantial heterogeneity in how frailty is measured in rheumatoid arthritis. We found few longitudinal studies making the impact of

frailty on clinical outcomes over time and the extent to which frailty is caused by rheumatoid arthritis unclear.

6.3 Introduction

Rheumatoid arthritis is the most common chronic inflammatory arthropathy, the incidence of which increases with age.[16,20,393] While advances in treatment of rheumatoid arthritis have resulted in marked improvement in outcomes and prognosis, rheumatoid arthritis continues to cause significant symptom burden, loss of function, morbidity, and reduced quality of life.[20,393] Frailty has been highlighted as an emerging concept in our understanding of the impact of musculoskeletal disorders.[16] Frailty is an age-related state of increased vulnerability leading to decompensation in response to physiological stress.[26] While most studies have focused on people aged over 65 years, frailty is also prevalent and associated with adverse health outcomes in younger populations.[9] Many measures exist to quantify frailty, of which the most widely used are the frailty phenotype[5] (a physical measure assessed by grip strength, walking speed, exhaustion, weight loss, and low physical activity) and the frailty index[6,35] (a cumulative count of age-related deficits including long term conditions, symptoms, functional limitation and physiological markers). Both constructs have potential overlap with features associated with rheumatoid arthritis.

Despite a rapid expansion of frailty research in the last two decades, including in the context of specific index conditions,[3] research on frailty in the context of inflammatory diseases in general, and rheumatoid arthritis in particular, is relatively recent.[16,394] Frailty has been reported to be prevalent in people with rheumatoid arthritis, including relatively young individuals (i.e. <65 years).[395] Others have explored associations between frailty and functional limitations in rheumatoid arthritis.[396] However, the diversity of measures used to quantify frailty, and overlap between features of rheumatoid arthritis and frailty constructs, means that understanding the relationship between frailty and rheumatoid arthritis requires careful consideration.

This systematic review seeks to synthesise data from observational studies of frailty in people with rheumatoid arthritis. We aim to assess (i) what frailty measures have been used in published studies including people with rheumatoid arthritis, (ii) what is the prevalence of frailty in people with rheumatoid arthritis across a range of ages, (iii) what is the association between frailty and features of rheumatoid arthritis such as disease activity, functional limitation, and

duration, and (iv) what is the association between frailty and adverse health outcomes (e.g. hospitalisation, mortality or quality of life) in people with rheumatoid arthritis.

6.4 Methods

This systematic review was conducted according to a pre-specified protocol (PROSPERO: CRD42021251960) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[397]

6.4.1 Eligibility criteria

Criteria for inclusion, defined according to PECOS (Population, Exposure, Comparator, Outcome, Setting and Study design),[398] including outcomes of interest are detailed in Table 6.1. Criteria were deliberately broad in terms of setting, frailty definition, and outcomes. Briefly, studies must include adults (≥18 years) with rheumatoid arthritis and assess frailty, although we expected studies may mainly involve 'older' populations. Studies were considered regardless of frailty measure, to allow comparison between different methods of identifying frailty. These could include validated measures of frailty (e.g. frailty phenotype or frailty index), adaptations of these measures where the adaptation was described, or unvalidated measures intended to capture frailty as long as the criteria used to define frailty within the study were fully described. We did not exclude studies on the basis of the criteria used to define rheumatoid arthritis (i.e. validated criteria, physician diagnosis, medical record/clinical codes or self-reported definitions were all eligible for inclusion). We included studies in any setting (community, outpatient, or inpatient). Observational studies with cross-sectional or cohort designs were eligible for inclusion. Experimental studies were excluded. When examining the association between frailty and clinical outcomes in those with rheumatoid arthritis, studies were expected to report the association between frailty and the outcome of interest. As in previous reviews of frailty,[37,253] we considered studies that describe this either as the association with the presence or absence of frailty or the association between the degree of frailty and the outcome.

Table 6.1 - Inclusion criteria

PECOS component	Description
Population	Adults (≥ 18 years old) with rheumatoid arthritis
Exposure	Frailty as assessed by any frailty measure
Comparator	People with rheumatoid arthritis not classified as frail
Outcomes	Primary outcome: Frailty prevalence Secondary outcomes: Mortality Hospital admission Major Adverse Cardiovascular Events Admission to long-term care facility Quality of life Fractures Disease activity (e.g. Disease Activity Score in 28 joints; DAS-28) Physical impairment or disability (e.g. Health Assessment Questionnaire – Disability Index; HAQ-DI)
Settings	Community (including care home/nursing home)

	Outpatient clinic Inpatient
Study design	Cross sectional or cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies, Grey literature. Studies not published in English.

6.4.2 Information sources and screening

We searched Medline, Embase, Web of Science Core Collection and Scopus databases from 2001 (as this was the date of the original description of the frailty phenotype and frailty index definitions[5,6]) to 8th April 2021 using a combination of keywords and Medical Subject Headings. The search structure was 'rheumatoid arthritis' and 'frail'. The full search strategy can be found in the supplementary appendix. Two independent reviewers screened all titles and abstracts and assessed full texts of all relevant articles for eligibility. Disagreements were resolved by consensus, involving a third reviewer if necessary. Hand-searching reference lists of relevant articles and forward-citation searching using Web of Science were also used to supplement electronic database searches.

6.4.3 Data extraction and quality assessment

Data were extracted from each of the eligible studies using a piloted data extraction form. Data extracted included details of the published study (publication reference, aim, setting), population (sample eligibility, recruitment method, age and sex), criteria used to define rheumatoid arthritis (e.g. American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria,[399] self-report, electronic medical records, etc.), frailty measure, any adaptation of the frailty measure used in the study, prevalence of frailty, and the association between frailty and clinical outcomes. For outcomes, we extracted data on the method used to assess the outcome, timeframe or length of follow-up, the magnitude of the association along with measure of

uncertainty, and any adjustment for potential confounders. Where there was variation between studies in the assessment of similar outcomes, we presented this data in supplementary tables. We used a version of the Newcastle-Ottawa tool, previously adapted to assess observational studies of frailty,[37] to quantify risk of bias (criteria shown in appendix 3). The Newcastle-Ottawa scale is frequently used to assess quality of observational studies. Previous reviews have also adapted elements of the scale to reflect the studies of interest to the review itself. For this review, we used an adaptation previously developed for observational studies of frailty. This adaptation altered the 'exposure' component to award two points if a study used validated measure of frailty implemented according to its original description. One point was awarded if studies used an alternative measure of frailty (e.g. an adapted or non-validated measure of frailty) but the criteria were described in sufficient detail to allow the assessment to be replicated. This adaptation was to reflect the fact that there is no 'gold-standard' measure of frailty and that frailty is assessed using a diverse range of measures within the literature. The scale was applied to all studies (cross sectional or longitudinal), with only the first 5 elements of the scale being relevant to the cross-sectional studies. This approach was taken to allow an identical approach to quality assessment for prevalence estimates from cross sectional or (baseline data from) longitudinal studies. Quality was assessed independently by two reviewers (PH and HM) with disagreements resolved by discussion and involving a third reviewer if necessary. Studies were not excluded on the basis of the quality assessment.

6.4.4 Synthesis

Findings of the included studies were summarised using a narrative synthesis. Methodological and demographic details of each study, along with quality assessment, were summarised using tables. Prevalence estimates were plotted stratified by age-group of the sample and with reference to the frailty measure used for each estimate. Findings related to other outcomes (characteristics of rheumatoid arthritis or clinical outcomes) were summarised using a Harvest plot.[256,400] Harvest plots can be used to display heterogenous data across a range of outcomes. Findings are displayed on a matrix with each bar representing a study. The position of the bar on the matrix indicates the relationship between frailty and a specific outcome (i.e. positive association, negative association, or

no association with frailty status), with the height of the bar indicating the sample size of the study and the colour indicating the frailty measure used.

6.5 Results

Database searches identified 601 titles and abstracts, after removal of duplicates, of which 91 were retained for full-text screening. From these, 17 eligible full texts were identified, describing 14 separate cohorts (three samples were analysed in two separate papers each). Numbers screened along with reasons for exclusion are shown in Figure 6.1.

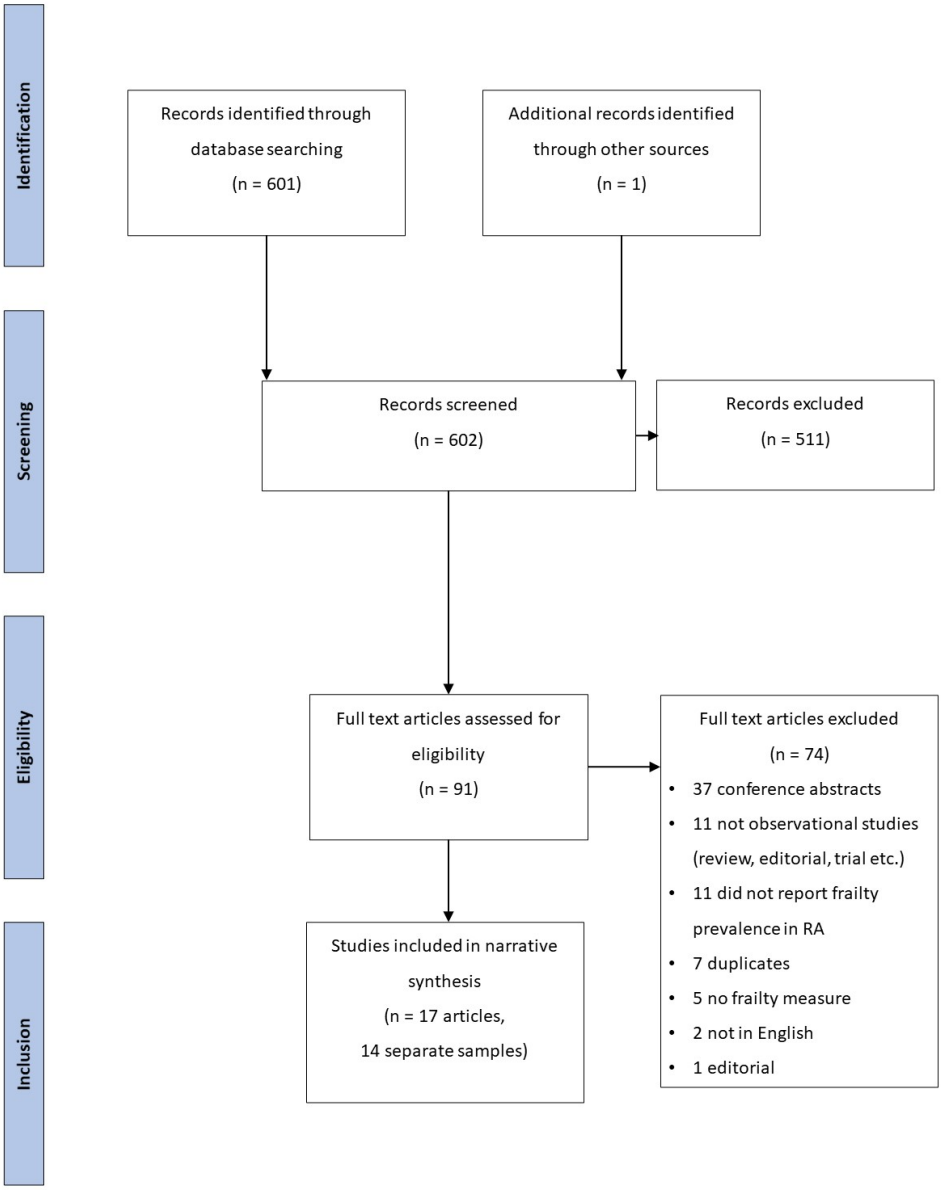

Figure 6.1 - PRISMA diagram of study selection

Baseline data for each of the included studies are shown in Table 6.2. Studies were from Japan (5 studies), USA (3 studies), Italy, Austria, Canada, Netherlands, Poland and UK (1 study each). Eleven studies identified rheumatoid arthritis according to the 2010 ACR/EULAR criteria,[399] while others used either 'clinician diagnosed' rheumatoid arthritis (3 studies), diagnostic codes from primary care records (1 study) or did not specify (2 studies). Mean age of the study samples ranged from 50.9 to 74.6 years. Only one study presented data on ethnicity,[401] and none commented on socioeconomic status.

The quality assessment of the included studies is summarised in Table 6.4. Most samples were recruited from rheumatology clinics. We judged most of these to be representative of people with rheumatoid arthritis as most people with the condition will be managed within specialist outpatient clinics and the sampling techniques of these studies were generally inclusive without applying further, restrictive exclusion criteria. Frailty measures used were generally validated or well-described. Few studies presented data on non-responders.

6.5.1 Frailty measurement

Across the 14 included studies, 11 different frailty measures were used. These are summarised in Table 6.3. The most commonly used measure was the frailty phenotype described by Fried et al (5 studies, 6 papers), followed by the Kihon frailty checklist (2 studies, 3 papers) and the SHARE frailty instrument (an adaptation of the frailty phenotype developed from the Survey for Health, Aging and Retirement in Europe, reported in 2 studies).

Of the 5 studies that used the frailty phenotype (based on grip strength, weight loss, physical activity, exhaustion, and walking speed), two also explored alternatives to grip strength, given the potential for the measurement of grip strength to be impacted by rheumatoid arthritis affecting the hands. Both used lower extremity strength as an alternative to grip strength to capture 'weakness'.

Table 6.2 - Characteristics of included studies

Author, Year	Country	Setting	Frailty measure	Rheumatoid arthritis definition	Total n	Age, years – mean (sd)	Eligible age range	N (%) women
Andrews 2017, Andrews 2019[396,402]	USA	Outpatient	Frailty phenotype	ACR	124	58 (10.8)	>18	59 (47.6%)
Bak 2020[403]	Poland	Inpatient	Tilburg frailty indicator	ACR/EULAR 2010	106	65.8 (5)	≥60	82 (77.4%)
Chang 2010[279]	USA	Community	Frailty phenotype	NA	11	74.1 (2.8)	≥65	11 (100%)
Haider 2019[395]	Austria	Outpatient	SHARE-FI	ACR/EULAR 2010	100	50.9 (9.7)	18-65	66 (66%)
Hippisley-Cox 2017[301]	UK	Community	Qfrailty	Primary Care clinical coding	10312	-	≥18	-

Kojima 2020[404]	Japan	Outpatient	Kihon checklist	ACR 2010	375	65.2 (9.7)	40-79	323 (86.1%)
Li 2019[405]	Canada	Outpatient (registry)	Frailty index	"Active RA"	2923	57.7 (12.7)	≥65	2290 (78.3%)
Minamino 2021[406]	Japan	Outpatient	Study of Osteoporotic Fracture frailty indicator	NA	306	63.5	≥18	306 (100%)
Oetsma 2020[407]	Netherlands	Outpatient	Groningen frailty indicator, Geriatric 8	rheumatologist diagnosed RA	80	74.6 (5.9)	≥65	53 (66.2%)
Salaffi 2019[408]*	Italy	Outpatient	SHARE-FI	ACR/EULAR	210	60.4 (13.5)	≥18	138 (65.7%)
Salaffi 2020[394]*	Italy	Outpatient	Comprehensive Rheumatologic	ACR/EULAR	219	60.4 (13.5)	≥18	138 (63%)

			Assessment of Frailty					
Tada 2019, Tada 2021[409,410]	Japan	Outpatient	Kihon checklist	ACR/EULAR	95	68 (5.5)	≥18	78 (82.1%)
Wysham 2020[401]	USA	Outpatient	Frailty phenotype	rheumatologist diagnosed RA	138	58 (10.8)	≥18	117 (84.8%)
Yoshii 2019[411]	Japan	Outpatient	Frailty phenotype	ACR/EULAR	441	64.5 (13.5)	≥18	337 (76.4%)
Yoshii 2020[412]	Japan	Outpatient	5-item frailty score	ACR/EULAR	739	71.3	≥18	-

Table 6.3 - Frailty measures used in included studies

Frailty measure	Components	Range and categorisation	Outcomes reported in included studies	Included studies
Frailty phenotype[5]	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI	Andrews 2017,[396] Andrew 2019,[402] Chang 2010,[279] Wysham 2020,[401] Yoshii 2019[411]
Kihon checklist[413]	Self-administered checklist (components: activities of daily living, exercise, falling, nutrition, oral health, cognition, depression)	Unweighted sum of components. Range 0-25. Pre-frail (4-7), Frail (≥8).	Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI	Kojima 2020,[404] Tada 2019,[409] Tada 2021[410]
Survey for Health, Aging and Retirement in Europe Frailty	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity). Conceptually based on the frailty phenotype with an alternative	Weighted score calculated and then categorised into robust, pre-frail, frail.	Frailty prevalence, Disease activity, HAQ-DI	Haider 2019,[395] Salaffi 2019[408]

Instrument (SHARE-FI)[227]	calculation for the final categorisation of frailty.			
Frailty index[6,35]	Count of health-related deficits (≥30, type and number of chosen deficits may vary between studies). Total present divided by number of possible deficits	Range 0-1 Sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24)	Hospitalisation, Fractures	Li 2019[405]
Comprehensive Rheumatologic Assessment of Frailty (CRAF)[394]	10 domains identified as relevant to the assessment of frailty in the context of rheumatological condition. Conceptually similar to the frailty index, cumulative deficit model (but with fewer deficits than the frailty index).	Range 0-1 Authors propose to categorise as robust (0-0.12), mild (0.12-0.24), moderate (0.24-0.36) and severe (>0.36) frailty.	Frailty prevalence, disease activity	Salaffi 2020[394]
5-Item frailty risk score[414]	5 components (weight loss, fatigue, short term memory decline, slow walking pace, low physical activity). Conceptually based on the frailty	1-2 criteria: Pre-frail ≥3 criteria: Frail	Frailty prevalence, Disease activity, HAQ-DI	Yoshii 2020[412]

	phenotype, with alteration of variables included.			
Tilburg frailty indicator[415]	15 questions across 3 domains (physical, psychological and social) Responses combined into unweighted sum.	Range 0-15 ≥5 indicates frailty	Frailty prevalence	Bak 2020[403]
Geriatric 8 score[416]	8 domains scored and summed (nutritional status, weight loss, body mass index, motor skills, psychological, number of medications, self-rated health, age)	Range 0-17 <14 indicates frailty	Frailty prevalence	Oetsma 2020[407]
Groningen frailty indicator[45]	15 items across 4 domains (physical, cognitive, social and psychological).	Range 0-15 ≥4 indicates frailty	Frailty prevalence, HAQ-DI	Oetsma 2020[407]
Study of Osteoporotic Fracture	3 components (weight loss, chair stand, exhaustion)	1 component: prefrail 2-3 components: frail	Frailty prevalence, Duration of rheumatoid	Minamino 2021[406]

frailty indicator			arthritis, Disease activity, HAQ-DI	
QFrailty[301]	Algorithm based on electronic medical records combining mortality (QMortality score) and hospital admission (QAdmission score) risk.	Categorised as mild, moderate and severe frailty.	Frailty prevalence	Hippisley-Cox 2017[301]
Table adapted from Hanlon et al 2020[37]				

Table 6.4 - Quality assessment of included studies (based on adapted Newcastle Ottawa Scale)

Author, Year	Representative	Selection of non-frail comparison	Ascertainment of exposure (frailty)	Non respondents	Outcome not present at start	Controls for age and sex	Control for other factors	Outcome assessment	Length of follow up	Adequacy of follow up	Cross-sectional score	Longitudinal score
Andrews 2017, Andrews 2019[396,402]	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Bak 2020[403]	0	1	2	0	-	-	-	-	-	-	3/5	-
Chang 2010[279]	1	1	1	0	-	-	-	-	-	-	3/5	-
Haider 2019[395]	1	1	2	0	-	-	-	-	-	-	3/5	-

Hippisley-Cox 2017[301]	1	1	1	0	-	-	-	-	-	-	3/5	-
Kojima 2020[404]	0	1	2	0	-	-	-	-	-	-	3/5	-
Li 2019[405]	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Minamino 2021[406]	1	1	2	0	-	-	-	-	-	-	4/5	-
Oetsma 2020[407]	1	1	2	0	-	-	-	-	-	-	4/5	-
Salaffi 2019[408]	1	1	2	1	-	-	-	-	-	-	5/5	-
Salaffi 2020[394]	1	1	1	1	-	-	-	-	-	-	4/5	-

Tada 2019, Tada 2021[409,410]	1	1	2	1	-	-	-	-	-	-	4/5	-
Wysham 2020[401]	1	1	2	0	-	-	-	-	-	-	4/5	-
Yoshii 2019[411]	1	1	2	0	-	-	-	-	-	-	4/5	-
Yoshii 2020[412]	1	1	1	0	-	-	-	-	-	-	3/5	-

6.5.2 Frailty prevalence

The prevalence of frailty in each of the studies identified is shown in Figure 6.2, stratified by age group. The prevalence in general adult populations with rheumatoid arthritis ranged from 10.1% (using the frailty phenotype) to 36% (using the Comprehensive Rheumatologic Assessment of Frailty (CRAF), taking 'moderate frailty' as the cut-off). Studies (or subsets of studies) with populations aged under 60 or 65 years had a frailty prevalence ranging from 2.4% (frailty phenotype) to 19.9% (Kihon checklist). In older populations, estimates ranged from 31.2% (Kihon checklist) to 55% (Geriatric 8 tool).

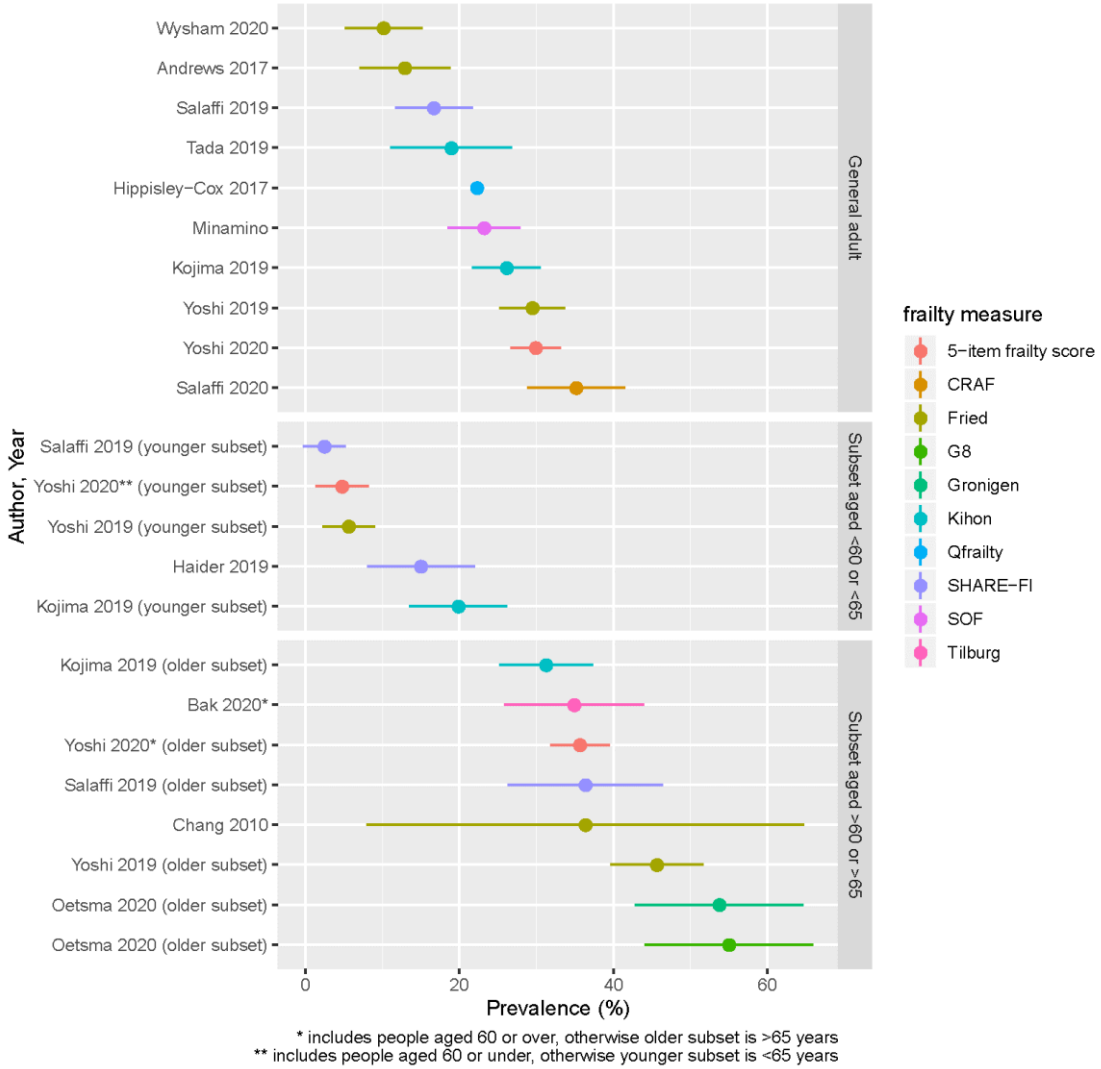

Figure 6.2 - Prevalence of frailty in included studies. Colours indicate frailty measure. Points indicate point estimate of for frailty prevalence, with bars indicating 95% confidence intervals. Stratified by age group. Ordered by frailty prevalence for ease of comparison.

While frailty prevalence is recognised to vary depending on the measure used, and therefore heterogeneity in these estimates is expected, the prevalence of frailty varied widely even among similar frailty definitions. For example, three studies applied the frailty phenotype to general adult populations with prevalence estimates of 10.1%, 12.9% and 28.5%, respectively. Two studies applied the SHARE-FI to populations aged under 65 years and found a prevalence of 2.5% and 15%, respectively. Therefore, estimates of frailty prevalence in rheumatoid arthritis appear to vary widely even between samples of similar ages applying similar measures of frailty.

One study assessed frailty using the standard frailty phenotype definition, and then using an alternative measure of weakness based on lower extremity strength rather than grip. This was to limit the impact of rheumatoid arthritis affecting the hands on the assessment of frailty. The prevalence of frailty using this alternative strength assessment was lower than the standard grip strength assessment (3.6% and 12.9%, respectively).

We did not attempt to meta-analyse any estimates of frailty prevalence as it is not valid to directly compare frailty prevalence assessed by different measures, and, even for those studies using similar measures, population demographics and exclusion criteria were too heterogenous to allow for a meaningful estimate.

6.5.3 Relationship between frailty and clinical characteristics and outcomes

Associations between frailty and clinical characteristics or outcomes in rheumatoid arthritis are summarised in figure 3. Most (8/10) of these studies were cross-sectional, showing associations between frailty and baseline measures of disease activity or physical function. These are discussed in greater detail below. The studies assessing outcomes were judged to be representative of people with rheumatoid arthritis as most recruited consecutive or non-selected patients from rheumatology outpatient departments (where most patients with rheumatoid arthritis undergoing treatment are managed). Frailty measures were either validated or well-described. Cross sectional characteristics were assessed similarly in people with and without frailty. As such these were judged to be a high-quality assessment of the cross-sectional associations

between frailty and features of rheumatoid arthritis but with limited assessment of the longitudinal impact of frailty or the causal role of frailty in the development of outcomes and complications.

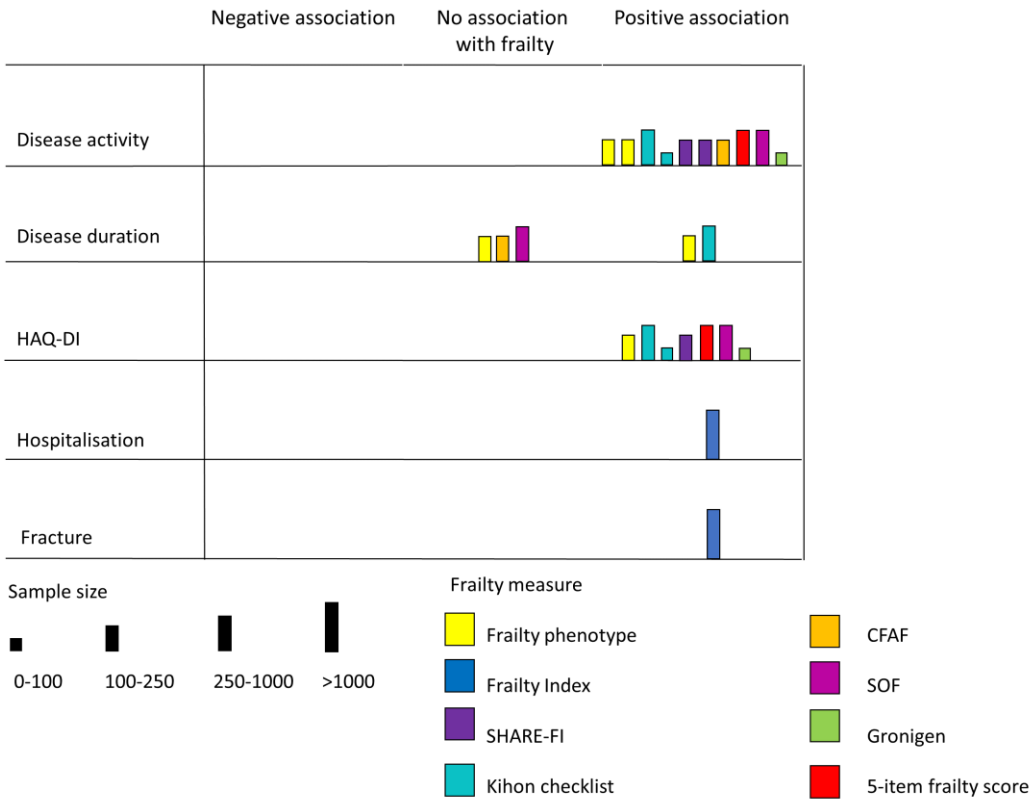

Figure 6.3 - Harvest plot of association between frailty and clinical outcomes. Each bar represents a study. The position of the bar on the matrix indicates the association between frailty and the outcome in question (positive association, negative association or neutral association). Colour indicates the frailty measure used in the study. The weight of the bar indicates the study sample size.

6.5.3.1 Rheumatoid arthritis disease activity

Ten studies, using seven different frailty measures and four different markers of rheumatoid arthritis disease activity (4 using Disease Activity Score in 28 joints (DAS-29), 2 using the Rheumatoid Arthritis Disease Activity Index (RADAI), 2 using Simple Disease Activity Index and 2 using Clinical Disease Activity Index (CDAI)) all showed a significant cross-sectional association between frailty status and activity of rheumatoid arthritis before adjustment for additional factors.[394,395,401,402,404,406-409,412] One study, using CDAI, found that this relationship was no longer evident after adjusting for age.[412] In contrast, two

other studies, showed that frailty remained associated with a higher baseline DAS-28 score after adjustment for age, sex, duration of rheumatoid arthritis and physical impairment (quantified using the Health Assessment Questionnaire – Disability Index (HAQ-DI)).[404,406]

Two studies presented data on prevalence or degree of frailty, stratified by disease activity (remission, low, medium or high). Tada and colleagues assessed frailty using the Kihon checklist and reported a prevalence of 6.7% in the remission group, 18% in people with low disease activity, and 47% in the medium or high disease activity group.[409] Salaffi and colleagues, analysing the CRAF, showed that none of the participants in remission or with low disease activity groups had scores above the threshold for 'moderate frailty', whereas among participants with high disease activity the median CRAF score was 0.34 (close to the threshold for 'severe frailty' of 0.36).[394]

One cohort study assessed the relationship between frailty and change in disease activity over time, reporting no significant association between frailty and change in RADAI over 3.7 years follow-up.[402]

Taken together these data show a consistent relationship between frailty and disease activity assessed using DAS28, however there was some inconsistency in this relationship when disease activity was assessed by different measures. The prevalence of frailty appears considerably higher in people with active disease. However, these were cross sectional assessments and no studies assessed whether frailty prevalence or severity is sensitive to changes in disease severity over time.

6.5.3.2 Physical function

Seven studies assessed the relationship between frailty and physical function using the HAQ-DI.[395,396,402-404,406,407,409,412] Each of these studies demonstrated an association between frailty and higher baseline HAQ-DI scores (indicating a greater degree of physical impairment). One of these studies also included a longitudinal analysis in which frailty at baseline (assessed using the frailty phenotype) was associated with worsening of HAQ-DI scores over 2-years follow-up, indicating that participants with frailty at baseline were more likely to

experience deterioration in physical function than robust participants.[402] This analysis was also adjusted for rheumatoid arthritis disease activity. Together these findings show a consistent relationship between frailty status, assessed through a range of measures, and greater physical impairment assessed using HAQ-DI.

6.5.3.3 Duration of rheumatoid arthritis

Five studies assessed the relationship between frailty and the duration of rheumatoid arthritis at baseline.[394,401,404,406,408] Findings were mixed, with three studies showing no association between frailty and disease duration.[394,401,406] By contrast, two studies showed that frailty was associated with greater duration of rheumatoid arthritis at the time of assessment,[404,408] however only one of these studies additionally adjusted for age in the analysis.[404]

6.5.3.4 Other outcomes

One study, using the frailty index approach to quantifying frailty in 2923 participants, assessed the relationship between frailty and all-cause hospitalisations.[405] Higher frailty index values were associated with a greater risk of hospitalisation during a mean follow-up of 3.7 years. This same study also showed that a higher frailty index was associated with a greater risk of osteoporotic fractures over the same follow-up period.

No studies assessed the relationship between frailty and mortality, cardiovascular events, or outcomes in response to treatment. Also, no studies assessed frailty at any other time-points following baseline, and therefore no analyses were identified of frailty trajectories in rheumatoid arthritis or of factors associated with worsening or amelioration of frailty.

6.6 Discussion

6.6.1 Summary of findings

In this systematic review we identified 17 papers, based on 14 different populations, reporting the prevalence of frailty in people with rheumatoid arthritis. Frailty was common in all studies, ranging from 10% to 36% among adult populations with rheumatoid arthritis, however there was considerable heterogeneity in both the measures used to identify frailty and the demographics of the populations studied (most notably age). There were 11 different measures used to identify frailty across the 14 cohorts, which limits the comparability of prevalence estimates. However, even among studies using similar measures, estimates of the frailty prevalence were variable. This may reflect differences in the underlying population (e.g. ethnicity, socioeconomic status, disease activity), inclusion criteria, or the application of frailty measures. All these factors may influence prevalence estimates of frailty. It is notable, therefore, that few studies reported data on ethnicity or socioeconomic status.

Nonetheless, frailty (however measured) was consistently associated with greater disease activity assessed through scores such as DAS-28, and with greater physical impairment indicated by HAQ-DI. The relationship with duration of rheumatoid arthritis was inconsistent, with some studies reporting an association between frailty and greater duration of rheumatoid arthritis. None assessed the prevalence of frailty in new-onset rheumatoid arthritis. Most studies were cross sectional, with only two reporting longitudinal follow-up (showing frailty to be associated with hospitalisations and fractures, and worsening physical function, respectively). Therefore, the prognostic significance of frailty in rheumatoid arthritis remains unclear, nor do we know anything about the likely trajectory of frailty over time or the sensitivity of frailty to changes in disease activity as a result of treatment with disease-modifying antirheumatic drugs.

6.6.2 Findings in context of previous literature

Estimates of frailty prevalence are understood to be limited by variability in how frailty is measured. Different frailty measures are based on different

characteristics, are underpinned by different theoretical constructs, and identify different populations. A recent systematic review estimated a pooled global prevalence of frailty in the general population at 7% (95% CI 5-9%) using a physical frailty model and 24% (22-26%) using a cumulative deficit model, however estimates vary widely depending on the underlying population demographics.[7] Despite these limitations in comparing frailty prevalence between studies, the estimates reported in this review indicate that frailty is common in people with rheumatoid arthritis compared to the general population. This is consistent with previous observations that frailty, identified using a frailty index, was common in phase 3-4 randomised controlled trials of people with rheumatoid arthritis.[417] As in this review, frailty in these trials was strongly associated with greater disease activity.

The cross-sectional nature of the included studies makes determining the extent to which the frailty is caused by rheumatoid arthritis difficult. The development of frailty is understood to be multifactorial. Furthermore, different approaches to identifying frailty (such as a frailty phenotype versus a cumulative deficit model, or a physical model versus one including psychological and social vulnerability) may have different causal pathways and mechanisms underlying them.[2,40] However, rheumatoid arthritis may lead to a range of states or complications (such as fatigue, sarcopenia, weight loss, and functional limitation) which may all contribute to the identification of frailty. Fatigue in rheumatoid arthritis may result from the underlying inflammatory process as well as symptoms, functional, emotional and psychological impact of the condition and treatments.[418] Weight loss and low body mass index, thought partly to be mediated through excess pro-inflammatory mediators such as IL-1 and TNF-alpha, are associated with greater erosive disease in rheumatoid arthritis as well as greater cardiovascular risk, physical disability, and mortality.[419-421] Rheumatoid arthritis, through a combination of systemic inflammation and reduced physical activity, may also result in sarcopenia which in turn contributes to the development of frailty.[422-426] These observations, along with the consistent association between frailty and greater disease activity, mean it is likely that rheumatoid arthritis – particularly if highly active or severe – leads to the development of features of frailty.

Conversely, frailty has a wide range of potential causes and associations, and it is unlikely that there is a single common pathway or mechanism underlying the development of frailty in people with rheumatoid arthritis. Co-existing frailty alongside rheumatoid arthritis may lead or contribute to functional limitations not exclusively attributable to rheumatoid arthritis itself. The rationale for frailty identification and assessment is to facilitate a broad and multidimensional evaluation of a person's needs and priorities. Given increasing rheumatoid arthritis in older age,[393] and the prevalence of multimorbidity among people with rheumatoid arthritis,[427] it is important to better understand whether incorporating frailty assessment into the management of rheumatoid arthritis would bring additional benefits beyond those measures already commonly used.

6.6.3 Implications

These findings highlight several important gaps in our understanding of frailty in the context of rheumatoid arthritis. The first is the prognostic significance of frailty in people with rheumatoid arthritis. Only one study, using a frailty index model, assessed the association between frailty and hospitalisations and none explored whether frailty is associated with mortality, cardiovascular events, or long-term care needs in people with rheumatoid arthritis. The association between frailty and these outcomes in the general population is well established. However, given the overlap between features of active or severe rheumatoid arthritis and frailty, it is not clear if assessment of frailty in the context of rheumatoid arthritis improves prediction of these outcomes.

The second gap is to disentangle the relationship between frailty and rheumatoid arthritis disease activity. Active rheumatoid arthritis may give rise to a range of features which may indicate frailty (fatigue, weakness, pain, functional limitation, etc.). Frailty may, therefore, be amenable to intervention. Frailty is recognised to be a dynamic state which changes over time. However, the degree to which frailty in rheumatoid arthritis is reversible is not clear. This question, like the association between frailty and clinical outcomes, would require longitudinal studies ideally with serial assessments of both frailty and disease activity.

A final, more nuanced, gap in our understanding is how these epidemiological measures of frailty translate to the experience and understanding of people living with rheumatoid arthritis and to the clinical impression of professionals involved in their care. While a range of physical, functional, and psychological features common in rheumatoid arthritis may be consistent with current definitions of frailty, this may not be how people living with rheumatoid arthritis would choose to characterise their experience. It is also not clear if frailty identified in such a way, particularly when it results from active rheumatoid arthritis, is equivalent to frailty as it would be understood by clinicians. Understanding the implications of frailty in rheumatoid arthritis therefore not only requires a fuller understanding of its epidemiology, but also the broader clinical implications and the utility of a frailty 'label'. For clinicians, understanding that there is uncertainty around the prognostic significance of frailty in people with rheumatoid arthritis is important. Recommendations for frailty based, for example, on limited life expectancy or the likelihood of functional decline may not be relevant for all individuals with rheumatoid arthritis who meet the criteria for frailty. For this reason, future research assessing the relationship between frailty and outcomes such as mortality and the development of disability in people with rheumatoid arthritis, as disentangling this from the impact of rheumatoid arthritis disease activity, is important to inform clinical decisions.

6.6.4 Strengths and limitations

Strengths of this review include a comprehensive search strategy with duplicate screening and data extraction. However, the search was limited to English language only and we excluded Grey literature. This could potentially lead to language or publication bias, respectively. We used an adapted version of the Newcastle-Ottawa scale (prespecified in our protocol) to maximise the comparability of assessment of cross-sectional and longitudinal studies (e.g., where both assessed prevalence). However, most studies identified and included were cross sectional, and this tool is not specific to the assessment of cross-sectional studies. It was not possible to conduct a meta-analysis of frailty prevalence due to the degree of heterogeneity. This was particularly evident in the measurement of frailty, as a range of different measures were used, and prevalence estimates are therefore not directly comparable. Studies were also

heterogenous in terms of their inclusion criteria, demographics, and definitions of rheumatoid arthritis. Studies were all from high-income countries with no data from low-and middle-income countries. Also, only one study presented data on the ethnicity of participants, and none assessed socioeconomic status, factors which may impact the prevalence of frailty. Finally, the studies included in this review were observational and mostly cross-sectional. It is therefore not possible to assess causal relationships.

6.6.5 Conclusion

Frailty in people with rheumatoid arthritis has been quantified in high income countries using a wide range of different approaches and is consistently demonstrated to be common, particularly among people with more active disease. Assessment of frailty among people with rheumatoid arthritis, including those aged under 65 years, is likely to identify people at greater risk of functional limitation. However, a relative lack of longitudinal studies and heterogeneity in the methods used to assess frailty mean that the clinical implications, prognostic significance, and potential reversibility remain unclear. There is a need for studies in low- and middle-income countries as well as studies with serial follow-up and repeated measures to understand the trajectories and outcomes of frailty in rheumatoid arthritis, as well as greater exploration of the implications of frailty from the perspective of patients and clinicians. Understanding these relationships in greater detail may reveal potential for interventions to ameliorate frailty in rheumatoid arthritis, limit its impact, and support people living with frailty.

Chapter 7 Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalisation and mortality: a longitudinal analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank

7.1 Chapter summary

This chapter presents an analysis of the UK Biobank cohort and the Scottish Early Rheumatoid Arthritis cohort addressing research question 1 (prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in people with rheumatoid arthritis.

The text and figures presented here are as published in Hanlon P, Morton F, Siebert S, Jani BD, Nicholl BI, Lewsey J, McAllister D, Mair FS. Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalisation and mortality: a longitudinal analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank. RMD open. 2022 Mar 1;8(1):e002111.

7.2 Abstract

Objective: To assess the prevalence of frailty in rheumatoid arthritis (RA) and its association with baseline and longitudinal disease activity, all-cause mortality, and hospitalisation.

Participants: People with RA identified from the Scottish Early Rheumatoid Arthritis (SERA) inception cohort (newly diagnosed, mean age 58.2 years) and UK Biobank (established disease identified using diagnostic codes, mean age 59 years). Frailty was quantified using the frailty index (both datasets) and frailty phenotype (UK Biobank only). Disease activity was assessed using Disease Activity Score in 28 joints (DAS28) in SERA. Associations between baseline frailty and all-cause mortality and hospitalisation were estimated after adjusting for age, sex, socioeconomic status, smoking and alcohol, plus DAS28 in SERA.

Results: Based on the frailty index, frailty was common in SERA (12% moderate, 0.2% severe) and UK Biobank (20% moderate, 3% severe). In UK Biobank 23% were identified as frail using frailty phenotype. Frailty index was associated with DAS28 in SERA, as well as age and female sex in both cohorts. In SERA, as DAS28 lessened over time with treatment, mean frailty index also decreased. The frailty index was associated with all-cause mortality (HR moderate/severe frailty vs robust 4.14 [95% CI 1.49-11.51] SERA, 1.68 [1.26-2.13] UK Biobank) and unscheduled hospitalisation (IRR 2.27 [1.45-3.57] SERA, 2.74 [2.29-3.29] UK Biobank). In UK Biobank, frailty phenotype also associated with mortality and hospitalisation.

Conclusion: Frailty is common in early and established RA and associated with hospitalisation and mortality. Frailty in RA is dynamic and, for some, may be ameliorated through controlling disease activity in early disease.

7.3 Key Messages

7.3.1 What is already known about this subject

- Frailty has been shown to be common in people with rheumatoid arthritis but its change over time and relationship with adverse clinical outcomes remain unclear.

7.3.2 What does this study add

- Frailty in early rheumatoid arthritis is dynamic and responsive to treatment: following diagnosis and initiation of disease modifying antirheumatic drugs, the mean frailty index fell and 46% of moderate frailty individuals transitioned to a mildly frail or robust state.

- Frailty, by two contrasting measures, was associated with greater risk of all-cause mortality and hospitalisation.

7.3.3 How might this impact on clinical practice or future developments

- Frailty may help identify people with rheumatoid arthritis at increased risk of adverse health outcomes.

- However, a label of frailty should be used with caution in people with active disease, for whom it may at least be partially reversible.

- Identification of frailty in people with rheumatoid arthritis should inform implementation of broad multidisciplinary assessment and intervention and focus on reversible factors.

7.4 Introduction

Frailty describes a state of increased vulnerability to adverse health outcomes caused by reduced physiological reserve.[3] Frailty is associated with age.[35] However, it also predicts hospitalisation and death in younger people (<65 years).[3,9] Frailty has also been found to be common in rheumatoid arthritis (RA), including in people <65 years.[395,396,408,409] However, most studies have been small and cross sectional with only one examining associations between frailty and any clinically significant outcome such as hospitalisation.[405,428]

There are a number of different operational definitions of frailty. The most commonly implemented are the frailty index (a count of age-related health deficits)[6] and the frailty phenotype (a specific syndrome based on a combination of low grip-strength, weight loss, exhaustion, low physical activity and slow walking pace).[5] Both measures are based on the identification of vulnerability to physiological decompensation, which distinguishes them from related concepts such as multimorbidity.[429] Multimorbidity is associated with mortality in people with RA,[430] however the relationship between frailty and these outcomes has not been widely explored in the context of RA.

Frailty and disease activity in RA are likely to share considerable overlap. Both the frailty phenotype[5] and the frailty index[6,35] share features with RA disease activity. Despite this, no study has assessed whether frailty in RA predicts clinical outcomes independently of disease activity, nor whether frailty, like disease activity, improves following treatment for RA. These questions are of clinical importance as they have implications for the optimal approach to the management of frailty in RA. Consequently, we assessed the prevalence of frailty in people with early and established RA; analysed change in frailty status in early RA in the period following diagnosis; and quantified the association between frailty and all-cause mortality and unscheduled hospitalisation.

7.5 Methods

7.5.1 Data sources

The Scottish Early Rheumatoid Arthritis (SERA) cohort is an inception cohort of people with newly diagnosed RA or undifferentiated arthritis recruited from 16 out of 17 specialist rheumatology units across Scotland.[23,431] SERA participants in the present study were recruited between March 2011 and April 2015. Participants were ineligible if they had previously received disease-modifying antirheumatic drug (DMARD) treatment for more than 4 weeks. Participants underwent a baseline assessment followed by 6-monthly follow-up visits.

UK Biobank is a population cohort study recruited between 2006 and 2010.[222] Participants had to be registered with a general practice and live within 20 miles of one of 22 assessment centres in England, Scotland or Wales. Participants underwent a baseline assessment including a questionnaire, interview, physical measurements and biological samples.

Date of initial assessment for either dataset was taken as baseline for this analysis. SERA and UK Biobank participants consented to data linkage to national records including inpatient hospital records and mortality registers (available until April 2017 for both datasets).

7.5.2 Study population: identifying rheumatoid arthritis

From the SERA dataset we selected patients who fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for RA at baseline assessment.[399]

From UK Biobank, we identified participants from baseline UK Biobank assessments who had a previous diagnostic code for RA from either linked primary care records or inpatient hospital records.

7.5.3 Frailty definition

7.5.3.1 Frailty index

In both UK Biobank and SERA we quantified frailty using the frailty index approach, based on the cumulative deficit model of frailty developed by Rockwood and Mitnitski.[6] A frailty index is a count of health related 'deficits' within an individual, calculated by summing all deficits present and dividing this by the total number of possible deficits, to give a value between 0 (no deficits) and 1 (all possible deficits). All deficits are weighted equally. Higher values indicate a greater degree of frailty.

There is a standardised method for constructing a frailty index.[36] There is no pre-specified list of deficits which must be included in the index. Rather, deficits are selected based on the variables available in a given dataset providing they meet the following criteria: (i) associated with poor health, (ii) increase in prevalence with age, (iii) cover a range of organ systems, and (iv) are neither too rare (i.e. <1% prevalence) nor ubiquitous within the target population. Deficits typically include comorbidities, symptoms, functional limitations and laboratory investigations. If data for a specific deficit is missing, this deficit is excluded from the numerator and the denominator. We excluded participants with missing data for >5% of deficits.

For UK Biobank, we used the frailty index previously developed by Williams et al.[22] For SERA, we constructed a frailty index based on 42 deficits (including similar comorbidities to the UK Biobank frailty index, as well as symptoms, laboratory deficits and functional measures previously used in a frailty index developed for RA clinical trials).[417] See appendix 5 for full list of deficits.

The frailty index was analysed as a numerical variable. In addition, for presentation of data in tables and hazard ratios, we categorised the frailty index into robust (0 to 0.12) and mild (>0.12 to 0.24), moderate (>0.24 to 0.36) and severe (>0.36) frailty based on the cut-points used in the electronic frailty index used in primary care within the UK.[56]

7.5.3.2 Frailty phenotype

For UK Biobank, we also assessed frailty using an adaptation of the frailty phenotype developed by Fried et al.[5] The frailty phenotype is based on five characteristics: low hand-grip strength, self-reported exhaustion, unintentional weight loss, low physical activity, and slow walking pace. People with three or more criteria are considered frail, while one or two criteria indicates 'pre-frailty'. We have previously adapted the original definitions of these criteria to UK Biobank data.[9]

SERA does not contain the necessary variables for the frailty phenotype.

7.5.4 Measures

Age and sex were recorded at time of recruitment in both datasets. For UK Biobank, disease duration was estimated as the time since the first recorded diagnostic code for RA (for SERA all participants were recruited at the point of diagnosis by a rheumatologist). As time since initial diagnostic code is a proxy measure, we did not attempt to differentiate early RA in UK Biobank. Socioeconomic status was based on an area-based measure (Townsend scores from linked 2001 census data in UK Biobank and Scottish Index of Multiple Deprivation in SERA).[388,432] Both measures are based data linkage to participants' postcodes and estimate socioeconomic status via a composite measure of various factors (Townsend scores based on percentage unemployment, percentage car ownership, percentage home ownership, and household overcrowding, Scottish Index of Multiple Deprivation based on income, employment, education, health, access to services, crime and housing).

Smoking status was categorised as current, previous or never. Alcohol intake was based on self-reported frequency of intake in UK Biobank and on self-reported weekly units in SERA.

7.5.5 Outcomes

In SERA, we assessed the relationship between baseline frailty and RA disease activity, assessed using the composite Disease Activity Score in 28 joints, CRP version (DAS28) based on 4 factors (tender joints, swollen joints, CRP and

patient global score). Physical function was assessed using the Health Assessment Questionnaire – Disability Index (HAQ-DI), and self-rated health was assessed using the visual analogue scale (0-100) from the EuroQol (EQ-5D) questionnaire. DAS28, HAQ-DI and self-rated health were assessed at baseline and then at 6-monthly follow-up intervals.

In both datasets, we assessed the relationship between frailty and both all-cause mortality and all-cause unscheduled hospitalisation (defined as any admission with an 'urgent' or 'emergency' code), identified through linkage to national mortality registers and hospital records, respectively. These linked datasets record all inpatient hospital episodes and recorded deaths in either Scotland (SERA) or for the entire UK (UK Biobank). Mean follow-up was 10 years in UK Biobank and 4 years in SERA. Participants were censored at death or end of available follow-up (April 2017), whichever occurred first.

7.5.6 Statistical analyses

7.5.6.1 Distributions of frailty

For SERA, the individual participant data are held within a secure safe-haven which only allows export of aggregate, non-disclosive data. Therefore, to allow us to describe the distribution of the frailty index, we assessed the fit of possible distributions for a frailty index (lognormal, exponential, Weibull and generalised-gamma) using the Kolmogorov-Smirnov test. The generalised-gamma distribution fitted well. These parameters were then exported from the safe-haven and used to plot the distribution of the frailty index.

For UK Biobank, we plotted the full distribution of the frailty index and described this distribution statistically.

To facilitate interpretation, we also calculated percentages of participants who were robust or had mild, moderate or severe frailty. These findings are presented as descriptive statistics only.

The frailty index distribution was summarised descriptively for each dataset separately. This is because the deficits included in each index differ, and the method used to identify RA also differed between SERA and UK Biobank.

7.5.6.2 Frailty and disease activity (SERA only)

For SERA, we assessed the relationship between the frailty index and activity of RA using the DAS28 score. We used generalised gamma regression to model the frailty index on age, sex and DAS28. The coefficients and variance covariance matrix from this model were then exported from the safe-haven and used to model the mean frailty index conditional on a specific age, sex and DAS28 value. We therefore modelled mean frailty index for men and women index at a range of ages (30 to 80 years) and DAS28 values (3.2 indicating the threshold for mild disease activity, and 5.1 indicating the threshold for active disease).

7.5.6.3 Frailty and outcomes – serial follow-up in SERA

To assess the change in frailty index over time, we re-calculated the frailty index at 6-monthly follow-up intervals. This period is concurrent with the commencement of disease-modifying treatment (reported elsewhere[431]). We did not formally assess treatment status. As comorbidities were only assessed at baseline, we carried baseline comorbidity status forward. For all other deficits (functional measures, symptoms, and blood results) the frailty index used follow-up values. Frailty index was treated as missing where these additional values were not assessed at follow-up, in which case the previous frailty index value was carried forward. We then plotted the mean frailty index at follow-up, as well as the mean DAS28 score, mean HAQ-DI score, and mean self-rated health (using the EQ-5D visual analogue scale) at each follow-up point. Participants were excluded where data on these outcomes were missing. We assessed these outcomes over the first 2 years of follow-up.

7.5.6.4 Frailty and outcomes – linked healthcare data

We used negative binomial regression to model the number of urgent or emergency admissions on the frailty index (SERA and UK Biobank) and the frailty phenotype (UK Biobank only). For all-cause mortality, we used Cox proportional hazards models to model mortality on frailty index. We fit three models for each outcome. Model 1 adjusted for age, sex and socioeconomic status. Model 2 additionally adjusted for smoking status and alcohol intake. Model 3 adjusted for variables in model 2, plus DAS28 (SERA only). Incidence rate ratios and hazard

ratios, respectively, were calculated with 95% confidence intervals. Participants with missing data for covariates were excluded from the adjusted analyses.

As a sensitivity analysis using the SERA dataset, an extended cox-PH model was used to model the effect of changing frailty index and DAS28 values on hospitalisation and mortality.

We fit models 1 and 2 using the frailty phenotype (UK Biobank only).

7.5.6.5 Patient and public involvement

No patients were involved in this research.

7.5.6.6 Ethical approval

UK Biobank has ethical approval from UK National Health Service research ethics service (16/NW/0274). This analysis was conducted under UK Biobank project 14151. SERA was approved by the West of Scotland Research Ethics Committee (10/S0704/20) and the analysis presented in this paper was approved by the SERA data access committee (project reference 2020042901).

7.6 Results

In SERA, 899 participants had RA at baseline, recruited at the time of diagnosis (median symptom duration 6 months). In UK Biobank, at baseline assessment, 3605 participants had a prior diagnostic code for RA in either primary care records or inpatient hospital records. Baseline characteristics are shown in Table 7.1.

7.6.1 Distributions of frailty

The mean frailty index was 0.16 in SERA and 0.19 in UK Biobank. The distribution of the frailty index in each of the datasets is shown in Figure 7.1. In SERA, 12.1% of participants had moderate frailty, with 0.2% having severe frailty. The prevalence was higher in UK Biobank, with 714 (20%) participants having moderate and 109 (3%) having severe frailty. All SERA participants had sufficient data to calculate the frailty index. In UK Biobank, 8 participants were excluded due to missing data for >5% of deficits.

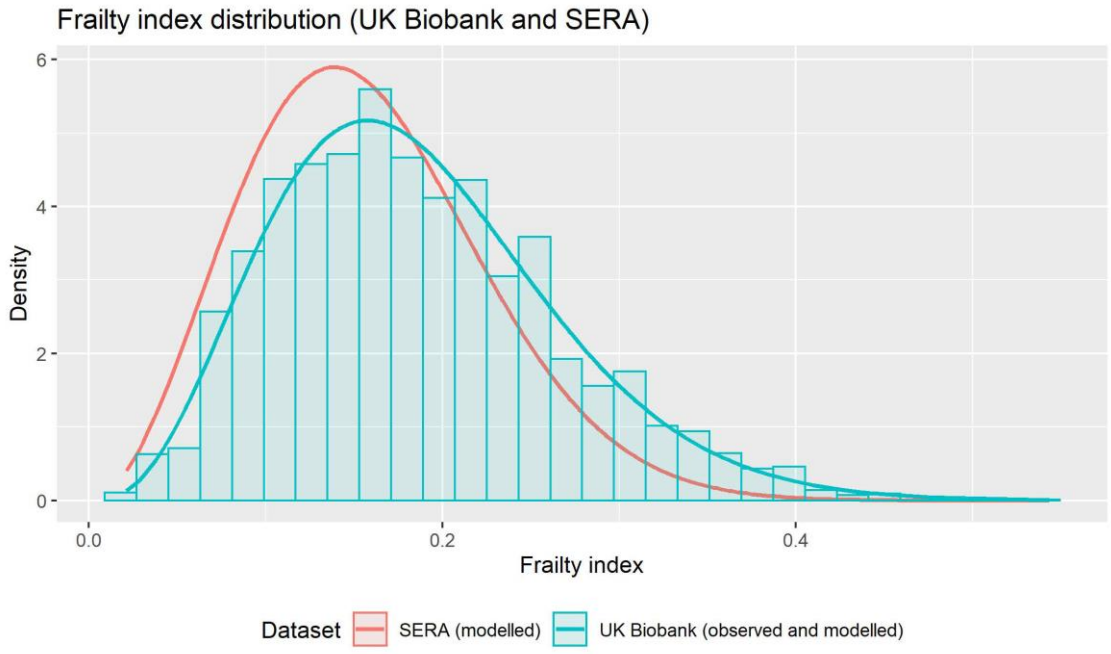

Figure 7.1 - Frailty index distribution (UK Biobank and SERA). This figure shows the distribution of the frailty index in UK Biobank participants (blue bars indicating observed values, blue line showing fitted distribution) and SERA participants (red line showing fitted distribution only – observed values analysed within a secure safe-haven and not exported).

Table 7.1 - Baseline demographic characteristics stratified by frailty status

	SERA				UK Biobank (Rheumatoid arthritis population only)							
	Total (n = 899)	Frailty Index			Total (n = 3605)	Frailty index*				Frailty phenotype**		
		Robust (n = 303)	Mild (n = 487)	Moderate/Severe (n = 109)		Robust (n = 773)	Mild (n = 2001)	Moderate (n = 714)	Severe (n = 109)	Robust (n = 788)	Pre-frail (n = 1775)	Frail (n = 781)
Mean age												
Years (sd)	58.3 (13.3)	56.0 (13.6)	58.5 (13.8)	63.7 (12.3)	59.5 (7.1)	59.2 (7.2)	59.5 (7.1)	59.8 (6.9)	58.2 (5.9%)	58.8 (7.1)	59.8 (7.1)	59.0 (7.0)
Sex												
Male (%)	313 (34.8%)	109 (36.0%)	171 (35.1%)	33 (30.3%)	1063 (29.5%)	255 (33.2%)	568 (28.4%)	208 (29.1%)	27 (24.8%)	278 (35.3%)	527 (29.7%)	193 (24.7%)
Female (%)	586 (65.2%)	194 (64.0%)	316 (64.9%)	76 (69.7%)	2542 (70.5%)	518 (66.8%)	1433 (71.6%)	506 (70.9%)	82 (75.2%)	510 (64.7%)	1248 (70.3%)	588 (75.3%)
SES												
Quintile 1 (deprived)	193 (21.6%)	60 (19.8%)	102 (21.1%)	31 (28.4%)	884 (24.5%)	115 (15.0%)	459 (23.0%)	255 (35.7%)	52 (47.7%)	132 (16.8%)	396 (22.3%)	270 (34.6%)
2	193 (21.6%)	58 (19.1%)	111 (23.0%)	24 (22.0%)	790 (21.9%)	169 (21.9%)	449 (22.4%)	148 (20.7%)	22 (20.2%)	173 (22.0%)	385 (21.7%)	181 (23.2%)
3	174 (19.4%)	62 (20.5%)	90 (18.6%)	22 (20.2%)	698 (19.4%)	161 (20.9%)	391 (19.5%)	129 (18.1%)	15 (13.8%)	167 (21.2%)	336 (18.9%)	142 (18.2%)
4	191 (21.3%)	69 (22.8%)	108 (22.4%)	14 (12.8%)	593 (16.5%)	162 (20.8%)	328 (16.4%)	91 (12.7%)	12 (11.0%)	145 (18.4%)	314 (17.7%)	98 (12.5%)
Quintile 5 (affluent)	144 (16.1%)	54 (17.8%)	72 (14.9%)	18 (16.5%)	639 (17.7%)	166 (21.4%)	373 (18.6%)	91 (12.7%)	8 (7.3%)	171 (21.7%)	343 (19.3%)	90 (11.5%)
Missing	0	0	0	0	0	0	0	0	0	0	1	0
Smoking												
Never	323 (35.9%)	115 (38.0%)	167 (34.3%)	41 (37.6%)	1624 (45.6%)	402 (52.5%)	894 (45.0%)	293 (41.6%)	35 (32.1%)	366 (46.7%)	810 (45.9%)	330 (42.9%)
Previous	326 (36.3%)	108 (35.6%)	181 (37.2%)	37 (33.9%)	1512 (42.4%)	295 (38.6%)	866 (43.6%)	303 (43.0%)	48 (44.0%)	346 (44.2%)	748 (42.4%)	317 (41.2%)
Current	249 (27.7%)	79 (26.1%)	139 (28.5%)	31 (28.4%)	429 (12.0%)	68 (8.9%)	227 (11.4%)	108 (15.3%)	26 (23.9%)	71 (9.1%)	205 (11.6%)	123 (16.0%)
Missing	1	1	0	0	40	8	14	10	0	5	12	11
RA duration												
Median years (IQR)	-	-	-	-	6.6 (3.0-10.7)	6.2 (3.0-11.2)	7.0 (3.2-11.0)	6.2 (2.7-9.8)	6.0 (2.8-9.4)	5.9 (2.7-10.0)	6.6 (3.0-10.8)	7.0 (3.6-10.6)
Mean DAS-28												
Score (sd)	4.9 (1.3)	4.1 (1.2)	5.2 (1.1)	6.0 (1.1)	-	-	-	-	-	-	-	-

Missing	65	31	30	4
Mean HAQ-DI				
Score (sd)	1.2 (0.8)	0.5 (0.5)	1.5 (0.6)	2.2 (0.6)
Missing	2	2	0	0
Mean self-rated health				
Score (sd)	55.4 (25.8)	25.9 (24.0)	50.0 (23.2)	39.2 (22.8)
Missing	7	3	3	1

SES: socioeconomic status, HAQ-DI: Health Assessment Questionnaire – Disability Index, DAS-28: Disease activity score in 28 joints. *8 UK Biobank participants had missing values for the frailty index and are excluded from columns stratified by frailty index. **262 UK Biobank participants had missing data for the frailty phenotype and are excluded from columns stratified by frailty phenotype status.

Using the frailty phenotype, 781 (23%) of UK Biobank participants met the criteria for frailty, while 1775 (53.1%) were classified as pre-frail (compared to 3% and 38%, respectively, in the cohort as a whole).[9] 44.7% (349/781) participants identified as frail were also moderate or severely frail by the frailty index criteria. Data for one or more criteria were missing for 262 (7.2%) people with RA (compared to 2% missing data for the cohort as a whole). Hand-grip strength was the most commonly missing variable. Descriptive statistics of participants with missing data are shown in appendix 5.

7.6.2 Frailty and disease activity (SERA only)

The modelled relationship between frailty and age, sex, and DAS28 in SERA is shown in Figure 7.2. Mean frailty index increased with age, was higher in women than in men, and was higher with more active disease.

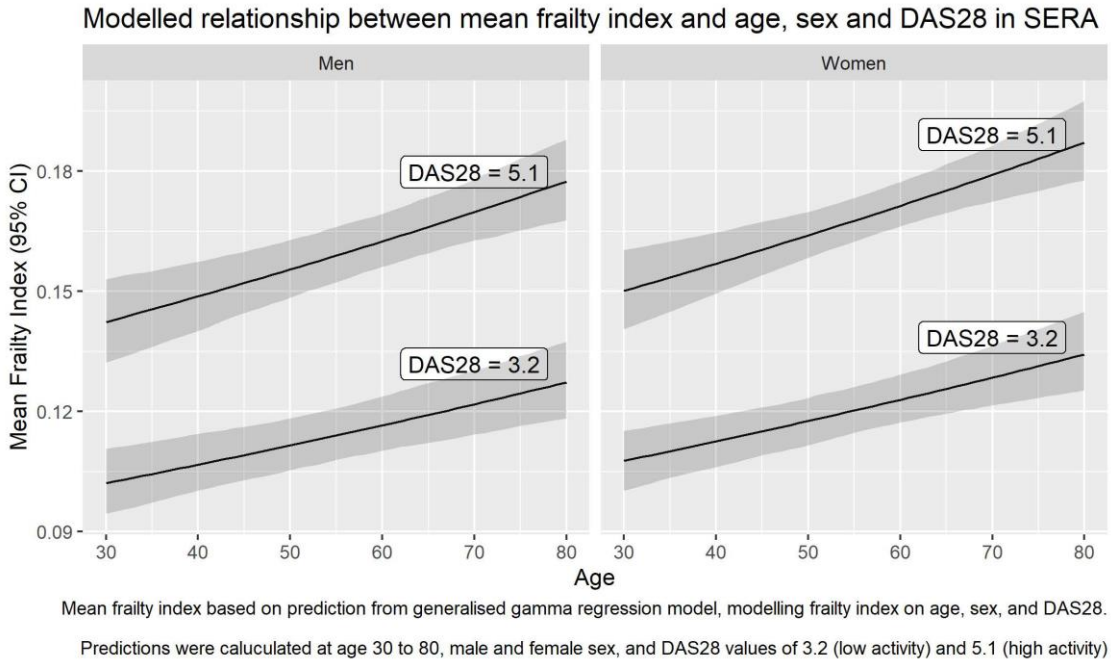

Figure 7.2 - Modelled relationship between frailty index, age, sex and DAS28 in SERA. This figure shows the predicted mean frailty index, based on generalised gamma regression models fitted to the SERA dataset, according to age (modelled within range 30-80 years), sex (male and female) and DAS28 (modelled at 3.2 indicating mild disease and 5.1 indicating active disease). Lines indicate point estimates for the mean frailty index, and shaded areas represent 95% confidence intervals.

7.6.3 Frailty and outcomes – serial follow-up in SERA

The change in mean frailty index in SERA over 2-year follow-up is shown in Figure 7.3, along with mean DAS28, HAQ-DI and self-rated health. Data for each measure was available for 834 participants, and this fell to 726, 645, 435 and

353 participants at 6, 12, 18 and 24 months, respectively. However, mean baseline frailty index values were similar between participants with and without missing follow-up data (e.g. 0.157 and 0.156 for those with and without missing data at 1 year). Mean frailty index, mean DAS28, and mean HAQ-DI fell after the initial baseline assessment and commencement of DMARD treatment, with improvement in self-rated health. This improvement in mean frailty index reflected a reduction in the overall prevalence of each of the functional measures that were reassessed, but not the laboratory values in the index (which did not substantially change) or comorbidities (which were not reassessed and therefore reflect baseline comorbidity prevalence). However, after 2 years follow-up, HAQ-DI scores, poor self-rated health and, to a lesser extent, disease activity were higher at the group level in participants with mild or moderate/severe frailty at baseline compared to participants who were robust at baseline (Figure 7.3). Of the 109 people who had moderate or severe frailty at baseline, 36 (33%) improved to mildly frail and 14 (13%) transitioned to a robust state in the first 6 months of follow-up. Despite these improvements, the mean frailty index at 2 years follow-up among those who were moderately or severely frail at baseline remained significantly higher than participants who were mildly frail or robust at baseline. This indicates that the frailty index is dynamic in early RA and fell concurrently with treatment and improvements in disease activity, physical function and self-rated health. However, despite these improvements, participants with a higher baseline frailty index tended to have a higher frailty index, higher disease activity, poorer physical function and poorer self-rated health throughout 2 years follow-up compared to participants with a lower baseline frailty index.

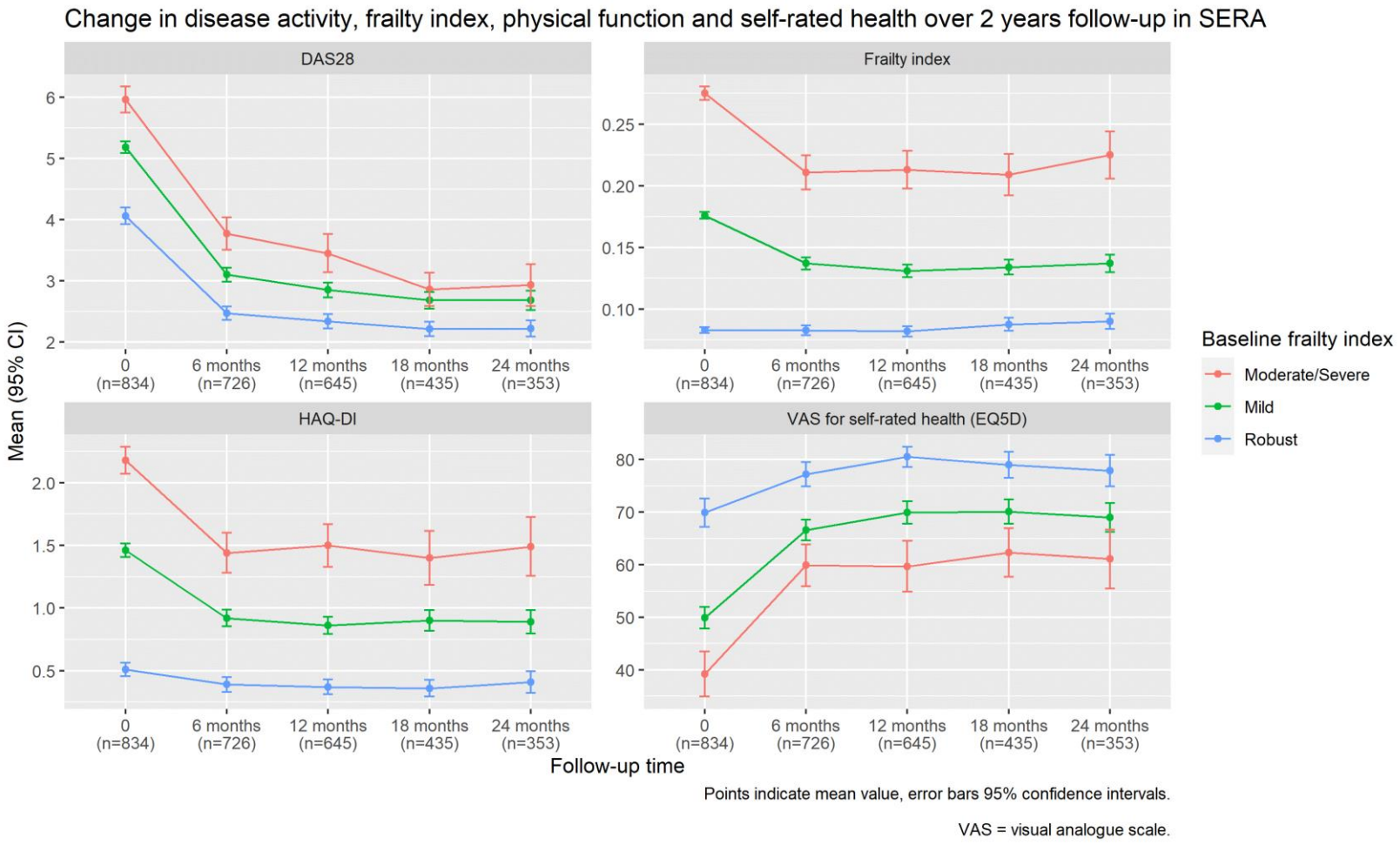

Figure 7.3 - Change in disease activity, frailty index, physical function and self-rated health over 2 years follow-up in SERA. Points indicate mean values for DAS28, frailty index, HAQ-DI and self-rated health, respectively. Error bars indicate 95% confidence intervals. Results are stratified by frailty status at baseline (robust, mild, or moderate/severe) based on the frailty index.

7.6.4 Frailty and outcomes – linked healthcare data

Associations between frailty and mortality and hospitalisation outcomes are shown in Table 7.2. In both SERA and UK Biobank, moderate/severe frailty (measured using the frailty index) was associated with a higher risk of both all-cause mortality and unscheduled hospitalisation in models adjusted for age, sex and socioeconomic status (model 1), plus smoking and alcohol intake (model 2) and, in SERA only, after additionally adjusting for DAS28. In UK Biobank, mild frailty was also associated with greater risk of mortality and hospitalisation, but in SERA the confidence interval for these estimates included the null. In the sensitivity analysis in SERA, the effect of frailty on both outcomes was similar using the time-varying model compared to using baseline values only.

Analyses of the frailty phenotype (UK Biobank only) demonstrated a greater risk of both mortality and hospitalisation associated with both pre-frailty and frailty.

Table 7.2 - Association between frailty and clinical outcomes (all-cause mortality and hospitalisation)

		All-cause mortality				Unscheduled hospitalisation			
Frailty level	N	Events (N)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Events (N)	Model 1 IRR (95% CI)	Model 2 IRR (95% CI)	Model 3 IRR (95% CI)
SERA: Frailty index (3 levels)*									
Robust	303	8	ref	ref	ref	152	ref	ref	ref
Mild	487	28	1.83 (0.83-4.02)	1.74 (0.79-4.29)	1.73 (0.7-4.29)	416	1.55 (1.17-2.64)	1.47 (1.12-1.94)	1.29 (0.93-1.77)
Moderate/ Severe	109	17	3.99 (1.7-9.35)	4.41 (1.85-10.49)	4.14 (1.49-11.51)	189	3.05 (2.09-4.47)	2.88 (1.97-4.20)	2.27 (1.45-3.57)
UK Biobank: Frailty index (3 levels)*									
Robust	773	79	ref	ref		618	ref	ref	
Mild	2001	279	1.39 (1.08-1.79)	1.36 (1.05-1.76)		2520	1.68 (1.44-1.97)	1.65 (1.41-1.93)	
Moderate/ Severe	823	158	1.84 (1.4-2.43)	1.68 (1.26-2.13)		1827	3.13 (2.62-3.74)	2.74 (2.29-3.29)	
UK Biobank: Frailty index (4 levels)									
Robust	773	79	ref	ref		618	ref	ref	
Mild	2001	279	1.39 (1.09-1.79)	1.36 (1.05-1.76)		2520	1.64 (1.41-1.92)	1.65 (1.41-1.93)	
Moderate	714	130	1.73 (1.3-2.3)	1.59 (1.19-2.13)		1443	2.54 (2.11-3.05)	2.47 (2.05-2.98)	
Severe	109	28	2.75 (1.78-4.27)	2.33 (1.49-3.64)		384	5.00 (3.58-6.99)	4.80 (3.43-6.73)	
UK Biobank: Frailty phenotype									
Robust	788	68	ref	ref		630	ref	ref	
Pre-frail	1775	224	1.45 (1.11-1.91)	1.37 (1.04-1.81)		2209	1.57 (1.34-1.84)	1.52 (1.29-1.78)	
Frail	781	158	2.54 (1.9-3.93)	2.30 (1.71-3.10)		1486	2.47 (2.07-2.99)	2.38 (1.97-2.87)	

Model 1: adjusted for age, sex and socioeconomic status
Model 2: adjusted for age, sex, socioeconomic status, smoking and alcohol intake
Model 3: adjusted for age, sex, socioeconomic status, smoking, alcohol intake and DAS28 (SERA only)
HR: Hazard ratio, IRR: incidence rate ratio, CI: Confidence interval

*Due to the small number of SERA participants in the severe frailty category (0.3%) these were collapsed into moderate/severe for analysis of SERA. For UK Biobank, the frailty index was analysed using 4-levels (robust, mild, moderate, severe) as pre-specified and then using 3-levels (robust, mild, moderate/severe) to mirror the analysis of SERA

7.7 Discussion

Frailty is common in both new onset and established RA. In SERA participants with early RA and in UK Biobank participants with established RA moderate/severe frailty was associated with greater risk of hospitalisation and mortality. In people with early RA, higher baseline frailty index was associated with greater disease activity, functional impairment, and poorer self-rated health. The frailty index was dynamic in early RA and as mean disease activity fell with initiation of treatment, so too did the mean frailty index. In SERA, the association between frailty and mortality and hospitalisation remained significant after adjustment for disease activity as well as sociodemographic factors. Frailty is therefore a clinically and prognostically significant marker in RA, although the degree of frailty is likely to fluctuate over time, particularly where it is driven by active RA.

This is the first study to assess frailty in people with early RA (at the point of specialist diagnosis). It is also the first study to assess changes in frailty status over time in RA, demonstrating that frailty in early RA can, at least for some people, improve significantly. This change is likely to reflect an improvement in functional impairment with the initiation of disease modifying treatment. Our hypothesis that improvements in the frailty index are driven by reductions in disease activity and improvements in physical impairment are consistent with previous cross sectional studies showing associations between frailty (albeit identified using different measures) and both higher disease activity and higher HAQ-DI scores.[394,395,401,402,404,406,407,409,412] It would also explain the higher prevalence of frailty observed in randomised controlled trials for RA,[417] as high disease activity is typically an explicit requirement for inclusion in these trials.

Our findings indicate that frailty has prognostic significance beyond that of high disease activity. Frailty was associated with all-cause mortality and hospitalisation after adjustment for DAS28. This is consistent with literature on frailty in general populations as well as other long-term conditions.[1,3,28,30] Although physical impairment and self-rated health improved after initial diagnosis, participants with moderate frailty at baseline had significantly higher HAQ-DI scores and poorer self-rated health at 2 years follow-up than robust participants or those with mild baseline frailty, despite larger reductions in

DAS28 from baseline levels. Our findings also show that while disease activity continues to gradually decline over 2 years on a group level, initial improvements in frailty, HAQ-DI and self-rated health plateaued or worsened over this period. This is consistent with previous observations from SERA, in which psychosocial baseline factors (such as functional disability, depression, and unemployment) were more predictive of functional status at 1-year than more traditionally used clinical markers such as disease activity, and supports calls for broad psychosocial factors beyond disease activity to be actively considered when assessing the impact of RA.[431]

Mean frailty index values were higher in UK Biobank than in SERA. This may reflect longer disease duration in UK Biobank participants. Previous studies have shown associations between frailty and duration of RA, however this has not been observed consistently across all studies.[394,401,404,412] Another possible explanation is differences in the variables included within the respective frailty indices. While there is no specific set of variables that should be included in a frailty index, and these usually vary between datasets, it is possible that differences in the available variables influenced the distribution of frailty. Both datasets included a similar range of comorbidities, however SERA included more measures of functional impairment (e.g. difficulty dressing, climbing stairs) than UK Biobank.

Our findings indicate that frailty may be a useful measure to identify people at greater risk of mortality, hospitalisation, and with greater functional limitation. However, given the close relationship with disease activity and frailty over time, care should be taken in applying a 'label' of frailty to people living with RA. The utility of identifying frailty in RA would depend on the intended purpose of the assessment. If frailty is used to identify people who may benefit from a broad, multidisciplinary assessment of health needs, this may be beneficial.[11] Such an assessment should include identification of reversible factors including, but not limited to, active RA, treatment of which might ameliorate frailty. However, without such an assessment, invoking frailty in the context of inflammatory conditions such as RA may inappropriately identify patients as frail and bias future assessments or interactions with healthcare professionals.

It is important for future research to explore longitudinal trends in frailty, including its correlation with other measures (such as HAQ-DI and quality of life) as well as which factors within the frailty construct are most amenable to change or intervention. The development of frailty is recognised to be multifactorial.[2,40] There may be multiple sub-types of frailty in RA: those for whom deficits leading to the identification of frailty are driven by active disease, and others for whom it is the result of other comorbidities, age-related decline in physiological function, or other factors. The trajectory, prognostic significance, and appropriate response to frailty may differ in each of these situations. It will also be important to explore how frailty in the context of RA differs from other measures, such as multimorbidity, which are also associated with increased mortality risk but have a different conceptual basis.[427,430]

This study is larger than previous studies of frailty in RA, and draws upon two independent data sources, each with different strengths. We compared two frailty measures, although each was adapted to available variables. Linkage to national hospital and mortality registers allowed reliable assessment of outcomes. However, both datasets had limitations in the variables available. SERA lacked any assessment of sensory function (e.g. vision, hearing) and had relatively few biochemical variables. UK Biobank, in contrast, has few measures of physical function. In SERA, some of these were identified from the HAQ-DI. Although this is consistent with previous applications of the frailty index method, the recognised floor effect of the HAQ-DI may limit the responsiveness of the frailty index to change.[433] It also means that the reduction in frailty following initiation of treatment is perhaps not surprising, as HAQ-DI is recognised to be responsive to treatment. In assessing the frailty index over SERA follow-up, we did not have any repeated assessment of comorbidities, and therefore had to assume baseline comorbidity status. It is possible that, for some participants, comorbidities may have changed over the 2 years follow-up which would have influenced the frailty index. Participants with RA in SERA were identified using the well-established ACR/EULAR criteria in people attending specialist rheumatology clinics, however in UK Biobank we had to rely on diagnostic codes from routine healthcare data being applied to a population-based cohort. The latter may have resulted in some misclassification. UK Biobank is also recognised to be unrepresentative of the general population,

being more affluent and including more people of predominantly White ethnicity than the general UK population. There is also potential for survival bias when assessing UK Biobank participants with RA, as participants were not recruited at the point of diagnosis. People with RA and more severe frailty may be more likely to die prior to recruitment and therefore not be included in UK Biobank. Analyses of UK Biobank are also susceptible to collider bias. For example, if people with either more severe RA or severe frailty were less likely to volunteer for UK Biobank (e.g. due to greater functional limitation) this could bias estimates of the association between frailty and RA, as well as the relationship between frailty and adverse outcomes in people with RA. A recent analysis of multimorbidity showed that UK Biobank may underestimate associations between higher long-term condition counts and mortality or hospitalisation.[434] The same may be true of frailty in this context, particularly as long-term conditions contribute heavily to the frailty index. Finally, our analysis of the frailty phenotype was limited to UK Biobank (as grip strength and walking speed were not assessed in SERA) and analysis of disease activity and change in frailty status was limited to SERA. As a result, not all analyses could be replicated in both datasets. Furthermore, there was more missing data for the frailty phenotype (particularly grip strength) in UK Biobank participants with RA compared to the cohort as a whole. It is possible that those with more active disease, pain or functional limitation were more likely to have missing data, which could bias the results.

Frailty is a common and prognostically significant factor in RA, however measured. Active RA is likely to drive at least some of the identification of frailty, however in early RA frailty may be partially reversible through treatment. Therefore, a label of ‘frailty’ should not be applied in early or active RA without reassessment following appropriate treatment and optimisation of RA activity. Frailty identification may be valuable in RA, however, should be done with caution and only where identification of reversible factors, broad assessment of health needs, and follow-up with reassessment are part of the clinical management.

Chapter 8 Frailty in COPD: a systematic review and study level meta-analysis of prevalence, trajectories, and relationship with clinical outcomes

8.1 Chapter summary

This chapter presents a systematic review of observational studies addressing research question 1 (the prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in the context of COPD.

The text and figures presented in the form in which it was submitted for publication. This has now been accepted and is currently in press: Hanlon P, Guo X, McGee E, Lewsey J, McAllister D, Mair, FS. Systematic review and meta-analysis of prevalence, trajectories, and clinical outcomes for frailty in COPD. Primary Care Respiratory Medicine (in press). Doi: 10.1038/s41533-022-00324-5

8.2 Abstract

Background: Frailty is common in people with COPD. This systematic review synthesises the measurement and prevalence of frailty in COPD, within-person trajectories of frailty over time, and associations between frailty and adverse health outcomes in people with COPD.

Methods: Medline, Embase and Web of Science searched (1 January 2001-8 September 2021). Searches supplemented by forward citation searching and hand-searching reference lists. Inclusion criteria: observational studies (using any frailty measure) in adults with COPD assessing frailty prevalence, trajectories, or association with health-related outcomes. Results synthesised using narrative synthesis and random-effects meta-analyses.

Results: 53 eligible studies used 11 different frailty measures. Most common were frailty phenotype (n=32), frailty index (n=5) and Kihon checklist (n=4). Sample size ranged 22-8074. Mean age ranged 50-88 years. Prevalence estimates varied between frailty definitions, setting, and age from 2.6% to 80.9%. Frailty changes over time and may improve as well as worsen. Frailty was associated with greater risk of mortality (5/7 studies), COPD exacerbation (7/11), and hospital admission (3/4). Using frailty phenotype (frail vs robust), the pooled hazard ratio for mortality was 1.80 (95% CI 1.24-2.63) and incident rate ratios were 1.42 (0.94-2.17) for COPD exacerbation and 1.46 (1.10-1.92) for hospitalisation. Frailty associated with greater airflow obstruction (11/14), dyspnoea (15/16), COPD severity (10/12), poorer quality of life (3/4) and greater disability (1/1).

Conclusion: Frailty is common among people with COPD and associated with an increased risk of adverse outcomes. Proactive identification of frailty may aid risk stratification and identification of individuals for whom interventions may be targeted.

8.3 Summary box

8.3.1 What is already known on the topic

Frailty is known to be common in people with COPD, however measures used and frailty prevalence estimates are highly variable.

Frailty is understood to be associated with a range of adverse health outcomes; however, these have not been systematically synthesised in the context of COPD.

8.3.2 What this study adds

Frailty prevalence, while common in COPD, varies considerably by age, frailty measure, and clinical setting.

Frailty trajectories are variable, and frailty may improve or worsen within individuals with COPD.

Frailty is associated with a range of adverse health outcomes (including mortality and hospitalisation), however its relationship with some outcomes (e.g. COPD exacerbations) is inconsistent.

8.3.3 How this study might affect research, practice or policy

Clinical services for people with COPD should seek to identify and respond to patients' frailty, however high prevalence and inconsistency in measurement present challenges for implementation.

Future research should explore strategies to improve frailty status in people with COPD and to mitigate its clinical impact.

8.4 Background

An increasing number of people worldwide are living with frailty.[7] Frailty describes a state of increased vulnerability to decompensation in response to physiological stress.[3,26] There is growing recognition of the importance of frailty in the management of noncommunicable diseases generally, and chronic respiratory diseases specifically.[3,435] In the context of chronic obstructive pulmonary disease (COPD) (a condition characterised by progressive decline in pulmonary function and periods of exacerbation, both of which may impact on function and independence) it has been argued that frailty may be a valuable concept to understand individual vulnerability to adverse clinical outcomes.[17,436,437]

While, at a conceptual level, frailty describes a state of increased vulnerability to physiological decompensation, there is no single universally accepted operational measure of frailty. Rather, multiple different measures, drawing on different theoretical models of aging, have been used to identify frailty within individuals.[3] Populations identified by different frailty definitions only partially overlap.[39] Frailty is also understood to be dynamic and may worsen or improve within individuals over time.

People with COPD are recognised to have a higher prevalence of frailty than the general population.[17] However, this prevalence is likely to differ by different frailty definitions as well as in different clinical settings. A previous systematic review has assessed the prevalence of frailty in people with COPD, however this review did not assess the impact of frailty on clinical outcomes.[17] Moreover, since its publication, a number of further studies focusing specifically on people with COPD have assessed the prevalence and implications of frailty.[438,439]

This systematic review aims to (i) review the different measures which have been used to quantify frailty in people with COPD; (ii) summarise the prevalence and trajectories of frailty in people with COPD across a range of settings and frailty definitions; and (iii) quantify the relationship between frailty and clinical outcomes in people with COPD.

8.5 Methods

This systematic review of observational studies was carried out according to a pre-specified protocol (PROSPERO CRD42021275574) and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[440,441]

8.5.1 Eligibility criteria

Observational studies (cross-sectional or cohort design) meeting the following criteria were included:

- Population: Adults aged ≥18 years with COPD
- Exposure: Frailty (any measure)
- Comparison: people with COPD without frailty
- Outcomes: Frailty prevalence (primary outcome), transitions in frailty status, mortality, hospitalisation, healthcare utilisation, quality of life, disability, COPD exacerbation, COPD severity, symptoms
- Setting: any (including community, outpatients, inpatients, residential care)

We included studies using any definition of frailty to allow comparison between different measures. Studies were included if they used a validated frailty measure or provided detailed criteria within the manuscript of the criteria used to identify frailty. We excluded studies that assessed frailty based on a single parameter or proxy measure (e.g., grip strength alone). We excluded studies not published in English, conference abstracts, and grey literature. For synthesis, studies were grouped by frailty definition and setting.

8.5.2 Search strategy

We searched three electronic databases (Medline, Embase and Web of Science Core Collection) using a combination of Medical Subject Headings and keyword

searches. The basic search structure was “Frailty” AND “COPD”. Full search terms for Medline are shown in Box 1 and were adapted for the other databases. Database searches were supplemented by forward citation searches of all eligible studies and hand-searching reference lists of relevant papers (included studies and relevant review articles).

8.5.3 Study selection

We screened titles and abstract of all records identified through database searching. Full texts of all potentially eligible articles were obtained and screened according to our eligibility criteria. Two reviewers, working independently, completed all stages of screening. Disagreements over eligibility were resolved by consensus, involving a third reviewer if necessary.

8.5.4 Data extraction

Two reviewers, working independently, extracted details of study publication (author, year, journal, location), setting (community, outpatient, inpatient, residential care, etc.), population (recruitment method, eligibility criteria, age, sex, socioeconomic status, comorbidities), frailty definition (including adaptations to the original definition), frailty prevalence, and the relationship between frailty and any clinical outcomes listed above.

8.5.5 Quality assessment

The methodological quality of the included studies was assessed using an adaptation of the Newcastle Ottawa Scale (previously adapted for systematic reviews of studies assessing frailty, included in supplementary material).[37] The initial 5 questions were used for all studies (cross sectional or longitudinal) with a further 6 for longitudinal studies.

8.5.6 Synthesis

We performed a narrative synthesis of frailty prevalence estimates, stratified by study setting and frailty definition. We synthesised studies assessing frailty and clinical outcomes using a combination of narrative synthesis and random effects meta-analysis. Meta-analysis was performed when at least two studies assessed

the same outcome, using the same frailty definition, using a similar statistical approach, and when heterogeneity was at an acceptable level (heterogeneity was assessing using the I^2 statistic). Where studies were too heterogeneous, a narrative synthesis was performed and summarised using Harvest plots. Harvest plots summarise heterogenous data using bars to represent individual studies placed on a matrix to indicate where the studies showed a positive, negative, or neutral association with a given outcome (we used $p<0.05$ to denote statistical significance).[256,400] Data processing and analysis was done using R (version 3.6.1).

Box 1: Medline Search Strategy (adapted for other databases):

1 exp Lung Diseases, Obstructive (MeSH)
2 exp Pulmonary Disease, Chronic Obstructive (MeSH)
3 emphysema$.mp.
4 (chronic$ adj3 bronchiti$).mp.
5 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6 (COPD or COAD or COBD).mp.
7 1 or 2 or 3 or 4 or 5 or 6

8 exp Frailty/ (MeSH)
9 exp Frail Elderly/ (MeSH)
10 frail$.tw.
11 8 or 9 or 10

12 7 and 11

Search conducted from inception to September 2021 in all databases

MeSH: Medical Subject Heading
$: Truncation tool
Adj3: adjacent (within 3 words)

8.6 Results

We identified 1402 unique titles and abstracts from electronic database searches, from which we retained 220 for full-text screening and finally identified 53 eligible studies (Figure 8.1). Sample size (with COPD) ranged from 22 to 8074 (median 192, IQR 103-149). Study characteristics and quality assessment are summarised in Table 8.1. Mean study age ranged from 50 to 88 (median 73, IQR 68-75). All studies were from high income or upper-middle income countries (Figure 8.2).

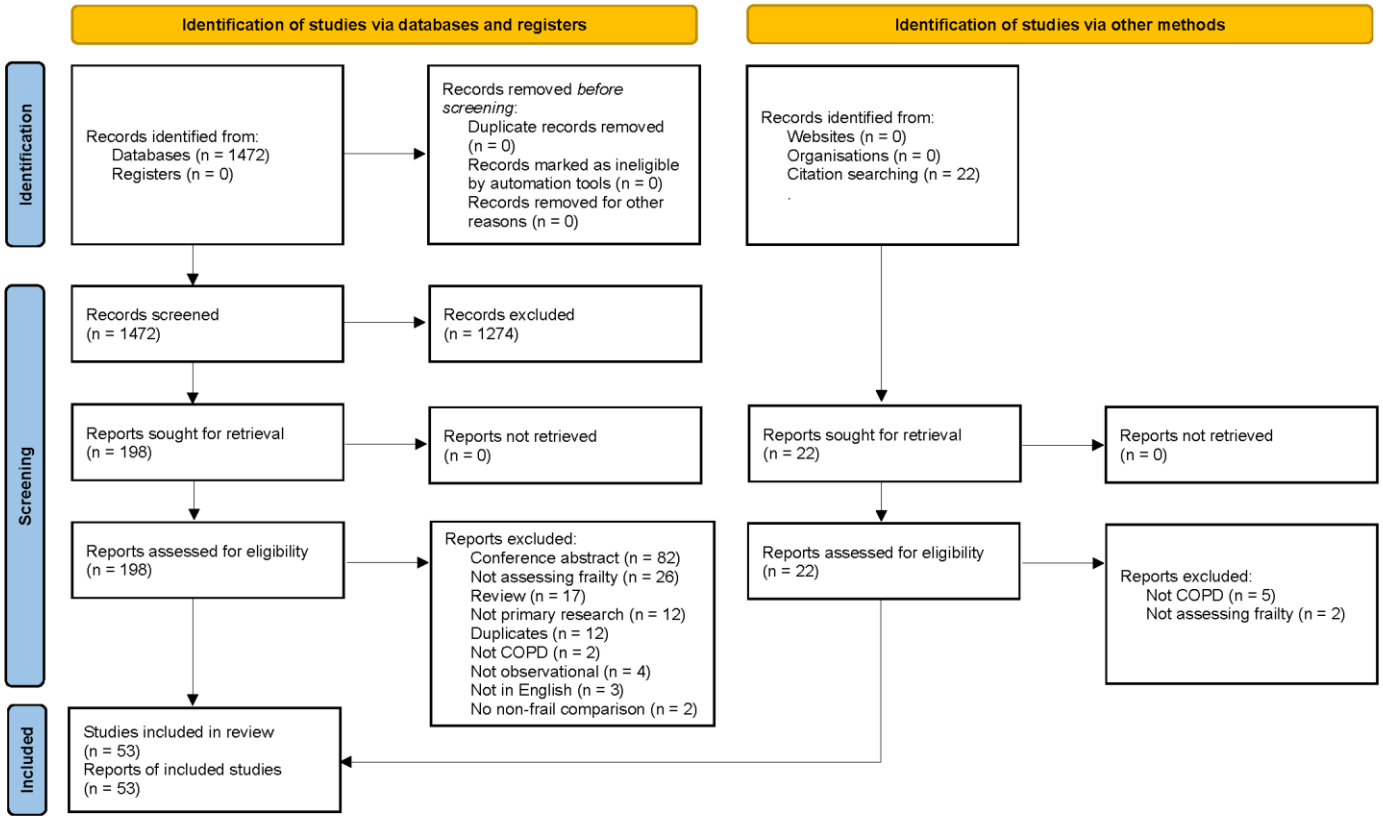

Figure 8.1 - PRISMA diagram of included studies

Table 8.1 - Characteristics of included studies

Author, Year	Country	Frailty measure	COPD definition	N with COPD	Mean age	Setting	Quality Assessment	Outcomes
Akgun 2016[442]	United States	Frailty phenotype	Electronic health records	182	50	community	3/5	Prevalence
Ambagtsheer 2019[262]	Australia	Frailty index	Electronic health records	98	88	residential care	2/5	Prevalence
Avila-Funes 2008[81]	Mexico	Frailty phenotype	Self-report	814	74	community	3/5	Prevalence
Bernabeu-Mora 2017[443]	Spain	Edmonton	GOLD criteria	103	71	inpatient	9/11	Prevalence, Hospital readmission, FEV1, Dyspnoea
Bernabeu-Mora 2020[444]	Spain	Frailty phenotype	GOLD criteria	119	67	outpatient	10/11	Prevalence, Frailty transitions, Exacerbation
Blaum 2005[445]	United States	Frailty phenotype	Electronic health records	230	74	community	2/5	Prevalence
Castellana 2021[446]	Italy	Frailty phenotype	Self-report	343	74	community	3/5	Prevalence
Chen 2010[283]	Taiwan	Frailty phenotype	Self-report	312	73	community	4/5	Prevalence
Chen 2018[447]	Taiwan	CFS	Electronic health records	125	77	outpatient	4/5	Prevalence, Exacerbation, Dyspnoea
Cheong 2019[285]	Singapore	Frailty phenotype	Self-report	239	66	community	3/5	Prevalence

Chin 2020[448]	Canada	CFS	Hospitalised with exacerbation of COPD	50	72	inpatient	2/5	Prevalence
Crow 2018[289]	United States	Frailty phenotype	Self-report	496	71	community	3/5	Prevalence
de Albuquerque 2012[449]	Brazil	Frailty phenotype	Self-report	22	74	community	/35	Prevalence
Dias 2020[450]	Brazil	FRAIL	GOLD criteria	153	69	outpatient	3/5	Prevalence, Exacerbation, FEV1, Dyspnoea, CAT
Fragoso 2012 [451]	United States	Frailty phenotype	Self-report	262	72	community	9/11	Prevalence, Frailty transitions
Fried 2001 [5]	United States	Frailty phenotype	Self-report	415	72	community	4/5	Prevalence
Gale 2018 [452]	United Kingdom	Frailty index	GOLD criteria	520	66	community	4/5	Prevalence, Exacerbation, FEV1, Dyspnoea, CAT
Galizia 2011 [453]	Italy	Frailty Staging System	Self-report	489	74	community	10/11	Prevalence, Mortality, Dyspnoea
Gephine 2020 [454]	France	Frailty phenotype	GOLD criteria	44	66	pulmonary rehab	4/5	Prevalence, Exacerbation, FEV1, Dyspnoea, QOL
Gu 2021 [455]	China	Frailty index	Clinician diagnosis of acute exacerbation of COPD	154	80	inpatient	9/11	Mortality

Hanlon 2018 [9]	United Kingdom	Frailty phenotype	Self-report	8074	58	community	2/5	Prevalence
Hirai 2019 [456]	Japan	Kihon	GOLD criteria	201	76	outpatient	3/5	FEV1, Dyspnoea, CAT
Ierodiakonou 2019 [457]	Greece	FiND	GOLD criteria	257	65	community	3/5	Prevalence, Exacerbation, FEV1, Dyspnoea, CAT
Kennedy 2019 [458]	United States	Frailty phenotype	GOLD criteria	902	68	outpatient	9/11	Prevalence, Mortality, Hospital admission, QOL
Kim 2020 [459]	South Korea	Frailty phenotype	Self-report	83	76	community	2/5	Prevalence
Kusunose 2017 [460]	Japan	Kihon	GOLD criteria	79	75	outpatient	2/5	Prevalence, Dyspnoea, CAT, QOL
Lahousse 2014 [309]	Netherlands	Frailty phenotype	GOLD criteria	172	75	community	3/5	Prevalence
Lahousse 2016 [461]	Netherlands	Frailty phenotype	GOLD criteria	172	75	community	10/11	Mortality, FEV1
Lai 2014 [462]	Taiwan	Frailty phenotype	Medical records	65	82	residential care	3/5	Prevalence
Lee 2014 [372]	China	Frailty phenotype	Self-report	236	74	community	2/5	Frailty transitions
Limpawattana 2017 [463]	Thailand	FRAIL	GOLD criteria	121	70	outpatient	2/5	Prevalence
Liotta 2017 [464]	Italy	Functional Geriatric Evaluation	Medical records	218	76	community	2/5	Prevalence
Luo 2021 [438]	China	Frailty phenotype	GOLD criteria	309	86	outpatient	9/11	Prevalence, Mortality, Exacerbation, Hospital admission, FEV1, Dyspnoea, CAT

Ma 2018 [465]	China	Frailty index	Self-report	205	72	community	2/5	Prevalence
Maddocks 2016 [466]	United Kingdom	Frailty phenotype	GOLD criteria	816	70	pulmonary rehab	10/11	Prevalence, Frailty transitions, Exacerbation
Medina-Mirapeix 2016 [467]	Spain	Edmonton	GOLD criteria	103	71	inpatient	2/5	Prevalence, Disability
Medina-Mirapeix 2018 [468]	Spain	Frailty phenotype	GOLD criteria	137	67	outpatient	3/5	Prevalence, Exacerbation, FEV1, Dyspnoea, CAT
Motokawa 2018 [332]	Japan	Kihon	Self-report	6	74	community	3/5	Prevalence
Nagorni-Obradovic 2014 [469]	Serbia	Frailty phenotype	Self-report	653	59	community	2/5	Prevalence
Oishi 2020 [470]	Japan	Kihon	American Thoracic Society guidelines	128	73	outpatient	2/5	Prevalence, Dyspnoea
Park 2013 [471]	United States	Tilburg	Self-report	211	71	community	2/5	Prevalence, Dyspnoea
Park 2021 [472]	South Korea	Tilburg	Self-report	417	65	community	3/5	Prevalence, FEV1
Pollack 2017 [342]	United States	Frailty phenotype	Self-report	537	73	community	2/5	Prevalence
Scarlata 2021	Italy	Frailty index	GOLD criteria	150	73	outpatient	9/11	Prevalence, Mortality, Exacerbation, FEV1, Dyspnoea, CAT
Serra-Prat 2016 [473]	Spain	Frailty phenotype	Self-report	44	80	community	2/5	Prevalence

ter Beek 2020 [474]	Netherlands	Frailty phenotype	GOLD criteria	57	61	pulmonary rehab	3/5	Prevalence
Uchmanowicz 2016 [475]	Poland	Tilburg	American Thoracic Society guidelines	102	63	outpatient	2/5	Prevalence
Valenza 2016 [476]	Spain	Frailty phenotype	American Thoracic Society guidelines	212	73	inpatient	2/5	Prevalence
Veronese 2017 [357]	Iceland	Frailty phenotype	Self-report	368	76	community	3/5	Prevalence
Warwick 2021 [477]	Canada	CFS	Hospitalised with exacerbation of COPD	390	68	inpatient (ITU)	9/11	Prevalence, Mortality
Xue 2019 [368]	China	Frailty phenotype	Self-report	23	79	outpatient	3/5	Prevalence
Yee 2020 [439]	United States	Frailty phenotype	GOLD criteria	280	68	outpatient	10/11	Prevalence, Mortality, Exacerbation, Hospital admission, FEV1, QOL
Zhang 2020 [478]	China	Frailty phenotype	Self-report	28	75	outpatient	2/5	Prevalence

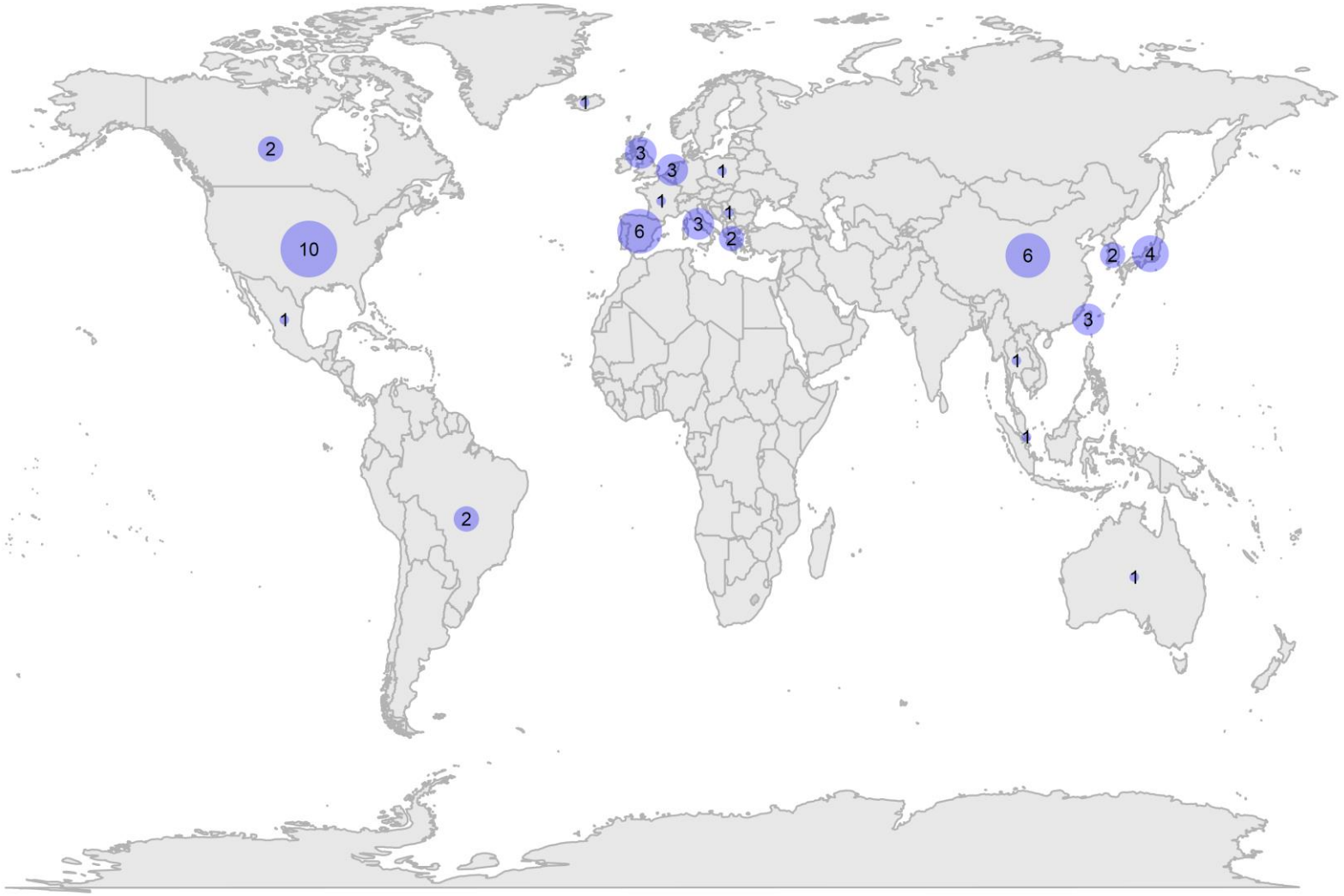

Figure 8.2 - Map showing the location of the included studies

8.6.1 Frailty measurement

The included studies used a total of 11 different frailty measures. The most common was the frailty phenotype (32 studies) followed by the frailty index (5 studies), Kihon checklist (4 studies), Clinical Frailty Scale (3 studies), Tilburg frailty indicator (3 studies), FRAIL scale (2 studies), Edmonton frailty indicator (2 studies), FiND (1 study), Study for Osteoporotic Fractures frailty score (1 study), Frailty staging system (1 study) and Functional Geriatric Evaluation (1 study). One study used three different measures.[456] These definitions are summarised in Table 8.2. While the frailty phenotype was the most commonly used measure, 27 of the 32 studies using this measure made some adaptation to the original frailty phenotype criteria.

Table 8.2 - Frailty measures used in included studies

Frailty measure	Components	Range and categorisation	Number of included studies
Frailty phenotype[5]	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	32
Frailty index[6,35]	Count of health-related deficits (≥30, type and number of chosen deficits may vary between studies). Total present divided by number of possible deficits	Range 0-1 Sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24)	5
Kihon checklist[413]	Self-administered checklist (components: activities of daily living, exercise, falling, nutrition, oral health, cognition, depression)	Unweighted sum of components. Range 0-25. Pre-frail (4-7), Frail (≥8).	4
Clinical frailty scale[49]	Clinical tool based on functional status.	Ranges 1 (very fit) to 9 (terminally ill). Some dichotomise as ≥5 = frail.	3
Tilburg frailty indicator[415]	15 questions across 3 domains (physical, psychological and social) Responses combined into unweighted sum.	Range 0-15 ≥5 indicates frailty	3
FRAIL scale[50]	5 components (weight loss, fatigue, weakness, ambulation, illness/comorbidity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	2
Edmonton frailty scale[47]	9 components: cognition, general health, functional independence, social support,	Score 0-17. Mild (7-8), moderate (9-10)	2

	medication, nutrition, mood, continence and functional performance.	and severe frailty (≥11).	
FiND[479]	Self-administered frailty screening tool. 5 items: difficulty walking 400m, difficulty climbing stairs, weight loss, exhaustion and low physical activity	Classed as disability (difficult walking or climbing stairs), frailty (no difficulty with walking or stairs but other deficits present) or robust (no deficits)	1
Study of Osteoporotic Fracture frailty indicator[480]	3 components (weight loss, chair stand, exhaustion)	1 component: prefrail 2-3 components: frail	1
Frailty staging system[481]	7 components (disability, mobility, cognition, vision, hearing, continence, social support).	Range 0-7. Mild (1) moderate (2-3) or severe frailty (≥4).	1
Functional geriatric assessment[482]	Multidimensional evaluation (physical, mental and functional status, socio/economic resources, environment)	Scored from -108 to 101 Robust (>50), frail (≤50, ≥10) and very frail (<10).	1
Table adapted from Hanlon et al 2020[37] and 2021			

8.6.2 Frailty prevalence

The prevalence of frailty was assessed in 47 studies. These are summarised in Figure 8.3, stratified by study setting and ordered by frailty definition and mean age in the included studies. Estimates of prevalence were highly heterogeneous, varying by setting and between frailty definitions. Prevalence ranged from 2.6% to 80.9% in 25 community-based studies and from 6.3% to 75.5% in 14 studies in outpatient settings. Prevalence varied by frailty measure (e.g. generally lower in studies using frailty phenotype). Prevalence was also higher in some studies with higher mean age (Figure 8.3). In other settings, prevalence ranged from 35.9% to 63.7% in hospital inpatients (4 studies), from 41.5% to 66.3% in residential care settings (2 studies) and 25.6% to 43.2% in populations recruited at the commencement of pulmonary rehabilitation programmes (3 studies).

Figure 8.3 - Plot showing the prevalence of frailty in each of the included studies. Studies are stratified by setting (community, outpatient, inpatient, intensive care (ITU), pulmonary rehabilitation and residential care). Within strata, studies are ordered by frailty measure (colour) and mean age (descending order on y-axis). Points indicate the prevalence estimate, lines indicate 95% confidence intervals.

8.6.3 Within-person frailty trajectories

Four studies assessed longitudinal changes in frailty over time. These varied in their setting, aim, and design. Two studies focused exclusively on people with COPD. Bernabeu-Mora et al (n=119) found that higher baseline muscle strength and lower exacerbation frequency were associated with improvement, while higher baseline dyspnoea was associated with worsening frailty status. Maddocks et al (n=816) found that people living with frailty were more likely not to complete pulmonary rehabilitation due to exacerbations or hospital admissions however, of those who did complete, 71/115 (61.3%) no longer met the criteria for frailty (74 pre-frail, 7 robust). People with baseline frailty also experienced greater improvements in dyspnoea, physical activity and health status following pulmonary rehabilitation than people who were not living with frailty at baseline.

Of the two studies of frailty trajectories among general populations (not limited to people with COPD), COPD was associated with worsening frailty status among women who were robust at baseline (adjusted odds ratio (OR) 2.66, 95% CI 1.10-6.44), however they did not find the same association in men (adjusted OR 0.61, 95% CI 0.34-1.11). COPD defined by obstructive spirometry was associated with worsening frailty status compared to people with no airway obstruction over 3 years follow-up (adjusted OR 1.58; 95% CI 1.17-2.13). Baseline frailty status was also associated with the development of respiratory impairment (defined as obstructive or restrictive pattern of spirometry) among people with no respiratory impairment at baseline (adjusted OR 1.42; 95% CI 1.11-1.82).

8.6.4 Frailty and clinical outcomes

Studies assessing the relationship between frailty and clinical outcomes (either cross-sectionally or prospectively) are summarised in Figure 8.4. These are explored in detail below.

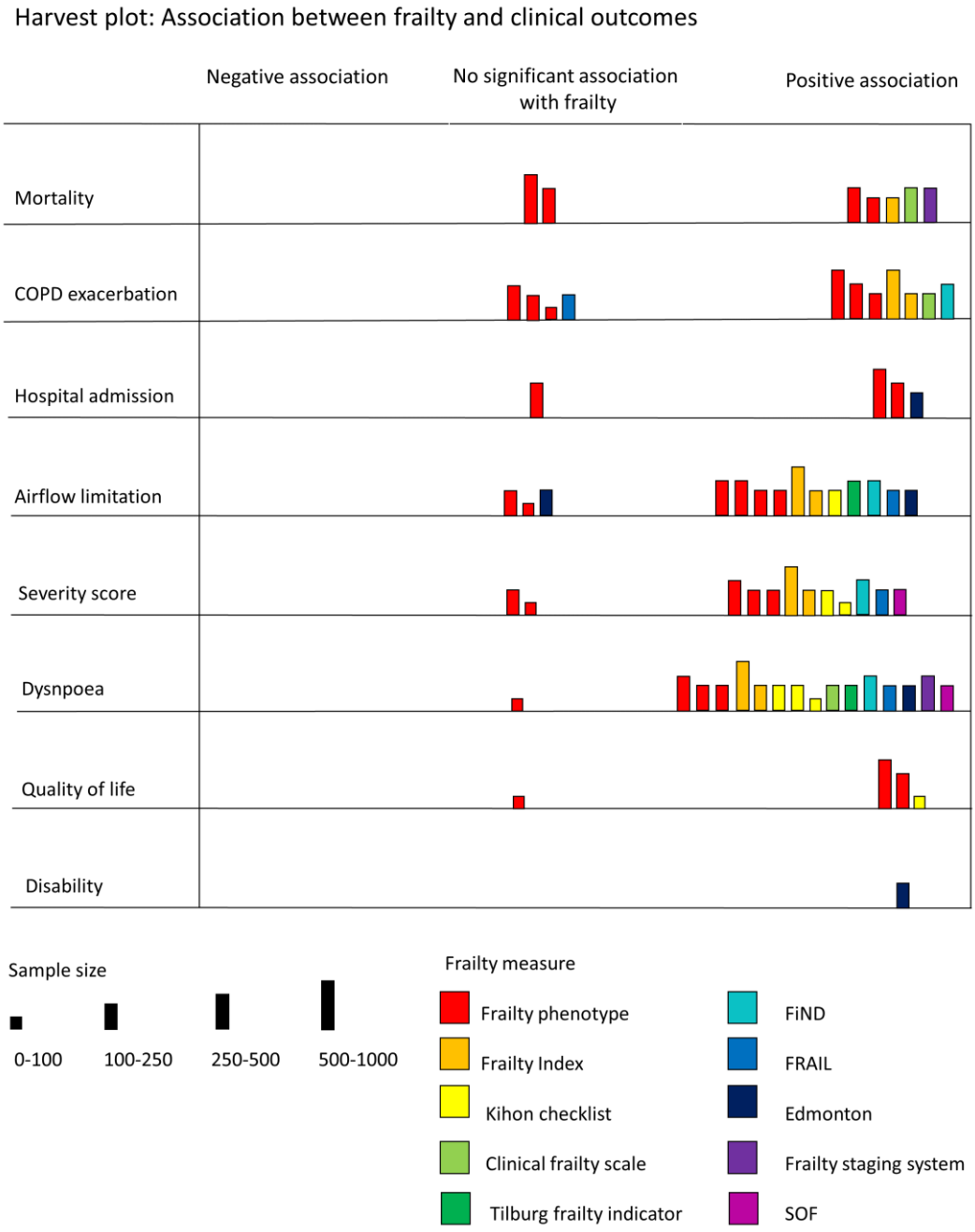

Figure 8.4 - Harvest plot showing the relationship between frailty and clinical outcomes in the included studies. Each bar represents a single study. Colour is used to indicate which frailty measure is used. Height of the bar indicates study sample size. The position of the bar on the matrix indicates the relationship between frailty and the outcome in question (positive association between frailty and the outcome, no significant association, or negative association between frailty and the outcome [i.e. frailty is protective]).

8.6.4.1 Mortality

Eight studies assessed the relationship between frailty and all-cause mortality in people with COPD.

Four of these were outpatient- or community-based studies which used the frailty phenotype definition. The pooled hazard ratio (HR) for mortality associated with frail compared to robust participants was 1.80; 95% CI 1.24-2.62 (Figure 8.5). Statistical heterogeneity was low (I2=0%) despite variation in study location (2 USA, 1 China, 1 Netherlands), adaptation of the frailty phenotype criteria, and covariates included in the adjusted models. One other community study (n=489) using the Frailty Staging system also showed an association between frailty and mortality. In an outpatient-based study using the frailty index (n=150) the association between frailty and mortality was not statistically significant (HR 2.1; 95% CI 0.7–5.8).

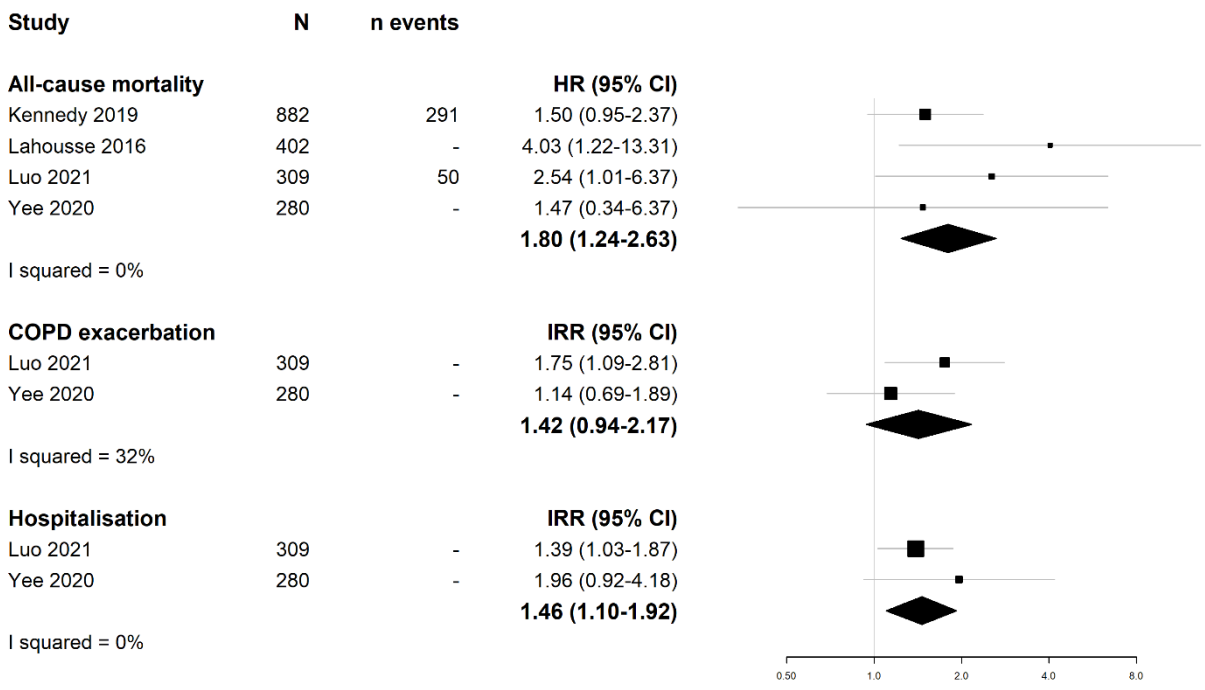

Figure 8.5 - Meta-analyses of random-effects meta-analysis of the relationship between frailty phenotype (frailty phenotype definition) and mortality, COPD exacerbation, and hospitalisation

Two studies assessed inpatient mortality. One used the Clinical Frailty Scale and assessed survival to discharge from intensive care (n=390). The other used a Frailty Index based on laboratory measures and compared people surviving to

hospital discharge (n=77) with people who did not (n=77) using propensity score matching. In both studies, a higher degree of frailty was associated with higher mortality.

8.6.4.2 Hospitalisation

Three outpatient-based studies assessed the relationship between the frailty phenotype and all-cause hospital admission. Hospitalisation rates among people living with frailty and COPD were high (2 studies reported mean 0.49 and 0.47 exacerbations per person per year, respectively, in people living with frailty compared to 0.20 and 0.21, respectively, in robust participants with COPD). In the two studies assessing the rate of exacerbations, the pooled incident rate ratio (IRR) was 1.46, 95% CI 1.10-1.92. In the remaining study the adjusted HR was 1.8, 95% CI 1.1-2.9. A fourth study assessed the relationship between frailty (Edmonton frailty indicator) and readmission within 90 days of COPD exacerbation. Severe frailty was strongly associated with readmissions (45% compared to 18% of robust participants, adjusted OR 5.19, 95% CI 1.26-21.50). Taken together there is consistent evidence that people living with frailty and COPD experience higher rates of hospital admission than robust individuals with COPD.

8.6.4.3 COPD exacerbation

Eleven studies reported the association between frailty status and COPD exacerbations. Only two of these were prospective studies, both of which used the frailty phenotype definition. On meta-analysing these two studies, incidence of COPD exacerbations was 42% higher in those who were frail compared to those who were not, however the confidence interval included the null (IRR 1.42, 95% CI 0.94-2.17, see figure 4). The remaining 9 studies assessed the unadjusted association between baseline frailty status and exacerbation frequency in the period prior to baseline (typically number of exacerbations, or frequent exacerbations defined as ≥2, in the past year). Six of these 9 studies reported an association between frailty and exacerbation frequency.

8.6.4.4 COPD severity

Fourteen studies assessed the cross-sectional relationship between frailty and either Forced Expiratory Volume in 1 second (FEV1); FEV1 as a percentage of predicted; or severity categories based on FEV1. Frailty was associated with a greater degree of airflow limitation in 11/14 of these studies.

Eight studies, comprising 7 different frailty measures, assessed the relationship between frailty and CAT score. All of these reported statistically significant (unadjusted) baseline associations between frailty and higher CAT scores.

8.6.4.5 Dyspnoea

Of the 16 studies comparing baseline dyspnoea in people with and without frailty, 13 used the modified MRC dyspnoea scale, of which 12 showed greater dyspnoea scores in people living with frailty. Three remaining studies also reported cross-sectional associations between frailty and self-reported dyspnoea. As mentioned above, baseline dyspnoea was also associated with worsening frailty status over 2 years follow-up in the only longitudinal study to assess this outcome.

8.6.4.6 Quality of life

Four studies assessed the cross-sectional relationship between frailty and quality of life. Three of these, all of which used the short-form 36 quality of life assessment, reported lower quality of life scores in participants with baseline frailty (2 frailty phenotype, 1 Kihon checklist). The remaining study used was small (n=55) and found no evidence of association between the frailty phenotype and quality of life according to the CCQ.

8.6.4.7 Disability

A single study assessed trajectories of activities of daily living limitation following hospital admission with COPD exacerbation. Frailty, measured using the Edmonton frailty indicator at the point of admission, was statistically significantly associated with functional decline measured 12 weeks after discharge (adjusted OR 3.97; 95% CI 1.13–13.92).

8.7 Discussion

8.7.1 Summary of findings

This systematic review summarises the existing literature on the prevalence, trajectories, and clinical implications of frailty in people with COPD. The prevalence of frailty varies by setting, age, and by method used to identify frailty, ranging between 2.6% and 80.9%. Nonetheless, our findings show that frailty is common among people with COPD. In inpatient settings, the prevalence of frailty was notably higher (between 36% and 64% using a variety of measures), as it was in people living in residential care and in pulmonary rehabilitation.

Our findings demonstrate that people living with COPD and frailty often experience a high frequency of exacerbations, tend to have more severe airflow limitation, higher prevalence of dyspnoea, and are at greater risk of readmission following hospital discharge and of mortality. Frailty in people with COPD varies over time, and these findings suggest that it may also be responsive to targeted intervention in the form of pulmonary rehabilitation. However, if people living with frailty are to benefit from this, efforts are needed to maximise their ability to participate and complete the programme.

8.7.2 Findings in context of previous literature

A previous systematic review, including 27 studies, assessed the prevalence of frailty in COPD but did not synthesise the relationship between frailty and clinical outcomes in COPD.[17] In this previous review, 13 studies used the frailty phenotype, with a pooled mean prevalence of 19%, 95% CI 14%-24%. Heterogeneity of these estimates was high. This previous study also reported that people with COPD had a two-fold higher odds of frailty prevalence than people without COPD (odds ratio 1.97, 95% CI 1.53-2.53). Our study builds on these findings by stratifying by setting, and also includes several more recent studies which specifically focused on frailty in COPD (rather than as a subset of a general population). Unlike the previous review, we did not meta-analyse prevalence estimates due to considerable variation in study inclusion criteria (e.g., the exclusion of people with cognitive impairment or mobility difficulty),

age range, and adaptations of the frailty phenotype criteria. These sources of heterogeneity limit the interpretability of a single pooled prevalence estimate.

The high prevalence of frailty in people with COPD likely represents complex inter-relationships between features of both frailty and COPD.[483-485] COPD gives rise to a range of extrapulmonary manifestations, such as sarcopenia and fatigue,[484,485] which may contribute to the manifestation of frailty. Depending on the frailty definition, these factors alone may be sufficient for an individual to be classified as frail (i.e., COPD may cause frailty, in this context).[1,2] Conversely, the development of COPD itself involves a complex interplay between environmental exposures and genetic susceptibility.[486] Accelerated lung aging has been proposed as one mechanism underlying this process.[487] Some have argued that the development of COPD should be best understood as an interplay between abnormalities in organ development and maintenance (susceptibility) and the cumulative effect of tissue injury and aging.[486,488] This is similar paradigm to the cumulative deficit model of frailty which is operationalised in the frailty index.[1,6,35] Under this framework, the development of COPD is a manifestation of the same processes underlying frailty, rather than a cause of frailty itself. In summary, depending on the theoretical model used to define frailty, COPD may be understood as both a cause and a consequence of frailty.

While frailty may result from the cumulative effect of acquired deficits, it may improve as well as worsen over time.[10] This review highlights that COPD may be a risk factor for worsening frailty, however also demonstrates that frailty in COPD may be responsive to targeted intervention, specifically pulmonary rehabilitation.[466] The improvement in frailty status with pulmonary rehabilitation was assessed in only one included study. However, these findings are consistent with emerging evidence on interventions targeting frailty in general populations. A recent meta-analysis of 46 interventions showed that interventions incorporating physical activity or nutritional supplementation could improve frailty status in some individuals.[375]

8.7.3 Implications

The high prevalence of frailty among people admitted to hospital with COPD, coupled with the higher rates of hospital readmission, indicate that identifying

frailty within respiratory inpatient services may offer opportunities for targeted interventions. However, it is likely that a high proportion of patients would meet the criteria for frailty. It is likely that appropriate clinical response will vary between individuals identified as frail. Individualisation of care, as well as holistic multidisciplinary approaches, are central tenets of frailty management. There is considerable overlap between these principles and the multidisciplinary care advocated for people with COPD. However, given the high prevalence of frailty, implementing this in practice requires considerable resource and coordination of multiple professionals.

Community prevalence of frailty was lower than among inpatients but still common and associated with adverse events, so proactive identification of frailty may aid risk stratification and identification of individuals for whom limited community resources may be targeted. Ideally, such effort should be integrated into existing systems for the monitoring and management of COPD, to minimise the additional burden on both patients and professionals. Responses to frailty in this context may include advance care planning as well as efforts to maximise function and identify potentially reversible aspects of frailty. Understanding factors that influence trajectories of frailty is an important area for future research, to inform the design and delivery of interventions. Also vital to these efforts would be exploring factors that may facilitate or act as barriers to participation in interventions designed to target frailty.

8.7.4 Strengths and limitations

Strengths of this review include a comprehensive search strategy supplemented by hand-searching reference lists and forward citation searching, followed by duplicate screening and data extraction. However, this review is limited by the exclusion of articles not published in English and of grey literature. The included studies themselves are all observational, meaning the observed relationships between frailty and clinical outcomes, or between COPD and frailty trajectories, cannot be assumed to be causal. Many studies defined COPD using either self-report or by coded diagnosis, and there is therefore a risk of some misclassification of COPD in these studies. Most studies had small sample sizes. Studies from lower-middle income counties were lacking, limiting the generalizability of prevalence estimates. Furthermore, most of the studies

assessing airflow limitation, COPD severity, and exacerbations were cross-sectional, further limiting inferences about the consequences of frailty in people with COPD. Most of the included studies contained detailed description of the population, and prospective studies adjusted for relevant potential confounders. However, description of non-responders and loss to follow-up was often limited. Furthermore, the potential confounders included in models assessing prospective outcomes (mortality, hospitalisations and exacerbations) varied widely between studies. Most notably, several did not adjust for severity of airflow limitation. Finally, the included studies were highly heterogenous in terms of inclusion criteria, frailty definitions, setting, and diagnostic criteria for COPD. Therefore, even among studies using the same model of frailty, differences in study populations and adaptation of frailty definition limited the synthesis of prevalence estimates.

8.7.5 Conclusion

Frailty is common in people with COPD and associated with disease severity, symptom burden, and with a range of adverse health outcomes. Frailty varies over time and may be responsive to interventions, including pulmonary rehabilitation. Proactive identification of frailty may aid risk stratification and identification of individuals for whom interventions, such as pulmonary rehabilitation, may be targeted.

Chapter 9 Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank

9.1 Chapter summary

This chapter presents an analysis of the UK Biobank cohort addressing research question 1 (prevalence of frailty) and research question 2 (the association between frailty and clinical outcomes) in people with COPD.

The figures and text are presented as published in Hanlon P, Lewsey J, Quint J, Jani BD, Nicholl B, McAllister DA, Mair FS. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. BMJ Open Resp Res 2022;1–9. doi: bmjresp-2022-001314

9.2 Abstract

Background: Frailty, a state of reduced physiological reserve, is common in people with chronic obstructive pulmonary disease (COPD). Frailty can occur at any age, however the implications in younger people (e.g., aged <65 years) with COPD is unclear. We assessed the prevalence of frailty in UK Biobank participants with COPD; explored relationships between frailty and FEV1; and quantified the association between frailty and adverse outcomes.

Methods: UK Biobank participants (n=3132, recruited 2006-2010) with COPD aged 40-70 years were analysed comparing two frailty measures (frailty phenotype and frailty index) at baseline. Relationship with FEV1 was assessed for each measure. Outcomes were mortality, Major Adverse Cardiovascular Event (MACE), all-cause hospitalisation, hospitalisation with COPD exacerbation, and community COPD exacerbation over 8 years follow-up.

Results: Frailty was common by both definitions (17% frail using frailty phenotype, 28% moderate and 4% severely frail using frailty index). The frailty phenotype, but not the frailty index, was associated with lower FEV1. Frailty phenotype [frail vs robust] was associated with mortality (hazard ratio 2.33; 95%CI 1.84-2.96), MACE (2.73; 1.66-4.49), hospitalisation (incidence rate ratio 3.39; 2.77-4.14) hospitalised exacerbation (5.19; 3.80-7.09), and community exacerbation (2.15; 1.81-2.54), as was frailty index [severe vs robust] (mortality (2.65; 95%CI 1.75-4.02), MACE (6.76; 2.68-17.04), hospitalisation (3.69; 2.52-5.42), hospitalised exacerbation (4.26; 2.37-7.68), and community exacerbation (2.39; 1.74-3.28)). These relationships were similar before and after adjustment for FEV1.

Conclusion: Frailty, regardless of age or measure, identifies people with COPD at risk of adverse clinical outcomes. Frailty assessment may aid risk stratification and guide targeted intervention in COPD and should not be limited to people aged >65 years.

9.3 Summary box

9.3.1 What is already known on this topic

- Frailty is common in people with COPD, including in younger people (e.g. those aged less than 65 years), however the clinical implications of COPD in this age group are poorly understood.

9.3.2 What this study adds

- Frailty in people with COPD aged 40-70 is associated with increased risk of mortality, hospital admission, major adverse cardiovascular events, and COPD exacerbations.
- This relationship is independent of the severity of airflow limitation.

9.3.3 How this study might affect research, practice or policy

- Current policies for frailty identification tend to focus exclusively on those aged 65 and over. These findings suggest that in people with COPD, identifying frailty in younger people may aid risk stratification an identification of those for whom interventions may be designed and targeted.

9.4 Introduction

Chronic obstructive pulmonary disease (COPD), characterised by fixed and progressive airflow obstruction, is the third leading cause of death worldwide.[489] COPD is also a condition associated with aging. While it is estimated that 10% of the adult population worldwide may be living with COPD,[489] the prevalence increases from <5% in people aged <65 years to >20% in people aged >85 years.[490] This has highlighted the need to understand the links between COPD and states associated with aging, such as frailty.[435,491] However, neither frailty nor COPD exclusively affect older people, and there is no clearly defined threshold above which frailty becomes a clinically meaningful concept. Most studies of frailty have focused exclusively on people over the age of 65, in whom frailty is more common. Frailty can affect people across a range of ages,[9,79] including people aged <65 years in whom it has been far less frequently studied. The clinical implications of frailty at younger ages remain unclear.

Frailty describes a state of reduced physiological reserve.[5] People living with frailty are more vulnerable to decompensation and adverse health outcomes in response to physiological stress. This confers an increased risk of a range of outcomes including mortality, hospital admission, adverse drug reactions and falls.[3] COPD is associated with a range of extrapulmonary complications including cardiovascular morbidity,[492] osteoporosis,[484] and muscle weakness,[485] all of which may contribute to frailty.

Frailty is highly prevalent in people with COPD.[17] Most previous studies have focused exclusively on people aged >65 years.[9,442,469,475] However, none of these studies have explored the clinical implications of frailty in younger people with COPD. Furthermore, while some studies have demonstrated an association between frailty and both severity of airflow limitation[452,456,461] and mortality in people with COPD,[438,453,493] these findings have been inconsistent.[439,443,458,468] It is also not clear if the relationship between frailty and adverse outcomes in COPD is independent of the severity of COPD assessed by airflow limitation.

This study seeks to address these gaps using data from the UK Biobank, a cohort of people aged 40 to 70, representing a relatively younger age-range than most previous studies. It will assess two models of frailty; the frailty index and the

frailty phenotype. We aim: (i) to assess the prevalence of frailty in UK Biobank participants with COPD; (ii) to explore the relationship between frailty and forced expiratory volume in 1 second (FEV1); and (iii) to quantify the association between frailty, and mortality, hospitalisations, major adverse cardiovascular events (MACE), and COPD exacerbations.

9.5 Methods

This is an observational analysis of the prevalence and impact of frailty, assessed using two different definitions, in UK Biobank participants with COPD.

9.5.1 Study population

UK Biobank is a large cohort, recruited by invitation between 2006 and 2010 (5% response rate). Participants were aged between 40 and 70 and had to be registered with a general practitioner and live within 20 miles of one of 22 assessment centres in England, Scotland and Wales. Participants underwent a baseline assessment questionnaire, nurse interview, physical assessment and provided biological samples. Informed consent was also given for linkage to healthcare records including primary care, hospital episode statistics, and national mortality records. Currently, linked primary care records are available for 218,570 of the original 502,533 participants. Participants with available primary care data are similar to the wider UK Biobank cohort in terms of age, sex, socioeconomic status, and self-reported long-term conditions (appendix 6). The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). All participants gave informed consent for participation in UK Biobank. Access to UK Biobank data was granted under project 14151.

9.5.2 Identifying COPD

Participants with COPD were identified from linked primary care data using a previously validated list of diagnostic codes (Read-codes).[494] This code list has been shown to have a high positive predictive value for COPD (86.5%). We included participants with any relevant code occurring prior to UK Biobank baseline assessment. We did not include people with self-reported COPD if they did not have a corresponding primary care Read code.

9.5.3 Spirometry

We assessed the severity of COPD using spirometry data. We relied primarily on spirometry values coded in primary care records in the two year period prior to baseline assessment, as the quality of spirometry undertaken in primary care is known to be high.[495]

Where no primary care measures were available, we used spirometry data from UK Biobank baseline assessment. These measurements were taken using a Vitalograph Pneumotrac 6800 according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. No post-bronchodilator measurements were taken. Criteria for acceptable spirometry values from UK Biobank assessment data were taken from previous UK Biobank studies and are described in full in appendix 6.[496]

We did not use spirometry to confirm the diagnosis of COPD as UK Biobank spirometry was not post-bronchodilator, and previous studies demonstrated that the addition of spirometry only marginally improves the positive predictive value of the diagnostic codes used to identify COPD.

For all analyses using spirometry, we performed sensitivity analyses based on primary care values and UK Biobank values separately.

9.5.4 Assessing frailty

We used two different definitions of frailty, the frailty index and the frailty phenotype, which we analysed in parallel. These are described briefly here with full details in chapter 3.

A frailty index is a non-weighted count of age-related deficits (including comorbidities, symptoms, functional limitations and laboratory values). The frailty index was originally developed by Rockwood and Mitnitski and includes a standard protocol for selecting deficits from a given dataset based on specific criteria.[6,35,36] Deficits should be associated with increasing age and with poor health status; be neither too rare (<1% prevalence) nor ubiquitous; and cover a range of organ systems.[36] We used the frailty index previously developed by Williams et al for UK Biobank.[22] Deficits are summed then divided by the total number of possible deficits to give a value between 0 (no deficits) and 1 (all possible deficits). We analysed the frailty index as a numerical variable. For estimating prevalence and for presentation in tables, we also categorised the frailty index into robust (0-0.12), mild (0.12-0.24), moderate (0.24-0.36) and severe (>0.36) frailty. Cut-points were selected based on the electronic frailty index used routinely in UK primary care.[56]

The frailty phenotype is based on five criteria: low grip strength, weight loss, slow walking speed, exhaustion, and low physical activity. Frailty is defined as the presence of 3 or more criteria, with 1 or 2 criteria indicating pre-frailty. We have previously adapted the original criteria by Fried et al to UK Biobank.[5,9] Briefly, cut-offs for grip strength were as per the original frailty phenotype description, weight loss was self-reported and (given the wording of the UK Biobank questionnaire) not specified to be 'unintentional', slow walking speed was self-reported (in contrast to the original frailty phenotype in which gait speed was measured) as were exhaustion and physical activity. Detailed comparison between the UK Biobank and original definitions for each component are in appendix 6.

9.5.5 Covariates

Baseline covariates were taken from UK Biobank assessment centre data. Age, sex and ethnicity were self-reported. Body mass index was calculated based on measured height and weight. Smoking was categorised as current, previous and never, based on self-report. Self-reported frequency of alcohol intake was categorised (never/special occasions, 1-3 times per month, 1-4 times per week, of daily/almost daily).

9.5.6 Outcomes

We assessed the following outcomes by linkage to prospective healthcare records: all-cause mortality; all-cause hospitalisations, major adverse cardiovascular event (MACE); hospitalisation with COPD exacerbation; community COPD exacerbation. Follow-up was 8 years.

Mortality was assessed through linkage to national mortality registers. Hospitalisations were defined as any hospital admission coded as 'urgent' or 'emergency' (excluding 'elective' admissions). MACE was defined using International Classification of Diseases 10th Revision (ICD-10) codes from mortality records (cardiovascular death) and hospital episode statistics (non-fatal myocardial infarction [I21] or stroke [I63-I64]). Hospitalised COPD exacerbations were defined using previously validated ICD-10 codes (acute exacerbation of COPD [J44.0 or J44.1] or lower respiratory tract infection [J22]

codes in any position, or COPD code [J44.9] in first position of a hospital episode).[497]

Community COPD exacerbations were identified using a previously validated combination of primary care diagnostic codes, symptom codes, and prescriptions.[498] We defined an exacerbation as either (i) a medical diagnosis of lower respiratory tract infection of acute exacerbation of COPD, (ii) prescription of COPD-specific antibiotic combined with oral corticosteroid prescription, or (iii) two or more respiratory symptoms recorded on the same day as prescription of COPD-specific antibiotics or oral corticosteroids. These criteria were applied after excluding events occurring on the same day as codes suggesting routine annual COPD reviews or provision of rescue medication.[498]

9.5.7 Statistical analysis

The overall distribution of each frailty measure was summarised descriptively using bar plots. The relationship between frailty and baseline characteristics was summarised using descriptive statistics (means and standard deviation or counts and percentages for continuous and categorical variables, respectively). For the frailty index, we summarised this data using categories of the frailty index (robust, mild, moderate, severe) as described above.

To assess the relationship between each frailty measure and adverse clinical outcomes we used Cox-proportional hazards models (for all-cause mortality and MACE, modelling time to first event for MACE) and negative binomial models (for all-cause hospitalisations, hospitalised COPD exacerbations, and community COPD exacerbations). For MACE, a cause-specific model was used, with participants dying of other causes being censored at death with event status set to ‘0’. All models were initially adjusted for age, sex, socioeconomic status, body mass index, smoking and alcohol frequency (model 1) and then additionally adjusted for FEV1 (expressed as a percentage of predicted FEV1 based on age, height and ethnicity) (model 2). Negative binomial models also included an offset term of log observation time. In all models, fractional polynomials were used to model non-linear associations between numerical variables (frailty index, age, socioeconomic status, and percent predicted FEV1) and outcomes. We assessed interactions using product terms between frailty and age, and

between frailty and percent predicted FEV1. Interaction terms were retained if they improved model fit (assessed using Akaike Information Criterion). This was to assess if the association between frailty and outcomes varied depending on age or severity of COPD.

In sensitivity analyses, we repeated all of the above analyses restricting the sample to those with primary care-based spirometry values (as UK Biobank spirometry data was not post-bronchodilator). We also repeated all analyses using FEV1 expressed as an absolute value instead of as a percentage of predicted FEV1.

Finally, in post-hoc analyses, we modelled the relationship between frailty and mortality, and between frailty and hospital admissions in the full cohort (with available primary care data) including a term for the interaction between frailty and COPD. This was to assess if any relationship between frailty and mortality or hospitalisation was similar in people with and without COPD.

All analyses were performed using R.

9.6 Results

We identified 3132 UK Biobank participants with a COPD-specific primary care diagnostic code prior to baseline assessment (Figure 9.1). Of these, 2820 had spirometry data (2203 of which were from primary care data recorded up to two years before baseline assessment, with 617 relying on UK Biobank spirometry), 3011 (96%) had complete data on frailty phenotype variables, and 3131 (99.9%) had sufficient data to calculate the frailty index. The total number of participants included in each analysis is shown in Figure 9.1. The prevalence of frailty was 17% (n=514) using the frailty phenotype, while with the frailty index 28% (n=872) had moderate frailty and 4% (n=121) had severe frailty (Figure 9.2). For both frailty measures, prevalence was higher in people with COPD than in the wider cohort (appendix 6). Baseline characteristics are shown in Table 9.1. The relationship between frailty and percent predicted FEV1 is shown in Figure 9.3. Airflow limitation was modestly lower in frailty based on the frailty phenotype (with considerable overlap in the distributions). However, this relationship was not seen between airflow limitation and the frailty index.

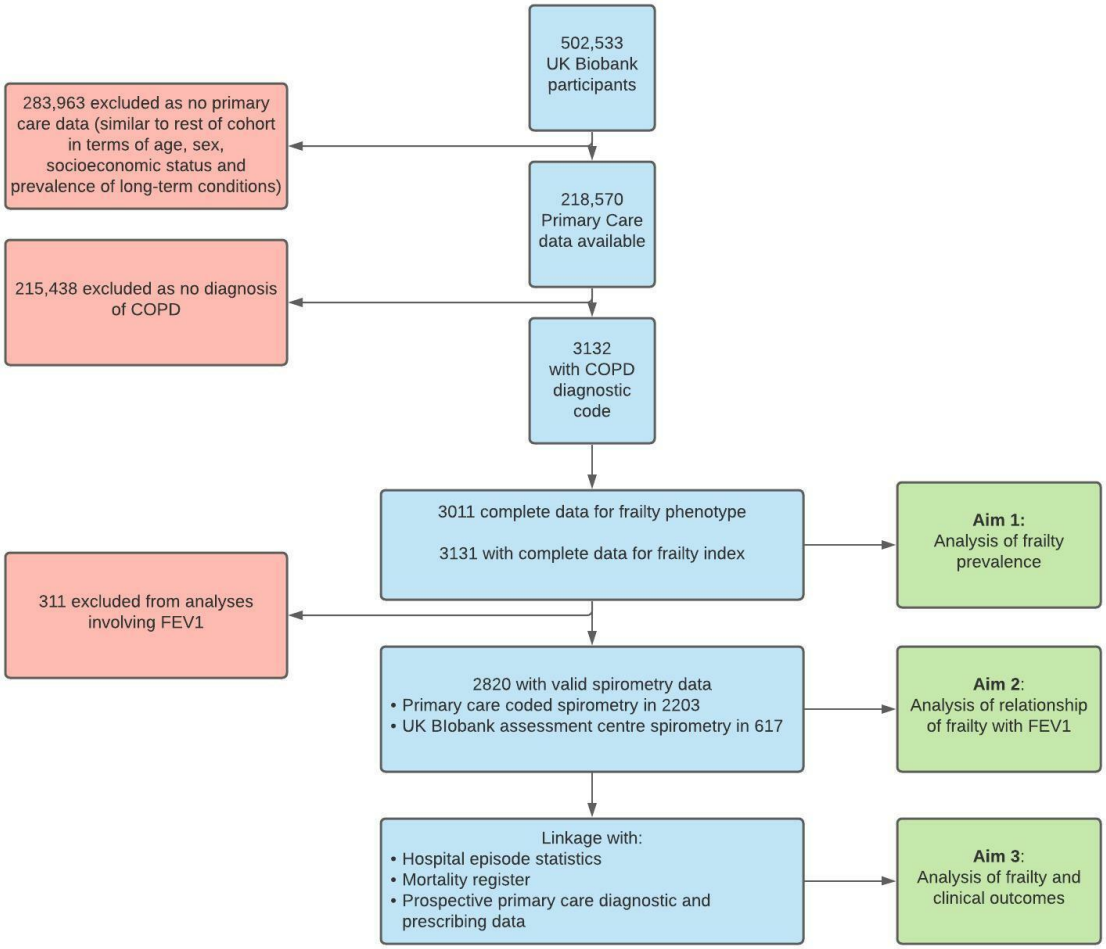

Figure 9.1 - Selection of participants. Flow diagram showing the selection of participants for inclusion in each of the three analyses. Prevalence estimates were based on participants with complete data for the frailty measure of interest.

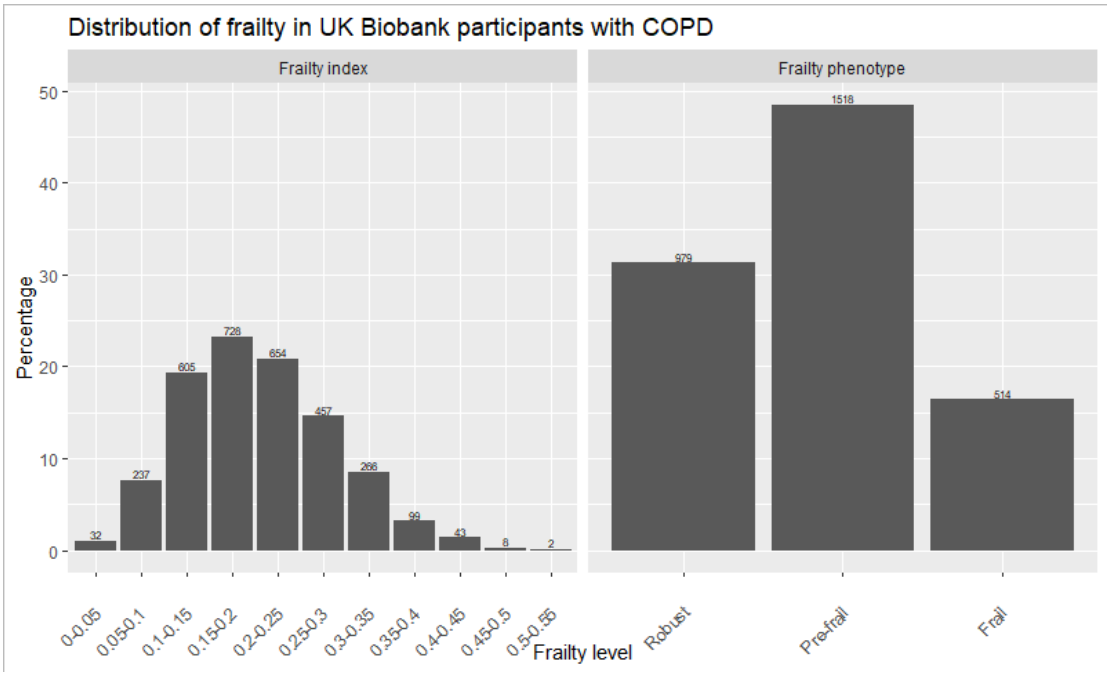

Figure 9.2 - Distribution of frailty in UK Biobank participants with COPD. Bar plot showing the distribution of each frailty measure in UK Biobank participants with COPD. The numbers above the bars indicate the total number of participants with each frailty status/frailty index value.

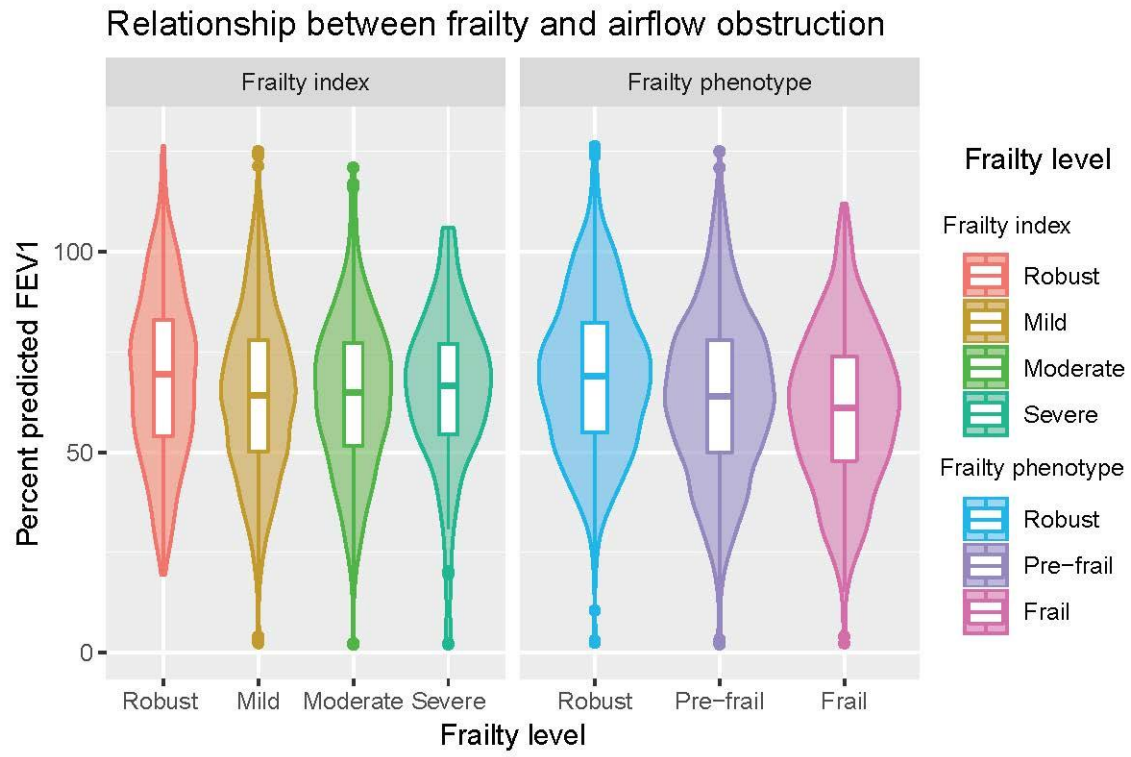

Figure 9.3 - Relationship between frailty and airflow obstruction. This plot shows the distribution of FEV1 values (expressed as a percentage of predicted FEV1 for each individual) stratified by frailty status. The Violin plots show the overall density. The Boxplots within these show the median and interquartile range.

Table 9.1 - Summary of baseline characteristics of UK Biobank participants with COPD, in total and by frailty status

	Total	Frailty phenotype			Frailty index			
		Robust	Pre-frail	Frail	Robust	Mild frailty	Moderate Frailty	Severe Frailty
Total N	3132	979	1518	514	467	1671	872	121
Age								
Mean (sd)	61.9 (5.9)	61.7 (5.9)	62.2 (5.8)	61.5 (5.9)	61.4 (6.3)	62.1 (5.9)	61.8 (5.7)	60.8 (5.6)
Sex								
Female (%)	1413 (45.1%)	409 (41.8%)	717 (47.2%)	235 (45.7%)	185 (39.6%)	749 (44.8%)	421 (48.3%)	58 (47.9%)
Male (%)	1718 (54.9%)	570 (58.2%)	801 (52.8%)	279 (54.3%)	282 (60.4%)	922 (55.2%)	451 (51.7%)	63 (52.1%)
Socioeconomic status								
Quintile 1 (most affluent)	367 (11.7%)	174 (17.8%)	158 (10.4%)	25 (4.9%)	79 (16.9%)	218 (13%)	65 (7.5%)	5 (4.1%)
Quintile 2	399 (12.7%)	170 (17.4%)	180 (11.9%)	42 (8.2%)	67 (14.3%)	236 (14.1%)	89 (10.2%)	7 (5.8%)
Quintile 3	520 (16.6%)	202 (20.6%)	240 (15.8%)	60 (11.7%)	97 (20.8%)	285 (17.1%)	121 (13.9%)	17 (14%)
Quintile 4	670 (21.4%)	191 (19.5%)	344 (22.7%)	104 (20.2%)	101 (21.6%)	355 (21.2%)	197 (22.6%)	17 (14%)
Quintile 5 (most deprived)	1170 (37.4%)	241 (24.6%)	593 (39.1%)	282 (54.9%)	121 (25.9%)	575 (34.4%)	399 (45.8%)	75 (62%)
Ethnicity								
White	3041 (97.1%)	960 (98.1%)	1478 (97.4%)	499 (97.1%)	446 (95.5%)	1628 (97.4%)	849 (97.4%)	118 (97.5%)
Other	66 (2.9%)	14 (1.9%)	31 (2.6%)	13 (2.9%)	6 (4.5%)	36 (2.6%)	22 (2.6%)	3 (2.5%)
BMI								
<18.5	52 (1.7%)	15 (1.5%)	18 (1.2%)	17 (3.3%)	7 (1.5%)	30 (1.8%)	14 (1.6%)	1 (0.8%)
18.5-24.9	853 (27.2%)	307 (31.4%)	410 (27%)	114 (22.2%)	171 (36.6%)	482 (28.8%)	183 (21%)	17 (14%)
25-29.9	1169 (37.3%)	439 (44.8%)	558 (36.8%)	141 (27.4%)	194 (41.5%)	666 (39.9%)	277 (31.8%)	32 (26.4%)
≥30	996 (31.8%)	218 (22.3%)	515 (33.9%)	229 (44.6%)	87 (18.6%)	472 (28.2%)	370 (42.4%)	67 (55.4%)

Smoking								
Never	494 (15.8%)	192 (19.6%)	238 (15.7%)	47 (9.1%)	96 (20.6%)	289 (17.3%)	93 (10.7%)	16 (13.2%)
Previous	1628 (52%)	541 (55.3%)	790 (52%)	249 (48.4%)	223 (47.8%)	887 (53.1%)	461 (52.9%)	57 (47.1%)
Current	972 (31%)	238 (24.3%)	477 (31.4%)	211 (41.1%)	134 (28.7%)	482 (28.8%)	309 (35.4%)	47 (38.8%)
Alcohol frequency								
Never/special occasions only	914 (29.2%)	194 (19.8%)	436 (28.7%)	237 (46.1%)	86 (18.4%)	427 (25.6%)	347 (39.8%)	54 (44.6%)
One to four times a week	1229 (39.2%)	434 (44.3%)	609 (40.1%)	151 (29.4%)	205 (43.9%)	694 (41.5%)	290 (33.3%)	40 (33.1%)
One to three times a month	327 (10.4%)	108 (11%)	156 (10.3%)	53 (10.3%)	48 (10.3%)	178 (10.7%)	85 (9.7%)	16 (13.2%)
Daily or almost daily	643 (20.5%)	243 (24.8%)	310 (20.4%)	72 (14%)	118 (25.3%)	367 (22%)	147 (16.9%)	11 (9.1%)
FEV1 (% predicted)								
>70%	1173 (37.5%)	449 (45.9%)	545 (35.9%)	147 (28.6%)	215 (46%)	607 (36.3%)	309 (35.4%)	42 (34.7%)
50-70%	1020 (32.6%)	321 (32.8%)	500 (32.9%)	172 (33.5%)	141 (30.2%)	561 (33.6%)	277 (31.8%)	41 (33.9%)
30-50%	518 (16.5%)	136 (13.9%)	264 (17.4%)	100 (19.5%)	68 (14.6%)	300 (18%)	141 (16.2%)	9 (7.4%)
<30%	109 (3.5%)	11 (1.1%)	65 (4.3%)	26 (5.1%)	15 (3.2%)	60 (3.6%)	30 (3.4%)	4 (3.3%)

The relationship between frailty and clinical outcomes is summarised in Figure 9.4. Using both the frailty index and the frailty phenotype definition, presence of frailty was associated with greater risk of all-cause mortality, MACE, all-cause hospitalisations, hospitalisation with COPD exacerbation, and community COPD exacerbation. For MACE, confidence intervals for different levels of frailty index, and for pre-frailty and frailty, were overlapping. The relative effect of frailty on each of these outcomes was similar before and after adjusting for airflow limitation, with only modest attenuation of the effect estimates.

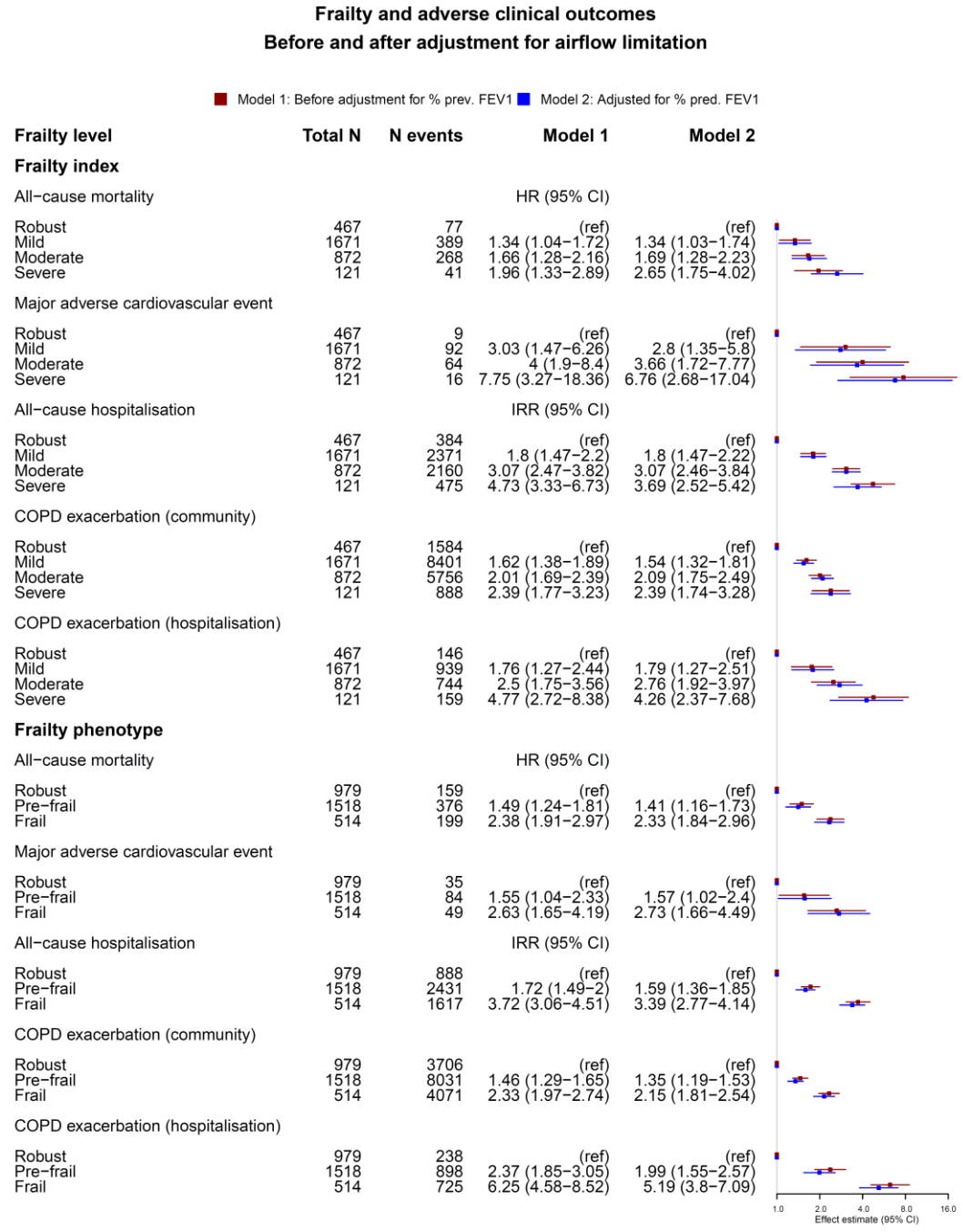

Figure 9.4 - Frailty and adverse clinical outcomes, before and after adjustment for airflow limitation. This figure shows hazard ratios (HR) and incidence rate ratios (IRR) for the association between frailty and clinical outcomes. Two models are presented, model 1 (adjusted for age, sex, socioeconomic status, smoking and alcohol frequency) and model 2 (adjusted for all covariates in model one plus forced expiratory volume in 1 second).

The predicted risk of clinical outcomes at different levels of frailty and airflow obstruction are shown in Figure 9.5 (all-cause mortality and MACE), Figure 9.6 (all-cause hospitalisation and hospitalised COPD exacerbations) and Figure 9.7 (community COPD exacerbations).

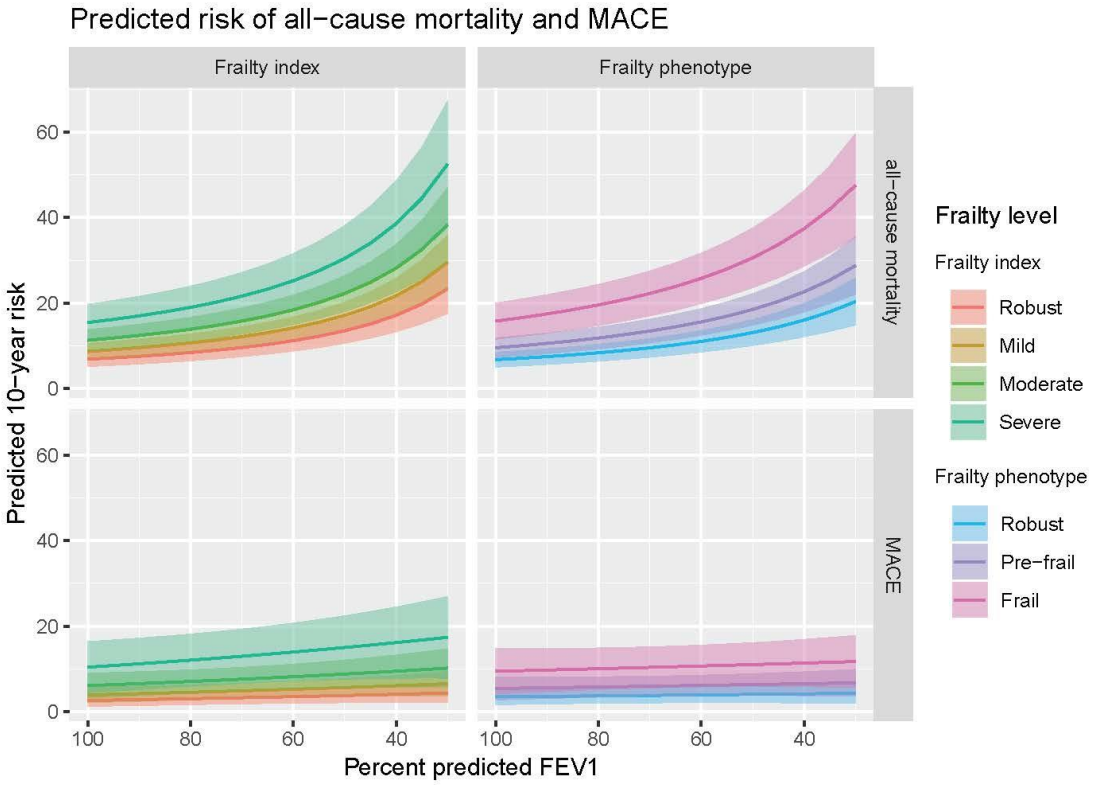

Figure 9.5 - Predicted risk of all-cause mortality and MACE. This plot shows the predicted 10-year risk of all-cause mortality (top two panels) and Major Adverse Cardiovascular Events (bottom two panels) based on frailty status and FEV1. Coloured lines indicate the point estimates for each level of frailty, with shaded areas showing the corresponding 95% confidence intervals. Results adjusted for age, sex, socioeconomic status, smoking and alcohol frequency.

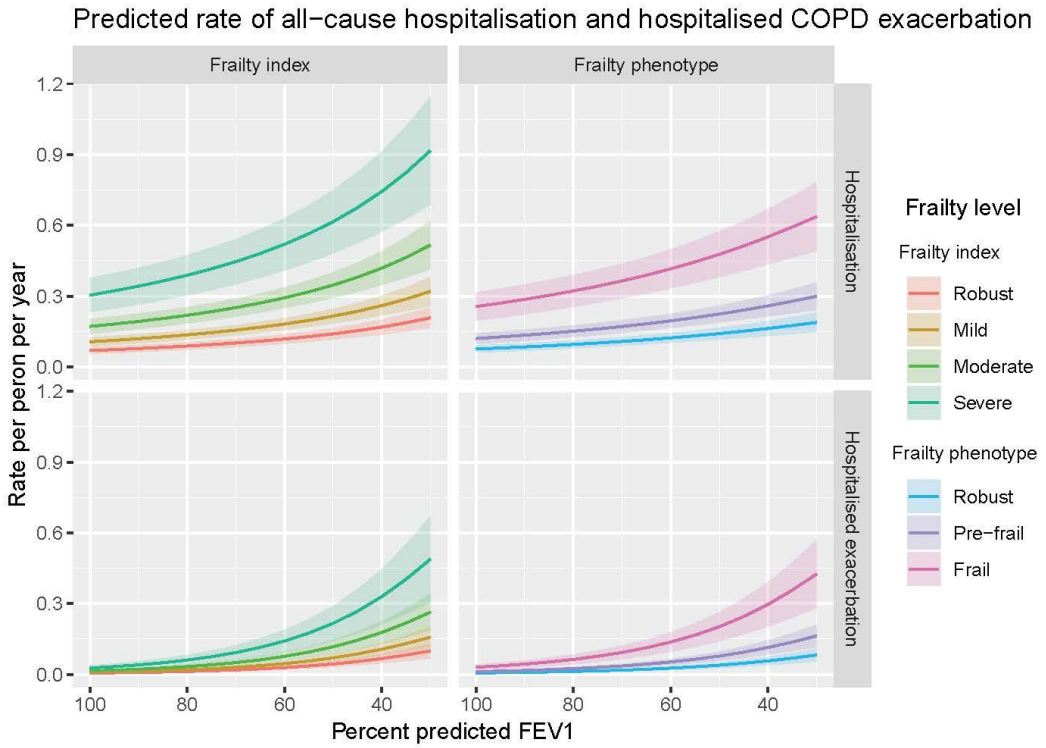

Figure 9.6 - Predicted rate of all-cause hospitalisation and hospitalised COPD exacerbation. This plot shows the predicted 10-year risk of all-cause hospitalisation (top two panels) and hospitalisation due to COPD exacerbation (bottom two panels) based on frailty status and FEV1. Coloured lines indicate the point estimates for each level of frailty, with shaded areas showing the corresponding 95% confidence intervals. Results adjusted for age, sex, socioeconomic status, smoking and alcohol frequency.

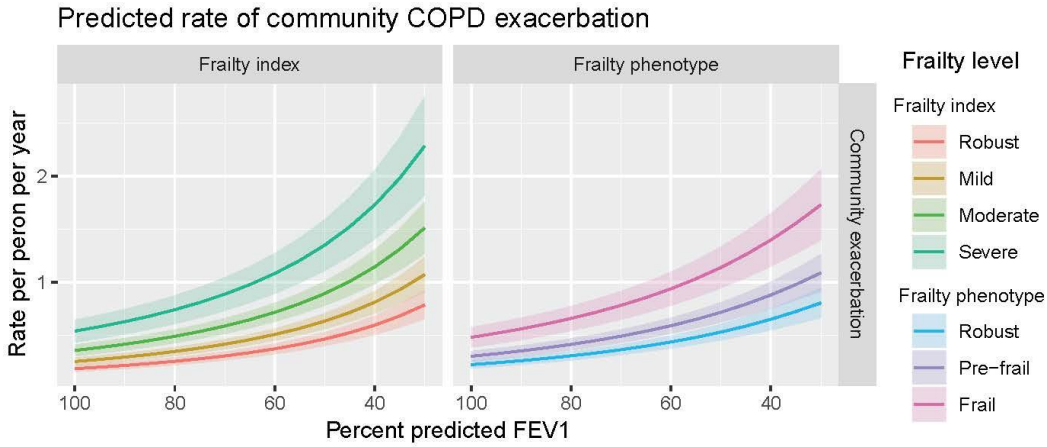

Figure 9.7 - Predicted rate of community COPD exacerbation. This plot shows the predicted 10-year risk of COPD exacerbation identified from primary care data, based on frailty status and FEV1. Coloured lines indicate the point estimates for each level of frailty, with shaded areas showing the corresponding 95% confidence intervals. Results adjusted for age, sex, socioeconomic status, smoking and alcohol frequency.

At all levels of frailty, the risk of all-cause mortality rose in a non-linear fashion with lower FEV1. There was no evidence of statistical interaction between either frailty definition and FEV1, or between age and either frailty or FEV1. This implies that, although the relative increase in mortality risk with frailty was similar at all levels of airflow obstruction, the absolute difference in mortality risk between 'robust' and 'frail' individuals was greatest in participants with lower FEV1. Furthermore, although the relative impact of frailty did not vary with age, absolute risk of outcomes is also therefore greater among older participants at any given level of frailty.

For MACE, the relationship with airflow limitation, as well as with frailty, was more modest. However, both were independently associated with a higher risk of MACE.

For hospitalisations and COPD exacerbations (hospitalised or community) there was a clear increase in risk with both airflow limitation and with frailty (Figure 9.6 and Figure 9.7). As with mortality and MACE, there was no evidence of statistical interaction.

In sensitivity analyses based on primary-care coded spirometry data all results were similar including the relationship between frailty and FEV1 and the relationship between frailty and clinical outcomes adjusting for FEV1. Findings were also similar when using raw FEV1 values rather than percent predicted FEV1. Finally, the relationship between frailty and mortality and between frailty and hospital admissions, on the relative scale, was similar between people with and without COPD (with no evidence of statistical interaction, shown in appendix 6).

9.7 Discussion

Frailty is common in 'middle-aged' as well as older people with COPD and is associated with a range of adverse health outcomes. In UK Biobank participants with COPD, aged between 40 and 70, frailty prevalence was 17% using the frailty phenotype, while using the frailty index 28% had moderate and 4% had severe frailty. The frailty phenotype, but not the frailty index, was associated with lower percent predicted FEV1. Both frailty definitions were associated with higher all-cause mortality, MACE, hospitalisations and both hospitalised and community COPD exacerbations. The relationship with each of these adverse outcomes was independent of the degree of airflow limitation, for both frailty definitions. However, the difference in absolute risk between frail and robust participants was greatest in those with severe airflow limitation. These findings demonstrate that frailty is a common and clinically significant concept in people with COPD, including those aged <65 years in whom it is not routinely identified and has been infrequently studied.

Our findings that frailty in COPD is associated with mortality independently of FEV1 is consistent with some previous studies,[438,453] although some have shown null associations after adjustment for age and FEV1.[439,458] These studies varied in their frailty definition, sample size, and length of follow-up. Frailty has also been associated with exacerbations in two cross sectional and one longitudinal study.[438,452,457] The association with MACE has not been described in previous studies of frailty in COPD.

Our findings that frailty was common in people with COPD is in keeping with previous epidemiological studies of frailty in COPD[17] as well as the wider literature on the broad physiological implications of COPD.[486] COPD impacts multiple organ systems and is often associated with muscle weakness, osteoporosis, and malnutrition.[484,485] The severity of COPD is best characterised by a multidimensional assessment reflecting these broad impacts. For example, the BODE index comprises four domains (body mass index, FEV1, dyspnoea assessed using the modified Medical Research Council scale, and exercise capacity based on the 6-minute walking distance). It is used to assess the severity of COPD, and is a superior predictor of mortality in COPD than FEV1 alone.[499] Domains of the BODE index have considerable overlap with features of

the frailty phenotype (e.g. weight loss and slow walking speed) and are commonly-used deficits within the frailty index. However, the extent to which frailty is caused by these features of COPD, or reflects a physiological decline distinct from COPD, is not clear. The development of frailty is multifactorial with multiple potential causal mechanisms. Many of these, including environmental exposures, systemic inflammation, and altered body composition, are closely linked to COPD (either as common causal factors, such as environmental exposures, or as sequelae of COPD that may contribute to the development of frailty). As frailty development is multifactorial, this is likely to vary between individuals, and may also differ depending on the measure used to define frailty.

Frailty is a dynamic concept. Longitudinal studies have shown that COPD is associated with the transition from a robust to a frail state using the frailty phenotype.[372,451] Conversely, some people with frailty and COPD undergoing pulmonary rehabilitation show a marked improvement in frailty status.[466] Therefore while COPD may be a risk factor for frailty progression, the shared features may offer opportunities for interventions targeting both frailty status and COPD. The observation that frailty may improve in the context of pulmonary rehabilitation, as described by Maddocks et al,[466] is consistent with recent reviews of interventions targeting frailty in general, in which exercise and nutritional interventions have shown the most promise in ameliorating frailty.[375] Identification of people with COPD and frailty may therefore be beneficial for both identification of risk and for targeted intervention. Our findings demonstrate that this identification should not be limited to 'older' people with COPD, as frailty is prevalent across a wide age range and associated with a range of clinically important outcomes.

Strengths of this study include its large sample size and prospective linkage to a wide range of healthcare outcomes. We also used validated definitions, based on linked diagnostic codes, to identify baseline COPD and subsequent exacerbations.[494,497,498] The range of variables available from the UK Biobank baseline assessment also allows the analysis of two separate measures of frailty. However, there are some important limitations. Our definition of the frailty phenotype was adapted from the original.[5,9] Unlike the original, weight loss was

not specified as unintentional in UK Biobank and walking speed was self-reported rather than measured. The frailty index was constructed according to the standard protocol, however there is a relative lack of functional measures and few measures of sensory or cognitive impairment. UK Biobank is also not nationally representative, with participants being on average more affluent, having fewer comorbidities, and more predominantly White ethnicity than the UK population. This lack of representativeness may lead to bias in the estimation of associations between exposure and outcomes. For example, UK Biobank appears to underestimate the risks of mortality, hospitalisation and major adverse cardiovascular events associated with high levels of multimorbidity.43 It is likely, therefore, that our estimates of the associations between frailty and adverse outcomes may be conservative. UK Biobank spirometry data is also not post-bronchodilator, however we used primary care spirometry data where possible (available for 70% of participants) which has been shown to be of high quality, and our findings were consistent when restricting our analysis to those with primary care spirometry alone.

9.8 Conclusion

Our findings demonstrate that frailty is common in people with COPD, including those under 65 years of age, and has clinically significant implications for this population regardless of which frailty definition is used. This relationship is independent of the degree of airflow limitation. Identification of frailty in people with COPD may aid risk stratification and identification of those who may benefit from targeted interventions. For this to be beneficial, frailty assessment would need to become integrated into the routine monitoring and management of COPD.

Chapter 10 Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions

10.1 Chapter summary

This chapter addresses research question 3 (the prevalence and implications of frailty in randomised controlled trials of drugs for each of the exemplar conditions). The analysis uses individual participant data from industry-sponsored drug trials, from which a frailty index is constructed and analysed. All three exemplar conditions are considered within this chapter.

The text and figures presented in this chapter are as published in Hanlon P, Butterly E, Lewsey J, Siebert S, Mair FS, McAllister DA. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. BMC medicine. 2020 Dec;18(1):1-2.

10.2 Abstract

Background: Frailty is common in clinical practice, but trials rarely report on participant frailty. Consequently, clinicians and guideline-developers assume frailty is largely absent from trials and have questioned the relevance of trial findings to people living with frailty. Therefore, we examined frailty in phase 3/4 industry-sponsored clinical trials of pharmacological interventions for three exemplar conditions: type 2 diabetes mellitus (T2DM), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD).

Methods: We constructed a 40-item frailty index (FI) in 19 clinical trials (7 T2DM, 8 RA, 4 COPD, mean age 42-65 years) using individual-level participant data. Participants with a FI >0.24 were considered 'frail'. Baseline disease severity was assessed using HbA1c for T2DM, Disease Activity Score-28 (DAS28) for RA, and % predicted FEV1 for COPD. Using generalised gamma regression, we modelled FI on age, sex and disease severity. In negative binomial regression we modelled serious adverse event rates on FI, and combined results for each index condition in a random-effects meta-analysis.

Results: All trials included participants with frailty: prevalence 7-21% in T2DM trials, 33-73% in RA trials, and 15-22% in COPD trials. Increased disease severity and female sex were associated with higher FI in all trials. The 99th centile of the FI ranged between 0.35 and 0.45. Frailty was associated with age in T2DM and RA trials, but not in COPD. Across all trials, and after adjusting for age, sex, and disease severity, higher FI predicted increased risk of serious adverse events; the pooled incidence rate ratios (per 0.1-point increase in FI scale) were 1.46 (95% CI 1.21-1.75), 1.45 (1.13-1.87) and 1.99 (1.43-2.76) for T2DM, RA and COPD, respectively.

Discussion: The upper limit of frailty in trials is lower than has been described in the general population. However, mild to moderate frailty was common, suggesting trial data may be harnessed to inform disease management in people living with frailty. Participants with higher FI experienced more serious adverse events, suggesting screening for frailty in trial participants would enable identification of those that merit closer monitoring.

Conclusion: Frailty is identifiable and prevalent among middle-aged and older participants in phase-3/4 drug trials and has clinically important safety implications.

10.3 Background

As average life expectancy rises and multimorbidity increases,[9] frailty is becoming an increasingly important consideration in the management of chronic disease.[3] Frailty describes a clinical state of decreased function across multiple physiological systems characterised by vulnerability to adverse health outcomes and decompensation in response to physiological stress.[3] A large number of measures exist to identify and quantify frailty, however two models have dominated the literature: the frailty index and the frailty phenotype.[3,26] The frailty index (FI) is based on a 'cumulative deficit' model wherein deficits including long-term conditions, symptoms, functional impairments, and laboratory abnormalities are counted.[6] Larger deficit counts indicate a greater degree of frailty. The main alternative to the FI, the frailty phenotype, identifies frailty where three of the following five specific criteria are met: unintentional weight loss, weakness, slow gait speed, exhaustion and low physical activity.[5] Although distinct concepts, there is considerable overlap in the populations identified by the frailty index and frailty phenotype.[288] Both approaches have been widely validated and associated with adverse health outcomes including mortality, hospitalisation and disability.[3]

Managing chronic illness in people living with frailty is challenging.[3,161] Not least because randomised controlled trials, which (via clinical guidelines) underpin safe and effective management, are said to exclude people with frailty.[161,500,501] As such, the applicability of trial findings to people living with frailty is not clear. This leaves clinicians uncertain about treatment effectiveness, which further complicates management of patients whose care is already complex and challenging.

Despite these concerns, direct evidence concerning frailty in clinical trials is scarce. Very few trials have measured frailty. Considering drug trials specifically, we found three (the HYVET and SPRINT studies of hypertension[502,503] and TOPCAT study of heart failure,[504]) which performed post-hoc analysis of frailty using the frailty index and a fourth (TRILOGY ACS for unstable angina), which assessed frailty using the frailty phenotype model in a subset of participants aged over 65 years.[505] Frailty was found to be prevalent in these trials, but as all four specifically targeted older people it is not known whether

frailty may also be found in the much larger and more influential body of trials not specifically targeted at older people. More recently, a pooled analysis of 14 cardiovascular trials in older people (153,696 participants, mean age 70.8 years) showed that a frailty index was associated with all-cause and cardiovascular mortality, as well as cardiovascular events.[91]

Hitherto, inferences about trial representativeness have largely been based on the observation that, on applying trial eligibility criteria to routine electronic health records, ineligible patients are older, frailer and have more comorbidities.[506] Recently, however, on directly measuring comorbidities using individual-level participant data (IPD) in 116 industry-funded trials we found that multimorbidity was common in trial participants.[244] Although frailty is associated with multimorbidity, it is a distinct entity[9] and it is not clear whether frailty is also common among trial participants. Moreover, since trial IPD contains rich data on physiological status (e.g. albumin, haemoglobin, body mass index), symptoms (e.g. breathlessness, fatigue), and function (e.g. impaired mobility), there is the potential to measure frailty.

In this study we use IPD from existing clinical trials for three exemplar chronic conditions (type 2 diabetes mellitus (T2DM), rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD)) to construct a frailty index. We then quantify the prevalence of frailty in these clinical trial populations and examine whether frailty is associated with serious adverse events in the clinical trials studied.

10.4 Methods

10.4.1 Study design and participants

IPD from industry-sponsored clinical trials were identified from two repositories: Clinical Study Data Request (CSDR) and the Yale University Open Data Access (YODA) project. Trials were selected according to a pre-specified protocol (Prospero CRD42018048202) as part of a wider project assessing multimorbidity in clinical trials. Trials were eligible for inclusion if they evaluated pharmacological treatments for a long-term condition, were registered with clinicaltrials.gov, started after 1st January 1990, were phase-2/3, -3, or -4, included ≥300 participants, and had an upper age limit ≥60 years (or no maximum). From this wider set of trials, we selected three exemplar conditions (T2DM, RA and COPD) in which to assess frailty. These conditions were chosen as frailty is common, and has been shown to affect younger people, in the context of these chronic conditions.[9,17,249,402] Furthermore, frailty is a clinically relevant concept in the management of these conditions, having been highlighted as an important factor influencing treatment targets.[507,508]

10.4.2 Procedures

We measured frailty using a frailty index approach, based on the cumulative deficit model of frailty described by Rockwood and Mitnitski.[35] A frailty index is a count of health-related deficits (including long term health conditions, laboratory abnormalities, symptoms and functional limitations) across a range of physiological and mental health domains. Each individual's frailty index value is calculated as the sum of deficits present, divided by the total number of deficits in the frailty index. For example, an individual with 8 out of a possible 40 deficits would have a frailty index of 0.2 (8/40). The frailty index was used to measure frailty in the HYVET, SPRINT and TOPCAT trials, is applicable at any age,[211,213,502-504,509] and can be calculated from any dataset where a sufficient number of deficits is recorded. It is therefore suitable for measuring frailty in our set of trials.

A standard procedure exists for selecting variables for inclusion as "deficits" in a frailty index.[36] Deficits should: (i) be associated with age and poorer health, (ii)

cover a range of physiological areas (e.g. physiological measures, physical function, long term conditions from different organ systems), and (iii) be neither ubiquitous in the target population nor be very rare (e.g. <1% prevalence in the target population). We applied these criteria to possible deficits identified from trial baseline data. Existing literature was used to judge if a deficit met the above criteria.

Symptoms and functional measures were identified using baseline quality of life and symptom questionnaires. We used the same deficits for all trials within each index condition. Deficits differed between index conditions as different questionnaires were used in the respective trials. Laboratory and anthropometric deficits (e.g. blood pressure, body mass index) were identified from baseline values. We excluded from the frailty index any deficit with >5% missing data. To assess if any variables were strongly correlated, we analysed all pairs of deficits using Pearson and Spearman's rank correlation coefficients (for pairs of binary and categorical deficits, respectively). Where there was high correlation (>0.3) only one of the correlated variables was included in the frailty index.[56] For each index condition, we identified 40 deficits to be included in the frailty index (details in chapter 3, Table 3.4, Table 3.5 and Table 3.6). Participants with complete data for at least 38 of these deficits were included in the analysis. The frailty index was calculated as the total number of deficits present divided by the total number of deficits with complete data for that individual.

We had intended to use medical history data to identify long term conditions, but this was frequently redacted (as a privacy measure) or not recorded. We therefore identified long-term conditions based on concomitant medications, using definitions we have previously published.[244]

10.4.3 Outcomes

Applying cut-off values to define frailty has proved controversial, with no consensus on a value above which a person should be identified as living with frailty. We therefore report the entire distribution of the frailty index for each trial. We also separately described the distribution in trial participants above 65 years. To facilitate comparison with the published literature, we also categorised the frailty index into no frailty (<0.12), mild (0.12-0.24), moderate

(0.24-0.36) and severe frailty (>0.36), based on cut-points used in the electronic frailty index (used in routine clinical practice).[56]

We assessed the relationship between frailty index and the following baseline characteristics: age, sex, and severity of the index condition. We assessed severity of T2DM by measuring glycated haemoglobin (HbA1c) as a proxy marker, while in RA we used the Disease Activity Score in 28 joints (DAS28) and for COPD the forced expiratory volume in one second as a percentage of predicted value (% predicted FEV1).

Finally, we assessed whether the frailty index at baseline predicts serious adverse events during trial follow-up. Trials record all adverse events occurring during the trial period regardless of their relationship (or lack of relationship) with the trial treatment. Certain adverse events are characterised as 'serious adverse events' (SAEs). SAEs are those meeting one or more of the following criteria: (i) results in death, (ii) is life threatening, (iii) results in hospitalisation, (iv) results in persistent or significant disability/incapacity, or (v) is a congenital abnormality/birth defect.

10.4.4 Statistical analysis

All analyses were conducted according to a pre-specified protocol.

All trial data were held within secure repositories that only permit export of aggregate, non-identifiable data. Therefore, to allow full description of the distribution of the frailty index for each trial while avoiding the risk of disclosure, we used statistical distributions to represent the frailty index. For each trial, we fitted the frailty index to each of the following distributions: lognormal, gamma, Weibull and generalised gamma. We then compared the fit of each distribution using Kolmogorov-Smirnov tests ($p>0.05$ taken as good fit, failing to reject the null hypothesis that the distributions were different). The generalised gamma distribution was found to fit the frailty index distribution well for all trials. Parameters describing the distribution for each trial were exported from the secure environments to allow us to report the distribution of the frailty index for each trial. We calculated the frailty distribution for the

whole trial population. We then repeated the process restricting the trial population to people over 65 years.

We then modelled frailty index on age, sex, and disease severity using generalised gamma regression models. Each trial was modelled separately. Non-linear relationships between age, disease severity and frailty index were explored using fractional polynomials. There was no improvement in model fit incorporating non-linear terms. The coefficients and variance-covariance matrices from these models were exported from the secure environments to allow us to report the mean frailty index for specific age, sex and disease severity combinations.

Within the secure environments, we fitted negative binomial models of serious adverse event rates on frailty index, age, sex and disease severity, exporting the coefficients and variance covariance matrices as before. For each index condition, we performed random-effects meta-analysis (using inverse variance weighting) to obtain overall estimates of the associations between serious adverse events and frailty index (adjusted for age, sex, and disease severity).

Data processing and analysis was performed using R (version 3.6.1). Meta-analyses were performed using RevMan5. All model outputs are available in appendix 7.

10.5 Results

10.5.1 Identification of studies

We identified 39 trials meeting our inclusion criteria for which IPD were available in the CSDR or YODA repositories. Of these, 19 trials (7 T2DM trials, 8 RA trials, and 4 COPD trials) contained IPD on a range of variables sufficient to calculate the frailty index. In the remaining 20 trials, data on functional deficits and/or laboratory measures were either redacted or not reported. The selection of trials is summarised in Figure 10.1. The characteristics of the included trials are summarised in Table 10.1.

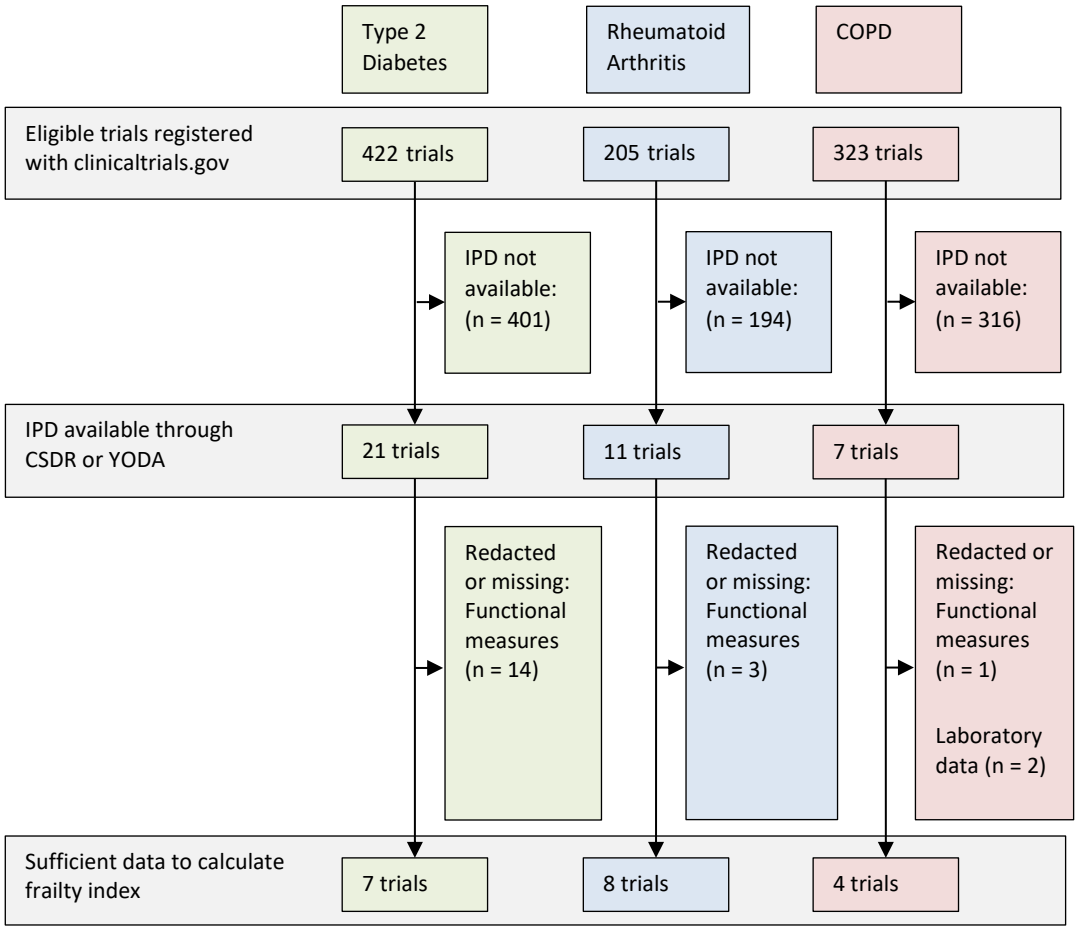

Figure 10.1 - Identification and selection of trials. Flow diagram of identification of trial individual participant data and inclusion in analysis.

Table 10.1 - Details of included trials

Trial ID	Sponsor	Drug	Comparison	Phase	Total participants	Age eligibility	N (%) aged ≥65	Mean (SD) age	N (%) female
T2DM									
NCT01106625	Janssen	Canagliflozin	Placebo	3	469	18-80 years	84 (17%)	56.7 (9.3)	230 (40%)
NCT01106677	Janssen	Canagliflozin	Placebo	3	1284	18-80 years	206 (16%)	55.4 (9.4)	679 (53%)
NCT00734474	Lilly	Dulaglutide	Sitagliptin, Placebo/Sitagliptin	3	1202	18-75 years	364 (30%)	54.1 (9.9)	643 (54%)
NCT01064687	Lilly	Dulaglutide	Exenatide, Placebo	3	978	≥18 years	197 (20%)	55.7 (9.8)	406 (42%)
NCT01075282	Lilly	Dulaglutide	Insulin	3	810	≥18 years	188 (23%)	56.7 (9.5)	393 (49%)
NCT01191268	Lilly	Dulaglutide	Insulin	3	884	≥18 years	280 (32%)	59.3 (9.2)	411 (57%)
NCT01624259	Lilly	Dulaglutide	Liraglutide	3	599	≥18 years	138 (23%)	56.7 (9.3)	312 (52%)
RA									
NCT00236028	Janssen	Infliximab	Methotrexate	3	1036	18-75 years	127 (12%)	50 (12.6)	733
NCT00264537	Janssen	Golimumab	Placebo	3	637	≥18 years	52 (8%)	49.5 (12.2)	528 (83%)
NCT00264550	Janssen	Golimumab	Placebo	3	444	≥18 years	38 (9%)	50.4 (11.3)	358 (81%)
NCT00361335	Janssen	Golimumab	Placebo	3	643	≥18 years	46 (7%)	49.4 (11.7)	517 (18%)
NCT00106535	Roche	Tocilizumab	Placebo	3	1196	≥18 years	173 (14%)	52.0 (12.2)	989 (83%)

NCT01119859	Roche	Tocilizumab	Adalimumab	4	326	≥18 years	75 (23%)	53.9 (12.7)	262 (81%)
NCT01007435	Roche	Tocilizumab	Placebo	3	1162	≥18 years	180 (15%)	50.1 (13.5)	904 (78%)
NCT01232569	Roche	Tocilizumab	Placebo	3	656	≥18 years	81 (12%)	52.1 (11.5)	555 (85%)
COPD									
NCT01316913	GSK	Umeclidinium bromide	Tiotropium	3	872	≥40 years	455 (52%)	64.6 (8.4)	280 (32%)
NCT01316900	GSK	Umeclidinium bromide	Tiotropium	3	846	≥40 years	364 (43%)	62.9 (9.0)	261 (31%)
NCT01957163	GSK	Umeclidinium bromide	Fluticasone, Placebo	3	619	≥40 years	299 (48%)	64.4 (8.1)	212 (32%)
NCT02119286	GSK	Umeclidinium bromide	Fluticasone, Placebo	3	620	≥40 years	270 (44%)	62.9 (8.2)	228 (37%)

10.5.2 Distribution of frailty

The distribution of the frailty index for each trial is shown in Figure 10.2, Figure 10.3 and Figure 10.4. Each trial included participants with a wide range of frailty index values and all trials included some participants with frailty. Distributions were similar within each index condition but differed substantially between the three conditions. Summary statistics for frailty in each trial, along with proportions in each category of frailty, are shown in Table 10.2. Taking an illustrative cut-off of 0.24 to indicate frailty, the proportion of trial participants with frailty ranged from 7% to 21% in T2DM trials, 33% to 73% in RA trials, and 15% to 22% in COPD trials.

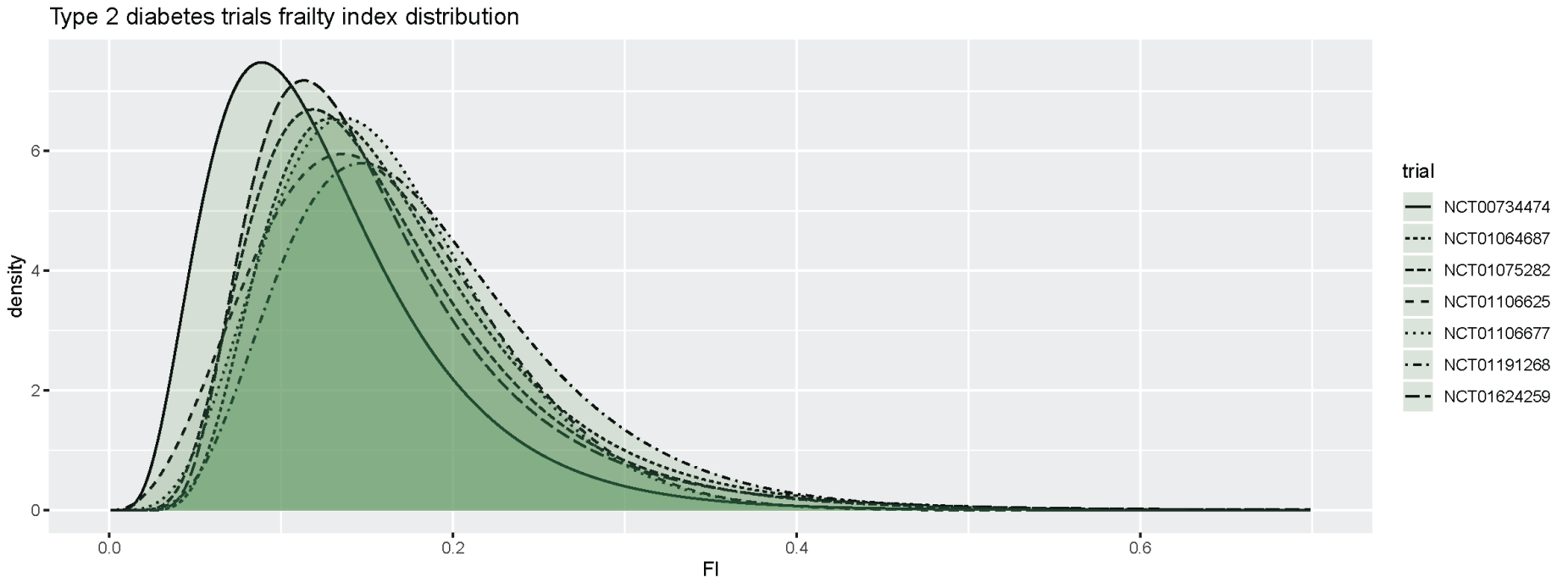

Figure 10.2 - Distribution of frailty index in each trial - Type 2 diabetes

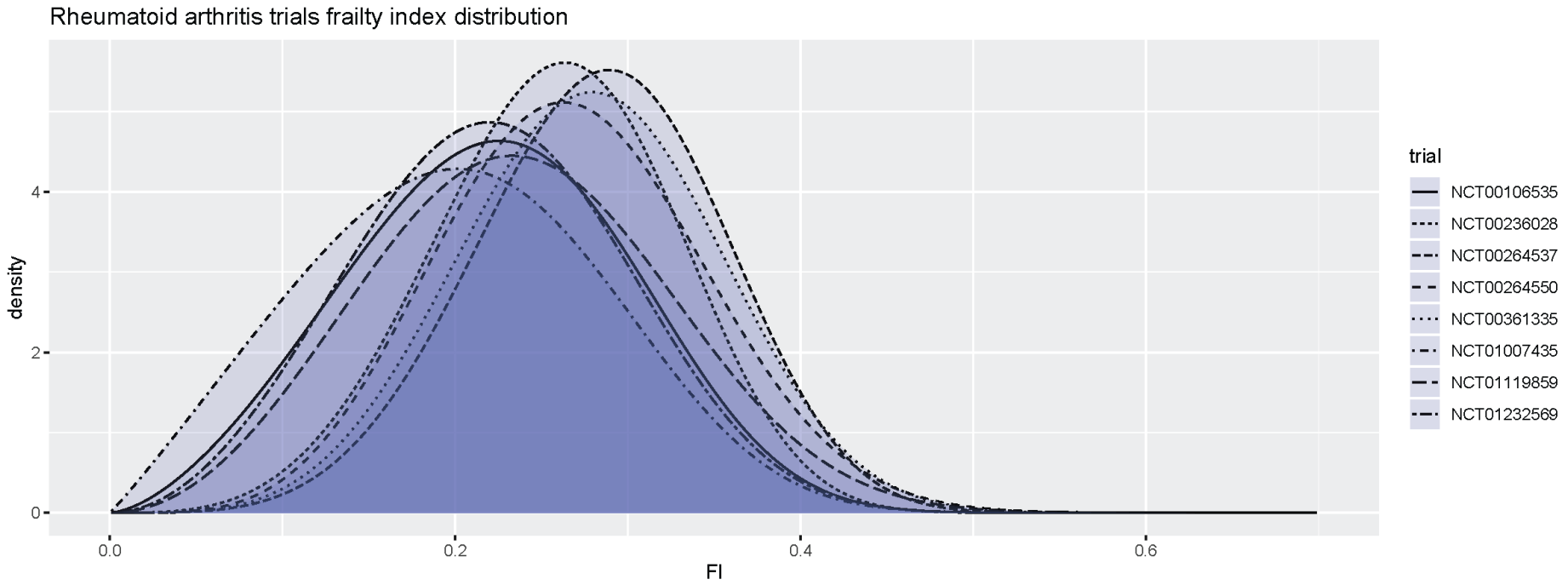

Figure 10.3 - Distribution of frailty index in each trial - Rheumatoid arthritis

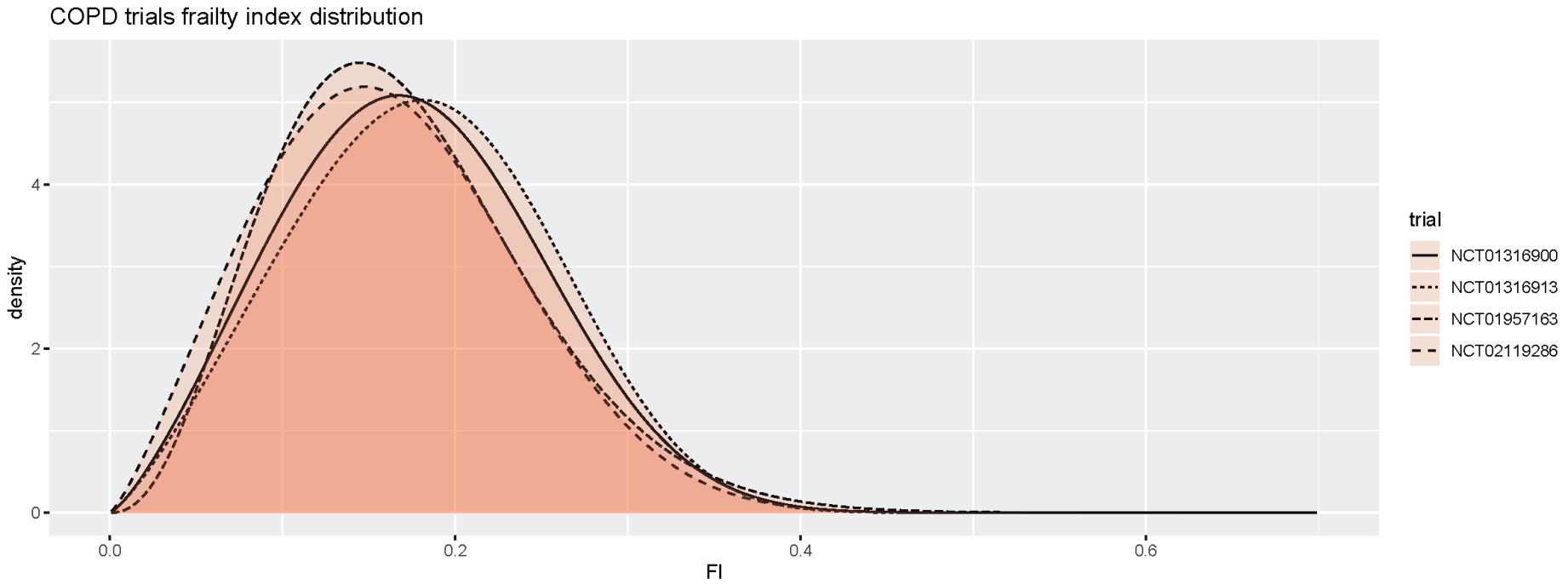

Figure 10.4 - Distribution of frailty index in each trial – COPD

Table 10.2 - Mean frailty index, 99th centile, and proportion of participants in frailty categories for each trial: whole trial population and those over 65 years

Trial	Whole sample						Participants aged ≥65 years						Number missing (%)
	Mean frailty index	99th centile	Frailty index Categories (%)				Mean frailty index	99th centile	Frailty index Categories (%)				
			0-0.12	0.12-0.24	0.24-0.36	>0.36			0-0.12	0.12-0.24	0.24-0.36	>0.36	
Type 2 diabetes													
NCT01106625	0.16	0.35	31.36	56.12	11.82	0.7	0.17	0.51	24.38	63.68	8.81	3.13	74 (16%)
NCT01106677	0.16	0.35	28.26	59.79	11.21	0.74	0.17	0.33	20.13	70.29	9.08	0.5	124 (10%)
NCT00734474	0.13	0.35	54.22	39.24	5.72	0.82	0.14	0.32	43.78	49.08	6.81	0.33	66 (5%)
NCT01064687	0.17	0.45	26.9	56.56	13.44	3.1	0.19	0.46	20.49	57.86	17.54	4.1	4 (0.4%)
NCT01075282	0.16	0.42	33.35	53.02	11.29	2.34	0.18	0.42	23.2	57.15	16.72	2.93	4 (0.5%)
NCT01191268	0.18	0.43	20.73	58.29	17.82	3.16	0.2	0.42	14.96	60.54	21.21	3.29	2 (0.2%)
NCT01624259	0.16	0.45	35.34	51.53	10.36	2.77	0.18	0.43	24.7	55.16	16.94	3.2	1 (0.2%)
RA													
NCT00236028	0.26	0.41	2.62	37.05	53.73	6.6	0.27	0.41	1.15	28.08	61.5	9.27	12 (2%)
NCT00264537	0.28	0.44	1.14	25.99	58.83	14.05	0.31	0.46	0.16	15.63	63.43	20.78	4 (0.6%)
NCT00264550	0.27	0.45	2.03	34.71	51.37	11.89	0.28	0.41	3.58	24.91	57.11	14.41	2 (0.5%)
NCT00361335	0.28	0.45	1.49	29.24	55.43	13.85	0.29	0.46	0.73	26.31	56.99	15.96	1 (0.2%)
NCT00106535	0.22	0.4	11.57	46.97	37.19	4.27	0.24	0.4	9.73	39.92	44.71	5.64	4 (0.3%)
NCT01007435	0.2	0.4	18.92	47.79	29.95	3.35	0.21	0.41	15.89	46.55	32.81	4.75	9 (3%)
NCT01119859	0.24	0.44	8.5	43.27	39.88	8.36	0.25	0.48	7.07	40.41	40.3	12.22	3 (0.3%)
NCT01232569	0.22	0.4	10.32	49.31	36.44	3.93	0.23	0.4	7.59	47.37	41.24	3.8	0 (0%)
COPD													
NCT01316900	0.18	0.35	24.62	55.68	18.9	0.8	0.17	0.35	25.83	57.28	16.3	0.58	33 (4%)
NCT01316913	0.18	0.35	22.04	55.71	21.56	0.69	0.18	0.35	24.64	55.33	19.38	0.65	19 (2%)
NCT01957163	0.17	0.37	27.13	55.71	15.74	1.42	0.17	0.36	28.32	56.89	13.79	1	0 (0%)
NCT02119286	0.16	0.35	30.74	53.91	14.67	0.68	0.16	0.33	30.75	56.81	12.1	0.34	2 (0.3%)

10.5.3 Relationship with baseline factors

Estimated mean frailty index by age, sex and disease severity is shown in Figure 10.5, Figure 10.6 and Figure 10.7. Disease severity at baseline was also associated with frailty index for COPD and, especially, for RA trials, but not for T2DM trials. Frailty was associated with female sex in all trials for all conditions. In the COPD trials the mean frailty index was not associated with age, but for all of the RA trials and all but one T2DM trials the mean frailty index increased with age. The variation by age was smaller than the variation between trials, however, and for all conditions frailty remained common even among the youngest participants. For example, the modelled proportion of 40-year-olds with a frailty index >0.24 ranged from 4% to 15%, 6% to 52%, and 20% to 27% in T2DM, RA and COPD respectively.

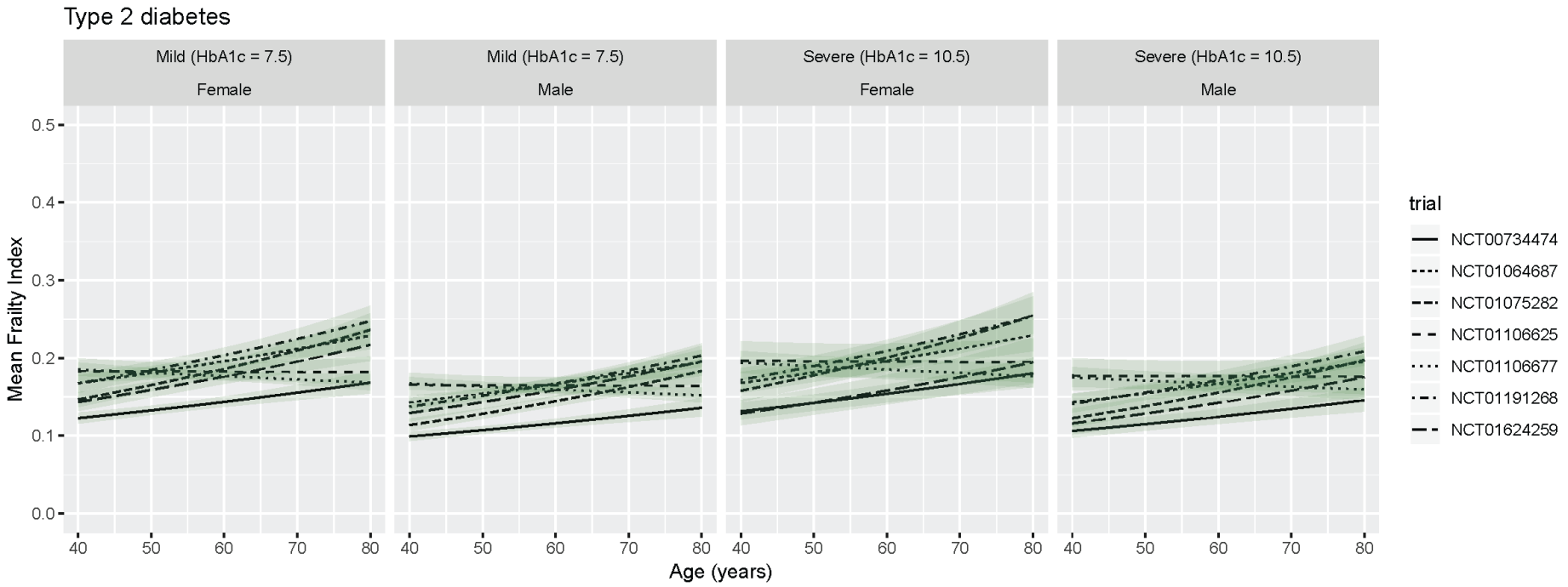

Figure 10.5 - Relationship between age, sex, disease severity and frailty index - Type 2 diabetes

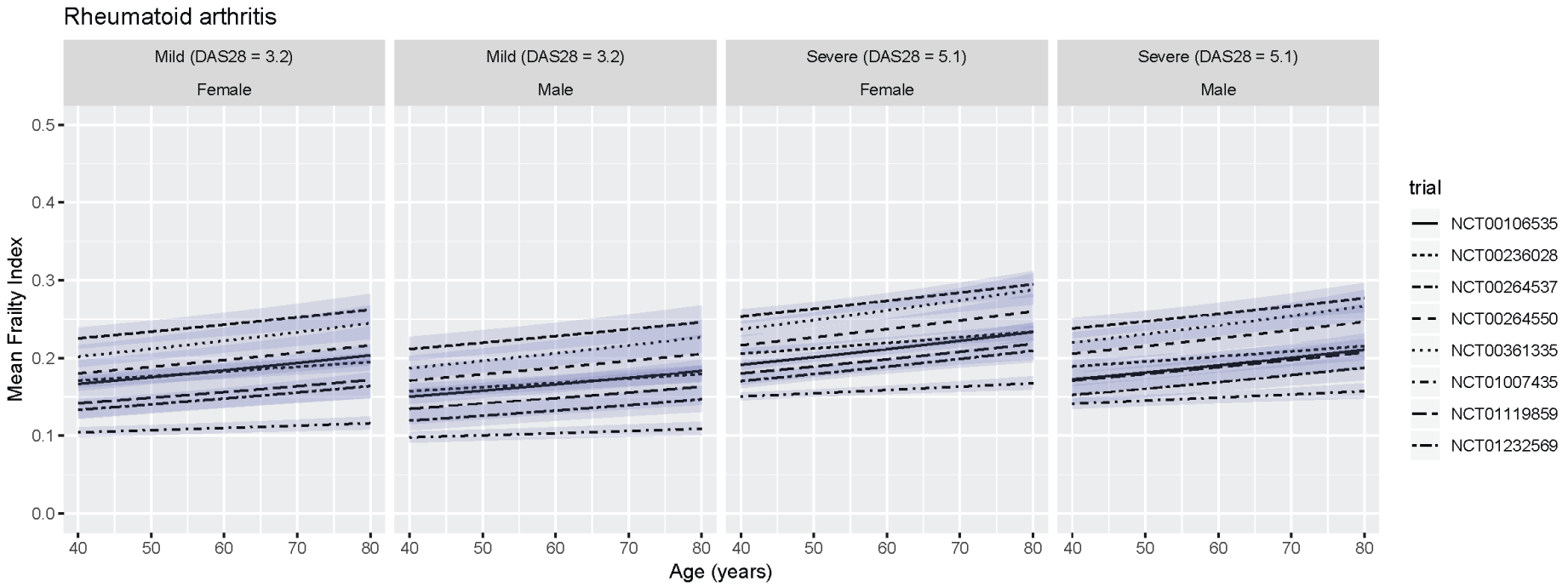

Figure 10.6 - Relationship between age, sex, disease severity and frailty index - Rheumatoid arthritis

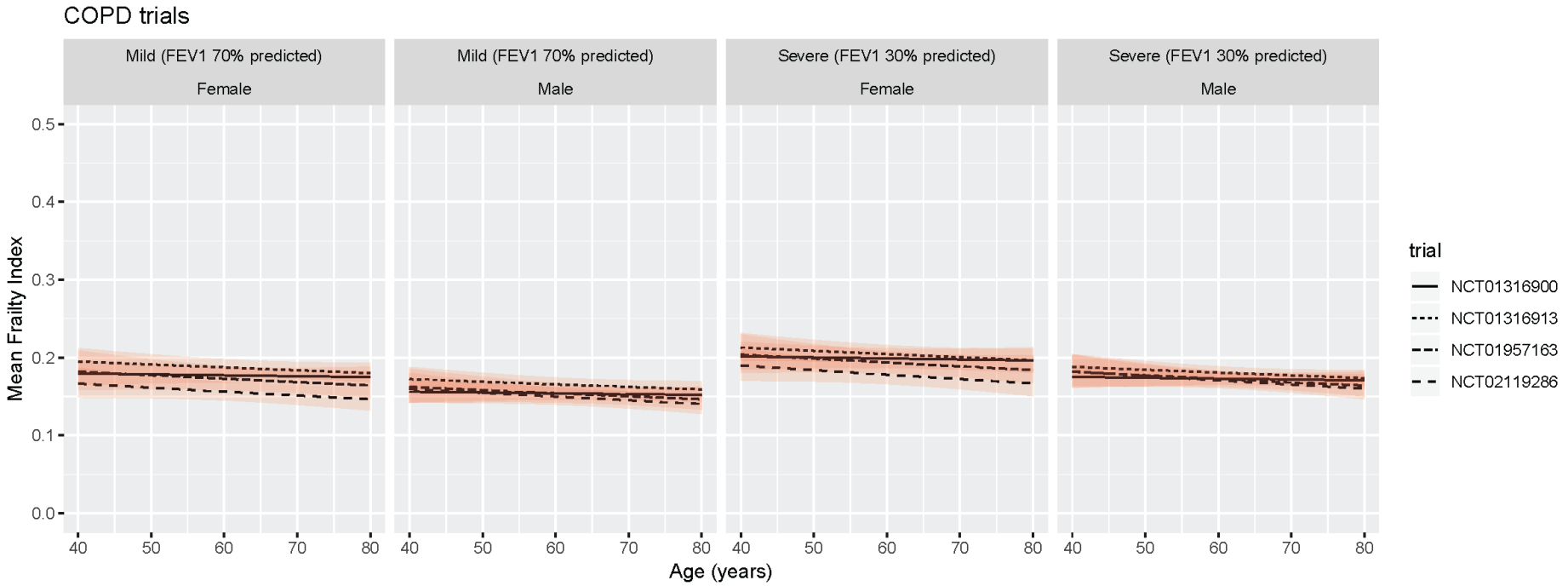

Figure 10.7 - Relationship between age, sex, disease severity and frailty index - COPD

10.5.4 Frailty index and Serious Adverse Events

The relationship between frailty index and the incidence of serious adverse events occurring during trial follow-up is summarised in Figure 10.8. When the trials within each condition were meta-analysed, a 0.1-point increment in frailty index at baseline was associated with a higher serious adverse event rate for all conditions (IRR 1.46 (95% CI 1.21-1.75) for T2DM, 1.45 (1.13-1.87) for RA, and 1.99 (1.43-2.76) for COPD). Heterogeneity between trials was high for RA, but low for T2DM and COPD. The full model outputs for each trial are shown in supplementary appendix 7. Therefore, for each condition, after adjusting for age, sex and disease severity, frailty index at baseline predicted subsequent serious adverse events.

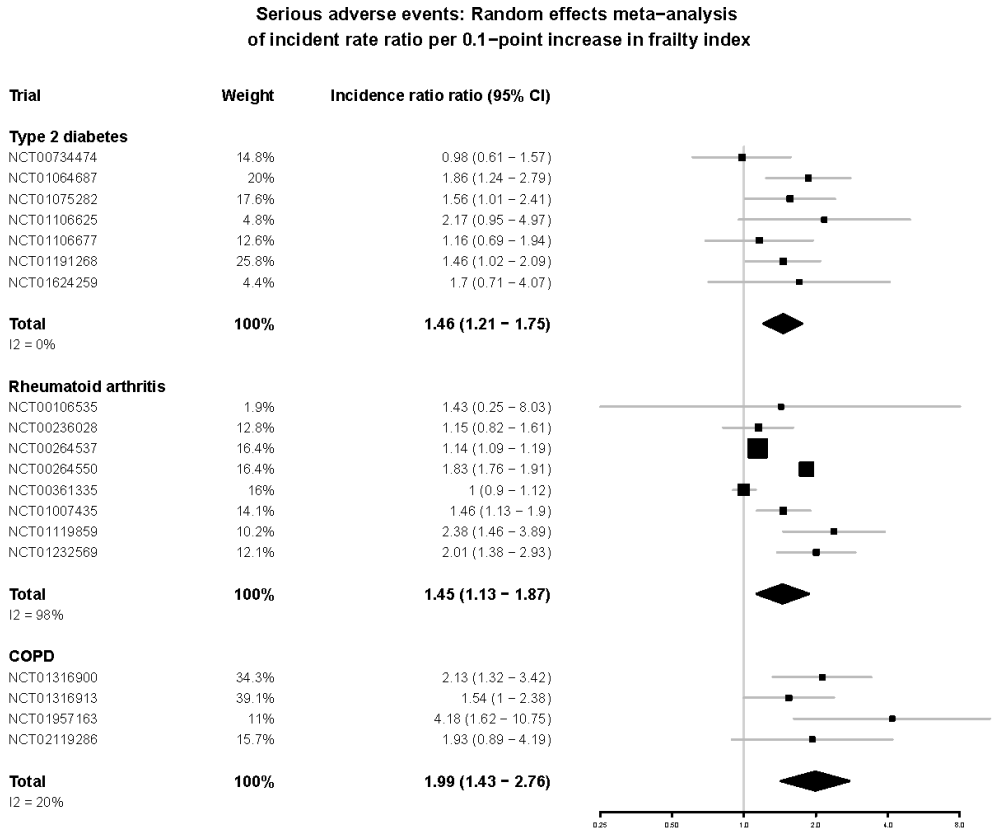

Figure 10.8 - Random-effects meta-analysis of incidence rate ratio of serious adverse events per 0.1 point increase in frailty index

10.6 Discussion

10.6.1 Summary of findings

Using individual-level participant data for 19 trials for three common and important chronic conditions - all with a mean age of less than 65 years - we found that frailty was highly prevalent among trial participants. The frailty index showed the expected relationships with sex, age (apart from in COPD) and disease severity and identified trial participants at higher risk of serious adverse events.

10.6.2 In context of existing literature

Few studies have attempted to measure frailty across multiple clinical trials. To our knowledge, this is the first to include trials not specifically targeting older populations (with most participants aged <65 years), and the first to do so for T2DM, RA or COPD. Our findings that frailty can be identified in trials are consistent with two large hypertension trials, HYVET and SPRINT,[502,503] which focused on hypertension management in older people, and one heart failure trial in older people,[504] which showed that frailty was relatively common in these trials. We extend these findings by showing that frailty is relatively common in "standard" industry-funded phase 3 trials in younger populations, and that it is associated with baseline characteristics and that frailty at baseline predicts the risk of serious adverse events, even after adjusting for age, sex and the severity of the index condition.

The frailty index in our analysis showed similar properties to observational studies of frailty using the frailty index approach.[35,36,213] As expected, the frailty index had a skewed distribution, was higher in women than men and for RA and T2DM was associated with age. We have previously shown, using UK Biobank data, that frailty is identifiable in younger as well as older people,[9] and the current work shows that this is also true of trials.

While many of the characteristics of the frailty index in the trial data are consistent with studies of frailty using observational cohorts and administrative data,[133] the maximum frailty index in the trials (based on the 99th centile of the frailty index distribution) was lower than is typically seen in observational

studies.[217] Since this difference was also evident among trial participants aged over 65, it cannot solely be attributed to the younger age of the trial participants. The extent to which this difference is due to trial eligibility criteria[506,510] (e.g. comorbidities, renal function etc) or other selection pressures on trial participation (such as the need to be able to undergo multiple trial visits or procedures) is unknown. This suggests that our findings hold for the range of frailty index values we observed in these trials, which is narrower than that observed in unselected populations.

Importantly, while the very frailest patients were rarely included in the clinical trials, we found people with moderate to severely frailty – who make up the bulk of those with frailty in the community – were commonly included as participants in clinical trials, despite those trials involving younger people aged under 65 years. Many trials require high disease activity/severity as an inclusion criterion, which is one potential explanation for the high prevalence of frailty in some trials, particularly in conditions like RA where there is overlap between functional limitations resulting from active disease and deficits included in the frailty index.

It is notable that the frailty index in the COPD trials was not associated with increasing age, as would be expected. A similar phenomenon was also observed in both the SPRINT and TOPCAT trials (of hypertension and heart failure, respectively), whereby younger trial participants showed relatively higher frailty index values compared to relatively older trial participants.[503,504] These COPD trials (as well as previous trials showing similar associations) may suggest that to be included in the trial, older people with COPD tended to be relatively less frail than similarly aged people with COPD in the general population. This could arise due to the trial selection process,[511] as an example of collider bias, whereby conditioning on a subsequent outcome (trial inclusion) influences the relationship between causally proximal characteristics such as age and frailty.[392] We conducted exploratory analyses of the association between age and the St George Respiratory Questionnaire score and EQ5D as these are known to increase with age in unselected populations.[512,513] Like the frailty index, these were not associated with age in the COPD trials. Furthermore, the mean frailty index is lower in the COPD trials, and the range of frailty index values is narrower,

compared to the frailty index distribution in previous observational studies of frailty in COPD.[452] This supports our speculation that the unexpected relationship between age and frailty index in these trials reflects differences between the trial population and people in the community with the same condition.

Frailty index was moderately associated with disease severity in COPD and RA. It would have been surprising had there been no association, as functional limitation and frailty, acting across multiple organ systems, are a well-recognised consequence of both diseases.[402,508] Moreover, FEV1 has long been established as a marker of general physiological reserve as well as of lung disease. The fact that the correlation was not stronger is perhaps of greater interest as it suggests that factors other than the severity of the index disease are important drivers of frailty. Moreover, frailty index predicted adverse events independently of disease severity, indicating that the frailty index contains important clinical information about trial participants beyond-that captured by disease-severity measures alone, possibly related to the increasing prevalence of multimorbidity.

10.6.3 Strengths and limitations

A strength of our study is that we used a standard well-validated approach to measure frailty,[36] across a large number of trials and a range of conditions, allowing comparison of findings between trials and between conditions. Our analysis also has some important limitations, however. The trials included were not a random sample, but instead were selected from trials that sponsors have made available to third party researchers for secondary analyses. Not all sponsors share IPD, and those that do share data do not make all trials available. Of the trials we did access, not all trials had sufficient data to identify deficits for inclusion in a frailty index.

The data used to compile the frailty index were not collected for the purpose of identifying frailty, although this is true of most studies using the frailty index. Moreover, medical history data were redacted in most of the included trials, so we were therefore reliant on concomitant medication data to define long term condition count-based deficits. Consequently, some conditions could only be included as part of a broader group (e.g. cardiovascular disease, obstructive

airways disease) rather than as a specific condition, while other conditions (those without specific drug treatments) could not be included.[244] This restricts the number of conditions that could be included in our frailty index, and may result in an under-estimate of the number of conditions present (e.g. in people with multiple cardiovascular conditions which are counted as a single category, or with conditions such as chronic kidney disease such could not be identified using prescribed medications). Furthermore, we used existing instruments, primarily designed to characterise the index condition, to measure functional deficits of frailty (e.g. reduced mobility and difficulty with household tasks were identified using St George Respiratory Questionnaire in the context of COPD and using the Health Assessment Questionnaire Disability Index in RA). It may be that instruments designed specifically to measure frailty would have improved sensitivity or specificity. Despite these limitations, and especially compared with most administrative data sources, trial data benefits from a wide range of physiological, biochemical, haematological and functional measures. Moreover, given the regulatory conditions under which trials are conducted, these data were collected, recorded and processed according to exacting standards.

10.6.4 Implications

Current guidelines caution against the extrapolation of trial evidence to people living with frailty,[161,507] and clinicians lack high-quality evidence about the benefits and harms of common treatments for people living with frailty. Our findings demonstrate that it is feasible to measure frailty, using an established, validated method – the frailty index – in standard industry-funded drug trials, and that on doing so significant numbers of trial participants have mild to moderate frailty. As such, while such trials cannot be claimed to be representative of people with frailty, particularly those with severe frailty who were very rarely found to be present, trials nonetheless contain important under-used information to help address current evidence gaps.

We were able to identify frailty in trials only because we were able to access trial IPD, which is complex and time-consuming. Moreover, several trials redacted data (and, less often, did not collect sufficient data) to allow us to calculate a frailty index. Both to allow clinicians to assess the degree to which frailty is under-represented in particular trials, and to understand whether and

how treatment effects differ by frailty (realistically only feasible via meta-analysis of multiple trials), there is a need to expand existing trial conduct and reporting standards,[514] to include standard measures of frailty. Our findings suggest that frailty is sufficiently common in trials for this to be a worthwhile exercise.

To that end standard approaches to the collection and reporting of medical history data (to allow accurate assessment of comorbidities to be included in a frailty index) as well as measures specifically designed to assess frailty (e.g. the frailty phenotype) should be incorporated into international standards for the conduct of trials. Ideally, the adoption of complementary measures such as the frailty index and frailty phenotype measures should be considered. The frailty index can be applied to routinely collected trial data but is likely to be more influenced by multimorbidity (and in turn, trial inclusion criteria) while the frailty phenotype may identify trial participants with more explicitly defined physiological frailty, some of whom may not have multimorbidity. Given the well-resourced and rigorous measurement and reporting usual in well-conducted trials the adoption of standard measures of frailty across trials is highly feasible and would allow estimation of the impact of frailty on treatment effects both for individual trials, and for meta-analyses of multiple trials. It would also enable identification of participants with increased frailty who are at increased risk of more serious adverse events, who might benefit from closer monitoring.

10.6.5 Conclusion

Contrary to the prevailing view[161,500] frailty, albeit not the most severe frailty, is common and readily measurable among clinical trial participants. This includes trials of relatively young populations. We have shown that participants with increased frailty at baseline also experience more serious adverse events, suggesting that such patients might merit closer monitoring and that screening for frailty should be considered for addition to future Consort checklists. Future research should evaluate whether frailty in trials is associated with treatment effectiveness. Both existing and future drug trials have the potential to inform the management of individuals living with frailty. Trialists therefore can and should routinely measure and report frailty. However, to do so frailty needs to become a standard measure within trials. Ideally, this would include both standardised assessment of comorbidities and baseline functional status (from which a frailty index could be consistently constructed) as well as physiological measurements to assess the frailty phenotype. There is also a need for research specifically targeting people with severe frailty, who were rarely included in these trials, and for whom the risks and benefits of treatments are most uncertain. Given ageing population demographics as well as the presence of frailty among relatively younger people, such measures would be central to understanding how treatments should be applied to the growing numbers of people living with frailty.

Chapter 11 Discussion

11.1 Chapter summary

This chapter presents a discussion of the findings presented in chapters 4 to 10. First, a summary of the findings for each research question will be presented, followed by strengths and limitations of the work as a whole. The findings will be discussed in the context of previous literature, before outlining potential implications for clinical practice, health policy and research. Finally, directions for future research relating to the thesis topics will be presented.

11.2 Summary of findings

This thesis sought to address three main research questions using three exemplar conditions (type 2 diabetes mellitus, rheumatoid arthritis, and COPD):

1. To assess the prevalence of frailty in each of the three exemplar long-term conditions

2. To quantify the association between frailty and clinical outcomes relevant to each of the three conditions.

3. To assess the prevalence of frailty within randomised controlled trials for each of these conditions and explore the implications of frailty within trial settings.

For each condition, frailty was found to be common but with prevalence estimates that varied widely depending on frailty measure, age, and clinical setting. In all three conditions frailty prevalence increased with age but was nonetheless common in people aged under 65 years. Regardless of frailty definition or age, frailty was associated with an increased risk of generic (e.g. mortality, hospitalisation) and disease specific (e.g. hypoglycaemia, rheumatoid arthritis disease activity, COPD exacerbations) adverse clinical outcomes. Finally, frailty could be identified and was present in randomised controlled trials of drugs treatments for each of the three exemplar conditions. However, the upper limit of frailty in trials (assessed using the 99th centile of the frailty

index distribution) was lower than is consistently observed in community-based populations studies, suggesting that severe frailty is rare in clinical trials. Frailty in trials was associated with increased rates of serious adverse events. Therefore, for each of the three exemplar conditions, frailty is common across a wide age range, with clinically significant negative outcomes, and is present albeit under-represented in clinical trials.

A more detailed summary of each research question is presented below, before considering the strengths and limitations, context, and implications of these findings.

11.2.1 Research question 1: What is the prevalence of frailty in each of the exemplar long-term conditions

Research question 1 was addressed through systematic reviews of observational studies. The literature was more mature for type 2 diabetes (118 included studies) and, to a lesser extent, COPD (56 included studies) than for rheumatoid arthritis (17 included studies). A few observations were common to each long-term condition, but there were also some important points of difference:

- Estimates of frailty prevalence varied considerably by frailty measure used (often lower in studies using the frailty phenotype than for other measures), age of study participants (with higher prevalence in older populations, but with frailty still identifiable in younger populations below the age of 65), and study setting (where community prevalence was lower than many outpatient-based studies, which in turn were lower than studies based in inpatient settings or residential care).

- In rheumatoid arthritis and COPD, frailty was more common among people with more severe or active disease. However, the relationship between glycaemia and frailty in type 2 diabetes inconsistent.

- For each exemplar condition, available prevalence estimates were almost exclusively from high-income or upper-middle income countries. There was also little examination in the existing literature for these conditions of how prevalence varies by factors such as

ethnicity or socioeconomic status, despite these factors being important determinants of prevalence at the population-level.

- Finally, our analysis of SERA demonstrated that estimates of frailty prevalence in rheumatoid arthritis are likely to be higher in those with active disease, but that frailty in this context may be, at least partly, reversible. This confirms that frailty is a dynamic process that may be responsive to intervention. Type 2 diabetes in general, and specifically higher HbA1c, were associated with incident frailty and with worsening frailty status. Frequent COPD exacerbations were also associated with worsening frailty, however successful completion of pulmonary rehabilitation appeared to lead to marked improvements in frailty status. Therefore, while frailty is indeed common in type 2 diabetes, rheumatoid arthritis and COPD, each of these conditions may also influence the dynamics and potential reversibility of frailty.

11.2.2 Findings for research question 2: Frailty and disease outcomes

Across each exemplar condition frailty was associated with a range of adverse outcomes; this included generic outcomes such as mortality and hospitalisation as well as disease-specific outcomes such as MACE, falls, and hypoglycaemia in type 2 diabetes, disease activity in rheumatoid arthritis, and MACE and acute exacerbations in COPD. For each of the three conditions, frailty was associated with all the adverse outcomes examined in the UK Biobank and SERA analyses, indicating that frailty identified individuals at increased risk of a broad range of outcomes. This pattern was also consistent irrespective of whether frailty was measured using the frailty phenotype or frailty index. The systematic reviews, in general, showed a similar pattern of consistent associations between frailty and a diverse range of adverse outcomes regardless of frailty definition.

While this general relationship between frailty and a range of adverse outcomes is not surprising, there were some specific features identified for each of the conditions that are relevant to clinical management:

- *Type 2 diabetes:* The absolute risk of adverse outcomes associated with frailty (which underpin current guideline recommendations about glycaemic control) differ in younger people compared to older people. For example, a given degree of frailty carries a much lower absolute risk of death at age 50 compared to age 70. Current frailty-related recommendations may not be directly transferable to 'younger-frail' people, as many of these recommendations are explicitly based on limited life expectancy in the context of frailty.

- *Rheumatoid arthritis:* Frailty is dynamic and at least partially reversible in people with early rheumatoid arthritis. Nonetheless, it is associated with adverse outcomes such as mortality and hospital admission even after adjustment for disease severity.

- *COPD:* Frailty is associated with a wide range of adverse outcomes including mortality, hospital admission, MACE and COPD exacerbations. In each case this relationship was independent of the severity of airflow limitation.

Overall, frailty was associated with disease-specific outcomes (e.g. hypoglycaemia in diabetes and acute exacerbations of COPD) as well as generic outcomes (e.g., mortality and hospitalisation). This has implications for the application of investigations and specific treatment for people with frailty, as discussed below.

11.2.3 Findings for research question 3: Prevalence and implications of frailty in clinical trials

The prevalence and implications of frailty in randomised controlled trials for pharmacological agents for each of the exemplar conditions, was answered via a secondary analysis of clinical trials where individual-level participant data was available. The findings showed that frailty is rarely explicitly measured in randomised controlled trials but can sometimes be retrospectively assessed using the frailty index approach. For 19 of 39 trials where we had access to IPD the frailty index could not be calculated because the trials either did not collect or else redacted data on participant's level of function. In those 19 trials for which

frailty could be assessed, moderate frailty was common within trial populations, albeit not as common as seen in general population studies. Frailty in trials was also associated with serious adverse events, indicating that it is a clinically important state even in the trial setting, where participants are believed to be generally healthier than other people with the same index conditions. In summary, frailty can be measured in existing randomised controlled trials with access to individual participant data, and moderate frailty is common and associated with clinically significant adverse outcomes. These findings indicate that frailty can be identified in clinical trials and that better recording and reporting of some parameters (e.g. comorbidities or functional limitation) could allow widespread estimation of frailty within clinical trials. This would allow assessment of trial representativeness in terms of frailty as well as analysis of how treatment decisions might be tailored to people living with frailty (e.g. by estimating whether treatment efficacy differs depending on frailty status, or whether frailty is associated with treatment-related harm).

11.2.4 Similarities and differences between conditions

The findings for each of the three conditions examined were consistent in many ways. First, within the published literature, frailty was identified using a wide range of measures in each condition, with the frailty phenotype being the most frequently used in each. Prevalence estimates were highly variable in each condition. Also, in the observational analyses, frailty was associated with mortality and hospitalisation in each condition, as well as with a range of 'disease-specific' clinical outcomes. Therefore, across all conditions examined, frailty was associated with a wide range of adverse outcomes including those related to the index condition.

There were also some differences in the findings between the conditions. First, frailty was associated with more severe or active disease in rheumatoid arthritis (based on DAS-28) and COPD (based on FEV1), however in diabetes there was inconsistency in the relationship between HbA1c and frailty. Both the UK Biobank analyses, and the analyses of trial data showed no overall association between frailty and HbA1c, and the published literature identified showed an inconsistent and often null relationship within the wider literature. Secondly, while there was evidence from the published literature of potential for

improvement in frailty status within all three conditions, for type 2 diabetes and for COPD frailty tended to worsen over time for most participants in most published studies which examined trajectories. This is in contrast to the findings relating to frailty in early rheumatoid arthritis from the SERA cohort, in which frailty improved following treatment of early active rheumatoid arthritis for a large proportion of participants. Finally, within the trial data, the distribution of frailty was similar in trials of the same index condition but differed between each condition examined. Participants of trials for rheumatoid arthritis had the highest mean frailty index values, which may reflect the relationship with high disease activity which was observed across the trial and SERA analyses.

11.3 Strengths and limitations

There are several strengths and weaknesses to the work presented in this thesis, many of which are summarised in the discussion sections of the respective manuscripts in chapters 4 to 10. This section presents a summary of the main strengths and weaknesses of this body of work as a whole, before providing more detailed discussion of two issues which are particularly pertinent to the weaknesses of this work. These are adaptation of frailty criteria, and the issue of selection bias.

General strengths of this work include:

- All analyses were prespecified. All three systematic reviews were conducted according to registered protocols and all secondary analyses followed analysis plans that pre-specified the population of interest, definition of exposures and outcomes, and approaches to statistical modelling.

- All analyses are reproducible with detailed search strategies, analysis syntax either provided as supplementary appendices to published papers or returned to UK Biobank for record. This supports an open research agenda in line with the principles of the Concordat on Open Research data.

- This thesis considers a broad range of frailty definitions, with no restriction on frailty definition placed on the systematic review eligibility criteria. Also, for UK Biobank, two contrasting models of frailty were used for all analyses. Given the differences between models of frailty outlined in the introduction and literature review, and the lack of consensus as to the best model with which to analyse frailty, it is important to allow comparison between different models where possible.

- The large sample size of UK Biobank allowed for a larger analytical sample than many disease-specific studies of frailty (as illustrated by the included studies in the systematic reviews, many of which were considerably smaller than the analyses presented within this thesis). Furthermore, there were low levels of missing data for frailty measures (<5%) and for covariates in the adjusted models (<3%). Complete case analysis was therefore used for all models.

- The focus on frailty in relatively younger populations (with many participants aged <65 years) is a strength as frailty in these populations is less well understood and has been recognised as an important gap in the literature. Similarly, relatively few studies have quantified frailty in clinical trials. These analyses are therefore novel and important addressing key gaps within the frailty literature.

Weaknesses relevant to this body of work include:

- Frailty definitions had to be adapted from their original description. This adaptation is described in detail in chapter 3 with discussion of its implications in the section below.

- Many of the findings are based on samples that are not representative. For example, UK Biobank is not a representative sample of the UK population. Specifically, UK Biobank participants are more affluent, more likely to be of white ethnicity, and have fewer long-term health conditions, than the UK population overall. Many of the studies included in the systematic reviews were also based on unrepresentative study populations. Finally, the trials in which the frailty index was calculated

using individual participant data were not a random or representative sample of the wider body of randomised controlled trials. These selected or unrepresentative samples can lead to biased results. This is discussed in greater detail below.

- For the observational analyses, linked healthcare data were used to identify outcomes. While this can give reliable and complete estimates for some outcomes (e.g. mortality or major adverse cardiovascular events) for other outcomes (e.g. hypoglycaemia or falls) it may have led to under-identification of outcomes.

- For all systematic reviews, only studies published in English were included. This was due to lack of resource for study translation and could have led to biased exclusion of studies published in other languages. However, very few studies were excluded based on language alone.

11.3.1 Adaptation of frailty criteria

In all analyses presented in this thesis, the measures used to identify and quantify frailty were adapted from the original descriptions. In the case of the frailty index, selecting deficits from the available data is standard practice.[36] This is not the case for the frailty phenotype, which is based on five pre-specified domains.[5] Despite this, most studies implementing the frailty phenotype have made some adaptation to the original Cardiovascular Health Study specification of each variable.[200] The way that either the frailty phenotype or the frailty index is specified is likely to influence the results of any given analysis.[200,515] The adaptation of either definition to the datasets used in this thesis is therefore likely to have influenced estimates of frailty prevalence.

The frailty phenotype was estimated using data from UK Biobank. Doing so has advantages as the frailty phenotype was shown in chapters 4, 6 and 8 to be the most commonly used measure within the existing literature for each of the exemplar conditions (and therefore use of this approach aids comparison with previous findings). It also utilises objective measurements in the form of grip strength. However, as is outlined in detail in the methods overview, the criteria used to identify weight loss, walking speed, exhaustion and low physical activity

were different from the original Cardiovascular Health Study definition.[5,9] Perhaps most notably, weight loss in the original definition was specified as being unintentional, whereas in the UK Biobank assessment centre participants were simply asked if they had lost weight. This broader definition of weight loss may not be as reliable an indicator of frailty as 'unintentional weight loss',[5] particularly when applied to a relatively younger population such as UK Biobank.[9] Furthermore, not all the included variables increase in prevalence with age within the range included in UK Biobank.[9] Despite this, each of the five variables included in the frailty phenotype are independently associated with mortality in the UK Biobank cohort as a whole.[9] Also, when used in combination, the prevalence of frailty in the whole cohort rises with age as expected. Therefore, while this adaptation cannot be assumed to fully reflect the original description of the frailty phenotype, and caution is required when inferring frailty from some specific aspect of the phenotype at an individual level, the UK Biobank adaptation exhibits the properties expected of a valid frailty measure.[9]

Adaptation of the frailty phenotype to available data sources is not unusual.[200] For example, among the 69 studies using the frailty phenotype in the systematic review of type 2 diabetes, 51 (74%) used an adaptation of the original description. The impact of adapting the frailty phenotype criteria has been explored in detail by Theou and colleagues.[200] They identified 262 different adaptations of the frailty phenotype from the published literature. Differences included number of criteria used (with some authors using only 4 of the 5 measures due to lack of available data), use of self-reported versus measured assessment of deficits (as was the case for walking speed and weight loss in UK Biobank), procedures for handling missing data (including complete case analysis and various approaches to imputation). The authors then implemented 262 different adaptations of the frailty phenotype to the Survey for Health, Ageing and Retirement in Europe. Within this dataset, prevalence of frailty ranged from 12.7% to 28.2% depending on the adaptation. Other properties, such as gender differences in prevalence and predictive ability for mortality, also differed between various adaptations of the frailty phenotype.[200] This indicates two important limitations for the analyses presented in this thesis. First is that the decisions made on how to specify the frailty phenotype (some based on the availability of data) are likely to have impacted on the findings themselves.

Secondly, as many of these decisions were based on the availability of data it is not possible to directly assess what impact these adaptations will have had. This should lead to caution, particularly when considering how best to apply findings such as prevalence estimates from UK Biobank.

Unlike the frailty phenotype the frailty index is designed to be defined using a diverse set of available data.[36] Nonetheless, both the available data and decisions about how it should be operationalised into a frailty index are likely to have had some impact on the overall findings of the analyses. Searle and colleagues, in describing the standard approach to constructing a frailty index, argue that a frailty index is valid providing it contains enough deficits (typically at least 30) meeting the defined criteria for inclusion in a frailty index (discussed in detail in the methods section).[36] In this thesis, for the randomised controlled trials data and for SERA, each included variable was assessed either empirically or with reference to previous literature to ensure that these criteria were met prior to inclusion in the index. For UK Biobank, a previously published frailty index was used in which the included deficits were selecting according to these criteria.[22] While this implies that each of the respective applications of the frailty index included in this thesis should be valid according to the established methodology of the frailty index, the available data and the way it is handled may still influence the findings themselves.[515]

One example of how the nature of the available data may influence the properties of a frailty index is in comparing self-reported with measured deficits. This issue was explored using data from The Irish Longitudinal Study of Ageing (TILDA).[515] Theou and colleagues used the standard frailty index approach to construct three separate frailty indices; one based on solely self-reported deficits, one on solely test-based measures, and one which combined the two. The authors found that while all three measures had the properties expected of a frailty index (e.g. right-skewed distribution, increase with age, and relationship with adverse health outcomes) the mean frailty index value was higher in the index using test-based measures (mean 0.17) than in the combined (mean 0.14) or self-reported (mean 0.12).[515] This implies that while each of these frailty indices may be ‘valid’ in terms of the method of their construction and their statistical properties, the generalizability of a given frailty index may

be limited by the variables that are included. Put another way, it may not be possible to accurately compare the prevalence of frailty between different study populations when the nature of the variables used to construct the frailty index differs between the studies.

This sensitivity of the frailty index to the type of variables included has implications for the interpretation of the findings of this thesis. For example, the frailty index constructed for clinical trials was limited by the redaction of medical history data. As a proxy, it was necessary to use concomitant medication data to approximate the presence of comorbidities for the frailty index. Similarly, the frailty indices in UK Biobank and SERA were based on a different list of deficits, with more functional measures used in SERA. This therefore limits the comparison of frailty prevalence between the two datasets.

11.3.2 Selection bias and risk of collider bias

As mentioned above, UK Biobank is not representative of the wider UK population, with participants being on average more affluent, having fewer long-term conditions, and being more likely to be of white ethnicity.[223] This has two important implications for the findings of this thesis. First, estimates of frailty prevalence derived from UK Biobank cannot be assumed to apply to the wider UK population, even within the age-range studied. Due to the previously described 'healthy volunteer bias', prevalence estimates from UK Biobank are likely to be conservative. The second issue is that, in the presence of selection bias such as this, estimates of the association between exposures (in this case frailty) and outcomes may be subject to collider bias.[516] This has the potential to influence the magnitude and direction of associations observed when conducting analyses in datasets subject to selection bias.[228,516]

A collider is a variable that is causally influenced by two or more other variables.[516] Collider bias may occur when analyses are conducted conditioning on a collider. This can take many forms but may occur when there is selection bias within a dataset. For example, if a variable influencing recruitment into a study (e.g. socioeconomic status) also exerts a causal influence on exposures (e.g. frailty) and outcomes (e.g. mortality), then estimates of the association between these exposures and outcomes will be biased if conducted in this

selected sample. In other words, by analysing this selected sample we have conditioned on a collider. There are therefore concerns that analyses of UK Biobank may be influenced by collider bias.

Some have argued that UK Biobank may produce spurious or biased results because of collider bias.[228,516] Others have attempted to compare the magnitude of associations between exposures and outcomes in UK Biobank to similar associations in surveys with higher response rates (and likely, therefore, to be more representative).[220] Batty et al published one such analysis and argued that relative effect estimates for UK Biobank were comparable to those from national health surveys.[220] However, even in Batty and colleagues' paper, the magnitude of association between some risk factors and mortality were notably different between UK Biobank and more representative surveys.[220] This suggests that, at least for some variables, collider bias does influence magnitude of effect estimates derived from UK Biobank data.

While conducting the work presented in this thesis, I sought to explore this issue further by comparing effect estimates from UK Biobank to routine healthcare data from a representative sample. It was not possible to make this comparison with frailty, as comparable measures of frailty are not available within routine healthcare data, and so this analysis was based on multimorbidity. The results are not presented in this thesis, as the study is not directly focused on frailty, but are published elsewhere.[226] Compared to a representative sample from the Secure Anonymised Information Linkage (SAIL) databank, multimorbidity identified using routine primary care data was less common in UK Biobank. At all levels of multimorbidity, the absolute risk of death, hospitalisation, and major adverse cardiovascular events was lower in UK Biobank than in SAIL. When assessing the relative risk of these outcomes associated with multimorbidity, estimates from UK Biobank and SAIL were similar at lower levels of multimorbidity (3 conditions or fewer) but at higher levels (e.g. more than three conditions) UK Biobank gave more conservative estimates of the risk of adverse outcomes. Estimates for some specific conditions were similar (e.g. hypertension, cardiovascular disease) whereas for other conditions (e.g. mental health conditions or chronic pain) UK Biobank underestimated the risk of mortality.[226] While magnitude of associations differed between the two datasets,

for multimorbidity counts and for individual long-term conditions, the direction of effect was similar between UK Biobank and SAIL (i.e. all conditions that were associated with increased mortality risk in SAIL were also associated with increased risk in UK Biobank). While these analyses do not specifically assess frailty, they do suggest that estimates of absolute risk (as presented in chapter 5 for type 2 diabetes) are likely to be conservative. Furthermore, it is possible to speculate that the risks associated with more severe frailty may be underestimated in UK Biobank in a similar way to higher levels of multimorbidity. In summary, collider bias is likely to have influenced the magnitude of effect estimates from UK Biobank presented in this thesis, however it is also likely that these estimates are conservative in this case.

11.4 Findings in context of other literature

The literature contextualising the observational findings for each of the conditions (chapters 5, 7 and 9) are summarised in their respective discussion sections, as well as expanded more fully in their accompanying systematic reviews (chapters 4, 6 and 8). The literature on the identification of frailty in trials is summarised in the discussion section of chapter 10. The text that follows here seeks to place the work within the context of the wider frailty literature, specifically highlighting work on the agreement between frailty definitions, and the emerging literature on trajectories of frailty over time.

11.4.1 Agreement between frailty measures

Findings for all three exemplar conditions demonstrated only partial overlap between the frailty index and frailty phenotype definitions. Discordance between frailty definitions is well recognised and has been described previously in unselected population-based studies.[38,39,288] This has led to differences of opinion as to the importance of this lack of agreement,[1,2,517] and the appropriateness of each of the respective frailty measures to identify people living with frailty.

In general, despite differences in frailty classification at the individual level, both the frailty phenotype and frailty index have consistently identified groups of individuals at increased risk of adverse outcomes.[28,53] Some advocate frailty

screening using either the frailty phenotype (or its derivatives) or the frailty index, arguing that either measure may adequately achieve the aim of risk stratifying a population in terms of frailty.[517] Others caution against the use of different tools to identify frailty when there may be clinically important differences between individuals identified as frail by different instruments, particularly when these differences are often poorly understood.[518]

A comparison of individual-level characteristics associated with discordance in frailty by either the frailty phenotype or frailty index showed greater discordance in younger people. Agreement was higher among the oldest participants (>80 years) with significant functional impairment or disability and many long-term conditions.[518] Some may argue, therefore, that where frailty is most marked and clinically obvious (e.g., with high multimorbidity combined with functional impairment) frailty measures are more likely to agree. However, it also suggests there may be clinically important subgroups of people living with frailty who may only be identified by some frailty measures (e.g. when frailty is characterised by cognitive impairment).[518] The clinical utility of frailty identification will depend on what subset of people are identified, and their specific characteristics. For example, some people identified by a frailty index (which may, for example, identify some people with cognitive frailty but fewer physical deficits) may merit a different clinical response to people with greater physical frailty and no cognitive impairment.

11.4.2 Changes in frailty over time

There is a growing body of literature assessing the trajectories of frailty. The findings for rheumatoid arthritis in this thesis based on SERA showed change in individual frailty index values over 2-years follow-up following initial diagnosis of rheumatoid arthritis, with an overall reduction in frailty at the group level. While the UK Biobank analyses in this thesis for type 2 diabetes and COPD only measured frailty at a single time-point, the systematic reviews identified some studies demonstrating individual-level change in frailty status, including improvement in some people with type 2 diabetes and COPD.

These findings relate to a broader literature assessing frailty trajectories in the population in general. Several studies using Generalised Estimating Equations

(which estimate population change over time) have shown that frailty, on average, progresses over time when quantified using a frailty index.[128,519,520] Other investigators have used random effects models to demonstrate acceleration of the accumulation of deficits over time, as well as exploring heterogeneity in the rate of deficit accumulation. There are indications that there is considerable between-person heterogeneity in frailty trajectories.[521] Some studies have sought to explore factors associated with specific trajectories or with fluctuations in the accumulation of deficits.[10] Fluctuations appear to increase with age, highlighting that the rate of frailty progression is not constant and may be subject to change.[522] Women, and people living in areas of higher socioeconomic deprivation, also appear to experience greater fluctuations in frailty status.[522] Changes in frailty status also appear to predict mortality more accurately than a single assessment of frailty.[212]

While these previous studies describe an overall trend of worsening frailty over time, albeit with individual-level differences, there are also a small number of studies indicating improvements in frailty. A systematic review, with searches conducted in 2018, identified 13 studies exploring factors associated with improvements in frailty status. These included younger age and never smoking. An absence of certain conditions, including diabetes, COPD and stroke, was also associated with greater probability of frailty improvement.[523] More recently, a study based in South Korea demonstrated that greater participation in social activities (defined as the number of different activities in which a person regularly participates) was associated with improvement in frailty status assessed by the FRAIL scale.[524]

The findings presented in this thesis add to this literature by presenting trends in frailty in early, active rheumatoid arthritis. This is clearly a more ‘selected’ population than the previous studies that have explored factors associated with frailty trajectories in general. However, the overall trend towards improvement indicates there are likely to be ‘special cases’, such as active rheumatoid arthritis, where frailty has the potential to follow a different trajectory than the population average. The broader challenge, therefore, is to identify what individual characteristics may be associated with potential for frailty

improvement, and to what extent these may be modifiable. This would be important to inform individualised responses to frailty.

11.5 Implications

11.5.1 Clinical implications

11.5.1.1 Frailty common in each condition and in settings not previously considered

Each of the chapters 4 to 9 makes the point that frailty should inform the management of the exemplar long-term conditions. The findings also highlight that the appropriate response to frailty should be tailored to the clinical context and underlying long-term condition. For example, this may include identifying reversible factors (such as active rheumatoid arthritis) or interventions with the potential to improve both frailty status and the underlying condition (e.g. pulmonary rehabilitation). The implications of frailty, when it is identified, may vary depending on the specific underlying long-term condition or clinical context. There is also a need to understand how interactions between multiple long-term conditions, and their respective treatments, may influence frailty and the individual more generally.

All three of the systematic reviews demonstrate that frailty, however measured, is common in each of the three long-term conditions. Furthermore, the analyses presented in chapters 5, 7 and 9, along with the analyses of trial data in chapter 10, demonstrate that this prevalence is not limited to older people. Proactive identification of frailty therefore has potential to be integrated into the routine management of these conditions and would be likely to identify many individuals at potentially increased risk of adverse clinical outcomes. This may therefore offer potential opportunities for intervention.

There are also uncertainties that remain, many of which are highlighted by the findings presented here.

- While frailty may be present and identifiable in younger people, the appropriate clinical response to frailty in younger age groups has not been widely studied. The considerably lower absolute risk of adverse outcomes

shown in the analysis of type 2 diabetes implies that recommendations based on older people living with frailty are not directly transferable to younger populations. Further research is needed to evaluate the appropriate clinical response to frailty in younger age groups, such as identifying reversible factors or understanding if frailty impacts the efficacy of treatment or increases susceptibility to treatment-related harms. In addition, there is a need to explore wider issues such as acceptability of the concept of frailty to patients and the views of healthcare professionals around frailty when applied to younger patients.

- In certain settings, frailty prevalence may be very high. For example, in hospital in-patients with COPD, frailty prevalence was frequently greater than 50%. The prevalence of moderate frailty was also notably high in clinical trials of rheumatoid arthritis, perhaps reflecting trial eligibility criteria requiring active rheumatoid arthritis. Two important implications follow: (i) when such a high proportion of individuals are identified as living with frailty, there is likely to be considerable heterogeneity within that population. Taking in-patients with COPD as an example, within the high proportion living with frailty there is likely to be variation in age and severity of COPD (both of which may independently influence prognosis); the presence of other underlying long-term conditions (such as cardiovascular disease, musculoskeletal disorders, or mental health problems, each of which may impact differently on treatment priorities); extent of functional limitation; and degree of social support. Appropriate responses to frailty are likely to differ between individuals within similar contexts, emphasising the importance of tailoring care to individuals living with frailty. (ii) The common drivers of frailty may well differ between clinical contexts (i.e. the factors leading to frailty in people with active rheumatoid arthritis may be quite different to those in people hospitalised with COPD and will also vary between individuals in each of these contexts). The apparent improvement in frailty status with treatment of active rheumatoid arthritis (chapter 8) and potential responsiveness of frailty to interventions such as pulmonary rehabilitation (chapter 9) implies that considering the factors leading to frailty, and their potential reversibility, may lead to opportunities for intervention.

- Finally, the high prevalence of frailty in some conditions and clinical contexts means that there will likely be considerable resource required to adequately respond to frailty if it is identified. Identifying frailty is likely to have very limited value or impact if it is not followed by appropriate individualised clinical assessment and response.

11.5.1.2 Relationship between frailty and disease specific outcomes may help inform management

The common findings across each of the chapters is that frailty is associated with increased risk of a wide range of adverse clinical outcomes. This includes outcomes such as mortality and hospital admission as well as disease specific outcomes such as hypoglycaemia in type 2 diabetes or acute exacerbations of COPD. This lack of specificity in the risks associated with frailty may present challenges when considering the most appropriate clinical response. On one hand, the greater risk of hypoglycaemia or falls may increase the risks associated with aggressive treatment (reflected in the rationale for higher HbA1c targets in older people with frailty in type 2 diabetes). Conversely, people living with frailty may have potentially more to gain from optimal treatment of some conditions (e.g. reducing cardiovascular risk in people with type 2 diabetes). Any treatment decision must balance risks and benefits, and the outcomes associated with frailty are often spread across both sides of the risk/benefit calculation. It is unlikely, therefore, that there is any single recommendation that can be made that will apply to all people living with frailty in any of the exemplar long-term conditions. Rather, the implications of frailty should be considered at the level of the individual patient. Patient priorities and shared decision making are central to making these judgements, and the observed associations described in this thesis may inform, but should not dictate, these interactions.

11.5.1.3 Caution in applying trial evidence to people with severe frailty

The final clinical implications of this work stem from the observation that people at the most severe end of the frailty spectrum appear to be excluded from many clinical trials. This creates uncertainty as to the applicability of trial recommendations to these people. Under-representativeness of frailty may limit applicability of trial evidence in several ways:

- *Heterogeneity in treatment effects*: It is possible that the efficacy of treatments may differ in people living with frailty. For example, this could occur if the physiological changes associated with frailty altered the pharmacokinetics or pharmacodynamics of a given treatment.

- *Heterogeneity in treatment-related risk*: the increased susceptibility to adverse health outcomes and physiological decompensation may lead to an increased risk of adverse events related to a given treatment, which may not be identified from trials in which people living with frailty are under-represented.

- *Difference in net benefit*: Even if the relative efficacy of treatments is the same for people with frailty (i.e., no heterogeneity in treatment efficacy) and risks of treatment are similar, the net benefit of a treatment may still be different for people living with frailty. This could occur in either direction (i.e., net benefit could be increased or decreased). Where frailty increases the absolute risk of the event the treatment is trying to prevent (e.g., cardiovascular events in a diabetes trial) then the net benefit of a treatment may be greater for people living with frailty. Conversely, if frailty increases the risk of competing events (e.g., death from other causes) then the net benefit of a given treatment may be less. For this reason, understanding the relationship between frailty and a range of diverse outcomes (as this thesis seeks to explore) is an important starting point when beginning to weigh up potential net benefits of treatments for people living with frailty.

- *Differences in treatment burden:* Even if quantification of treatment effects and event rates suggests treatments may be beneficial for people living with frailty, the associated functional limitations and risk of decompensation may mean that the impact of a given treatment on a person's experience of chronic illness may still be greater for people living with frailty. Multiple treatments may increase treatment burden (the effort and work required for a person to take on the tasks associated with managing their long-term health condition).[525] If trials are under-

representative of frailty, trial evidence may not reflect this increased burden placed upon patients.

This lack of trial representativeness is not a new concern. For example, the NICE multimorbidity guideline cautions against the application of disease-specific clinical guidelines to people with multimorbidity on the grounds that many trials are not representative.[162] However, despite these concerns, judging trial representativeness is challenging as trials generally do not report characteristics such as frailty or multimorbidity. Our findings suggest that severe frailty is generally lacking from trial populations. However, for many trials, it remains difficult to judge this representativeness. More standard reporting of measures such as comorbidity, as well as specific collection of data relating to frailty, would greatly improve our ability to assess trial representativeness in terms of frailty. However, as discussed above, variation in how frailty is measured and how these measures are applied may also influence prevalence estimates.

11.5.2 Policy implications

There are three main implications of the research findings which are relevant for health policy. These stem from the core finding shared across each of the exemplar conditions, that frailty is identifiable and has clinically significant implications in younger as well as older people. These implications include:

- **Research question 1 – frailty prevalence:** In each condition frailty was present in people aged <65, most commonly in people living in areas of high socioeconomic deprivation. The identification of frailty in younger populations has implications for prevention. There is a need for health policy addressing modifiable risk factors for frailty to address, rather than exacerbate, existing health inequalities. Risk factors tend to cluster within individuals and particularly within areas of high socioeconomic deprivation. Furthermore, data from the Whitehall II cohort suggests that social inequalities are associated with increased risk of developing frailty. However, the relationship between inequalities and mortality was no longer evident once frailty had developed.[12] Therefore, approaches to mitigate the impact of frailty at younger ages need to address primary prevention. If such approaches are to reduce, rather than exacerbate,

health inequalities they must address upstream determinants of poor health and acknowledge the burden placed on individuals who may face multiple potential targets for behaviour change.[526]

- **Research question 2 – frailty and clinical outcomes:** Frailty, as expected, was associated with a range of adverse outcomes. However, the findings that frailty changes within individuals, and is reversible in certain circumstances, has implications for system-level responses to frailty. Current policy priorities (such as anticipatory care planning), while clearly important for many people living with frailty, may not be the optimal or most appropriate initial response to frailty, particularly in younger people. Taking type 2 diabetes as an example, among younger people with frailty absolute 10-year mortality risk was considerably lower than in older people living with frailty, however risks associated with uncontrolled hyperglycaemia appeared greater in the context of frailty. In this context, some people may benefit more from assessment of risk factors and interventions aiming to optimise diabetes management. Some people in such a situation may not agree with an emphasis on anticipatory care planning. Therefore, policy around frailty should include sufficient flexibility to allow judgement to be applied to the appropriate response to frailty when it is identified (particularly if frailty across a broad age spectrum is to be recognised and managed). These judgements may be influenced by individual patient priorities as well as factors such as age, underlying conditions, potential for reversibility, with no single factor dictating what is most appropriate for an individual.

- **Research question 3 – frailty in clinical trials:** Our findings that frailty was identifiable using individual participant data (where this was available) from trials not designed to assess frailty suggests that research funders and trial regulators could mandate the reporting of frailty within clinical trials. Some of the challenges faced in this analysis (such as having to rely on medication data to identify long-term conditions) also highlights a need to improve the reporting of characteristics (such as comorbidities) within clinical trials. Such changes to policies around trial

reporting could potentially improve assessments of the applicability of trial evidence to specific groups, such as people living with frailty.

Proactive identification of frailty is increasingly becoming part of healthcare policy recommendations.[517] The findings of this thesis present two main points of consideration for such policies: what patient groups should be prioritised for frailty assessment; and what is the intended purpose of frailty identification? Both questions have important implications for what resources are needed to support frailty assessment and what pathways need to be in place to facilitate appropriate response to frailty.

In England, currently, general practices are contractually required to identify frailty in people aged over 65. The findings of this thesis suggest that a strict age cut-off such as this may mean that younger people, particularly those with specific long-term conditions, may be living with frailty and but not be identified. Given the relationship between frailty and clinically important outcomes identified here, it may be appropriate for policy to reflect the possibility of frailty at younger ages. However, it does not necessarily follow that frailty should be proactively identified in all people regardless of age, or even in the context of specific long-term conditions. The lower prevalence means that there will be potentially significant opportunity cost in terms of resources required to identify individuals.

11.5.3 Implications for future research

While the findings of this thesis indicate that frailty is not uncommon in younger people with each of these conditions; the true prevalence among younger people is not yet clear. The main barrier from these analyses is the lack of a representative sample, given the limitations of UK Biobank discussed above. Therefore, studies of frailty in representative samples of each of these conditions would be necessary to provide a more reliable answer to the first research question of the prevalence of frailty in each of these long-term conditions. Ideally such studies would also explore how frailty prevalence varies by socioeconomic status and ethnicity, as these were notably absent from the literature identified in the systematic reviews and are characteristics on which UK Biobank is particularly under-representative. Given the marked socio-

economic gradient seen in the UK Biobank analyses, it is likely that the true impact of frailty in younger individual occurs in areas of highest socioeconomic deprivation. Therefore, the under-representation of these groups (or lack of detailed reporting) within frailty research is an important gap to be addressed.

The analyses relating to the relationship between frailty and adverse clinical outcomes demonstrated a diverse range of potential adverse outcomes. However, this was generally limited to those outcomes that could be identified through routine healthcare linkage. Future research would be required to gain a fuller understanding of the breadth and complexity of the consequences of frailty. This would include examining patient reported outcomes such as quality of life in greater depth, and ideally over longitudinal follow-up. The systematic reviews presented here demonstrated that few such analyses have been conducted in these conditions.

All the findings of this thesis were observational. While these can offer important insights that can inform clinical practice, they do not offer direct or definitive evidence as to the most appropriate clinical response to frailty in the context of these long-term conditions. For example, while the findings suggest that concerns about hypoglycaemia risk in people with frailty and type 2 diabetes may be well founded, we currently lack evidence from randomised controlled trials to inform the optimal treatment targets in people living with frailty. Similarly, the responsiveness of frailty in active rheumatoid arthritis (as suggested from the SERA analyses), or potential to improve frailty with pulmonary rehabilitation in COPD (from the systematic review findings) would be ideally evaluated further in randomised controlled trials. For some such questions, such as the response of the frailty index to treatment in rheumatoid arthritis, the findings using trial individual participant data suggest that some of this may be possible using data from existing trials and that designing future trials with measures of frailty is both feasible and desirable.

The findings relating to frailty in clinical trials, namely that frailty is rarely measured, often present, but under-represented within clinical trials, has several implications for future trials, trial conduct, and evidence synthesis:

- Frailty is likely to be present to some degree in most trials and is a marker of risk for Serious Adverse Events. People identified as living with frailty may therefore merit closer monitoring in trials.

- It is clearly feasible to recruit people with at least moderate frailty into standard randomised controlled trials. Given the current uncertainty over the applicability of guidelines recommendations to people living with frailty, and broader concerns about trial representativeness, recruitment of people living with frailty into trials should be facilitated and encouraged.

- Frailty can be measured within trials. This includes many existing trials, in which frailty may be estimable using a frailty index approach from previously collected data. However, given the complexities over frailty measurement, and the lack of direct comparability between frailty measures, it may also be possible and desirable to purposefully measure frailty at the point of trial recruitment.

- Trial exclusion criteria likely act as a barrier to recruitment of people with most severe frailty into trials. Uncertainty over optimal treatment approaches to people living with severe frailty is likely to require specific trials designed and targeted at the needs of this specific patient group.

- The presence of frailty within trials offers a possible opportunity to better inform the application of treatment recommendations to people living with frailty. Given their relatively small numbers, and the limitations of subgroup analyses, this would ideally require pooling of data from many trials. These findings show that when individual participant data is made available, frailty assessment is feasible. However, to meaningfully answer clinical questions, either wider data sharing or standardised reporting of frailty within trials would be required to allow sufficient statistical power to assess questions such as treatment efficacy within people living with frailty.

There is also a need to consider the potential unintended consequences of recommending frailty assessment, particularly in younger people. Frailty may well be seen as a pejorative or inappropriate term to many patients, or indeed to some healthcare professionals. While identifying frailty may have clinical utility in identifying individuals at increased risk of adverse outcomes, for whom individualised treatment approaches may be targeted, this is not the only possible response to perceived 'frailty'. These dilemmas highlight the need for a broad discussion, involving patients, clinicians, and policy makers, around the meaning and nature of frailty. Ideally this would be supported by research beyond the purely quantitative findings presented in this thesis.

11.6 Future directions

The findings shown demonstrate that existing models of frailty identify greater relative risks of adverse outcomes in each of the exemplar conditions and among at younger ages than are frequently studied. However, the clinical utility of applying this concept, particularly to younger patients, is not clear and needs further research. This is a broad question and requires a range of complementary methodologies. These include:

- *Research into the mechanisms underlying the development of frailty in younger ages*. Ideally this would be based on longitudinal data with long-term life-course follow-up (e.g., birth cohorts). The influence of genetic predisposition, environmental exposures, behavioural risk factors, biomarkers for frailty development, and the interaction between these factors are all potentially useful avenues for inquiry. While existing research has explored elements of each of these, cohorts in which frailty has been assessed so far have lacked the long-term life-course follow-up to assess these factors at an individual level.

- *Context-specific risk prediction.* Frailty is clearly associated with a range of adverse outcomes. However, the outcomes which are most relevant to predict, and which are most likely to influence care, may vary between clinical context and patient groups. Having identified associations with a range of adverse outcomes in three distinct long-term conditions, future work should explore what specific points in the patients' interactions with

the healthcare system would be most appropriate to identify frailty, what outcomes it would be most informative to predict, and what frailty model may be optimal for this purpose. There is also a need to assess the relationships between frailty and outcomes in other long-term conditions not considered in this thesis. Answering these questions will be important in the translation of frailty epidemiology into the routine management of specific long-term conditions.

- *Identifying frailty in trials*. Having demonstrated the feasibility of identifying frailty in trials at a large scale, next steps could explore how frailty identification could become more widespread and commonplace within trial conduct. The application of the frailty index to variables already collected routinely in many trials offers an attractive opportunity to make the quantification of frailty a 'standard' measure in trials of conditions where frailty is a relevant clinical indicator. Conversely, future work could explore what insights may emerge from applying alternative frailty models, such as the frailty phenotype, within clinical trials. This would require additional resource as well as broader acceptance of the relevance of frailty. As such, pilot work to assess additional frailty measures in trials for conditions in which frailty is highly relevant may be an appropriate next step. The findings presented in this thesis suggest that type 2 diabetes, rheumatoid arthritis, and COPD may all be potentially relevant exemplar conditions in which to explore this possibility.

- *Exploring patient and public understanding of frailty*. While the term frailty is in common usage, its meaning in this context is often quite different to the concept outlined in the scientific literature. A few studies have explored public attitudes to frailty in the context of aging more generally. However, particularly if the utility and appropriateness of frailty assessment in younger patients with multimorbidity and chronic disease is to be understood, a deeper appreciation of the public understanding of the term is required. There is a danger that frailty may be seen as a pejorative term, with negative connotations for patients and healthcare professionals. If frailty identification is to facilitate

individualisation of care, aiming to optimise risks and benefits and maximise function, this will need to go alongside a wider public discourse about the meaning of frailty and the intentions behind its identification.

- *Exploring professionals' and policymakers' understanding of frailty.* As with patients and the public, the attitudes of healthcare professionals and those involved in health policy to frailty, including its meaning and connotations, are important if insights about frailty are to be translated into healthcare delivery. In particular, appreciation of the potential reversibility of frailty may be lacking. Broad dialogue and engagement, including research bringing together diverse expertise and attitudes, will be important next steps going alongside expansion of our understanding of frailty.

11.7 Conclusion

Frailty is a complex and variably defined state which affects many people living with type 2 diabetes, rheumatoid arthritis and COPD. Frailty in each of these conditions does not just affect older people but can be identified in a substantial minority of people aged under 65 years. In each of these conditions, however, frailty status may change within an individual, most notably showing potential reversibility among people with early, active rheumatoid arthritis. Frailty is associated with a wide range of adverse outcomes in each of these conditions and assessing frailty may therefore help identify individuals at greatest risk.

The implications of frailty at the individual level may also vary with factors such as age and underlying long-term conditions. For example, in type 2 diabetes absolute risk of adverse outcomes such as mortality varied considerably with age as well as frailty status, meaning that optimal treatment strategies may differ between people with similar degrees of frailty at different ages. Potential reversibility was seen in all three conditions, but the mechanisms and appropriate interventions are likely to differ between underlying conditions. Overall these findings highlight the need for an individualised response to frailty that includes consideration of a wide range of possible risks and outcomes, seeks to identify reversible factors, and establishes patient priorities.

Finally, frailty is present but under-represented in randomised controlled trials for these conditions. Therefore, if trial evidence is to be harnessed to better inform judgements about how frailty should inform clinical management, trials will need to both recruit more people living with frailty and facilitate more widespread quantification of frailty in existing trials. These challenges notwithstanding, integrating frailty assessment into the routine management of many long-term conditions has the potential to inform targeted, individualised interventions aimed at optimising care.

Bibliography

1. Howlett SE, Rutenberg AD, Rockwood K. The degree of frailty as a translational measure of health in aging. *Nature Aging* 2021; **1**(8): 651-65.

2. Fried LP, Cohen AA, Xue Q-L, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. *Nature Aging* 2021; **1**(1): 36-46.

3. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *The Lancet* 2019; **394**(10206): 1365-75.

4. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. *European journal of internal medicine* 2016; **31**: 3-10.

5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2001; **56**(3): M146-M57.

6. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *The Scientific World Journal* 2001; **1**: 323-36.

7. O'Caoimh R, Sezgin D, O'Donovan MR, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. *Age and Ageing* 2020; **50**(1): 96-104.

8. Spiers GF, Kunonga TP, Hall A, et al. Measuring frailty in younger populations: a rapid review of evidence. *BMJ open* 2021; **11**(3): e047051.

9. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *The lancet Public Health* 2018; **3**(7): e323-e32.

10. Welstead M, Jenkins ND, Russ TC, Luciano M, Muniz-Terrera G. A Systematic review of frailty trajectories: their shape and influencing factors. *The Gerontologist* 2020. 61(8):e463-75.

11. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *The Lancet* 2019; **394**(10206): 1376-86.

12. Dugravot A, Fayosse A, Dumurgier J, et al. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: a 24-year follow-up of the Whitehall II cohort study. *Lancet Public Health* 2020; **5**(1): E42-E50.

13. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and multimorbidity: a systematic review and meta-analysis. *The Journals of Gerontology: Series A* 2019; **74**(5): 659-66.

14. Guthrie B, Thompson A, Dumbreck S, et al. Better guidelines for better care: accounting for multimorbidity in clinical guidelines–structured examination of exemplar guidelines and health economic modelling. NIHR Journals Library, Southampton (UK); 2017. PMID: 28459515.

15. Sinclair AJ, Rodriguez-Mañas L. Diabetes and frailty: two converging conditions? *Canadian journal of diabetes* 2016; **40**(1): 77-83.

16. Salaffi F, Farah S, Carlo MD. Frailty syndrome in musculoskeletal disorders: An emerging concept in rheumatology. *Acta Biomedica* 2020; **91**(2): 274-96.

17. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K. The relationship between COPD and frailty: a systematic review and meta-analysis of observational studies. *Chest* 2018; **154**(1): 21-40.

18. Sinclair AJ, Abdelhafiz AH, Forbes A, Munshi M. Evidence-based diabetes care for older people with Type 2 diabetes: a critical review. *Diabetic Medicine* 2019; **36**(4): 399-413.

19. Sinclair AJ, Abdelhafiz A, Dunning T, et al. An international position statement on the management of frailty in diabetes mellitus: summary of recommendations 2017. *The Journal of frailty & aging* 2018; **7**(1): 10-20.

20. Espinoza G, Maldonado G, Narvaez J, Guerrero R, Citera G, Rios C. Beyond Rheumatoid Arthritis Evaluation: What are We Missing? *Open access rheumatology : research and reviews* 2021; **13**: 45-55.

21. Bousquet J, Dinh-Xuan AT, Similowski T, et al. Should we use gait speed in COPD, FEV1 in frailty and dyspnoea in both? *European Respiratory Journal* 2016; **48**(2): 315-9.

22. Williams DM, Jylhävä J, Pedersen NL, Hägg S. A frailty index for UK Biobank participants. *The Journals of Gerontology: Series A* 2019; **74**(4): 582-7.

23. Dale J, Paterson C, Tierney A, et al. The Scottish Early Rheumatoid Arthritis (SERA) study: an inception cohort and biobank. *BMC musculoskeletal disorders* 2016; **17**(1): 1-8.

24. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet* 2012; **380**(9836): 37-43.

25. Andrew MK, Mitnitski AB, Rockwood K. Social Vulnerability, Frailty and Mortality in Elderly People. *PLOS ONE* 2008; **3**(5): e2232.

26. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The lancet* 2013; **381**(9868): 752-62.

27. Junius-Walker U, Onder G, Soleymani D, et al. The essence of frailty: a systematic review and qualitative synthesis on frailty concepts and definitions. *European journal of internal medicine* 2018; **56**: 3-10.

28. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. *Age and ageing* 2018; **47**(2): 193-200.

29. Chang S-F, Lin P-L. Frail phenotype and mortality prediction: a systematic review and meta-analysis of prospective cohort studies. *International journal of nursing studies* 2015; **52**(8): 1362-74.

30. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016; **70**(7): 722-9.

31. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. *Journal of the American Medical Directors Association* 2015; **16**(12): 1027-33.

32. Bouillon K, Kivimaki M, Hamer M, et al. Measures of frailty in population-based studies: an overview. *BMC geriatrics* 2013; **13**(1): 64.

33. Bunt S, Steverink N, Olthof J, Van Der Schans CP, Hobbelen JS. Social frailty in older adults: a scoping review. European journal of ageing. 2017 Sep;14(3):323-34.

34. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. *The journal of nutrition, health & aging* 2013; **17**(9): 726-34.

35. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2007; **62**(7): 722-7.

36. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatrics* 2008; **8**(1): 24.

37. Hanlon P, Fauré I, Corcoran N, Butterly E, Lewsey J, McAllister D, Mair FS. Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis. *The Lancet Healthy Longevity*. 2020 Dec 1;1(3):e106-16.

38. Theou O, Brothers TD, Pena FG, Mitnitski A, Rockwood K. Identifying Common Characteristics of Frailty Across Seven Scales: Journal of the American Geriatrics Society; 2014 May;62(5):901-6.

39. Aguayo GA, Donneau A-F, Vaillant MT, et al. Agreement between 35 published frailty scores in the general population. *American journal of epidemiology* 2017; **186**(4): 420-34.

40. Rockwood K, Howlett SE. Fifteen years of progress in understanding frailty and health in aging. BMC medicine. 2018 Dec;16(1):1-4.

41. Fan J, Yu C, Guo Y, et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. *The Lancet Public Health* 2020; **5**(12): e650-e60.

42. Nguyen QD, Moodie EM, Forget MF, Desmarais P, Keezer MR, Wolfson C. Health heterogeneity in older adults: exploration in the Canadian longitudinal study on aging. *Journal of the American Geriatrics Society* 2021; **69**(3): 678-87.

43. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: a systematic review and meta-analysis. *Ageing research reviews* 2019; **50**: 81-8.

44. Kulminski AM, Ukraintseva SV, Kulminskaya IV, Arbeev KG, Land K, Yashin AI. Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: lessons from the Cardiovascular Health Study. *Journal of the American Geriatrics Society* 2008; **56**(5): 898-903.

45. Steverink N. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). *The gerontologist* 2001; **41**: 236.

46. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg frailty indicator: psychometric properties. *Journal of the American Medical Directors Association* 2010; **11**(5): 344-55.

47. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. *Age and ageing* 2006; **35**(5): 526-9.

48. Roppolo M, Mulasso A, Gobbens RJ, Mosso CO, Rabaglietti E. A comparison between uni-and multidimensional frailty measures: prevalence, functional status, and relationships with disability. *Clinical interventions in aging* 2015; **10**: 1669.

49. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Cmaj* 2005; **173**(5): 489-95.

50. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *The journal of nutrition, health & aging* 2012; **16**(7): 601-8.

51. van Kan GA, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. *Journal of the American Medical Directors Association* 2008; **9**(2): 71-2.

52. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. *BMC geriatrics* 2020; **20**(1): 1-18.

53. Kojima G. Frailty defined by FRAIL scale as a predictor of mortality: a systematic review and meta-analysis. *Journal of the American Medical Directors Association* 2018; **19**(6): 480-3.

54. Martins BA, Visvanathan R, Barrie H, et al. Frailty prevalence using Frailty Index, associated factors and level of agreement among frailty tools in a cohort of Japanese older adults. *Archives of gerontology and geriatrics* 2019; **84**: 103908.

55. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. Journal of the American Geriatrics Society. 2013 Sep;61(9):1537-51.

56. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age and ageing* 2016; **45**(3): 353-60.

57. Pajewski NM, Lenoir K, Wells BJ, Williamson JD, Callahan KE. Frailty Screening Using the Electronic Health Record Within a Medicare Accountable Care Organization. *The Journals of Gerontology: Series A* 2019; **74**(11): 1771-7.

58. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *The Lancet* 2018; **391**(10132): 1775-82.

59. McAlister F, van Walraven C. External validation of the Hospital Frailty Risk Score and comparison with the Hospital-patient One-year Mortality Risk Score to predict outcomes in elderly hospitalised patients: a retrospective cohort study. *BMJ quality & safety* 2019; **28**(4): 284-8.

60. NHS England. Electronic Frailty Index. https://www.england.nhs.uk/ourwork/clinical-policy/older-people/frailty/efi/#why-is-clinical-judgement-important-can-clinicians-not-just-use-the-results-of-the-tool. [accessed March 2022]

61. Munyombwe T, West RM, Pendleton N, Clegg A. Mapping between the Electronic Frailty Index and a Research Standard Frailty Index: Findings from the Community Ageing Research 75+(CARE 75+) Cohort Study. *Advances in Geriatric Medicine and Research* 2020; **4**(3).

62. Hollinghurst J, Housley G, Watkins A, Clegg A, Gilbert T, Conroy SP. A comparison of two national frailty scoring systems. *Age and ageing* 2021; **50**(4): 1208-14.

63. Peña FG, Theou O, Wallace L, Brothers TD, Gill TM, Gahbauer EA, Kirkland S, Mitnitski A, Rockwood K. Comparison of alternate scoring of variables on the performance of the frailty index. BMC geriatrics. 2014 Dec;14(1):1-9.

64. Theou O, Brothers TD, Rockwood MR, Haardt D, Mitnitski A, Rockwood K. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. Age and ageing. 2013 Sep 1;42(5):614-9.

65. Bennett S, Song X, Mitnitski A, Rockwood K. A limit to frailty in very old, community-dwelling people: a secondary analysis of the Chinese longitudinal health and longevity study. *Age and ageing* 2013; **42**(3): 372-7.

66. Yu P, Song X, Shi J, et al. Frailty and survival of older Chinese adults in urban and rural areas: results from the Beijing Longitudinal Study of Aging. *Archives of gerontology and geriatrics* 2012; **54**(1): 3-8.

67. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *Cmaj* 2011; **183**(8): E487-E94.

68. Li G, Ioannidis G, Pickard L, et al. Frailty index of deficit accumulation and falls: Data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort. *BMC Musculoskeletal Disorders* 2014; **15**(1): 185.

69. Mitnitski A, Howlett SE, Rockwood K. Heterogeneity of human aging and its assessment. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2017; **72**(7): 877-84.

70. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and co-morbidity in relation to frailty: how much do they overlap? *Archives of gerontology and geriatrics* 2012; **55**(2): e1-e8.

71. Kamaruzzaman S, Ploubidis GB, Fletcher A, Ebrahim S. A reliable measure of frailty for a community dwelling older population. *Health and quality of life outcomes* 2010; **8**(1): 1-14.

72. King-Kallimanis BL, Kenny RA, Savva GM. Factor structure for the frailty syndrome was consistent across Europe. Journal of clinical epidemiology. 2014 Sep 1;67(9):1008-15.

73. Miller AJ, Theou O, McMillan M, Howlett SE, Tennankore KK, Rockwood K. Dysnatremia in relation to frailty and age in community-dwelling adults in the National Health and Nutrition Examination Survey. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2017; **72**(3): 376-81.

74. Armstrong JJ, Mitnitski A, Launer LJ, White LR, Rockwood K. Frailty in the Honolulu-Asia Aging Study: deficit accumulation in a male cohort followed to 90% mortality. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2015; **70**(1): 125-31.

75. Hao Q, Song X, Yang M, Dong B, Rockwood K. Understanding risk in the oldest old: frailty and the metabolic syndrome in a Chinese community sample aged 90+ years. *The journal of nutrition, health & aging* 2016; **20**(1): 82-8.

76. Blodgett JM, Theou O, Howlett SE, Rockwood K. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *GeroScience* 2017; **39**(4): 447-55.

77. Ravindrarajah R, Lee DM, Pye SR, et al. The ability of three different models of frailty to predict all-cause mortality: results from the European Male Aging Study (EMAS). *Archives of gerontology and geriatrics* 2013; **57**(3): 360-8.

78. Hoogendijk EO, Theou O, Rockwood K, Onwuteaka-Philipsen BD, Deeg DJ, Huisman M. Development and validation of a frailty index in the Longitudinal Aging Study Amsterdam. *Aging clinical and experimental research* 2017; **29**(5): 927-33.

79. Blodgett JM, Rockwood K, Theou O. Changes in the severity and lethality of age-related health deficit accumulation in the USA between 1999 and 2018: a population-based cohort study. *The Lancet Healthy Longevity* 2021; **2**(2): e96-e104.

80. Bandeen-Roche K, Xue Q-L, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2006; **61**(3): 262-6.

81. Avila-Funes JA, Helmer C, Amieva H, et al. Frailty among community-dwelling elderly people in France: the three-city study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2008; **63**(10): 1089-96.

82. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. *Journal of the American Geriatrics Society* 2009; **57**(9): 1532-9.

83. Coelho T, Paul C, Gobbens RJ, Fernandes L. Frailty as a predictor of short-term adverse outcomes. *PeerJ* 2015; **3**: e1121.

84. Fugate Woods N, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society* 2005; **53**(8): 1321-30.

85. Jung H-W, Kim S-W, Ahn S, et al. Prevalence and outcomes of frailty in Korean elderly population: comparisons of a multidimensional frailty index with two phenotype models. *PloS one* 2014; **9**(2): e87958.

86. García-García FJ, Carcaillon L, Fernandez-Tresguerres J, et al. A new operational definition of frailty: the Frailty Trait Scale. *Journal of the American Medical Directors Association* 2014; **15**(5): 371. e7-. e13.

87. Bouillon K, Sabia S, Jokela M, et al. Validating a widely used measure of frailty: are all sub-components necessary? Evidence from the Whitehall II cohort study. *Age* 2013; **35**(4): 1457-65.

88. Bilotta C, Nicolini P, Casè A, Pina G, Rossi S, Vergani C. Frailty syndrome diagnosed according to the Study of Osteoporotic Fractures (SOF) criteria and adverse health outcomes among community-dwelling older outpatients in Italy. A one-year prospective cohort study. *Archives of gerontology and geriatrics* 2012; **54**(2): e23-e8.

89. Forti P, Rietti E, Pisacane N, Olivelli V, Maltoni B, Ravaglia G. A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. *Archives of gerontology and geriatrics* 2012; **54**(1): 16-20.

90. Wallace LMK, Theou O, Kirkland SA, et al. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. *PloS one* 2014; **9**(3): e90475.

91. Farooqi MA, Gerstein H, Yusuf S, Leong DP. Accumulation of Deficits as a Key Risk Factor for Cardiovascular Morbidity and Mortality: A Pooled Analysis of 154 000 Individuals. *Journal of the American Heart Association* 2020; **9**(3): e014686.

92. Aguayo GA, Vaillant MT, Donneau A-F, et al. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer, and total mortality in an elderly general population in England: An observational study. *PLos Med* 2018; **15**(3): e1002543.

93. Lan X, Li H, Wang Z, Chen Y. Frailty as a predictor of future falls in hospitalized patients: A systematic review and meta-analysis. *Geriatric nursing* 2020; **41**(2): 69-74.

94. United Nations. World Population Prospects 2019. 2019. https://population.un.org/wpp/. [accessed March 2022]

95. Wagner K-H, Brath H. A global view on the development of non communicable diseases. *Prev Med* 2012; **54**: S38-S41.

96. Head A, Fleming K, Kypridemos C, Schofield P, Pearson-Stuttard J, O'Flaherty M. Inequalities in incident and prevalent multimorbidity in England, 2004–19: a population-based, descriptive study. *The Lancet Healthy Longevity* 2021; **2**(8): e489-e97.

97. Hanlon P, McCallum M, Jani BD, McQueenie R, Lee D, Mair FS. Association between childhood maltreatment and the prevalence and complexity of

multimorbidity: A cross-sectional analysis of 157,357 UK Biobank participants. *Journal of comorbidity* 2020; **10**: 2235042X10944344.

98. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *The Lancet Public Health* 2017; **2**(8): e356-e66.

99. Savela SL, Koistinen P, Stenholm S, et al. Leisure-time physical activity in midlife is related to old age frailty. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2013; **68**(11): 1433-8.

100. Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2014; **69**(1): 73-8.

101. Strandberg T, Sirola J, Pitkälä K, Tilvis R, Strandberg A, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. *International journal of obesity* 2012; **36**(9): 1153-7.

102. Strandberg TE, Stenholm S, Strandberg AY, Salomaa VV, Pitkälä KH, Tilvis RS. The "obesity paradox," frailty, disability, and mortality in older men: a prospective, longitudinal cohort study. *American journal of epidemiology* 2013; **178**(9): 1452-60.

103. Atkins JL, Delgado J, Pilling LC, et al. Impact of low cardiovascular risk profiles on geriatric outcomes: evidence from 421,000 participants in two cohorts. *The Journals of Gerontology: Series A* 2019; **74**(3): 350-7.

104. Strandberg AY, Trygg T, Pitkälä KH, Strandberg TE. Alcohol consumption in midlife and old age and risk of frailty: Alcohol paradox in a 30-year follow-up study. *Age and ageing* 2018; **47**(2): 248-54.

105. Gale CR, Cooper C, Aihie Sayer A. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. Age and ageing. 2014 Oct 12;44(1):162-5.

106. Majid Z, Welch C, Davies J, Jackson T. Global frailty: the role of ethnicity, migration and socioeconomic factors. *Maturitas* 2020; **139**: 33-41.

107. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society* 2012; **60**(8): 1487-92.

108. Lang IA, Hubbard RE, Andrew MK, Llewellyn DJ, Melzer D, Rockwood K. Neighborhood deprivation, individual socioeconomic status, and frailty in older adults. Journal of the American Geriatrics Society. 2009 Oct;57(10):1776-80.

109. Szanton SL, Seplaki CL, Thorpe RJ, Allen JK, Fried LP. Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. *J Epidemiol Community Health* 2010; **64**(01): 63-7.

110. Franse CB, van Grieken A, Qin L, Melis RJ, Rietjens JA, Raat H. Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PloS one* 2017; **12**(11): e0187946.

111. O'Caoimh R, Galluzzo L, Rodríguez-Laso Á, et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. *Annali dell'Istituto superiore di sanita* 2018; **54**(3): 226-38.

112. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *International journal of epidemiology* 2013; **42**(6): 1640-8.

113. Syddall H, Roberts HC, Evandrou M, Cooper C, Bergman H, Sayer AA. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. *Age and Ageing* 2010; **39**(2): 197-203.

114. Niederstrasser NG, Rogers NT, Bandelow S. Determinants of frailty development and progression using a multidimensional frailty index: Evidence from the English Longitudinal Study of Ageing. *PLoS One* 2019; **14**(10): e0223799.

115. Chen S, Honda T, Narazaki K, Chen T, Kishimoto H, Kumagai S. Physical frailty and risk of needing long-term care in community-dwelling older adults: a 6-year prospective study in Japan. *The journal of nutrition, health & aging* 2019; **23**(9): 856-61.

116. García-Nogueras I, Aranda-Reneo I, Peña-Longobardo L, Oliva-Moreno J, Abizanda P. Use of health resources and healthcare costs associated with frailty: The FRADEA study. *The journal of nutrition, health & aging* 2017; **21**(2): 207-14.

117. Comans TA, Peel NM, Hubbard RE, Mulligan AD, Gray LC, Scuffham PA. The increase in healthcare costs associated with frailty in older people discharged to a post-acute transition care program. *Age and ageing* 2016; **45**(2): 317-20.

118. Han L, Clegg A, Doran T, Fraser L. The impact of frailty on healthcare resource use: a longitudinal analysis using the Clinical Practice Research Datalink in England. *Age and ageing* 2019; **48**(5): 665-71.

119. Nikolova S, Heaven A, Hulme C, West R, Pendleton N, Humphrey S, Cundill B, Clegg A. Social care costs for community-dwelling older people living with frailty. Health & Social Care in the Community. 2022 May;30(3):e804-11.

120. Hajek A, Bock J-O, Saum K-U, et al. Frailty and healthcare costs—longitudinal results of a prospective cohort study. *Age and ageing* 2018; **47**(2): 233-41.

121. Ensrud KE, Kats AM, Schousboe JT, et al. Frailty phenotype and healthcare costs and utilization in older women. *Journal of the American Geriatrics Society* 2018; **66**(7): 1276-83.

122. Reeves D, Pye S, Ashcroft DM, Clegg A, Kontopantelis E, Blakeman T, van Marwijk H. The challenge of ageing populations and patient frailty: can primary care adapt?. Bmj. 2018 Aug 28;362.

123. Gwyther H, Shaw R, Jaime Dauden E-A, et al. Understanding frailty: a qualitative study of European healthcare policy-makers' approaches to frailty screening and management. *BMJ Open* 2018; **8**(1): e018653.

124. NHS England. Updated guidance on supporting routine frailty identification and frailty care through the GP Contract 2017/2018. 2017. https://www.england.nhs.uk/wp-content/uploads/2017/04/supporting-guidance-on-frailty-update-sept-2017.pdf. [accessed March 2022]

125. Alderwick H, Dixon J. The NHS long term plan. bmj. 2019 Jan 7;364..

126. Levinson W, Born K, Wolfson D. Choosing Wisely Campaigns: A Work in Progress. *JAMA* 2018; **319**(19): 1975-6.

127. Fenning SJ, Smith G, Calderwood C. Realistic Medicine: Changing culture and practice in the delivery of health and social care. *Patient education and counseling* 2019; **102**(10): 1751-5.

128. Hoogendijk EO, Rockwood K, Theou O, et al. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. *Age and ageing* 2018; **47**(5): 727-33.

129. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. J Epidemiol Community Health. 2015 Apr 1;69(4):316-21.

130. Orkaby AR, Nussbaum L, Ho Y-L, et al. The burden of frailty among US veterans and its association with mortality, 2002–2012. *The Journals of Gerontology: Series A* 2019; **74**(8): 1257-64.

131. Mousa A, Savva GM, Mitnitski A, et al. Is frailty a stable predictor of mortality across time? Evidence from the Cognitive Function and Ageing Studies. *Age and ageing* 2018; **47**(5): 721-7.

132. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. *Ageing research reviews* 2013; **12**(2): 719-36.

133. Gordon E, Peel N, Samanta M, Theou O, Howlett S, Hubbard R. Sex differences in frailty: a systematic review and meta-analysis. *Experimental gerontology* 2017; **89**: 30-40.

134. Gordon E, Hubbard R. Physiological basis for sex differences in frailty. *Current opinion in physiology* 2018; **6**: 10-5.

135. Shi J, Yang Z, Song X, et al. Sex differences in the limit to deficit accumulation in late middle-aged and older Chinese people: results from the Beijing Longitudinal Study of Aging. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2014; **69**(6): 702-9.

136. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ open* 2018; **8**(3): e018195.

137. Hyde Z, Flicker L, Smith K, et al. Prevalence and incidence of frailty in Aboriginal Australians, and associations with mortality and disability. *Maturitas* 2016; **87**: 89-94.

138. Hyde Z, Smith K, Flicker L, et al. Mortality in a cohort of remote-living Aboriginal Australians and associated factors. *Plos One* 2018; **13**(4): 12.

139. Barrett P, Twitchin S, Kletchko S, Ryan F. The living environments of community-dwelling older people who become frail: another look at the living standards of older New Zealanders survey. Te Puna Whakaaro 2006, 28, 133-157.

140. Franse CB, van Grieken A, Qin L, Melis RJ, Rietjens JA, Raat H. Ethnic differences in frailty: a cross-sectional study of pooled data from community-dwelling older persons in the Netherlands. *BMJ open* 2018; **8**(8): e022241.

141. Brothers TD, Theou O, Rockwood K. Frailty and migration in middle-aged and older Europeans. Archives of Gerontology and Geriatrics. 2014 Jan 1;58(1):63-8.

142. Walkden GJ, Anderson EL, Vink MP, Tilling K, Howe LD, Ben-Shlomo Y. Frailty in older-age European migrants: Cross-sectional and longitudinal analyses of the Survey of Health, Aging and Retirement in Europe (SHARE). Social science & medicine. 2018 Sep 1;213:1-1.

143. Thompson MQ, Theou O, Yu S, Adams RJ, Tucker GR, Visvanathan R. Frailty prevalence and factors associated with the frailty phenotype and frailty index: findings from the North West Adelaide health study. *Australasian journal on ageing* 2018; **37**(2): 120-6.

144. Woo J, Goggins W, Sham A, Ho S. Social determinants of frailty. *Gerontology* 2005; **51**(6): 402-8.

145. Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. *BMC geriatrics* 2015; **15**(1): 1-7.

146. Theou O, Blodgett JM, Godin J, Rockwood K. Association between sedentary time and mortality across levels of frailty. *Cmaj* 2017; **189**(33): E1056-E64.

147. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. The association between sedentary behaviour, moderate-vigorousphysical activity and frailty in NHANES cohorts. *Maturitas* 2015; **80**(2): 187-91.

148. Rietman ML, Van Der A D, Van Oostrom S, et al. The association between BMI and different frailty domains: a U-shaped curve? *The journal of nutrition, health & aging* 2018; **22**(1): 8-15.

149. Hernández Morante JJ, Gómez Martínez C, Morillas-Ruiz JM. Dietary factors associated with frailty in old adults: a review of nutritional interventions to prevent frailty development. *Nutrients* 2019; **11**(1): 102.

150. Linardakis M, Smpokos E, Papadaki A, Komninos ID, Tzanakis N, Philalithis A. Prevalence of multiple behavioral risk factors for chronic diseases in adults aged 50+, from eleven European countries—the SHARE study (2004). *Prev Med* 2013; **57**(3): 168-72.

151. Blue S, Shove E, Carmona C, Kelly MP. Theories of practice and public health: understanding (un) healthy practices. *Critical Public Health* 2016; **26**(1): 36-50.

152. Romero-Ortuno R. Frailty Index in Europeans: Association with determinants of health. *Geriatrics & gerontology international* 2014; **14**(2): 420-9.

153. Haapanen M, Perälä M, Salonen M, et al. Early life stress and frailty in old age: the Helsinki birth cohort study. *BMC geriatrics* 2018; **18**(1): 1-8.

154. Iavicoli I, Leso V, Cesari M. The contribution of occupational factors on frailty. *Archives of gerontology and geriatrics* 2018; **75**: 51-8.

155. The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. *The Lancet* 1997; **349**(9062): 1341-6.

156. Woodhouse PR, Khaw K-T, Plummer M. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. *Journal of hypertension* 1993; **11**(11): 1267-74.

157. Payne RA, Mendonca SC, Elliott MN, et al. Development and validation of the Cambridge Multimorbidity Score. *CMAJ* 2020; **192**(5): E107-E14.

158. Zhu Y, Edwards D, Mant J, Payne RA, Kiddle S. Characteristics, service use and mortality of clusters of multimorbid patients in England: a population-based study. *BMC Med* 2020; **18**: 1-11.

159. Jani BD, Hanlon P, Nicholl BI, et al. Relationship between multimorbidity, demographic factors and mortality: findings from the UK Biobank cohort. *BMC Med* 2019; **17**(1): 74.

160. Ho IS, Azcoaga-Lorenzo A, Akbari A, Black C, Davies J, Hodgins P, Khunti K, Kadam U, Lyons RA, McCowan C, Mercer S. Examining variation in the measurement of multimorbidity in research: a systematic review of 566 studies. The Lancet Public Health. 2021 Aug 1;6(8):e587-97.

161. Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. *Bmj* 2016; **354**: i4843.

162. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. NICE guideline [NG56]. 2016. https://www.nice.org.uk/guidance/conditions-and-diseases/multiple-long-term-conditions. [Accessed March 2022]

163. Quach LT, Primack J, Bozzay M, Madrigal C, Erqou S, Rudolph JL. The Intersection of Physical and Social Frailty in Older Adults. *Rhode Island Medicine*; **104**(4): 16-9.

164. Bessa B, Ribeiro O, Coelho T. Assessing the social dimension of frailty in old age: A systematic review. *Arch Gerontol Geriatr*; **78**: 101-13.

165. Lacas A, Rockwood K. Frailty in primary care: a review of its conceptualization and implications for practice. *BMC Med* 2012; **10**(1): 1-9.

166. Andrew MK. Let's Put the Pieces Together: Frailty, Social Vulnerability, the Continuum of Care, Prevention and Research are Key Considerations for a Dementia Care Strategy. *HealthcarePapers* 2016; **16**(2): 34-9.

167. Andrew MK, Keefe JM. Social vulnerability from a social ecology perspective: a cohort study of older adults from the National Population Health Survey of Canada. *BMC geriatrics* 2014; **14**(1): 1-14.

168. Wallace LMK, Theou O, Pena F, Rockwood K, Andrew MK. Social vulnerability as a predictor of mortality and disability: cross-country differences in the survey of health, aging, and retirement in Europe (SHARE). *Aging Clinical and Experimental Research* 2015; **27**(3): 365-72.

169. Ma L, Sun F, Tang Z. Social frailty is associated with physical functioning, cognition, and depression, and predicts mortality. *The journal of nutrition, health & aging* 2018; **22**(8): 989-95.

170. Bessa B, Coelho T, Ribeiro Ó. Social frailty dimensions and frailty models over time. *Archives of Gerontology and Geriatrics* 2021; **97**: 104515.

171. Gale CR, Westbury L, Cooper C. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age and ageing. 2018 May 1;47(3):392-7.

172. Jarach CM, Tettamanti M, Nobili A, D'avanzo B. Social isolation and loneliness as related to progression and reversion of frailty in the Survey of Health Aging Retirement in Europe (SHARE). *Age and Ageing* 2021; **50**(1): 258-62.

173. Giné-Garriga M, Jerez-Roig J, Coll-Planas L, et al. Is loneliness a predictor of the modern geriatric giants? Analysis from the survey of health, ageing, and retirement in Europe. *Maturitas* 2021; **144**: 93-101.

174. Sha S, Xu Y, Chen L. Loneliness as a risk factor for frailty transition among older Chinese people. *BMC geriatrics* 2020; **20**(1): 1-11.

175. Maltby J, Hunt SA, Ohinata A, Palmer E, Conroy S. Frailty and social isolation: comparing the relationship between frailty and unidimensional and multifactorial models of social isolation. *Journal of Aging and Health* 2020; **32**(10): 1297-308.

176. Davies K, Maharani A, Chandola T, Todd C, Pendleton N. The longitudinal relationship between loneliness, social isolation, and frailty in older adults in England: a prospective analysis. *The Lancet Healthy Longevity* 2021; **2**(2): e70-e7.

177. Hoogendijk EO, Suanet B, Dent E, Deeg DJ, Aartsen MJ. Adverse effects of frailty on social functioning in older adults: Results from the Longitudinal Aging Study Amsterdam. *Maturitas* 2016; **83**: 45-50.

178. Hoogendijk EO, Smit AP, van Dam C, et al. Frailty combined with loneliness or social isolation: an elevated risk for mortality in later life. *Journal of the American Geriatrics Society* 2020; **68**(11): 2587-93.

179. Dibello V, Zupo R, Sardone R, et al. Oral frailty and its determinants in older age: a systematic review. *The Lancet Healthy Longevity* 2021; **2**(8): e507-e20.

180. Cesari M, Canevelli M. How many frailties exist? *The Lancet Healthy Longevity* 2021; **2**(10): e615.

181. World Health Organization. Integrated care for older people: guidelines on community-level interventions to manage declines in intrinsic capacity. Geneva: World Health Organization; 2017.

182. Fontana L, Kennedy BK, Longo VD, Seals D, Melov S. Medical research: treat ageing. *Nature News* 2014; **511**(7510): 405.

183. Kane AE, Gregson E, Theou O, Rockwood K, Howlett SE. The association between frailty, the metabolic syndrome, and mortality over the lifespan. *GeroScience* 2017; **39**(2): 221-9.

184. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Weinberg AD. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *American journal of public health* 2010; **100**(S1): S105-S12.

185. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge gaps in cardiovascular care of the older adult population: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. *Circulation* 2016; **133**(21): 2103-22.

186. Walker D, Gale C, Lip G, et al. Editor's Choice-Frailty and the management of patients with acute cardiovascular disease: A position paper from the Acute Cardiovascular Care Association. *European Heart Journal: Acute Cardiovascular Care* 2018; **7**(2): 176-93.

187. Li Q, Wang S, Milot E, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. *Aging cell* 2015; **14**(6): 1103-12.

188. Kalyani RR, Varadhan R, Weiss CO, Fried LP, Cappola AR. Frailty status and altered dynamics of circulating energy metabolism hormones after oral glucose in older women. *The journal of nutrition, health & aging* 2012; **16**(8): 679-86.

189. Kalyani RR, Varadhan R, Weiss CO, Fried LP, Cappola AR. Frailty status and altered glucose-insulin dynamics. *The journals of gerontology Series A, Biological sciences and medical sciences* 2012; **67**(12): 1300-6.

190. Kalyani RR, Varadhan R, Weiss CO, Fried LP, Cappola AR. The frailty syndrome and glucose and insulin measurements from the oral glucose tolerance test. *Diabetes* 2011; **60**(SUPPL. 1): A380.

191. Blaum CS, Xue QL, Tian J, Semba RD, Fried LP, Walston J. Is hyperglycemia associated with frailty status in older women? *Journal of the American Geriatrics Society* 2009; **57**(5): 840-7.

192. Akki A, Yang H, Gupta A, et al. Skeletal muscle ATP kinetics are impaired in frail mice. *Age* 2014; **36**(1): 21-30.

193. Moore AZ, Biggs ML, Matteini A, et al. Polymorphisms in the mitochondrial DNA control region and frailty in older adults. *PLoS One* 2010; **5**(6): e11069.

194. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *Journal of the American Geriatrics Society* 2007; **55**(6): 864-71.

195. Van Epps P, Oswald D, Higgins P, et al. Frailty has a stronger association with inflammation than age in older veterans. *Immun Ageing* 2016; **13**(1): 1-9.

196. Richards CD. Innate immune cytokines, fibroblast phenotypes, and regulation of extracellular matrix in lung. *Journal of Interferon & Cytokine Research* 2017; **37**(2): 52-61.

197. Straub RH. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. *Arthritis Res Ther* 2014; **16**(1): 1-15.

198. Ghachem A, Fried LP, Legault V, et al. Evidence from two cohorts for the frailty syndrome as an emergent state of parallel dysregulation in multiple physiological systems. *Biogerontology* 2021; **22**(1): 63-79.

199. Fried LP, Xue Q-L, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2009; **64**(10): 1049-57.

200. Theou O, Cann L, Blodgett J, Wallace LM, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. Ageing research reviews. 2015 May 1;21:78-94.

201. Young AC, Glaser K, Spector TD, Steves CJ. The identification of hereditary and environmental determinants of frailty in a cohort of UK twins. *Twin Research and Human Genetics* 2016; **19**(6): 600-9.

202. Sathyan S, Verghese J. Genetics of frailty: a longevity perspective. *Translational Research* 2020; **221**: 83-96.

203. Haapanen MJ, Perälä M-M, Osmond C, et al. Infant and childhood growth and frailty in old age: the Helsinki Birth Cohort Study. *Aging clinical and experimental research* 2019; **31**(5): 717-21.

204. Herr M, Robine J-M, Aegerter P, Arvieu J-J, Ankri J. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. *Annals of epidemiology* 2015; **25**(9): 674-80. e1.

205. van der Linden B, Cheval B, Sieber S, Kliegel M, Cullati S. Adverse childhood experiences are associated with frailty in old age. Innovation in Aging. 2018 Nov;2(Suppl 1):892.

206. Van der Linden BWA, Cheval B, Sieber S, et al. Life course socioeconomic conditions and frailty at older ages. *The Journals of Gerontology: Series B* 2020; **75**(6): 1348-57.

207. Jazwinski SM, Kim S. Examination of the dimensions of biological age. *Frontiers in genetics* 2019; **10**: 263.

208. Carvalho ACA, Mendes MLT, da Silva Reis MC, Santos VS, Tanajura DM, Martins-Filho PRS. Telomere length and frailty in older adults—A systematic review and meta-analysis. *Ageing research reviews* 2019; **54**: 100914.

209. Hägg S, Jylhävä J, Wang Y, Czene K, Grassmann F. Deciphering the genetic and epidemiological landscape of mitochondrial DNA abundance. *Human Genetics* 2021; **140**(6): 849-61.

210. Feridooni H, Kane A, Ayaz O, et al. The impact of age and frailty on ventricular structure and function in C57BL/6J mice. *The Journal of physiology* 2017; **595**(12): 3721-42.

211. Mitnitski A, Rockwood K. The rate of aging: the rate of deficit accumulation does not change over the adult life span. *Biogerontology* 2016; **17**(1): 199-204.

212. Stolz E, Hoogendijk EO, Mayerl H, Freidl W. Frailty changes predict mortality in four longitudinal studies of aging. *The journals of gerontology Series A, Biological sciences and medical sciences* 2020. 76(9):1619-1626

213. Rockwood K, Mogilner A, Mitnitski A. Changes with age in the distribution of a frailty index. *Mechanisms of ageing and development* 2004; **125**(7): 517-9.

214. Drubbel I, Numans ME, Kranenburg G, Bleijenberg N, de Wit NJ, Schuurmans MJ. Screening for frailty in primary care: a systematic review of the psychometric properties of the frailty index in community-dwelling older people. *Bmc Geriatrics* 2014; **14**(1): 1-13.

215. Sutton JL, Gould RL, Daley S, et al. Psychometric properties of multicomponent tools designed to assess frailty in older adults: a systematic review. *BMC geriatrics* 2016; **16**(1): 1-20.

216. Walston JD, Bandeen-Roche K. Frailty: a tale of two concepts. *BMC Med* 2015; **13**(1): 1-3.

217. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mechanisms of ageing and development* 2006; **127**(5): 494-6.

218. Theou O, Rockwood K. Comparison and clinical applications of the frailty phenotype and frailty index approaches. *Frailty in Aging* 2015; **41**: 74-84.

219. Allen N, Sudlow C, Downey P, et al. UK Biobank: Current status and what it means for epidemiology. *Health Policy and Technology* 2012; **1**(3): 123-6.

220. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. bmj. 2020 Feb 12;368.

221. Manolio TA, Collins R. Enhancing the Feasibility of Large Cohort Studies. *JAMA* 2010; **304**(20): 2290-1.

222. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015; **12**(3): e1001779.

223. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *American journal of epidemiology* 2017; **186**(9): 1026-34.

224. Keyes KM, Westreich D. UK Biobank, big data, and the consequences of non-representativeness. *The Lancet* 2019; **393**(10178): 1297.

225. Stamatakis E, Owen KB, Shepherd L, Drayton B, Hamer M, Bauman AE. Is Cohort Representativeness Passé? Poststratified Associations of Lifestyle Risk Factors with Mortality in the UK Biobank. *Epidemiology (Cambridge, Mass)* 2021; **32**(2): 179.

226. Hanlon P, Jani BD, Nicholl B, Lewsey J, McAllister DA, Mair FS. Associations between multimorbidity and adverse health outcomes in UK Biobank and the SAIL Databank: A comparison of longitudinal cohort studies. *PLos Med* 2022; **19**(3): e1003931.

227. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC geriatrics. 2010 Dec;10(1):1-2.

228. Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020; **11**(1): 5749.

229. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *International journal of epidemiology* 2010; **39**(2): 417-20.

230. Britsemmer K, Ursum J, Gerritsen M, van Tuyl L, van Schaardenburg D. Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis:

slight improvement over the 1987 ACR criteria. *Annals of the rheumatic diseases* 2011; **70**(8): 1468-70.

231. van der Helm-van AH, Zink A. What is rheumatoid arthritis? Considering consequences of changed classification criteria. Annals of the Rheumatic Diseases. 2017 Feb 1;76(2):315-7.

232. Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. *Annals of the rheumatic diseases* 2014; **73**(1): 114-23.

233. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *New England Journal of Medicine* 2010; **363**(10): 905-17.

234. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 2000; **43**(3): 506-14.

235. Bruce B, Fries JF. The Stanford health assessment questionnaire: dimensions and practical applications. *Health and quality of life outcomes* 2003; **1**(1): 1-6.

236. Krishnan E, Häkkinen A, Sokka T, Hannonen P. Impact of age and comorbidities on the criteria for remission and response in rheumatoid arthritis. *Annals of the rheumatic diseases* 2005; **64**(9): 1350-2.

237. Aoki T, Ito H, Ogura T, Hirata A, Nishiwaki Y, Kameda H. Association of age with the non-achievement of clinical and functional remission in rheumatoid arthritis. *Scientific reports* 2020; **10**(1): 1-6.

238. Krishnan E, Sokka T, Häkkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. *Arthritis Rheum* 2004; **50**(3): 953-60.

239. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 2003; **48**(6): 1530-42.

240. Kind P, Hardman G, Macran S. UK population norms for EQ-5D, 1999.

241. Janssen B, Szende A. Population norms for the EQ-5D. *Self-reported population health: an international perspective based on EQ-5D* 2014: 19-30.

242. Cavrini G, Broccoli S, Puccini A, Zoli M. EQ-5D as a predictor of mortality and hospitalization in elderly people. *Qual Life Res* 2012; **21**(2): 269-80.

243. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials. gov results database—update and key issues. *New England Journal of Medicine* 2011; **364**(9): 852-60.

244. Hanlon P, Hannigan L, Rodriguez-Perez J, et al. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. *BMC Med* 2019; **17**(1): 201.

245. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Archives of internal medicine* 2006; **166**(9): 1021-6.

246. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. *Chest* 2007; **132**(2): 456-63.

247. Ståhl E, Lindberg A, Jansson S-A, et al. Health-related quality of life is related to COPD disease severity. *Health and quality of life outcomes* 2005; **3**(1): 1-8.

248. US Food and Drug Administration Authority. What is a serious adverse event? . https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event [accessed April 2022]

249. Sinclair AJ, Rodriguez-Manas L. Diabetes and Frailty: Two Converging Conditions? *Canadian journal of diabetes* 2016; **40**(1): 77-83.

250. Chode S, Malmstrom TK, Miller DK, Morley JE. Frailty, Diabetes, and Mortality in Middle-Aged African Americans. *The journal of nutrition, health & aging* 2016; **20**(8): 854-9.

251. National Institute for Health and Care Excellence. Type 2 Diabetes in Adults: Management (NICE Guideline 28). 2019. https://www.nice.org.uk/guidance/ng28. [accessed May 2022]

252. Santos-Eggimann B, Sirven N. Screening for frailty: older populations and older individuals. *Public health reviews* 2016; **37**(1): 7.

253. Hanlon P, Fauré I, Corcoran N, et al. Identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: a systematic review protocol. *BMJ Open* 2020; **10**(9): e037476.

254. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010; **25**(9): 603-5.

255. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020; **368**: l6890.

256. Ogilvie D, Fayter D, Petticrew M, et al. The harvest plot: a method for synthesising evidence about the differential effects of interventions. *BMC medical research methodology* 2008; **8**(1): 8.

257. Adame Perez SI, Senior PA, Field CJ, Jindal K, Mager DR. Frailty, Health-Related Quality of Life, Cognition, Depression, Vitamin D and Health-Care

Utilization in an Ambulatory Adult Population With Type 1 or Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Cross-Sectional Analysis. *Canadian journal of diabetes* 2019; **43**(2): 90-7.

258. Aguayo GA, Hulman A, Vaillant MT, et al. Prospective association among diabetes diagnosis, HbA1c, glycemia, and frailty trajectories in an elderly population. *Diabetes Care* 2019; **42**(10): 1903-11.

259. Aguilar-Navarro SG, Mimenza-Alvarado AJ, Corona-Sevilla I, et al. Cerebral vascular reactivity in frail older adults with vascular cognitive impairment. *Brain Sciences* 2019; **9**(9): 214.

260. Al Snih S, Graham JE, Ray LA, Samper-Ternent R, Markides KS, Ottenbacher KJ. Frailty and incidence of activities of daily living disability among older Mexican Americans. *Journal of Rehabilitation medicine* 2009; **41**(11): 892-7.

261. Almeida OP, McCaul K, Hankey GJ, et al. Duration of diabetes and its association with depression in later life: The Health In Men Study (HIMS). *Maturitas* 2016; **86**: 3-9.

262. Ambagtsheer RC, Beilby J, Seiboth C, Dent E. Prevalence and associations of frailty in residents of Australian aged care facilities: findings from a retrospective cohort study. *Aging Clinical and Experimental Research* 2020 Sep;32(9):1849-56.

263. Anjos DMD, Moreira BD, Pereira DS, et al. Impact of Type-2 Diabetes Time Since Diagnosis on Elderly Women Gait and Functional Status. *Physiother Res Int* 2017; **22**(2): 8.

264. Atif M, Saleem Q, Asghar S, Malik H, Ahmad N. Extent and Predictors of Poor Glycaemic Control among Elderly Pakistani Patients with Type 2 Diabetes Mellitus: A Multi-Centre Cross-Sectional Study. *Med Lith* 2019; **55**(1): 11.

265. Azmon M, Gayus N, Michal H, Olmer L, Cukierman-Yaffe T. The Association between Glucose Control and Functional Indices in Older People with Diabetes. International Journal of Endocrinology. 2018 Dec 23;2018.

266. Bello-Chavolla OY, Aguilar-Salinas CA, Avila-Funes JA. Geriatric Syndromes and Not Cardiovascular Risk Factors are Associated with Cognitive Impairment among Mexican Community-Dwelling Elderly with Type 2 Diabetes. *Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion* 2017; **69**(3): 166-72.

267. Boas N, Salome GM, Ferreira LM. Frailty syndrome and functional disability among older adults with and without diabetes and foot ulcers. *Journal of Wound Care* 2018; **27**(7): 409-16.

268. Bouillon K, Kivimaki M, Hamer M, et al. Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. *Journal of the American Medical Directors Association* 2013; **14**(11): 851.e1-6.

269. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, et al. Midlife contributors to socioeconomic differences in frailty during later life: a prospective cohort study. *The Lancet Public Health* 2018; **3**(7): e313-e22.

270. Cacciatore F, Testa G, Galizia G, et al. Clinical frailty and long-term mortality in elderly subjects with diabetes. *Acta diabetologica* 2013; **50**(2): 251-60.

271. Cakmur H. Frailty among elderly adults in a rural area of Turkey. *Medical science monitor : international medical journal of experimental and clinical research* 2015; **21**: 1232-42.

272. Calado LB, Ferriolli E, Moriguti JC, Martinez EZ, Da Costa Lima NK. Frailty syndrome in an independent urban population in Brazil (FIBRA study): A cross-sectional populational study. *Sao Paulo Medical Journal* 2016; **134**(5): 385-92.

273. Carneiro JA, Ramos GCF, Barbosa ATF, de Mendonca JMG, da Costa FM, Caldeira AP. Prevalence and factors associated with frailty in non-institutionalized older adults. *Rev Bras Enferm* 2016; **69**(3): 408-15.

274. Castrejon-Perez RC, Aguilar-Salinas CA, Gutierrez-Robledo LM, Cesari M, Perez-Zepeda MU. Frailty, diabetes, and the convergence of chronic disease in an age-related condition: a population-based nationwide cross-sectional analysis of the Mexican nutrition and health survey. *Aging clinical and experimental research* 2018; **30**(8): 935-41.

275. Castrejón-Pérez RC, Borges-Yáñez SA, Gutiérrez-Robledo LM, Ávila-Funes JA. Oral health conditions and frailty in Mexican community-dwelling elderly: a cross sectional analysis. *BMC public health* 2012; **12**(1): 773.

276. Castrejon-Perez RC, Gutierrez-Robledo LM, Cesari M, Perez-Zepeda MU. Diabetes mellitus, hypertension and frailty: A population-based, cross-sectional study of Mexican older adults. *Geriatrics & gerontology international* 2017; **17**(6): 925-30.

277. Castro-Rodriguez M, Carnicero JA, Garcia-Garcia FJ, et al. Frailty as a Major Factor in the Increased Risk of Death and Disability in Older People With Diabetes. *Journal of the American Medical Directors Association* 2016; **17**(10): 949-55.

278. Cesari M, Leeuwenburgh C, Lauretani F, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *The American journal of clinical nutrition* 2006; **83**(5): 1142-8.

279. Chang SS, Weiss CO, Xue Q-L, Fried LP. Patterns of comorbid inflammatory diseases in frail older women: the Women's Health and Aging Studies I and II. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2010; **65**(4): 407-13.

280. Chang Y-W, Chen W-L, Lin F-G, et al. Frailty and its impact on health-related quality of life: a cross-sectional study on elder community-dwelling preventive health service users. *PloS one* 2012; **7**(5).

281. Chao CT, Wang J, Chien KL, NTUH COGN. Both pre-frailty and frailty increase healthcare utilization and adverse health outcomes in patients with type 2 diabetes mellitus. *Cardiovascular Diabetology* 2018; **17**: 13.

282. Chaves PH, Semba RD, Leng SX, et al. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2005; **60**(6): 729-35.

283. Chen C-Y, Wu S-C, Chen L-J, Lue B-H. The prevalence of subjective frailty and factors associated with frailty in Taiwan. *Archives of gerontology and geriatrics* 2010; **50**: S43-S7.

284. Chen LJ, Chen CY, Lue BH, Tseng MY, Wu SC. Prevalence and associated factors of frailty among elderly people in Taiwan. *International Journal of Gerontology* 2014; **8**(3): 114-9.

285. Cheong CY, Nyunt MS, Gao Q, Gwee X, Choo RW, Yap KB, Wee SL, Ng TP. Risk factors of progression to frailty: findings from the Singapore Longitudinal Ageing Study. The journal of nutrition, health & aging. 2020 Jan;24(1):98-106.

286. Chhetri JK, Zheng Z, Xu X, Ma C, Chan P. The prevalence and incidence of frailty in Pre-diabetic and diabetic community-dwelling older population: results from Beijing longitudinal study of aging II (BLSA-II). *BMC geriatrics* 2017; **17**(1): 47.

287. Chiu CJ, Cheng YY. Utility of geriatric syndrome indicators for predicting subsequent health care utilization in older adults in Taiwan. *International Journal of Environmental Research and Public Health* 2019; **16**(3): 456.

288. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. *Journal of the American Geriatrics Society* 2009; **57**(5): 830-9.

289. Crow RS, Lohman MC, Titus AJ, et al. Mortality Risk Along the Frailty Spectrum: Data from the National Health and Nutrition Examination Survey 1999 to 2004. *Journal of the American Geriatrics Society* 2018; **66**(3): 496-502.

290. Calado LB, Ferriolli E, Moriguti JC, Martinez EZ, Lima NKD. Frailty syndrome in an independent urban population in Brazil (FIBRA study): a cross-sectional populational study. *Sao Paulo Medical Journal* 2016; **134**(5): 385-92.

291. da Silva AP, da Pureza DY, Landre CB. Frailty syndrome in elderly patients with type 2 diabetes mellitus. *Acta Paul Enferm* 2015; **28**(6): 503-9.

292. Danon-Hersch N, Rodondi N, Spagnoli J, Santos-Eggimann B. Prefrailty and chronic morbidity in the youngest old: an insight from the Lausanne cohort Lc65+. *Journal of the American Geriatrics Society* 2012; **60**(9): 1687-94.

293. de León González ED, Hermosillo HG, Beltran JAM, et al. Validation of the FRAIL scale in Mexican elderly: results from the Mexican Health and Aging Study. *Aging clinical and experimental research* 2016; **28**(5): 901-8.

294. Doi T, Makizako H, Tsutsumimoto K, et al. Transitional status and modifiable risk of frailty in Japanese older adults: A prospective cohort study. *Geriatrics & Gerontology International* 2018; **18**(11): 1562-6.

295. Espinoza SE, Hazuda HP. Frailty prevalence and neighborhood residence in older Mexican Americans: the San Antonio longitudinal study of aging. *Journal of the American Geriatrics Society* 2015; **63**(1): 106-11.

296. Espinoza SE, Jung I, Hazuda H. Lower frailty incidence in older Mexican Americans than in older European Americans: the San Antonio Longitudinal Study of Aging. *Journal of the American Geriatrics Society* 2010; **58**(11): 2142-8.

297. Espinoza SE, Jung I, Hazuda H. Frailty transitions in the San Antonio Longitudinal Study of Aging. *Journal of the American Geriatrics Society* 2012; **60**(4): 652-60.

298. Ferri-Guerra J, Aparicio-Ugarriza R, Salguero D, Baskaran D, Mohammed YN, Florez H, Ruiz JG. The association of frailty with hospitalizations and mortality among community dwelling older adults with diabetes. The Journal of frailty & aging. 2020 Feb;9(2):94-100.

299. Garcia-Esquinas E, Graciani A, Guallar-Castillon P, Lopez-Garcia E, Rodriguez-Manas L, Rodriguez-Artalejo F. Diabetes and risk of frailty and its potential mechanisms: a prospective cohort study of older adults. *Journal of the American Medical Directors Association* 2015; **16**(9): 748-54.

300. Hasan SS, Kow CS, Verma RK, Ahmed SI, Mittal P, Chong DWK. An evaluation of medication appropriateness and frailty among residents of aged care homes in Malaysia: A cross-sectional study. *Medicine* 2017; **96**(35): e7929.

301. Hippisley-Cox J, Coupland C. Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study. *BMJ (Clinical research ed)* 2017; **358**: j4208.

302. Howrey BT, Al Snih S, Markides KS, Ottenbacher KJ. Frailty and diabetes among Mexican American older adults. *Annals of epidemiology* 2018; **28**(7): 421-6.e1.

303. Hubbard RE, Andrew MK, Fallah N, Rockwood K. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. *Diabetic medicine : a journal of the British Diabetic Association* 2010; **27**(5): 603-6.

304. Hyde Z, Smith K, Flicker L, et al. HbA1c Is Associated with Frailty in a Group of Aboriginal Australians. *The Journal of frailty & aging* 2019; **8**(1): 17-20.

305. Khan H, Kalogeropoulos AP, Georgiopoulou VV, et al. Frailty and risk for heart failure in older adults: the health, aging, and body composition study. *American heart journal* 2013; **166**(5): 887-94.

306. Khandelwal D, Goel A, Kumar U, Gulati V, Narang R, Dey A. Frailty is associated with longer hospital stay and increased mortality in hospitalized older patients. *The journal of nutrition, health & aging* 2012; **16**(8): 732-5.

307. Kirkwood RN, Borem IL, Sampaio RF, et al. Frailty Status and Gait Parameters of Older Women With Type 2 Diabetes. *Canadian journal of diabetes* 2019; **43**(2): 121-7.

308. Kitamura A, Taniguchi Y, Seino S, et al. Combined effect of diabetes and frailty on mortality and incident disability in older Japanese adults. *Geriatrics and Gerontology International* 2019; **19**(5): 423-8.

309. Lahousse L, Maes B, Ziere G, et al. Adverse outcomes of frailty in the elderly: the Rotterdam Study. *European journal of epidemiology* 2014; **29**(6): 419-27.

310. Lee JSW, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. *The journal of nutrition, health & aging* 2011; **15**(10): 857-62.

311. Lee JSW, Auyeung T-W, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *Journal of the American Medical Directors Association* 2014; **15**(4): 281-6.

312. Lee S, Harada K, Bae S, et al. Relationship between chronic kidney disease with diabetes or hypertension and frailty in community-dwelling Japanese older adults. *Geriatrics and Gerontology International* 2017; **17**(10): 1527-33.

313. Lekan DA, McCoy TP. Frailty risk in hospitalised older adults with and without diabetes mellitus. *Journal of clinical nursing* 2018; **27**(19-20): 3510-21.

314. Li CL, Stanaway FF, Lin JD, Chang HY. Frailty and health care use among community-dwelling older adults with diabetes: A population-based study. *Clinical Interventions in Aging* 2018; **13**: 2295-300.

315. Li G, Prior JC, Leslie WD, et al. Frailty and risk of fractures in patients with type 2 diabetes. *Diabetes Care* 2019; **42**(4): 507-13.

316. Li J, Nie S, Wang S, et al. Operationalization of Frailty Index in Diabetic Older Patients. *Journal of the American Medical Directors Association* 2016; **17**(3): 273-4.

317. Li Y, Zou Y, Wang S, et al. A Pilot Study of the FRAIL Scale on Predicting Outcomes in Chinese Elderly People With Type 2 Diabetes. *Journal of the American Medical Directors Association* 2015; **16**(8): 714.e7-.e12.

318. Li YX, Jiang XY, Stone C, et al. A new physical-cognitive scale for assessment of frailty in Chinese Han elderly. *Neurological Research* 2019; **41**(8): 728-33.

319. Liccini A, Malmstrom TK. Frailty and Sarcopenia as Predictors of Adverse Health Outcomes in Persons With Diabetes Mellitus. *Journal of the American Medical Directors Association* 2016; **17**(9): 846-51.

320. Lin CH, Chou CY, Liu CS, Huang CY, Li TC, Lin CC. Association between frailty and subclinical peripheral vascular disease in a community-dwelling geriatric population: Taichung Community Health Study for Elders. *Geriatrics and Gerontology International* 2015; **15**(3): 261-7.

321. MacKenzie HT, Tugwell B, Rockwood K, Theou O. Frailty and diabetes in older hospitalized adults: the case for routine frailty assessment. Canadian Journal of Diabetes. 2020 Apr 1;44(3):241-5.

322. Matsuzawa T, Sakurai T, Kuranaga M, Endo H, Yokono K. Predictive factors for hospitalized and institutionalized care-giving of the aged patients with diabetes mellitus in Japan. *The Kobe journal of medical sciences* 2011; **56**(4): E173-83.

323. McAlister FA, Lethebe BC, Lambe C, Williamson T, Lowerison M. Control of glycemia and blood pressure in British adults with diabetes mellitus and

subsequent therapy choices: a comparison across health states. *Cardiovascular diabetology* 2018; **17**(1): 27.

324. McAlister FA, Youngson E, Eurich DT. Treated glycosylated hemoglobin levels in individuals with diabetes mellitus vary little by health status: A retrospective cohort study. *Medicine* 2016; **95**(24): e3894.

325. McAlister FA, Youngson E, Eurich DT. Treatment Deintensification Is Uncommon in Adults With Type 2 Diabetes Mellitus: A Retrospective Cohort Study. *Circulation Cardiovascular quality and outcomes* 2017; **10**(4).

326. McClure R, Villain A. Greater adherence to a Mediterranean Diet is associated with better gait speed in older adults with type 2 diabetes mellitus. *Clinical Nutrition Espen* 2019; **32**: 33-9.

327. Merchant RA, Chen MZ, Tan LWL, Lim MY, Ho HK, van Dam RM. Singapore Healthy Older People Everyday (HOPE) Study: Prevalence of Frailty and Associated Factors in Older Adults. *Journal of the American Medical Directors Association* 2017; **18**(8): 734.

328. Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. Testosterone, sex hormone–binding globulin, and frailty in older men. *Journal of the American Geriatrics Society* 2007; **55**(4): 548-55.

329. Molist-Brunet N, Sevilla-Sánchez D, Puigoriol-Juvanteny E, González-Bueno J, Solà-Bonada N, Cruz-Grullón M, Espaulella-Panicot J. Optimizing drug therapy in frail patients with type 2 diabetes mellitus. Aging Clinical and Experimental Research. 2020 Aug;32(8):1551-9.

330. Moreira Bd.e S, Dos Anjos DM, Pereira DS, et al. The geriatric depression scale and the timed up and go test predict fear of falling in community-dwelling elderly women with type 2 diabetes mellitus: a cross-sectional study. *BMC geriatrics* 2016; **16**: 56.

331. Moreira BdS, Sampaio RF, Diz JBM, et al. Factors associated with fear of falling in community-dwelling older adults with and without diabetes mellitus:

Findings from the Frailty in Brazilian Older People Study (FIBRA-BR). *Experimental gerontology* 2017; **89**: 103-11.

332. Motokawa K, Watanabe Y, Edahiro A, et al. Frailty Severity and Dietary Variety in Japanese Older Persons: A Cross-Sectional Study. *The journal of nutrition, health & aging* 2018; **22**(3): 451-6.

333. Nadruz W, Jr., Kitzman D, Windham BG, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. *The journals of gerontology Series A, Biological sciences and medical sciences* 2017; **72**(7): 958-64.

334. Nelson JM, Dufraux K, Cook PF. The relationship between glycemic control and falls in older adults. *Journal of the American Geriatrics Society* 2007; **55**(12): 2041-4.

335. Ng TP, Feng L, Nyunt MSZ, Larbi A, Yap KB. Frailty in older persons: multisystem risk factors and the Frailty Risk Index (FRI). *Journal of the American Medical Directors Association* 2014; **15**(9): 635-42.

336. Nguyen AT, Nguyen LH, Nguyen TX, et al. Frailty prevalence and association with health-related quality of life impairment among rural community-dwelling older adults in Vietnam. *International Journal of Environmental Research and Public Health* 2019; **16**(20): 3869.

337. Nguyen TTH, Vu HTT, Nguyen TN, et al. Assessment of nutritional status in older diabetic outpatients and related factors in Hanoi, Vietnam. *Journal of Multidisciplinary Healthcare* 2019; **12**: 601-6.

338. Nishimura A, Harashima S, Hosoda K, Arai H, Inagaki N. Sex-related differences in frailty factors in older persons with type 2 diabetes: a cross-sectional study. *Ther Adv Endocrinol Metab* 2019; **10**: 14.

339. Orkaby AR, Lunetta KL, Sun FJ, et al. Cross-Sectional Association of Frailty and Arterial Stiffness in Community-Dwelling Older Adults: The Framingham

Heart Study. *The journals of gerontology Series A, Biological sciences and medical sciences* 2019; **74**(3): 373-9.

340. Ottenbacher KJ, Graham JE, Al Snih S, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. *American journal of public health* 2009; **99**(4): 673-9.

341. Pilotto A, Noale M, Maggi S, Addante F, Tiengo A, Perin PC, Rengo G, Crepaldi G. Hypoglycemia is independently associated with multidimensional impairment in elderly diabetic patients. BioMed Research International. 2014 Feb 13;2014.

342. Pollack LR, Litwack-Harrison S, Cawthon PM, et al. Patterns and Predictors of Frailty Transitions in Older Men: The Osteoporotic Fractures in Men Study. *Journal of the American Geriatrics Society* 2017; **65**(11): 2473-9.

343. Presley CA, Chipman J, Min JY, et al. Evaluation of Frailty as an Unmeasured Confounder in Observational Studies of Antidiabetic Medications. *J Gerontol Ser A-Biol Sci Med Sci* 2019; **74**(8): 1282-8.

344. Raji MA, Al Snih S, Ostir GV, Markides KS, Ottenbacher KJ. Cognitive status and future risk of frailty in older Mexican Americans. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2010; **65**(11): 1228-34.

345. Ricci NA, Pessoa GS, Ferriolli E, Dias RC, Perracini MR. Frailty and cardiovascular risk in community-dwelling elderly: a population-based study. *Clinical interventions in aging* 2014; **9**: 1677-85.

346. Saum KU, Müller H, Stegmaier C, Hauer K, Raum E, Brenner H. Development and Evaluation of a Modification of the F ried Frailty Criteria Using Population-Independent Cutpoints. *Journal of the American Geriatrics Society* 2012; **60**(11): 2110-5.

347. Simpson SH, Lin M, Eurich DT. Medication Adherence Affects Risk of New Diabetes Complications: A Cohort Study. *The Annals of pharmacotherapy* 2016; **50**(9): 741-6.

348. Sirola J, Pitkala K, Tilvis R, Miettinen T, Strandberg TE. Definition of frailty in older men according to questionnaire data (RAND-36/SF-36): The Helsinki Businessmen Study. *The journal of nutrition, health & aging* 2011; **15**(9): 783-7.

349. Tamura Y, Ishikawa J, Fujiwara Y, et al. Prevalence of frailty, cognitive impairment, and sarcopenia in outpatients with cardiometabolic disease in a frailty clinic. *BMC geriatrics* 2018; **18**(1): 264.

350. Tang Z, Wang C, Song X, et al. Co-occurrence of cardiometabolic diseases and frailty in older Chinese adults in the Beijing Longitudinal Study of Ageing. *Age and ageing* 2013; **42**(3): 346-51.

351. Tepper S, Alter Sivashensky A, Rivkah Shahar D, Geva D, Cukierman-Yaffe T. The Association between Mediterranean Diet and the Risk of Falls and Physical Function Indices in Older Type 2 Diabetic People Varies by Age. *Nutrients* 2018; **10**(6).

352. Thein FS, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is associated with diabetes and adversely impact functional status and mortality. *Postgraduate medicine* 2018; **130**(6): 561-7.

353. Tuttle LJ, Bittel DC, Bittel AJ, Sinacore DR. Early-Onset Physical Frailty in Adults With Diabesity and Peripheral Neuropathy. *Canadian journal of diabetes* 2018; **42**(5): 478-83.

354. Vaingankar JA, Chong SA, Abdin E, et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. *Geriatrics & Gerontology International* 2017; **17**(10): 1444-54.

355. van Hateren KJJ, Hendriks SH, Groenier KH, et al. Frailty and the relationship between blood pressure and mortality in elderly patients with type 2 diabetes (Zwolle Outpatient Diabetes project Integrating Available Care-34). *Journal of hypertension* 2015; **33**(6): 1162-6.

356. Vaz Fragoso CA, Gahbauer EA, Van Ness PH, Gill TM. Sleep–wake disturbances and frailty in community-living older persons. *Journal of the American Geriatrics Society* 2009; **57**(11): 2094-100.

357. Veronese N, Sigeirsdottir K, Eiriksdottir G, et al. Frailty and Risk of Cardiovascular Diseases in Older Persons: The Age, Gene/Environment Susceptibility-Reykjavik Study. *Rejuvenation research* 2017; **20**(6): 517-24.

358. Veronese N, Stubbs B, Fontana L, et al. Frailty Is Associated with an Increased Risk of Incident Type 2 Diabetes in the Elderly. *Journal of the American Medical Directors Association* 2016; **17**(10): 902-7.

359. Wang C-P, Lorenzo C, Espinoza SE. Frailty attenuates the impact of metformin on reducing mortality in older adults with type 2 diabetes. *Journal of endocrinology, diabetes & obesity* 2014; **2**(2).

360. Wang C-P, Lorenzo C, Habib SL, Jo B, Espinoza SE. Differential effects of metformin on age related comorbidities in older men with type 2 diabetes. *Journal of diabetes and its complications* 2017; **31**(4): 679-86.

361. Watanabe Y, Hirano H, Arai H, et al. Relationship Between Frailty and Oral Function in Community-Dwelling Elderly Adults. *Journal of the American Geriatrics Society* 2017; **65**(1): 66-76.

362. Weinstein G, Lutski M, Goldbourt U, Tanne D. Physical frailty and cognitive function among men with cardiovascular disease. *Archives of gerontology and geriatrics* 2018; **78**: 1-6.

363. Wong CH, Weiss D, Sourial N, et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in

Montreal: a cross-sectional study. *Aging clinical and experimental research* 2010; **22**(1): 54-62.

364. Wong TY, Sofia Massa M, O'Halloran AM, Kenny RA, Clarke R. Cardiovascular risk factors and frailty in a cross-sectional study of older people: Implications for prevention. *Age and Ageing* 2018; **47**(5): 714-20.

365. Woo J, Yang X, Lui LT, et al. Utility of the FRAIL Questionnaire in Detecting Heart Failure with Preserved Ejection Fraction. *Journal of Nutrition, Health and Aging* 2019; **23**(4): 373-7.

366. Wu C, Smit E, Xue Q-L, Odden MC. Prevalence and correlates of frailty among community-dwelling Chinese older adults: the China Health and Retirement Longitudinal Study. *The Journals of Gerontology: Series A* 2018; **73**(1): 102-8.

367. Wu IC, Shiesh S-C, Kuo P-H, Lin X-Z. High oxidative stress is correlated with frailty in elderly chinese. *Journal of the American Geriatrics Society* 2009; **57**(9): 1666-71.

368. Xue Q, Qin MZ, Jia J, Liu JP, Wang Y. Association between frailty and the cardio-ankle vascular index. *Clinical Interventions in Aging* 2019; **14**: 735-42.

369. Yanagita I, Fujihara Y, Eda T, et al. Low glycated hemoglobin level is associated with severity of frailty in Japanese elderly diabetes patients. *Journal of diabetes investigation* 2018; **9**(2): 419-25.

370. Zaslavsky O, Walker RL, Crane PK, Gray SL, Larson EB. Glucose Levels and Risk of Frailty. *The journals of gerontology Series A, Biological sciences and medical sciences* 2016; **71**(9): 1223-9.

371. Orkaby AR, Lunetta KL, Sun FGJ, et al. Cross-Sectional Association of Frailty and Arterial Stiffness in Community-Dwelling Older Adults: The Framingham Heart Study. *J Gerontol Ser A-Biol Sci Med Sci* 2019; **74**(3): 373-9.

372. Lee JSW, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *Journal of the American Medical Directors Association* 2014; **15**(4): 281-6.

373. Sinclair AJ, Abdelhafiz AH, Rodriguez-Manas L. Frailty and sarcopenia - newly emerging and high impact complications of diabetes. *Journal of diabetes and its complications* 2017; **31**(9): 1465-73.

374. Angulo J, El Assar M, Rodriguez-Manas L. Frailty and sarcopenia as the basis for the phenotypic manifestation of chronic diseases in older adults. *Molecular Aspects of Medicine* 2016; **50**: 1-32.

375. Travers J, Romero-Ortuno R, Bailey J, Cooney M-T. Delaying and reversing frailty: a systematic review of primary care interventions. *Br J Gen Pract* 2019; **69**(678): e61-e9.

376. American Diabetes Association. 12. Older adults: standards of medical care in diabetes—2019. *Diabetes Care* 2019; **42**(Supplement 1): S139-S47.

377. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA internal medicine* 2015; **175**(3): 356-62.

378. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *New England Journal of Medicine* 2011; **365**(21): 2002-12.

379. Miller ME, Williamson JD, Gerstein HC, et al. Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD trial. *Diabetes Care* 2014; **37**(3): 634-43.

380. Chiang JI, Jani BD, Mair FS, et al. Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review. *Plos one* 2018; **13**(12): e0209585.

381. Chiang JI, Hanlon P, Li T-C, et al. Multimorbidity, mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts. *PLos Med* 2020; **17**(5): e1003094.

382. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *European Journal of Public Health* 2019; **29**(1): 182-9.

383. Strain WD, Hope SV, Green A, Kar P, Valabhji J, Sinclair AJ. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative. *Diabetic medicine : a journal of the British Diabetic Association* 2018; **35**(7): 838-45.

384. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. *PloS one* 2016; **11**(9): e0162388.

385. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *Journal of clinical epidemiology* 1994; **47**(11): 1245-51.

386. Stirland LE, González-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ* 2020; **368**: m160.

387. Wallace E, McDowell R, Bennett K, Fahey T, Smith SM. Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study. *BMJ open* 2016; **6**(9).

388. Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North: Routledge; 1988.

389. Aguayo GA, Donneau AF, Vaillant MT, Schritz A, Franco OH, Stranges S, Malisoux L, Guillaume M, Witte DR. Agreement between 35 published frailty

scores in the general population. American journal of epidemiology. 2017 Aug 15;186(4):420-34.

390. Miller ME, Williamson JD, Gerstein HC, et al. Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD Trial. *Diabetes care* 2014; **37**(3): 634-43.

391. Barranco R, Gomez-Peralta F, Abreu C, et al. Incidence and care-related costs of severe hypoglycaemia requiring emergency treatment in Andalusia (Spain): the PAUEPAD project. *Diabetic Medicine* 2015; **32**(11): 1520-6.

392. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology* 2003; **14**(3): 300-6.

393. Salaffi F, Di Carlo M, Carotti M, Farah S, Ciapetti A, Gutierrez M. The impact of different rheumatic diseases on health-related quality of life: a comparison with a selected sample of healthy individuals using SF-36 questionnaire, EQ-5D and SF-6D utility values. *Acta Bio-medica: Atenei Parmensis* 2019; **89**(4): 541-57.

394. Salaffi F, Di Carlo M, Farah S, Carotti M. The Comprehensive Rheumatologic Assessment of Frailty (CRAF): development and validation of a multidimensional frailty screening tool in patients with rheumatoid arthritis. *Clinical and experimental rheumatology* 2020; **38**(3): 488-99.

395. Haider S, Grabovac I, Berner C, et al. Frailty in seropositive rheumatoid arthritis patients of working age: a cross-sectional study. *Clin Exp Rheumatol* 2019; **37**: 585-92.

396. Andrews JS, Trupin L, Yelin EH, Hough CL, Covinsky KE, Katz PP. Frailty and reduced physical function go hand in hand in adults with rheumatoid arthritis: a US observational cohort study. *Clinical rheumatology* 2017; **36**(5): 1031-9.

397. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLos Med* 2009; **6**(7): e1000097.

398. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int* 2018; **121**(Pt 1): 1027.

399. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62**(9): 2569-81.

400. Crowther M, Avenell A, MacLennan G, Mowatt G. A further use for the Harvest plot: a novel method for the presentation of data synthesis. *Research Synthesis Methods* 2011; **2**(2): 79-83.

401. Wysham KD, Shoback DM, Andrews JS, Katz PP. Sex differences in frailty and its association with low bone mineral density in rheumatoid arthritis. *Bone reports* 2020; **12**: 100284.

402. Andrews JS, Trupin L, Wysham KD, Hough CL, Yelin EH, Katz PP. The Impact of Frailty on Changes in Physical Function and Disease Activity Among Adults With Rheumatoid Arthritis. *ACR open rheumatology* 2019; **1**(6): 366-72.

403. Bak E, Mlynarska A, Marcisz C, Bobinski R, Sternal D, Mlynarski R. Factors that affect the assessment of the quality of life of rheumatoid arthritis patients depending on the prevalence of frailty syndrome. *Health and quality of life outcomes* 2020; **18**(1): 216.

404. Kojima M, Kojima T, Waguri-Nagaya Y, Takahashi N, Asai S, Sobue Y, Nishiume T, Suzuki M, Mitsui H, Kawaguchi Y, Kuroyanagi G. Depression, physical function, and disease activity associated with frailty in patients with rheumatoid arthritis. Modern rheumatology. 2021 Sep 3;31(5):979-86.

405. Li G, Chen M, Li X, et al. Frailty and risk of osteoporotic fractures in patients with rheumatoid arthritis: Data from the Ontario Best Practices Research Initiative. *Bone* 2019; **127**: 129-34.

406. Minamino H, Katsushima M, Torii M, et al. Habitual fish intake negatively correlates with prevalence of frailty among patients with rheumatoid arthritis. *Scientific reports* 2021; **11**(1): 5104.

407. Oetsma S, Boonen A, Starmans M, Peeters R, van Onna M. Validation of two frailty questionnaires in older patients with rheumatoid arthritis: a cross-sectional study. *Clinical and experimental rheumatology* 2020; **38**(3): 523-8.

408. Salaffi F, Di Carlo M, Farah S, Di Donato E, Carotti M. Prevalence of frailty and its associated factors in patients with rheumatoid arthritis: a cross-sectional analysis. *Clinical Rheumatology* 2019; **38**(7): 1823-30.

409. Tada M, Yamada Y, Mandai K, Hidaka N. Correlation between frailty and disease activity in patients with rheumatoid arthritis: Data from the CHIKARA study. *Geriatrics & gerontology international* 2019; **19**(12): 1220-5.

410. Tada M, Yamada Y, Mandai K, Hidaka N. Relationships of the stand-up time to falls and fractures in patients with rheumatoid arthritis: Results from the CHIKARA study. *International journal of rheumatic diseases* 2021; **24**(2): 246-53.

411. Yoshii I, Chijiwa T, Sawada N. Validity of adopting a Health Assessment Questionnaire Disability Index less than 0.5 as a target in elderly rheumatoid arthritis patients. *Clinical Rheumatology* 2019; **38**(12): 3351-60.

412. Yoshii I, Kondo M. Clinical Characteristics of frailty in Japanese Rheumatoid Arthritis Patients. *The Journal of frailty & aging* 2020; **9**(3): 158-64.

413. Satake S, Senda K, Hong YJ, et al. Validity of the K ihon Checklist for assessing frailty status. *Geriatrics & gerontology international* 2016; **16**(6): 709-15.

414. Yamada M, Arai H. Predictive value of frailty scores for healthy life expectancy in community-dwelling older Japanese adults. *Journal of the American Medical Directors Association* 2015; **16**(11): 1002. e7-. e11.

415. Gobbens RJ, Schols JM, Van Assen MA. Exploring the efficiency of the Tilburg Frailty Indicator: a review. *Clinical interventions in aging* 2017; **12**: 1739.

416. Bellera C, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Annals of Oncology* 2012; **23**(8): 2166-72.

417. Hanlon P, Butterly E, Lewsey J, Siebert S, Mair FS, McAllister DA. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. *BMC Med* 2020; **18**(1): 1-12.

418. Nikolaus S, Bode C, Taal E, van de Laar MA. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken)* 2013; **65**(7): 1128-46.

419. Santo RC, Fernandes KZ, Lora PS, Filippin LI, Xavier RM. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. *Journal of cachexia, sarcopenia and muscle* 2018; **9**(5): 816-25.

420. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum* 2004; **50**(11): 3450-7.

421. Book C, Karlsson MK, Åkesson K, Jacobsson LT. Early rheumatoid arthritis and body composition. *Rheumatology (Oxford)* 2009; **48**(9): 1128-32.

422. Mochizuki T, Yano K, Ikari K, Okazaki K. Sarcopenia-associated factors in Japanese patients with rheumatoid arthritis: A cross-sectional study. *Geriatrics & gerontology international* 2019; **19**(9): 907-12.

423. Giles JT, Ling SM, Ferrucci L, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. *Arthritis Care & Research: Official Journal of the American College of Rheumatology* 2008; **59**(6): 807-15.

424. Petermann-Rocha F, Chen M, Gray SR, Ho FK, Pell JP, Celis-Morales C. Factors associated with sarcopenia: A cross-sectional analysis using UK Biobank. *Maturitas* 2020; **133**: 60-7.

425. Munro R, Capell H. Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. *Annals of the rheumatic diseases* 1997; **56**(5): 326-9.

426. Doğan SC, Hizmetli S, Hayta E, Kaptanoğlu E, Erselcan T, Güler E. Sarcopenia in women with rheumatoid arthritis. *European journal of rheumatology* 2015; **2**(2): 57.

427. McQueenie R, Nicholl BI, Jani BD, et al. Patterns of multimorbidity and their effects on adverse outcomes in rheumatoid arthritis: a study of 5658 UK Biobank participants. *BMJ open* 2020; **10**(11): e038829.

428. Hanlon P, Morton F, Siebert S, et al. Frailty in people with rheumatoid arthritis: a systematic review of observational studies [version 1; peer review: awaiting peer review]. . *Wellcome Open Research* 2021; **6**(244).

429. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2004; **59**(3): M255-M63.

430. Canning J, Siebert S, Jani BD, Mair FS, Nicholl BI. Examining the relationship between rheumatoid arthritis, multimorbidity and adverse health-related outcomes: a systematic review protocol. Journal of comorbidity. 2020 Mar 5;10:2235042X20906657.

431. Kronisch C, McLernon DJ, Dale J, et al. Brief report: Predicting functional disability: One-year results from the Scottish early rheumatoid arthritis inception cohort. *Arthritis rheumatol* 2016; **68**(7): 1596-602.

432. Scottish Executive. Scottish index of multiple deprivation 2006 technical report. *Office of the Chief Statistician, Scottish Executive* 2006: 10.

433. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). *Arthritis Care Res (Hoboken)* 2011; **63**(S11): S4-S13.

434. Hanlon P, Jani BD, Nicholl B, Lewsey J, McAllister DA, Mair FS. Associations between multimorbidity and adverse health outcomes in UK Biobank and the SAIL Databank: A comparison of longitudinal cohort studies. PLoS medicine. 2022 Mar 7;19(3):e1003931.

435. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease. *Chronic Respiratory Disease* 2017; **14**(1): 85-99.

436. Bousquet J, Dinh-Xuan AT, Similowski T, et al. Should we use gait speed in COPD, FEV1 in frailty and dyspnoea in both? : Eur Respiratory Soc; 2016.

437. Charbek E, Espiritu JR, Nayak R, Morley JE. Frailty, Comorbidity, and COPD. *Journal of Nutrition, Health and Aging* 2018; **22**(8): 876-9.

438. Luo J, Dai Zhang WT, Dou L-Y, Sun Y. Impact of Frailty on the Risk of Exacerbations and All-Cause Mortality in Elderly Patients with Stable Chronic Obstructive Pulmonary Disease. *Clinical Interventions in Aging* 2021; **16**: 593.

439. Yee N, Locke ER, Pike KC, et al. Frailty in chronic obstructive pulmonary disease and risk of exacerbations and hospitalizations. *International Journal of COPD* 2020; **15**: 1967-76.

440. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *Journal of Clinical Epidemiology* 2021; **134**: 103-12.

441. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *International Journal of Surgery* 2010; **8**(5): 336-41.

442. Akgun KM, Tate JP, Oursler KK, et al. Association of chronic obstructive pulmonary disease with frailty measurements in HIV-infected and uninfected Veterans. *AIDS* 2016; **30**(14): 2185-93.

443. Bernabeu-Mora R, Garcia-Guillamon G, Valera-Novella E, Gimenez-Gimenez LM, Escolar-Reina P, Medina-Mirapeix F. Frailty is a predictive factor of readmission within 90 days of hospitalization for acute exacerbations of chronic obstructive pulmonary disease: a longitudinal study. *Therap* 2017; **11**(10): 383-92.

444. Bernabeu-Mora R, Oliveira-Sousa SL, Piedad Sanchez-Martinez M, Garcia-Vidal JA, Gacto-Sanchez M, Medina-Mirapeix F. Frailty transitions and associated clinical outcomes in patients with stable COPD: A longitudinal study. *PLoS ONE* 2020; **15**(4).

445. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *Journal of the American Geriatrics Society* 2005; **53**(6): 927-34.

446. Castellana F, Lampignano L, Bortone I, et al. Physical Frailty, Multimorbidity, and All-Cause Mortality in an Older Population From Southern Italy: Results from the Salus in Apulia Study. *Journal of the American Medical Directors Association* 2021; **22**(3): 598-605.

447. Chen PJ, Yang KY, Perng WC, Lin KC, Wang KY. Effect of dyspnea on frailty stages and related factors in Taiwanese men with COPD. *International Journal of Copd* 2018; **13**: 2463-9.

448. Chin M, Voduc N, Huang S, Forster A, Mulpuru S. Practical lessons in implementing frailty assessments for hospitalised patients with COPD. *BMJ open qual* 2020; **9**(1): 01.

449. de Albuquerque Sousa ACP, Dias RC, Maciel ÁCC, Guerra RO. Frailty syndrome and associated factors in community-dwelling elderly in Northeast Brazil. *Archives of gerontology and geriatrics* 2012; **54**(2): e95-e101.

450. Dias LD, Ferreira ACG, da Silva JLR, Conte MB, Rabahi MF. Prevalence of Frailty and Evaluation of Associated Variables Among COPD Patients. *International Journal of Chronic Obstructive Pulmonary Disease* 2020; **15**: 1349-56.

451. Fragoso CAV, Enright PL, McAvay G, Van Ness PH, Gill TM. Frailty and respiratory impairment in older persons. *The American journal of medicine* 2012; **125**(1): 79-86.

452. Gale NS, Albarrati AM, Munnery MM, et al. Frailty: A global measure of the multisystem impact of COPD. *Chronic respiratory disease* 2018; **15**(4): 347-55.

453. Galizia G, Cacciatore F, Testa G, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clin Exp Res* 2011; **23**(2): 118-25.

454. Gephine S, Grosbois JM, Saey D, Maltais F, Mucci P. Effects of home-based pulmonary rehabilitation on physical frailty in people with COPD and chronic respiratory failure. *European Respiratory Journal Conference: European Respiratory Society International Congress, ERS* 2020; **56**(Supplement 64).

455. Gu J-J, Liu Q, Zheng L-J. A Frailty Assessment Tool to Predict In-Hospital Mortality in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *International Journal of Chronic Obstructive Pulmonary Disease* 2021; **16**: 1093.

456. Hirai K, Tanaka A, Homma T, et al. Comparison of three frailty models and a sarcopenia model in elderly patients with chronic obstructive pulmonary disease. *Geriatrics & gerontology international* 2019; **19**(9): 896-901.

457. Ierodiakonou D, Kampouraki M, Poulonirakis I, et al. Determinants of frailty in primary care patients with COPD: the Greek UNLOCK study. *BMC pulmonary medicine* 2019; **19**(1): 63.

458. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. *Annals of the American Thoracic Society* 2019; **16**(2): 217-24.

459. Kim S, Jung HW, Won CW. What are the illnesses associated with frailty in community-dwelling older adults: The Korean frailty and aging cohort study. *Korean Journal of Internal Medicine* 2020; **35**(4): 1004-13.

460. Kusunose M, Oga T, Nakamura S, Hasegawa Y, Nishimura K. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: Are they independent entities? *BMJ Open Respir Res* 2017; **4**(1).

461. Lahousse L, Ziere G, Verlinden VJ, et al. Risk of Frailty in Elderly With COPD: A Population-Based Study. *J Gerontol A Biol Sci Med Sci* 2016; **71**(5): 689-95.

462. Lai HY, Chang HT, Lee YL, Hwang SJ. Association between inflammatory markers and frailty in institutionalized older men. *Maturitas* 2014; **79**(3): 329-33.

463. Limpawattana P, Putraveephong S, Inthasuwan P, Boonsawat W, Theerakulpisut D, Chindaprasirt J. Frailty syndrome in ambulatory patients with COPD. *International Journal of Copd* 2017; **12**: 1193-8.

464. Liotta G, O'Caoimh R, Gilardi F, et al. Assessment of frailty in community-dwelling older adults residents in the Lazio region (Italy): A model to plan regional community-based services. *Archives of Gerontology and Geriatrics* 2017; **68**: 1-7.

465. Ma L, Tang Z, Zhang L, Sun F, Li Y, Chan P. Prevalence of Frailty and Associated Factors in the Community-Dwelling Population of China. *Journal of the American Geriatrics Society* 2018; **66**(3): 559-64.

466. Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax* 2016; **71**(11): 988-95.

467. Medina-Mirapeix F, Bernabeu-Mora R, Garcia-Guillamon G, Novella EV, Gacto-Sanchez M, Garcia-Vidal JA. Patterns, trajectories, and predictors of functional decline after hospitalization for acute exacerbations in men with moderate to severe chronic obstructive pulmonary disease: A longitudinal study. *PLoS ONE* 2016; **11**(6).

468. Medina-Mirapeix F, Bernabeu-Mora R, Gimenez-Gimenez LM, Escolar-Reina P, Gacto-Sanchez M, de Oliveira-Sousa SL. Physical frailty characteristics have a differential impact on symptoms as measured by the CAT score: an observational study. *Health Qual Life Outcomes* 2018; **16**(1): 140.

469. Nagorni-Obradovic LM, Vukovic DS. The prevalence of COPD co-morbidities in Serbia: results of a national survey. *NPJ Prim Care Respir Med* 2014; **24**: 14008.

470. Oishi K, Matsunaga K, Harada M, et al. A new dyspnea evaluation system focusing on patients' perceptions of dyspnea and their living disabilities: The linkage between copd and frailty. *Journal of Clinical Medicine* 2020; **9**(11): 1-13.

471. Park SK, Richardson CR, Holleman RG, Larson JL. Frailty in people with COPD, using the National Health and Nutrition Evaluation Survey dataset (2003-2006). *Heart & lung : the journal of critical care* 2013; **42**(3): 163-70.

472. Park SK. Frailty in Korean patients with chronic obstructive pulmonary disease, using data from the Korea National Health and Nutrition Examination Survey, 2015 and 2016. *Applied Nursing Research* 2021; **59**: 151417.

473. Serra-Prat M, Papiol M, Vico J, Palomera E, Sist X, Cabre M. Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. *European Geriatric Medicine* 2016; **7**(6): 531-7.

474. ter Beek L, van der Vaart H, Wempe JB, et al. Coexistence of malnutrition, frailty, physical frailty and disability in patients with COPD starting a pulmonary rehabilitation program. *Clinical Nutrition* 2020; **39**(8): 2557-63.

475. Uchmanowicz I, Jankowska-Polanska B, Chabowski M, Uchmanowicz B, Fal AM. The influence of frailty syndrome on acceptance of illness in elderly patients with chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* 2016; **11**: 2401-7.

476. Valenza MC, Torres-Sanchez I, Cabrera-Martos I, Rodriguez-Torres J, Gonzalez-Jimenez E, Munoz-Casaubon T. Physical Activity as a Predictor of Absence of Frailty in Subjects With Stable COPD and COPD Exacerbation. *Respiratory Care* 2016; **61**(2): 212-9.

477. Warwick M, Fernando SM, Aaron SD, Rochwerg B, Tran A, Thavorn K, Mulpuru S, McIsaac DI, Thompson LH, Tanuseputro P, Kyeremanteng K. Outcomes and resource utilization among patients admitted to the intensive care unit following acute exacerbation of chronic obstructive pulmonary disease. Journal of intensive care medicine. 2021 Sep;36(9):1091-7.

478. Zhang Y, Zhang Y, Li Y, Chan P, Ma L. Reliability and validity of the self-reported frailty screening questionnaire in older adults. Therapeutic advances in chronic disease. 2020 Feb;11:2040622320904278.

479. Cesari M, Demougeot L, Boccalon H, et al. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. *PloS one* 2014; **9**(7): e101745.

480. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Archives of internal medicine* 2008; **168**(4): 382-9.

481. Lachs MS, Feinstein AR, Cooney Jr LM, et al. A simple procedure for general screening for functional disability in elderly patients. *Annals of internal medicine* 1990; **112**(9): 699-706.

482. Scarcella P, Liotta G, Marazzi M, Carbini R, Palombi L. Analysis of survival in a sample of elderly patients from Ragusa, Italy on the basis of a primary care level multidimensional evaluation. *Archives of gerontology and geriatrics* 2005; **40**(2): 147-56.

483. Bousquet J, Dinh-Xuan AT, Similowski T, et al. Should we use gait speed in COPD, FEV1 in frailty and dyspnoea in both? *European Respiratory Journal* 2016; **48**(2): 315-9.

484. Barnes P, Celli B. Systemic manifestations and comorbidities of COPD. *European respiratory journal* 2009; **33**(5): 1165-85.

485. Natanek SA, Gosker HR, Slot IG, et al. Heterogeneity of quadriceps muscle phenotype in chronic obstructive pulmonary disease (COPD); implications for stratified medicine? *Muscle Nerve* 2013; **48**(4): 488-97.

486. Agustí A, Faner R. COPD beyond smoking: new paradigm, novel opportunities. *The Lancet Respiratory Medicine* 2018; **6**(5): 324-6.

487. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest* 2009; **135**(1): 173-80.

488. Rutten EP, Gopal P, Wouters EF, et al. Various mechanistic pathways representing the aging process are altered in COPD. *Chest* 2016; **149**(1): 53-61.

489. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet* 2012; **380**(9859): 2095-128.

490. Incalzi RA. Epidemiological overview and clinical picture of COPD in the elderly. *Journal of Gerontology and Geriatrics* 2016; **64**: 119-25.

491. Singer JP, Lederer DJ, Baldwin MR. Frailty in pulmonary and critical care medicine. *Annals of the American Thoracic Society* 2016; **13**(8): 1394-404.

492. Sin DD, Man SP. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proceedings of the American Thoracic Society* 2005; **2**(1): 8-11.

493. Lahousse L, Ziere G, Verlinden VJ, et al. Risk of Frailty in Elderly With COPD: A Population-Based Study. *The journals of gerontology* 2016; **Series A, Biological sciences and medical sciences. 71**(5): 689-95.

494. Quint JK, Müllerova H, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open* 2014; **4**(7): e005540.

495. Rothnie KJ, Chandan JS, Goss HG, Muellerova H, Quint JK. Validity and interpretation of spirometric recordings to diagnose COPD in UK primary care. *International journal of chronic obstructive pulmonary disease* 2017; **12**: 1663.

496. De Matteis S, Jarvis D, Hutchings S, et al. Occupations associated with COPD risk in the large population-based UK Biobank cohort study. *Occupational and environmental medicine* 2016; **73**(6): 378-84.

497. Rothnie KJ, Müllerová H, Thomas SL, et al. Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. *Clin Epidemiol* 2016; **8**: 771.

498. Rothnie KJ, Müllerová H, Hurst JR, et al. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. *PLOS ONE* 2016; **11**(3): e0151357.

499. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2004; **350**(10): 1005-12.

500. Ridda I, Lindley R, MacIntyre RC. The challenges of clinical trials in the exclusion zone: the case of the frail elderly. *Australasian Journal on Ageing* 2008; **27**(2): 61-6.

501. van der Cammen TJ, Crome P. Persistent exclusion of older people from clinical trials of cardiovascular and antithrombotic medicinal products. Springer; 2018.

502. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med* 2015; **13**(1): 78.

503. Pajewski NM, Williamson JD, Applegate WB, et al. Characterizing frailty status in the systolic blood pressure intervention trial. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2016; **71**(5): 649-55.

504. Sanders NA, Supiano MA, Lewis EF, et al. The frailty syndrome and outcomes in the TOPCAT trial. *European journal of heart failure* 2018; **20**(11): 1570-7.

505. White HD, Westerhout CM, Alexander KP, et al. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: Insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *European Heart Journal: Acute Cardiovascular Care* 2016; **5**(3): 231-42.

506. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama* 2007; **297**(11): 1233-40.

507. Sinclair A, Morley JE, Rodriguez-Manas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for

Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *Journal of the American Medical Directors Association* 2012; **13**(6): 497-502.

508. Dalal DS, Duran J, Brar T, et al. Efficacy and safety of biological agents in the older rheumatoid arthritis patients compared to Young: A systematic review and meta-analysis. Seminars in arthritis and rheumatism; 2019: Elsevier; 2019. p. 799-807.

509. Collerton J, Martin-Ruiz C, Davies K, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. *Mechanisms of ageing and development* 2012; **133**(6): 456-66.

510. Scichilone N, Basile M, Battaglia S, Bellia V. What proportion of chronic obstructive pulmonary disease outpatients is eligible for inclusion in randomized clinical trials? *Respiration* 2014; **87**(1): 11-7.

511. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *Journal of clinical epidemiology* 1999; **52**(12): 1143-56.

512. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D: Springer Netherlands Dordrecht; 2014.

513. Weatherall M, Marsh S, Shirtcliffe P, Williams M, Travers J, Beasley R. Quality of life measured by the St George's Respiratory Questionnaire and spirometry. *European Respiratory Journal* 2009; **33**(5): 1025-30.

514. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of internal medicine* 2010; **152**(11): 726-32.

515. Theou O, O 'Connell M, King-Kallimanis B, O'Halloran A, Rockwood K, Kenny R. Measuring frailty using self-report and test-based health measures. *Age and ageing* 2015; **44**(3): 471-7.

516. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. *International journal of epidemiology* 2018; **47**(1): 226-35.

517. Morley JE, Vellas B, Van Kan GA, et al. Frailty consensus: a call to action. *Journal of the American Medical Directors Association* 2013; **14**(6): 392-7.

518. Xue Q-L, Tian J, Walston JD, Chaves PHM, Newman AB, Bandeen-Roche K. Discrepancy in Frailty Identification: Move Beyond Predictive Validity. *The Journals of Gerontology: Series A* 2019; **75**(2): 387-93.

519. Machado-Fragua MD, Hoogendijk EO, Struijk EA, et al. High dephospho-uncarboxylated matrix Gla protein concentrations, a plasma biomarker of vitamin K, in relation to frailty: The Longitudinal Aging Study Amsterdam. *European Journal of Nutrition* 2020; **59**(3): 1243-51.

520. Li G, Papaioannou A, Thabane L, Cheng J, Adachi JD. Frailty change and major osteoporotic fracture in the elderly: data from the global longitudinal study of osteoporosis in women 3-year Hamilton cohort. *Journal of Bone and Mineral Research* 2016; **31**(4): 718-24.

521. Stolz E. HM, É. Rásky, W. Freidl. Does Sample Attrition Affect the Assessment of Frailty Trajectories Among Older Adults? A Joint Model Approach: Gerontology; 2018.

522. Stolz E, Mayerl H, Freidl W. Fluctuations in frailty among older adults. *Age and Ageing* 2019; **48**(4): 547-52.

523. Kojima G, Taniguchi Y, Iliffe S, Urano T, Walters K. Factors Associated With Improvement in Frailty Status Defined Using the Frailty Phenotype: A Systematic Review and Meta-analysis. *Journal of the American Medical Directors Association* 2019; **20**(12): 1647-9.e2.

524. Jang AR, Won CW, Sagong H, Bae E, Park H, Yoon JY. Social factors predicting improvement of frailty in community-dwelling older adults: Korean

Frailty and Aging Cohort Study. *Geriatrics & Gerontology International* 2021; **21**(6): 465-71.

525. Mair FS, May CR. Thinking about the burden of treatment. Bmj. 2014 Nov 10;349.

526. Hanlon P, Blane DN, Macdonald S, Mair FS, O'Donnell CA. Our response to rising frailty in younger people must address prevention burden. *The Lancet Healthy Longevity* 2021; **2**(5): e245.

Appendices

Appendix 1: Manuscript describing the selection of trial individual participant data and the quantification of comorbidities in clinical trials

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Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis

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Abstract

Background: Clinicians are less likely to prescribe guideline-recommended treatments to people with multimorbidity than to people with a single condition. Doubts as to the applicability of clinical trials of drug treatments (the gold standard for evidence-based medicine) when people have co-existing diseases (comorbidity) may underlie this apparent reluctance. Therefore, for a range of index conditions, we measured the comorbidity among participants in clinical trials of novel drug therapies and compared this to the comorbidity among patients in the community.

Methods: Data from industry-sponsored phase 3/4 multicentre trials of novel drug therapies for chronic medical conditions were identified from two repositories: Clinical Study Data Request and the Yale University Open Data Access project. We identified 116 trials ($n = 122{,}969$ participants) for 22 index conditions. Community patients were identified from a nationally representative sample of 2.3 million patients in Wales, UK. Twenty-one comorbidities were identified from medication use based on pre-specified definitions. We assessed the prevalence of each comorbidity and the total number of comorbidities (level of multimorbidity), for each trial and in community patients.

Results: In the trials, the commonest comorbidities in order of declining prevalence were chronic pain, cardiovascular disease, arthritis, affective disorders, acid-related disorders, asthma/COPD and diabetes. These conditions were also common in community-based patients.
Mean comorbidity count for trial participants was approximately half that seen in community-based patients. Nonetheless, a substantial proportion of trial participants had a high degree of multimorbidity. For example, in asthma and psoriasis trials, 10–15% of participants had ≥ 3 conditions overall, while in osteoporosis and chronic obstructive pulmonary disease trials 40–60% of participants had ≥ 3 conditions overall.

Conclusions: Comorbidity and multimorbidity are less common in trials than in community populations with the same index condition. Comorbidity and multimorbidity are, nevertheless, common in trials. This suggests that standard, industry-funded clinical trials are an underused resource for investigating treatment effects in people with comorbidity and multimorbidity.

Keywords: Randomised controlled trials, Comorbidity, Multimorbidity

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Background

Drug treatments that have been recommended in evidence-based clinical guidelines are less likely to be prescribed to people with multimorbidity (defined as people with two or more conditions) [1–5]. One reason for this difference in prescribing is that the populations included in clinical trials, which underpin evidence-based guidelines, are believed to be unrepresentative of people with multimorbidity [6, 7].

Comorbidity (the presence of other conditions in addition to a specified index condition) [8] may influence the effectiveness of treatments for specific conditions through competing risks, drug-drug, drug-disease and disease-disease interactions, altering the balance of risks and benefits [9–11]. Underrepresentation of people with multimorbidity in clinical trials is therefore concerning.

However, most studies examining clinical trial representativeness have done so by analysing routine clinical practice data (e.g. from disease registers and electronic health records) to which trial eligibility criteria have been applied [12–17]. Since factors other than eligibility criteria are likely to influence which people are recruited to clinical trials [18], such approaches provide only indirect evidence about the prevalence of comorbidity and multimorbidity in trial participants.

We examined the prevalence of comorbidity and multimorbidity among 122,969 participants from 116 industry-funded trials of novel drug therapies for 22 index conditions and compared these results with comorbidity and multimorbidity prevalence in 2.3 million patients living in the community.

Methods

Study design

This cross-sectional analysis compares the distribution of comorbidity and multimorbidity in participants enrolled in 116 industry-sponsored trials and a representative community sample from the UK. All analyses were pre-specified (Additional file 1).

Data sources and participants

Trials

We accessed individual-level participant data (IPD) from industry-sponsored trials from two repositories: the Clinical Study Data Request (CSDR) and the Yale University Open Data Access (YODA) project (on 21 November 2016 and 18 May 2018, respectively). From this set, trials were selected according to a pre-specified protocol (Prospero CRD42018048202) [19]. Briefly, eligible trials were registered with the US Clinical Trials register (clincialtrials.gov), had a start date on or after 1 January 1990 (based on scoping showing that trials where IPD was available had started on or after this date), were phase 2/3, 3 or 4, recruited ≥ 300 participants, had an upper age limit ≥ 60 years (or no maximum) and evaluated drugs for a selected set of chronic conditions (Fig. 1). Conditions were chosen on the basis that they require long-term pharmacological therapy. We selected a range of cardiovascular, respiratory, gastrointestinal, musculoskeletal, metabolic, autoimmune and connective tissue, and urological and otolaryngological disorders. A full list of eligible conditions is shown in Additional file 1: Table S1.8. Trials for neoplastic, infectious, affective, psychotic or developmental disorders were excluded, as were trials of primary prevention in general populations without an index condition (see Additional file 1). Only randomised participants were included in analyses. We also searched the National Institutes of Health (NIH) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) repository in August 2017, but no trials from this source were eligible because of lack of reported data on comorbidities.

Community sample

A community sample was identified using the Secure Anonymised Information Linkage (SAIL) Databank, which is a repository of health and administrative data covering 70% of Wales's population of three million [20]. This sample is nationally representative in terms of age, sex and socioeconomic status (Additional file 2). We included people registered with a participating primary care practice between 1 January 2011 and 1 January 2012 (2,289,583 people). This time period was chosen after accessing the primary care data, prior to further analysis, as coding of prescribing data was most complete from this point onwards.

Index conditions

For trial data, index conditions were defined by the treatment indication, described in the trial registration. Trials were then grouped by index condition.

For the community sample, we used codes from the Read classification system to identify people with each index condition. Read codes are a coding scheme used in UK primary care electronic health records [21]. The index condition definitions were adapted from published literature and from definitions used in the Quality & Outcomes Framework, a pay-for-performance programme which has incentivised coding for common chronic conditions (Additional file 3) [1, 22, 23]. For defining asthma, hypertension, type 2 diabetes, migraine and thromboembolic disease, prescribed medications were also used, alongside diagnostic codes, to confirm that conditions were receiving active pharmacological treatment [1].

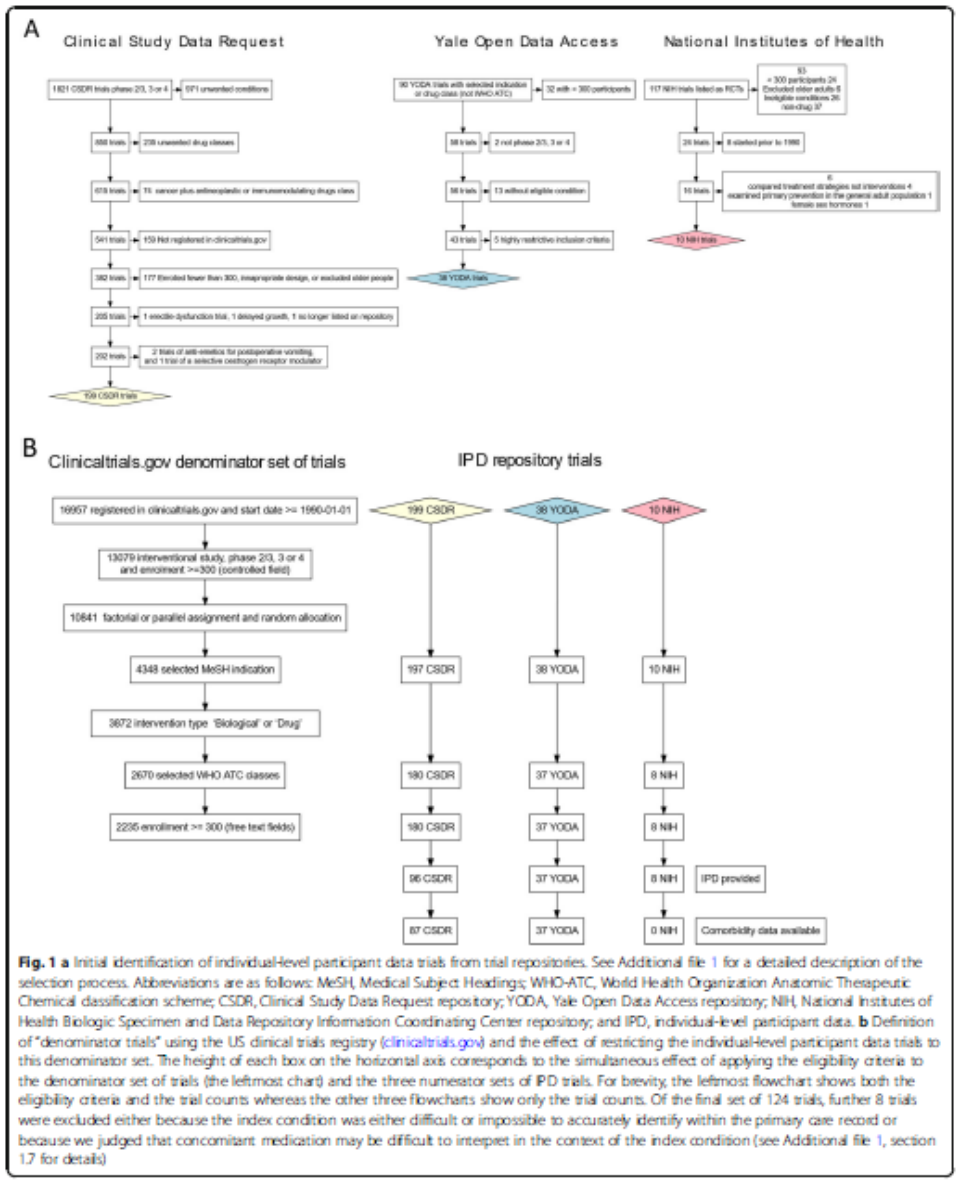

Fig. 1 a Initial identification of individual-level participant data trials from trial repositories. See Additional file 1 for a detailed description of the selection process. Abbreviations are as follows: MeSH, Medical Subject Headings; WHO-ATC, World Health Organization Anatomic Therapeutic Chemical classification scheme; CSDR, Clinical Study Data Request repository; YODA, Yale Open Data Access repository; NIH, National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center repository; and IPD, individual-level participant data. **b** Definition of "denominator trials" using the US clinical trials registry (clinicaltrials.gov) and the effect of restricting the individual-level participant data trials to this denominator set. The height of each box on the horizontal axis corresponds to the simultaneous effect of applying the eligibility criteria to the denominator set of trials (the leftmost chart) and the three numerator sets of IPD trials. For brevity, the leftmost flowchart shows both the eligibility criteria and the trial counts whereas the other three flowcharts show only the trial counts. Of the final set of 124 trials, further 8 trials were excluded either because the index condition was either difficult or impossible to accurately identify within the primary care record or because we judged that concomitant medication may be difficult to interpret in the context of the index condition (see Additional file 1, section 1.7 for details)

Quantifying comorbidities

Medical history data was frequently redacted in the trial datasets to maintain patient confidentiality, and even when provided, different terminologies were used. In contrast, all the trials providing data on concomitant medication used the World Health Organization Anatomic Therapeutic Chemical (WHO-ATC) system, the de facto standard for drug coding in clinical trials [24]. We therefore used concomitant medication data to identify 21 comorbidities in both the trial and community datasets.

Trials either reported the ATC codes directly or reported preferred terms often along with the drug route. In the latter case, we used RxNorm (the US drug metathesaurus) [25], the UK British National Formulary [21] and manual review to assign ATC codes. Trial concomitant medications were defined as any drug started on or before the randomisation date.

For the community sample, we used the NHS Business Authority ATC to Read code lookup table (as processed by the OpenPrescribing project) [26]. For drugs not found in the lookup table, we manually mapped Read code-defined drugs to ATC codes. Any drug prescribed during 2011 was included.

The following comorbidities (detailed in Additional file 4) were identified based on medication use: cardiovascular disease, chronic pain, arthritis, affective disorders, acid-related disorders, asthma/chronic obstructive pulmonary disease, diabetes mellitus, osteoporosis, thyroid disease, thromboembolic disease, inflammatory conditions, benign prostatic hyperplasia, gout, glaucoma, urinary incontinence, erectile dysfunction, psychotic disorders, epilepsy, migraine, parkinsonism and dementia. These drug-based definitions were developed in consultation with a steering committee comprising clinicians, epidemiologists and statisticians and were finalised before the analysis of the primary care data.

For each patient/participant, and within each index condition, we summed the number of individual comorbidities, not including the index condition, to obtain a comorbidity count.

Statistical analysis

Individual-level participant data were held on the YODA repository for one trial sponsor, on the CSDR secure platform for the other trial sponsors and on the SAIL secure platform for the community sample. These platforms only allow export of non-disclosive aggregate-level data. We could not, therefore, include all individual-level data in a single model.

Therefore, for each trial, we summed the number of participants with each comorbidity count and exported this from each secure environment, along with the age-sex distribution of participants. For each indication, we obtained the number of community patients with each comorbidity count within age-sex-specific strata and directly standardised these to a weighted average of the trial age-sex distributions.

We used simulation to obtain uncertainty intervals. For single trials and community patients, we sampled from Dirichlet distributions [27]. For indications with multiple trials, we fitted a Poisson regression model, similar to a random effects meta-analysis, to the mean count. Taking posterior samples from this model, we applied the probability mass function for the Poisson distribution to obtain the proportion with comorbidity counts ranging from 0 to 12. In both cases, we obtained 1000 samples, from which we calculated the following pre-specified statistics: the ratio of mean counts of conditions, the ratio of the proportion with a count ≥ 2 and the proportion of community patients with a count greater than the trial median count. For each statistic, lower and upper uncertainty intervals were obtained as the 2.5th and 97.5th rank percentiles.

Data were prepared using Structured-query Language (SQL) and R (Vienna, Austria). The Dirichlet sampling was performed using R, and the Poisson model was fitted in Just Another Gibbs Sampler (JAGS - http://mcmc-jags.sourceforge.net/). Aggregated data and code required to run these models, along with full model descriptions, are available in Additional file 5. The statistical analysis plan, with version history, is available at https://github.com/dmcalli2/dynamic_protocols/blob/master/defining_comorbidities_SAIL.md.

Additionally, we compared data elements obtained from clinicaltrials.gov for trials where we had access to IPD and included in our analysis, to other trials for which no individual-level participant data was obtained (other trials) using descriptive statistics.

Ethical approval

This project had approval from the University of Glasgow, College of Medicine, Veterinary and Life Sciences ethics committee (200160070). SAIL analyses were approved by SAIL Information Governance Review Panel (Project 0830).

Results

Of the 124 trials meeting our inclusion criteria and made available via the CSDR and YODA repositories, 116 (including 122,969 participants for 22 index conditions) provided concomitant medication data allowing us to identify comorbidities. We had initially planned to include trials from the NIH BioLINCC repository, but found that none of the 8 trials which met our eligibility criteria provided sufficient data on comorbidities to be included in the analysis (Fig. 1). Index conditions are summarised in Table 1. Additional file 6 contains a

summary of the characteristics of each trial. Additional file 7 shows summary statistics of the community sample for each index condition. Trials included in this analysis and trials which met our eligibility criteria but were not included (either because we did not obtain IPD or because the data we needed to perform these analyses had been redacted) were broadly similar in terms of the trial start dates, study design, excluding conditions and the number of participants enrolled as well as the clinical indications and drug classes studied (Additional file 8). However, we found that trials for inflammatory bowel disease and rheumatoid arthritis, as well as trials of immunosuppressant drugs, were somewhat overrepresented. We also found that while 11.3% of the IPD trials were phase 4 trials, 20.9% of non-IPD trials were phase 4, and that a lower proportion of IPD trials than non-IPD trials were very large (Additional file 8: Figure S8.1).

For each index condition, most comorbidities were more common in community patients than in the trials (Fig. 2). In community patients, the seven commonest comorbidities, from most to least common, were chronic pain, cardiovascular disease, arthritis, affective disorders, acid-related disorders, asthma or COPD, and diabetes. These conditions were common across all index conditions, although the ordering varied somewhat. For example, cardiovascular disease was commoner than chronic pain for both type 2 diabetes and COPD. This difference in ordering was evident for *both* the community sample and the trials. Indeed, for most index conditions, those comorbidities which were commonest in the community were also commonest for the trials.

For each of the comorbidities assessed, prevalence varied between trials. Some trials had a prevalence close to that of

Table 1 Trial participants and community patients with each index condition

Index condition	Trials	Trial participants	Community-based sample
Cardiometabolic			
Type 2 diabetes mellitus	21	23,750	82,473
Atrial fibrillation	1	18,033	43,330
Hypertension	8	5151	310,691
Thromboembolism	4	9362	9162
Respiratory			
Asthma	4	1623	191,160
COPD	7	5256	57,378
Pulmonary fibrosis	2	1063	1465
Pulmonary hypertension	1	406	759
Inflammatory			
Axial spondyloarthritis	2	458	1982
Inflammatory bowel disease	12	9241	12,514
Psoriasis	7	7568	52,810
Psoriatic arthritis	3	1331	3523
Rheumatoid arthritis	11	7662	13,809
Systemic lupus erythematosus	2	1693	1033
Musculoskeletal			
Osteoarthritis	1	1320	124,521
Osteoporosis	7	14,497	38,212
Neurological			
Dementia	7	6253	13,871
Migraine	5	3069	19,562
Parkinson's disease	3	1368	4727
Restless legs syndrome	2	676	11,480
Urological			
Benign prostatic hyperplasia	5	2210	19,906
Erectile dysfunction	1	606	65,736

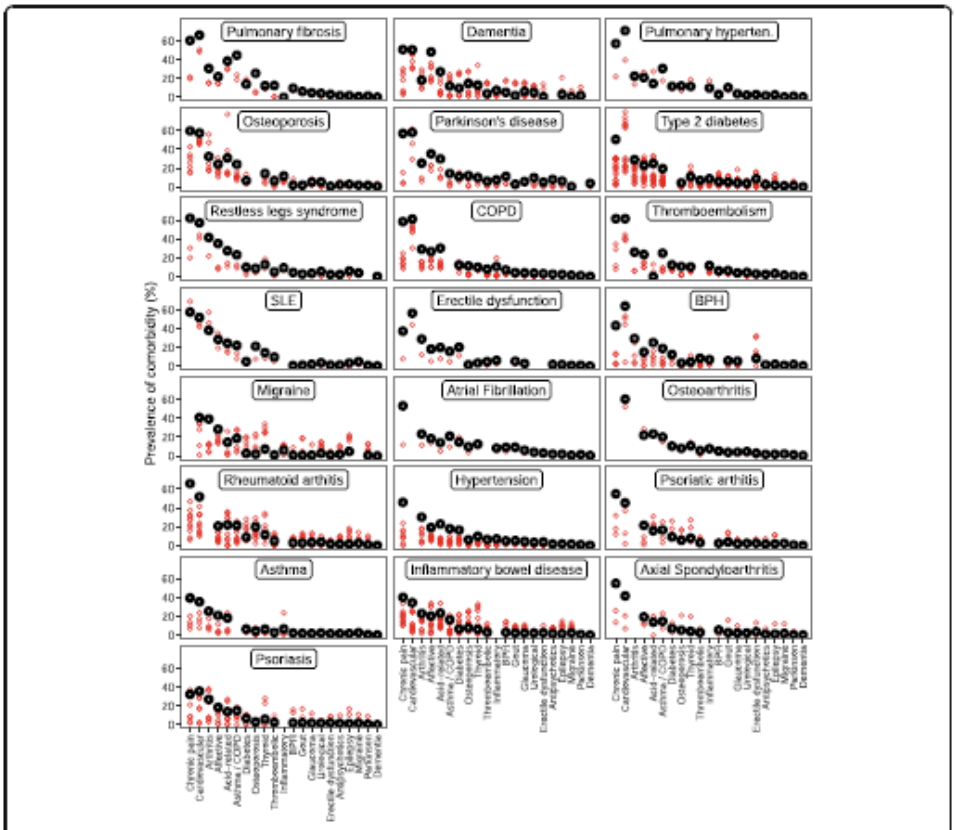

Fig. 2 Scatterplot of the prevalence for each comorbidity for each index condition, for the community-based sample and for clinical trial participants. Black circles indicate the community-based cohort and red circles trials. The *x*-axis is sorted according to the prevalence of the comorbidities in the community-based sample. The sort order was obtained by ranking the comorbidities from commonest to least common for each index condition, then by taking the median across all index conditions. The individual panels are sorted by the mean comorbidity count for each index condition, from highest to lowest. Where the index condition was judged to be the same as the comorbid condition, the comorbidity was not defined, which accounts for apparently missing points on the graph. So, for example, for people in the community sample who had migraine, the most common comorbidity was chronic pain with the next most common being cardiovascular disease

the primary care population, while in other trials the prevalence was much lower (Fig. 2 and Additional file 9). This pattern was similar across all index conditions, and for all comorbidities assessed. No specific comorbidities stood out as being consistently underrepresented. Conversely, none was found to be well represented across all trials.

Figure 3 shows the distribution of the comorbidity counts for trial participants and community-based patients. For each index condition, the comorbidity distribution for community-based patients lay to the right of the trial distribution (i.e. more comorbidities in community patients compared to trial participants). The community-based counts were *standardised* to the age-sex distributions of the trial participants for the relevant condition. However, the standardisation made little difference to the estimates (Additional file 10) so only the age-sex standardised results are presented. For the trial participants, where there were multiple trials per condition, the proportions were obtained from the *modelled* mean comorbidity counts for each index condition (see Table 2), under the assumption that the proportion of trial participants with each comorbidity count follows a

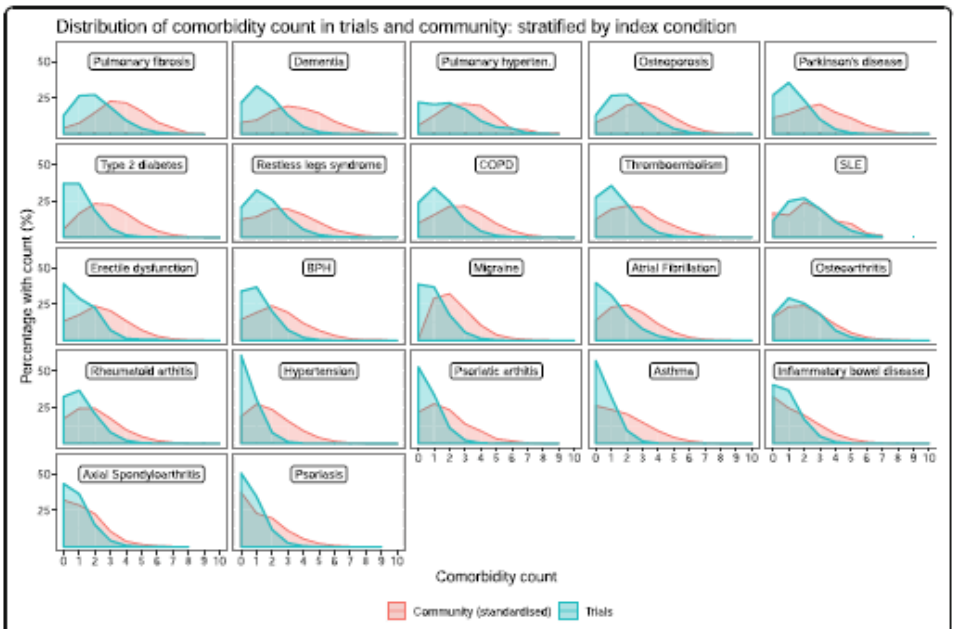

Fig. 3 Proportion with each comorbidity count in trials and community: stratified by index condition. This plot indicates the proportion of comorbidity counts for each index condition. The height of the plot indicates the percentage of participants/patients with a particular count for each index condition. For community-based patients, the proportion of patients with each comorbidity count has been standardised to the trial populations; this was done by applying age-sex-specific proportions to the age-sex distributions of the trial participants. For the trial participants, where there were multiple trials per condition, the proportion with each comorbidity was obtained from the modelled mean comorbidity counts for each index condition (see Table 2), under the assumption that the proportion of trial participants with each comorbidity count follows a Poisson distribution. Where there was only a single trial for a given condition (e.g. osteoarthritis), raw proportions are given. See Additional file 5 for further details of these analyses

Poisson distribution. Where there was only a single trial for a given condition (e.g. osteoarthritis), raw proportions are shown (see Additional file 5 for details). Comorbidity counts varied by index condition. Lower counts were evident for conditions such as asthma, inflammatory bowel disease and psoriasis. Conditions with higher comorbidity counts were those with a later age of onset. For most index conditions, the mean comorbidity counts were between 1.5-fold higher and 3-fold higher for community-based patients than for trial participants (Table 2).

Nonetheless, in absolute terms, comorbidity was common in both settings (Table 2). Most community-based patients had two or more comorbidities (i.e. three or more conditions overall) and would therefore be considered to have a high degree of multimorbidity under many definitions [28]. In trials, a significant proportion also had two or more comorbidities. This ranged from 10 to 15% for conditions such as asthma and psoriasis to around 40–60% for conditions with an older age of onset such as osteoporosis, dementia and pulmonary fibrosis.

On examining individual trials, the mean comorbidity count was the same or higher in the community than for every trial (Fig. 4). Nonetheless, there was considerable variation, even within the same index conditions. For some trials, the mean comorbidity counts were almost the same as in the community; for others, there was more than a twofold difference. In additional analyses, to explore this variation, we plotted the mean comorbidity count for each trial against trial-level characteristics such as the start date, phase, sponsor and total number of excluding conditions within the eligibility criteria, without observing any associations (Additional file 11).

Discussion

We examined comorbidity and multimorbidity using individual-level participant data from 116 trials (122,969

Table 2 Comorbidity counts in trial participants and in the community, ordered according to the mean comorbidity counts in the community

Indication	Mean comorbidity count			% with comorbidity count > 2	
	Community (standardised to trials)	Trials	Ratio between mean counts (community:trials)	Community	Trials
Pulmonary fibrosis	3.61 (3.49–3.75)	2.17 (1.03–3.92)	1.87 (0.90–3.49)	0.88 (0.86–0.91)	0.61 (0.28–0.90)
Dementia	3.44 (3.38–3.49)	1.56 (1.10–2.18)	2.27 (1.58–3.11)	0.82 (0.81–0.83)	0.46 (0.30–0.64)
Pulmonary hypertension	3.27 (3.01–3.53)	2.09 (1.93–2.26)	1.57 (1.39–1.75)	0.80 (0.75–0.84)	0.58 (0.53–0.63)
Osteoporosis	3.01 (2.99–3.03)	2.07 (1.43–2.95)	1.50 (1.02–2.10)	0.79 (0.79–0.80)	0.60 (0.42–0.79)
Parkinson's disease	3.00 (2.90–3.10)	1.36 (0.78–2.18)	2.37 (1.37–3.86)	0.75 (0.73–0.77)	0.39 (0.18–0.64)
Type 2 diabetes mellitus	2.95 (2.94–2.96)	0.79 (0.43–1.32)	4.06 (2.23–6.83)	0.78 (0.78–0.78)	0.27 (0.19–0.36)
Restless legs syndrome	2.85 (2.81–2.89)	1.68 (0.83–2.98)	1.89 (0.96–3.42)	0.74 (0.73–0.75)	0.48 (0.20–0.80)
Pulmonary disease, chronic obstructive	2.76 (2.75–2.78)	1.46 (1.00–2.07)	1.96 (1.33–2.78)	0.75 (0.74–0.75)	0.43 (0.26–0.61)
Thromboembolism	2.52 (2.48–2.56)	1.33 (0.80–2.00)	2.00 (1.24–3.13)	0.68 (0.67–0.70)	0.38 (0.19–0.59)
Systemic lupus erythematosus	2.51 (2.35–2.68)	2.30 (1.08–4.12)	1.22 (0.60–2.32)	0.69 (0.65–0.73)	0.63 (0.29–0.92)
Erectile dysfunction	2.44 (2.43–2.45)	1.08 (0.99–1.17)	2.27 (2.08–2.47)	0.69 (0.69–0.69)	0.32 (0.29–0.36)
Benign prostatic hyperplasia	2.37 (2.34–2.40)	1.11 (0.70–1.69)	2.24 (1.40–3.36)	0.66 (0.66–0.67)	0.30 (0.16–0.50)
Migraine	2.33 (2.31–2.35)	0.98 (0.63–1.42)	2.50 (1.65–3.73)	0.70 (0.69–0.71)	0.26 (0.13–0.42)
Atrial fibrillation	2.22 (2.20–2.23)	1.08 (1.07–1.10)	2.05 (2.01–2.08)	0.63 (0.63–0.64)	0.29 (0.29–0.30)
Osteoarthritis	2.14 (2.13–2.15)	1.79 (1.72–1.86)	1.20 (1.15–1.24)	0.61 (0.61–0.61)	0.54 (0.51–0.56)
Rheumatoid arthritis	2.07 (2.03–2.10)	1.14 (0.87–1.51)	1.84 (1.37–2.39)	0.59 (0.58–0.60)	0.32 (0.22–0.44)
Hypertension	1.91 (1.90–1.91)	0.50 (0.36–0.69)	3.88 (2.76–5.28)	0.54 (0.54–0.54)	0.09 (0.05–0.15)
Psoriatic arthropathy	1.84 (1.78–1.89)	0.67 (0.38–1.09)	2.96 (1.71–4.88)	0.51 (0.50–0.53)	0.15 (0.06–0.30)
Asthma	1.81 (1.81–1.82)	0.58 (0.35–0.92)	3.32 (1.97–5.24)	0.51 (0.50–0.51)	0.12 (0.05–0.23)
Inflammatory bowel disease	1.55 (1.52–1.58)	0.92 (0.68–1.18)	1.73 (1.32–2.28)	0.44 (0.43–0.45)	0.23 (0.15–0.33)
Axial spondyloarthritis	1.42 (1.34–1.50)	0.88 (0.43–1.58)	1.79 (0.90–3.31)	0.40 (0.37–0.43)	0.22 (0.07–0.47)
Psoriasis	1.35 (1.34–1.37)	0.69 (0.48–0.99)	2.02 (1.36–2.80)	0.39 (0.39–0.40)	0.15 (0.08–0.26)

participants) from seven industry sponsors of novel drug treatments for 22 common index conditions. We assessed the same comorbidities for the same index conditions from a nationally representative community sample of 2.3 million people. Comorbidity and multimorbidity were consistently lower in trial populations than in community patients, but were nonetheless common in both.

Our estimates of comorbidity in the community are consistent with previous findings: comorbidity was common, and for some conditions (e.g. COPD and osteoporosis), it was almost ubiquitous [1, 28]. To our knowledge, however, ours is the first study to compare comorbidity and multimorbidity patterns in the community to those in clinical trial populations by directly analysing comorbidity counts using individual-level trial participant data. In so doing, we confirmed that the mean comorbidity count for trials was approximately half that observed in the community.

We also found that, although patients with comorbidity or multimorbidity were underrepresented in many trials, comorbidity and multimorbidity were nonetheless common. For around half of the index conditions, the proportion of trial participants with ≥ 2 comorbidities (i.e. with three conditions and therefore highly multimorbid [28]) was above 30%. Given the ubiquity of multimorbidity among patients in the community [1, 28], it is perhaps unsurprising that comorbidity and multimorbidity are so common in industry-funded trials of novel drugs. However, we do not think that this unexpectedly high prevalence has previously been noted.

This finding is important because of current uncertainty as to the treatment of people with multimorbidity. Guidelines on the treatment of multimorbidity express reservations about the applicability of trial evidence to people with multimorbidity [29]. Moreover, in clinical practice, people with comorbidity (who, by definition, have multimorbidity) are less likely to receive certain drug treatments recommended across a range of disease-specific guidelines [2–5]. Our findings that comorbidity and multimorbidity are underrepresented in clinical trials would support a cautious approach by guideline developers to the routine extrapolation of evidence. However, the finding that comorbidity and multimorbidity are

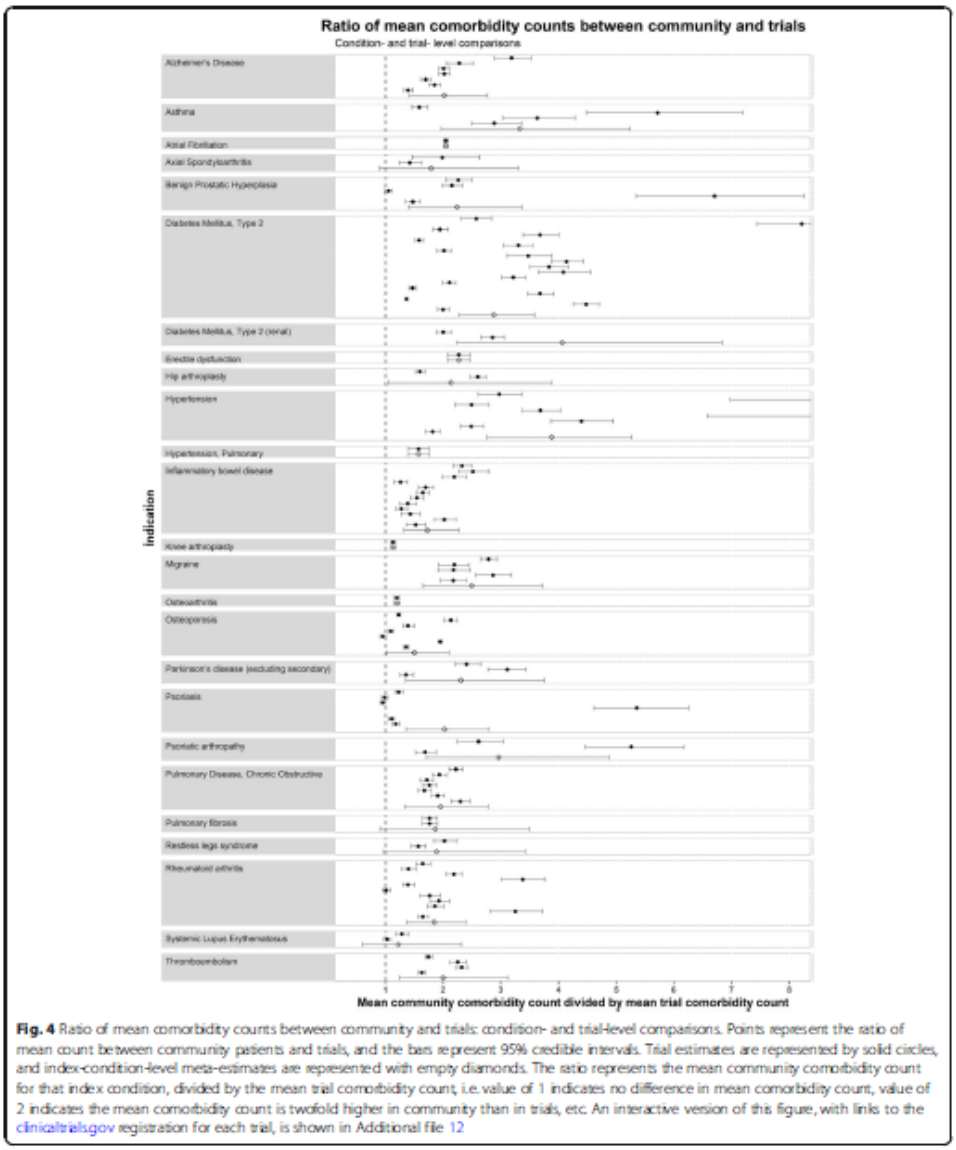

Fig. 4 Ratio of mean comorbidity counts between community and trials: condition- and trial-level comparisons. Points represent the ratio of mean count between community patients and trials, and the bars represent 95% credible intervals. Trial estimates are represented by solid circles, and index-condition-level meta-estimates are represented with empty diamonds. The ratio represents the mean community comorbidity count for that index condition, divided by the mean trial comorbidity count, i.e. value of 1 indicates no difference in mean comorbidity count, value of 2 indicates the mean comorbidity count is twofold higher in community than in trials, etc. An interactive version of this figure, with links to the clinicaltrials.gov registration for each trial, is shown in Additional file 12

common in clinical trials is important, because it suggests that trial data could potentially provide an important resource to allow treatment effects to be estimated in people with multimorbidity. These findings have implications for both triallists and for guideline developers.

The first implication for triallists and guideline developers relates to making better use of existing evidence.

One way of doing so is via individual participant-level data meta-analyses. For this reason, we agree with the Alltrials initiative, and others, that sharing of IPD from clinical trials is crucial. Such analyses have helped resolve previous controversies about the efficacy of drugs in different sub-groups, showing, for example, that aspirin is similarly efficacious in men and women [30–34]. Similar analyses have the potential to resolve similar controversies concerning comorbidity and multimorbidity [29, 35], potentially changing clinical practice, either by providing reassurance that trial findings can be applied to people with multimorbidity or by providing robust evidence to the contrary.

However, compared to meta-analysis of published results, IPD meta-analysis is costly and challenging. If trials are to be widely used to inform clinicians and guideline developers as to the efficacy of different treatments in the presence of comorbidity or multimorbidity, trials must publish results according to comorbidity subgroups. Doing so will be challenging, however, because there are multiple different potential patterns of comorbidity. This is true even if only a small number of comorbid diseases are considered. There are, for example, 64 different possible ways that six conditions can occur together. Whether important and clinically relevant patterns of comorbidity can be identified from among such combinations remains an active and unresolved research question [36]. Nonetheless, we found that those comorbidities which were common in the community were also common in trials. Consequently, if clinically meaningful patterns of comorbidity and multimorbidity can be identified among people in the community, it may be possible to identify similar sub-groups among trial participants.

In the absence of consensus on which patterns of comorbidity should be grouped together, we propose that trials report treatment effects according to the presence/absence of common comorbidities, as well as by multimorbidity counts. Ideally, comorbidities would be defined using medical history data collected in a systematic and standardised manner across trials. In the absence of standardised medical histories [9, 37], some insights may be obtained from existing trials using drug-defined comorbidities, particularly where the focus is on conditions closely associated with particular drug classes (e.g. diabetes and glucose-lowering drugs) or on overall measures of multimorbidity, such as a count.

Despite these challenges, using clinical trial data to estimate treatment effects in people with comorbidity or multimorbidity remains appealing because of limitations in the alternatives. For example, observational datasets rich in multimorbidity, such as electronic health records, are used to estimate treatment effects. However, despite methodological advances in this use of observational data, it remains controversial, as unmeasured confounding can result in apparent treatment benefits when none really exist [9, 38].

The second implication for triallists relates to eligibility criteria and recruitment. For many indications, there was little difference in comorbidity counts between some trials and the community sample, whereas for other trials within the same indication the differences were large. This suggests that, even for standard industry-funded phase 3/4 trials, increasing the recruitment of comorbid participants is feasible. There is therefore potential for future trials to become more representative in terms of multimorbidity. In exploratory analyses, the differences in comorbidity between trials for similar indications were not related to start date, phase, sponsor or total number of exclusion criteria. Additional work is needed to identify the selection processes driving inclusion or exclusion of people with comorbidity so that trials can be made more representative. In addition, it will be important for future research to examine how conditions cluster in people with multimorbidity and whether this differs between clinical trial participants and people in the community in order to improve analysis and reporting of treatment effects as well as trial design.

The strengths of our study include large numbers and that the comorbidity definitions and analyses were prespecified before making comparisons. However, there are several limitations. First, the trials collected medical history data in a variety of incommensurable ways. Consequently, we used concomitant medications to define comorbidities. This meant that some important conditions that are not treated with specific medications (e.g. chronic kidney disease) could not be identified reliably, whereas some other conditions which share treatments (e.g. asthma and COPD) had to be combined into broader categories. The use of some medications was so heterogenous as to preclude meaningful categorisation, and we did not attempt to use such drugs in any definition (for example, since amitriptyline is widely used in the treatment of chronic pain [39], we did not include it in our definition of affective disorders). Despite these limitations, some conditions are well defined by medications, and importantly, the same definitions were applied across trial and community data. Our community sample was taken from Wales because, while being broadly similar to the rest of the UK, it provides access to electronic medical records from a large and representative sample covering 70% of the population [40]. The Welsh population is broadly similar to the UK population in demography, and the findings are likely to be applicable to other high-income countries, but do require replication in other contexts. In order to facilitate this, we provide standard comorbidity definitions as well as data on the distribution of comorbidity counts, age and sex at

the level of individual trials. A further limitation is that the included trials were not a random sample of all trials for these index conditions. Not all sponsors share trial data. Those who do share data do not make all trials available. Differences between trials that do or do not provide IPD may be a potential source of bias [41]. As such, we believe that the sharing of data by trial sponsors is to be encouraged, so as to minimise bias arising from the availability of a limited set of trials. Nonetheless, the included trials were similar to a wider body of registered trials across a range of characteristics (Additional file 8).

Conclusion

Clinical trial populations have a lower prevalence of comorbidity and multimorbidity than unselected community populations. Clinicians should exercise caution when applying disease-specific evidence and guidelines to people with comorbidity or multimorbidity. Nonetheless, comorbidity and multimorbidity are common in clinical trials. Given the limitations of observational data for estimating treatment effects, this suggests that standard industry-funded clinical trials are an underused resource for estimating treatment effects in multimorbidity. We would recommend that future disease-specific guidelines need to incorporate information concerning likely treatment effects in the context of the specific index condition and comorbidity or multimorbidity. To enable guideline developers to do so, triallists should at least report the prevalence of multimorbidity and a range of comorbidities among trial participants and should consider reporting treatment effect estimates stratified by comorbidity and/or multimorbidity. More general multimorbidity guidelines could also usefully include information in relation to this within any future guideline to permit more specific guidance for clinicians dealing with people with multimorbidity.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12916-019-1427-1.

Additional file 1. Selection-of-trials-protocol.pdf: Protocol for selection of clinical trials individual participant data and search of wider body of registered trials from clinicaltrials.gov.

Additional file 2. Representativeness-of-community-data-sail.pdf: Analysis of the representativeness of the community sample.

Additional file 3. Selection-of-patients-and-participants-from-primary-care-data-read-codes.pdf: Read codes used to identify index conditions.

Additional file 4. Defining-comorbidity-protocol.pdf: Protocol detailing the identification of comorbidities from clinical trial data.

Additional file 5. More-detailed-statistical-analysis.pdf: Model description and code required for analyses. Detailed description of statistical methods.

Additional file 6. Trials-characteristics.pdf: Summary of characteristics of included trials.

Additional file 7. Characteristics-of-primary-care-populations-with-each-of-the-trial-indications.pdf: Summary statistics of community sample for each index condition.

Additional file 8. Summary-Statistics-Comparing-Ipd-Trials-To-Wider-Body-Of-Trials-From-Clinicaltrials.Gov.Pdf: Comparison of included trials with registered trials on clinicaltrials.gov for which individual participant data were not available.

Additional file 9. Proportion-with-each-comorbidity-for-trials-and-sail.pdf: Analysis of the prevalence of each comorbidity, within each index condition, in trial participants and the community sample.

Additional file 10. Comorbidity-counts-for-trials-and-primary-care.pdf: Summary comorbidity counts.

Additional file 11. Explore-relationship-of-trial-mean-comorbidity-counts-to-trial-characteristics.pdf: Analysis of characteristics based on trial meta-data and relationship to comorbidity counts.

Additional file 12. Figure-4-interactive.svg: Interactive version of Fig. 4 with hyperlinks to trial registration.

Abbreviations

COPD: Chronic obstructive pulmonary disease; CSRD: Clinical Study Data Request; IPD: Individual-level participant data; SAIL: Secure Anonymised Information Databank; WHO-ATC: World Health Organization Anatomic Therapeutic Chemical classification; YODA: Yale University Open Data Access

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Authors' contributions

DM, SW, BG, SD and MW conceived the study with PH and FSM commenting on the study design. DM acquired the data from trials and SAIL. DM, PH and LH conducted the statistical analysis and interpretation of the data. NW advised on the statistical analysis. PH wrote the first draft with support from DM. All authors reviewed the manuscript and made critical changes for intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

All data released from the respective safe havens (YODA, CSDR and SAIL) has been made available via the supplementary appendix. Potentially disclosive data can be accessed by applying to the original data holders who were reported in the "Methods" section.

Ethics approval and consent to participate

This project had approval from the University of Glasgow, College of Medicine, Veterinary and Life Sciences ethics committee (200160070). SAIL

analyses were approved by SAIL Information Governance Review Panel (Project 0830).

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References

1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380:37–43.
2. Bursi F, Vassallo R, Weston SA, Killian JM, Roger VL. Chronic obstructive pulmonary disease after myocardial infarction in the community. Am Heart J. 2010;160:95–101.
3. Quipourt V, Jooste V, Cottet V, Faivre J, Bouvier A-M. Comorbidities alone do not explain the undertreatment of colorectal cancer in older adults: a French population-based study. J Am Geriatr Soc. 2011;59:694–8.
4. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med. 2013;11:263.
5. Wang Philip S, Avorn J, Brookhart MA, et al. Effects of noncardiovascular comorbidities on antihypertensive use in elderly hypertensives. Hypertension. 2005;46:273–9.
6. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med. 2006;4:104–8.
7. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297:1233–40.
8. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009;7:357–63.
9. Boyd CM, Kent DM. Evidence-based medicine and the hard problem of multimorbidity. J Gen Intern Med. 2014;29:552–3.
10. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. BMJ. 2015;350:h176.
11. Bohm M, Pogue J, Kindermann I, Pora J, Koon T, Yusuf S. Effect of comorbidities on outcomes and angiotensin converting enzyme inhibitor effects in patients with predominantly left ventricular dysfunction and heart failure. Eur J Heart Fail. 2014;16:325–33.
12. Battaglia S, Basile M, Spatafora M, Scichilone N. Are asthmatics enrolled in randomized trials representative of real-life outpatients? Respiration. 2015;89:383–9.
13. Scichilone N, Basile M, Battaglia S, Bellia V. What proportion of chronic obstructive pulmonary disease outpatients is eligible for inclusion in randomized clinical trials? Respiration. 2014;87:11–7.
14. Fanning L, Ilomaeki J, Bell JS, Darzins P. The representativeness of direct oral anticoagulant clinical trials to hospitalized patients with atrial fibrillation. Eur J Clin Pharmacol. 2017;73:1427–36.
15. Saunders C, Byrne CD, Guthrie B, et al. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? Diabet Med. 2013;30:300–8.
16. Sen A, Goldstein A, Chakrabarti S, et al. The representativeness of eligible patients in type 2 diabetes trials: a case study using GIST 2.0. J Am Med Inform Assoc. 2017;25(3):239–47.
17. Leinonen A, Koponen M, Hartikainen S. Systematic review: representativeness of participants in RCTs of acetylcholinesterase inhibitors. PLoS One. 2015;10:e0124500.
18. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999;52:1143–56.
19. Assessing heterogeneity in treatment efficacy by age, sex and comorbidity. PROSPERO 2018 CRD42018048202. 2018. at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018048202.)
20. Lyons RA, Jones KH, John G, et al. The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak. 2009;9:3.
21. Available from National Health Service (NHS) digital. at https://digital.nhs.uk/services/.
22. McQueenie R, Ellis DA, McConnachie A, Wilson P, Williamson AE. Morbidity, mortality and missed appointments in healthcare: a national retrospective data linkage study. BMC Med. 2019;17:2.
23. Roland M. Linking physicians' pay to the quality of care — a major experiment in the United Kingdom. N Engl J Med. 2004;351:1448–54.
24. Anatomic Therapeutic Chemical Index. World Health Organization. 2019. (https://www.whocc.no/atc_ddd_index/.) Accessed March 2019.
25. Unified Medical Language System RxNorm. (https://www.nlm.nih.gov/research/umls/rxnorm/.) Accessed March 2019.
26. The OpenPrescribing project. University of Oxford. available at (https://openprescribing.net/) Accessed March 2019.
27. Gelman A, Carlin JB, Stern HA, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. London: Chapman and Hall/CRC; 2013.
28. Fortin M, Stewart M, Poitras M-E, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. Ann Fam Med. 2012;10:142–51.
29. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. J Am Geriatr Soc. 2012;60:E1–E25.
30. Simmonds MC, Higginsa JPT, Stewartb LA, Tierneyb JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. Clinical Trials. 2005;2:209–17.
31. Cholesterol Treatment Trialists C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
32. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929–35.
33. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA. 2002;288:2441–8.
34. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377:31–41.
35. National Institute for Health and Care Excellence. NICE guideline 56: Multimorbidity: clinical assessment and management. 2016. Available from https://www.nice.org.uk/guidance/ng56 Accessed March 2019.
36. The Academy of Medical Sciences. Multimorbidity: a priority for global health research (available from https://acmedsci.ac.uk/file-download/82222577). 2018. Accessed March 2019.
37. Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. PLoS One. 2012;7.
38. D'Agostino RB. Estimating treatment effects using observational data. JAMA. 2007;297:314–6.
39. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006;166:1021–6.
40. Health at a Glance, OECD Indicators 2017. available from https://www.oecd.org/unitedkingdom/Health-at-a-Glance-2017-Key-Findings-UNITED-KINGDOM.pdf) Accessed March 2019.
41. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ. 2012;344:d7762.

Publisher's Note

Appendix 2: Protocol manuscript for systematic review of observational studies of frailty in type 2 diabetes

Open access Protocol

BMJ Open

Identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: a systematic review protocol

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ABSTRACT

Introduction Diabetes mellitus is common and growing in prevalence, and an increasing proportion of people with diabetes are living to older age. Frailty is, therefore, becoming an important concept in diabetes. Frailty is associated with older age and describes a state of increased susceptibility to decompensation in response to physiological stress. A range of measures have been used to quantify frailty. This systematic review aims to identify measures used to quantify frailty in people with diabetes (any type); to summarise the prevalence of frailty in diabetes; and to describe the relationship between frailty and adverse clinical outcomes in people with diabetes.

Methods and analysis Three electronic databases (Medline, Embase and Web of Science) will be searched from 2000 to November 2019 and supplemented by citation searching of relevant articles and hand searching of reference lists. Two reviewers will independently review titles, abstracts and full texts. Inclusion criteria include: (1) adults with any type of diabetes mellitus; (2) quantify frailty using any validated frailty measure; (3) report the prevalence of frailty and/or the association between frailty and clinical outcomes in people with diabetes; (4) studies that assess generic (eg, mortality, hospital admission and falls) or diabetes-specific outcomes (eg, hypoglycaemic episodes, cardiovascular events, diabetic nephropathy and diabetic retinopathy); (5) cross-sectional and longitudinal observational studies. Study quality will be assessed using the Newcastle–Ottawa Scale for observational studies. Clinical and methodological heterogeneity will be assessed, and a random effects meta-analysis performed if appropriate. Otherwise, a narrative synthesis will be performed.

Ethics and dissemination This manuscript describes the protocol for a systematic review of observational studies and does not require ethical approval.

PROSPERO registration number CRD42020163109.

Strengths and limitations of this study

- This systematic review will provide a comprehensive overview of the prevalence and implications of frailty in people with diabetes.
- We will include a broad range of frailty definitions and clinical outcomes relevant to diabetes.
- There is likely to be significant heterogeneity between population characteristics and frailty definitions in included studies.
- By including only English language articles, there is a chance of language bias in the results of the review.
- We exclude Grey literature, which may lead to publication bias.

INTRODUCTION

Diabetes mellitus (hereafter 'diabetes') describes a collection of metabolic disorders, with distinct pathological processes, that are characterised by elevated blood glucose.[1] The most common are type 1 and type 2 diabetes. Type 1 diabetes is caused by insulin deficiency resulting from destruction of pancreatic beta cells, usually by an autoimmune process.[2] Type 2 diabetes describes a relative insulin deficiency caused by beta-cell dysfunction and insulin resistance of target organs.[2] Both are associated with a range of complications including macrovascular disease, retinopathy, nephropathy and neuropathy.[3] The prevalence of diabetes is increasing across the world.[4] Population demographics are also shifting towards an ageing population.[5] Among people above the age of 65, the prevalence of diabetes can be as high as 30%.[6] Diabetes in older people is, therefore, a growing clinical and public health priority. One factor with important implications for disease management in older age is frailty.[7]

Frailty is a state characterised by reduced functional reserve across multiple physiological systems.[8] People living with frailty have impaired resolution of homaeostasis following physiological stressors.[8] Frailty, therefore, carries an increased risk of a range of adverse health outcomes, such as falls, cognitive decline, hospital admission and mortality.[9] Frailty is widely recognised

to be a multidimentional and dynamic state, associated with older age and with a range of non-communicable diseases.[9] However, there is no single universally accepted operational definition of frailty. Rather, a wide range of definitions have been used in both research and clinical practices.[10]

The two dominant paradigms in the frailty literature are the frailty phenotype and the frailty index. The frailty phenotype, described by Fried *et al*, defines frailty as the presence of three or more out of five features: low hand grip strength, unintentional weight loss, low physical activity, exhaustion and slow walking pace.[11] The presence of one or two of these features is classified as a prefrail state. The frailty index, described by Rockwood and Mitnitski, is based on a Cumulative Deficit Model of frailty, whereby frailty is identified by counting the number of health 'deficits' present in an individual.[12] At least 30 deficits are required to construct a frailty index, all of which must increase in prevalence with age, be associated with poor health and not saturate too early (ie, be universally present among older people).[13] Both the frailty phenotype and the frailty index have been associated with adverse health outcomes in a range of older populations; however, the populations identified as frail by each are different.[14] Since their original description, a wide range of other frailty instruments, as well as adaptations of the frailty index and phenotype, have been developed for both epidemiological studies and for clinical practice.[9 10]

The relationship between diabetes and frailty is complex. Diabetes is associated with a higher prevalence of frailty.[15–18] Both type 1 and type 2 diabetes lead to microvascular and macrovascular complications that have important physical, cognitive and functional consequences, which may contribute to the development of frailty.[6] Hyperglycaemia is also recognised to directly impact muscle mass and quality, exacerbating age-related sarcopaenia and, in turn, physical function.[19] However, the association between frailty and poor functional outcomes in people with diabetes is only partially explained by direct complications of diabetes.[17 20]

The importance of frailty in the context of diabetes is increasingly recognised in clinical guidelines.[7] Specifically, higher glycated haemoglobin (HbA1c) targets are recommended in the context of frailty, in part due to the increased risks associated with hypoglycaemia.[21] Despite this, up to 40% of older people with diabetes may be overtreated (with HbA1c<7%).[22 23] Conversely, poor glycaemic control and associated vascular complications risk causing, or accelerating the progression of, frailty.[24]

One recent meta-analysis demonstrated a consistent relationship between frailty and mortality, hospitalisation and cardiovascular events in the context of diabetes.[25] We are not aware of any systematic review to assess the prevalence of frailty in diabetes, or to consider a broader range of outcomes relevant to the management of diabetes.

To enhance understanding of the implications and management of diabetes within an ageing population, it is important to fully describe the association between diabetes and frailty. Given the risks of both over treatment and under treatment of diabetes in the context of frailty, it is important to understand the associations between frailty and a range of potential outcomes in diabetes. This includes generic outcomes such as mortality and hospitalisation and disability and disease-specific outcomes such as retinopathy, neuropathy and hypoglycaemic events. An understanding of the range and complexity of these associations is required to inform clinical decisions around treatment priorities and to underpin future research. This includes quantifying the prevalence of frailty in people with diabetes, and the impact that different frailty definitions might have on this prevalence. This manuscript describes the protocol of a systematic review aiming to synthesise existing evidence relating to these questions.

Aims

The systematic review will aim to:

- Identify which frailty measures have been used to assess frailty in people with diabetes (any type, including mixed/unspecified).
- Quantify the prevalence of frailty among people with diabetes.
- Describe the association between frailty and both generic (eg, mortality) and disease-specific (eg, hypoglycaemia) clinical outcomes in the context of diabetes.

METHODS AND ANALYSIS

The review will be conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[26] Where a meta-analysis is undertaken, we will report findings according to the Meta-analyses Of Observational Studies in Epidemiology checklist.

Eligibility criteria for inclusion

The eligibility criteria for this review are summarised in table 1 and explained in more detail below.

Population

We will include studies analysing data from people with any form of diabetes.

While frailty is a state associated with increasing age, there is evidence that frailty is identifiable in relatively younger people, particularly in certain contexts such as multimorbidity (two or more coexisting long-term conditions) or in areas of high socioeconomic deprivation. We will, therefore, include studies of adults of any age (≥18 years). However, we anticipate that most studies will focus predominantly on 'older' populations.

From an initial scoping of the literature, it is likely that many studies describing frailty in population-based studies measure unspecified 'diabetes' rather than explicitly type 1 or type 2 diabetes. We will, therefore, include any study that includes people with any type of diabetes (including type 1, type 2 diabetes, secondary or monogenic diabetes, or people with unspecified diabetes). Given that frailty is

Table 1 Inclusion criteria

PECOS component	Description
Population	Adults (≥18 years old) Diabetes (any type, including mixed or unspecified)
Exposure	Frailty as assessed by any frailty measure
Comparator	People with diabetes not classified as frail
Outcomes	Generic: ► Mortality ► Major adverse cardiovascular events ► Hospital admission ► Admission to long-term care facility ► Falls ► Number of clinic attendances ► Quality of life ► Disability/functional status Diabetes specific: ► HbA1c (cross-sectional association, or longitudinal) ► Glycaemic variability ► Hypoglycaemic episodes ► Diabetic retinopathy (cross-sectional association, or longitudinal) ► Diabetic nephropathy (cross-sectional association, or longitudinal) – Include development of end-stage renal disease ► Diabetic foot complications (cross-sectional association or longitudinal) ► Treatment burden (eg, Diabetic Treatment Burden Questionnaire)
Settings	Community (including care home/nursing home) Outpatient clinic Inpatient
Study design	Cross-sectional or longitudinal Cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies and Grey literature

PECOS, Population, Exposure, Comparator, Outcome, Setting and Study design.

a state associated with older age, and that type 2 diabetes is both more prevalent than type 1 diabetes and becomes more prevalent with age, it is likely that most (but not all) people with diabetes in the relevant populations will have type 2 diabetes. Studies of type 1, type 2 diabetes and those of unspecified diabetes will be considered separately in any subsequent analysis.

We will include studies focusing purely on people with diabetes, or population-based studies that report results for people with diabetes separately.

Exposure

The 'exposure' of interest is frailty. Many epidemiological measures and clinical tools have been developed to identify frailty for research or clinical practice.[10]

To be eligible for inclusion, a study must use a measure that explicitly seeks to quantify frailty. We will include measures developed primarily as epidemiological tools (eg, the frailty phenotype and frailty index).[11 12] We will also include measures designed primarily for clinical practice (eg, the Clinical Frailty Scale).[27]

Studies focusing solely on comorbidity (ie, no additional measures to identify 'frailty') will be excluded unless these are explicitly operationalised as a 'frailty index'. In this case, studies would generally be expected to include additional deficits (such as symptoms, functional limitations and laboratory measures). Studies that use a single parameter as a proxy for frailty (eg, grip strength alone and self-rated health) will be excluded.

Comparator

Studies that report the prevalence of frailty will be eligible for inclusion if they report the prevalence of frailty in diabetes only. Studies should report the number or proportion of participants with and without frailty (or with varying degrees of frailty, depending on the measure used).

For assessing the association between frailty and clinical outcomes in the context of diabetes, studies should report the association between frailty and the outcome of interest. This may be reported either as the association with the presence or absence of frailty (in the case of a

Box 1 Medline search

1. Exp Frailty/
2. Exp Frail Elderly/
3. Frail*.tw
4. 1 or 2 or 3
5. Exp Diabetes Mellitus
6. Diabet*.tw
7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin ?depend).tw
9. (insulin* depend* or insulin ?depend*).tw
10. 5 or 6 or 7 or 8 or 9
11. Exp Diabetes Insipidus/
12. Diabet* insipidus.tw
13. 11 or 12
14. 10 not 13
15. 4 and 14

binary or categorical measure) or the association between the degree of frailty and the outcome (in the case of a continuous or ordinal measure of frailty).

Outcomes

Outcomes of interest are summarised in table 1. We will include studies assessing any of these outcomes as long as the association is specifically quantified in people with diabetes and frailty.

Setting

We will include studies of community-dwelling patients, outpatient populations or hospital inpatients.

For the purposes of this review, given the focus on frailty, people living in long-term care facilities (eg, care homes and nursing homes) will be considered to be 'community dwelling'. Therefore, any study including, or specifically recruiting, nursing home residents will be eligible for inclusion.

Identification of studies

Electronic searches

Medline, Embase and Web of Science (core collection) databases will be search using a combination of Medical Subject Headings and keyword searches (online supplementary file 1). The terms used for the Medline search are shown in box 1. These terms will be adapted for the other databases. Searches will be from 2000 to November 2019. The year 2000 was chosen as the start date as the first seminal paper operationalising the concept of frailty in an epidemiological study was published in 2001. Articles published prior to this date are, therefore, unlikely to be relevant. No language restriction will be applied to the search, but only English language articles will be included at the screening level. This language restriction is a pragmatic decision; however, we acknowledge that this may lead to a language bias in the results, potentially excluding relevant studies published in other languages.

Identifying additional articles

Electronic searches will be supplemented by hand searching reference lists of relevant articles. A citation search of all relevant articles will also be carried out using the Web of Science citation search tool.

Data collection and analysis

Selection of studies

Two reviewers, working independently, will screen all titles and abstracts of records identified in the database searches. PECOS (population, exposure, comparator, outcome, setting and study design) criteria outlined above will be used to determine eligibility. Where there is disagreement, studies will be retained for full-text screening.

Full texts of all potentially eligible studies will be screened independently by two reviewers. Disagreements about eligibility will be resolved by consensus, involving a third reviewer where necessary.

Data extraction

A standard data extraction form will be designed and piloted before being applied to each of the included studies. Extracted data will include:

Study details

- Author.
- Year
- Location.
- Setting (community, outpatient and residential care).
- Method of recruitment (eg, random sample, postal invitation and consecutive patients).
- Method of assessment (face to face, survey and linkage to healthcare records).

Population

- Age.
- Sex.
- Ethnicity.
- Socioeconomic status.
- Comorbidities.
- Medications.
- Social circumstances (eg, living independently, requiring carers, family support and so on).
- Smoking status.
- Physical activity.

Diabetes details

- Type of diabetes.
- Method of confirmation (self-report, medical records and clinical assessment).
- Measure of control (eg, HbA1c).
- Medication (eg, proportion taking insulin, oral antidiabetics and so on).
- Presence and severity of complications (eg, retinopathy, nephropathy, neuropathy, ulceration and Charcot arthropathy).

Frailty definition

- Frailty measure used.
- Definitions for each component of the frailty measure (eg, cut-points used for continuous measures and

method of assessment (questionnaire, interview and so on)).

Frailty prevalence

Outcomes (generic):

- Mortality.
- Major adverse cardiovascular events.
- Hospital admission.
- Admission to long-term care facility.
- Falls.
- Number of clinic attendances.
- Quality of life.
- Disability/functional status

Outcomes (diabetes specific):

- HbA1c (cross-sectional association or longitudinal).
- Glycaemic variability.
- Hypoglycaemic episodes.
- Diabetic retinopathy (cross-sectional association or longitudinal).
- Diabetic nephropathy (cross-sectional association or longitudinal).
- Diabetic foot complications (cross-sectional association or longitudinal).
- Treatment burden (eg, Diabetic Treatment Burden Questionnaire).

As we include a wide range of outcomes, it is likely that the way outcomes are assessed will vary depending on the outcome in question. Studies may also assess similar outcomes (eg, hospital admission) in different ways (eg, number of admissions over specified follow-up, time to first admission and presence or absence of admission during follow-up). For the outcomes listed above, we will extract data regardless of the method of assessment. Heterogeneity in the way outcome data were collected will be used to inform the approach to data synthesis (ie, meta-analysis vs narrative synthesis). For each outcome reported, we will record:

- The method of outcome assessment (eg, linkage to healthcare records, face-to-face assessment, questionnaire and so on).
- Method of analysis (eg, time to event, mean difference and so on).
- The association between frailty and the outcome (eg, prevalence, OR, HR and so on).
- Adjustment for any potential confounders.
- Length of follow-up over which the outcome was assessed.
- Method of analysis of competing risks when assessing each outcome.

Where available, we will also extract data on both relative (eg, HRs) and absolute (eg, events per 1000 people) associations with outcomes.

Assessment of methodological quality

The Newcastle–Ottawa Scale will be used to assess the risk of bias for each study (online supplementary file 2).[28] This scale is widely used for the assessment of observational studies, and has frequently been adapted to the context of specific systematic reviews. We have adapted the criteria in order to be explicit about how the 'exposure assessment' related to frailty: specifically, awarding one point for the use of a validated frailty assessment measure. For cross-sectional studies, only the first five elements of the scale were relevant to quality assessment (the remainder concerning the longitudinal assessment of outcomes). We will use this subsection of the Newcastle–Ottawa Scale to assess the quality of cross-sectional studies to allow direct comparability with the baseline assessments of longitudinal studies (from which we will also extract data on frailty prevalence). In assessing the comparability of frail/non-frail groups, age will be taken as the most important factor for which studies should account.

Data synthesis

The appropriate method of data synthesis will be determined after assessment of the heterogeneity of the included studies, in terms of population selection and demographics, frailty definition and method of outcome assessment.

With regards to the prevalence of frailty, different frailty measures will be considered separately (ie, we will not perform a meta-analysis of frailty prevalence measured using different scales). We will also consider community studies separately from studies focussing on outpatient clinic populations (as these may represent people with more severe diabetes), inpatients or people living in residential care. We will also assess the inclusion criteria and demographics of the sample population, with particular attention to age (as frailty is strongly associated with age) and sex (as women tend to have a higher prevalence of frailty than men) to determine the most appropriate method of synthesis. Where samples have been drawn from populations with a markedly different age/sex structure, a pooled estimate of the mean prevalence of frailty across these studies is unlikely to be a meaningful summary. Similarly, other inclusion criteria used by the individual studies (such as excluding 'institutionalised' people, people with cognitive impairment and people with impaired mobility unable to attend an assessment) may disproportionately impact on the estimation of frailty prevalence. The appropriateness, or otherwise, of a meta-analysis of frailty prevalence will be judged only after examination of these aspects of the included studies.

For the assessment of outcomes, the approach to synthesis will also be judged based on heterogeneity of the method of outcome assessment and the analytic approach. As above, different frailty measures will be considered separately.

If appropriate, we will combine these in a random effects meta-analysis (anticipating heterogeneity in the true association). As well as a pooled estimate and 95% CIs, we will also calculate the prediction interval to assess the range of plausible estimates from the observed data. Heterogeneity will be quantified using the I^2 statistic. Where heterogeneity is present, we will attempt to explore potential sources of heterogeneity using subgroup analyses (eg, by method of determining frailty, age of sample population

and method of outcome assessment). By doing so, we propose to explore factors that may influence the estimates reported in observational studies in the presence of heterogeneity, rather than provide a definitive single estimate.[29] We will use funnel plots to assess for potential publication bias.

Only those studies that are judged to be sufficiently comparable will be included in meta-analyses. For outcomes where there are too few studies, or the included studies are too heterogenous to permit a meaningful meta-analysis (eg, in terms of outcome definition or method of assessing frailty), we will perform a narrative synthesis of the study findings. This will report the methods used to identify frailty along with the prevalence and association with outcomes, to explore the impact of the method of assessment on the observed relationship. This will be reported alongside detail of the recruitment strategy, age profile and characteristics of each sample included.

Patient and public involvement

No patients were involved in the development of this review.

ETHICS AND DISSEMINATION

This systematic review will provide an overview of the prevalence of frailty in diabetes and the relationship between frailty and adverse health outcomes in people with diabetes.

As the prevalence of both frailty and diabetes increase, it will become increasingly important for clinical guidelines for the treatment of diabetes to explicitly consider the needs of people living with frailty.[7] Quantifying the prevalence of frailty in diabetes will allow the scale of this challenge to be better appreciated. By including any reported definition of frailty within our inclusion criteria, this review will demonstrate which of the wide range of frailty instruments and measures have been used to study frailty in diabetes. It will also be possible to compare if and how prevalence and association with outcomes differs depending on the frailty definition used.

Given the likely heterogeneity in frailty definitions, as well as inherent differences in the populations studied, it may not be possible to undertake a meta-analysis of the findings of this review. If this is the case, we propose to conduct a detailed narrative synthesis, systematically describing and synthesising details of the populations under study as well as the details of frailty definitions used.

We also propose to search for and extract data for a wide range of clinical outcomes. Given the multidimentional nature of frailty,[8] and the vulnerability to decompensation that is inherent to any frailty definition,[9] it is likely that frailty will be associated with a range of adverse outcomes. The challenge in translating these associations into meaningful recommendations is understanding the balance of these risks, and how they might inform clinical decisions and recommendations. The balance of risks in diabetes, and treatment priorities, may differ depending on the degree of frailty experienced by an individual. The associations may also differ in their nature or magnitude depending on the method used to identify frailty. This review will aim to provide an overview of what is known about the relationship between frailty and both generic and disease-specific outcomes. This is likely to inform priorities for future research into the consequences of frailty in diabetes.

As this project is a systematic review, ethical approval is not required. Patients or the public were not involved in the development of this protocol.

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Contributors All authors contributed to the conception and design of the proposed study. PH, DM and FM developed the data sources and search strategy. PH, IF, NC, DM and FM refined the inclusion criteria. PH, IF, NC, DM and FM developed the data extraction template which was piloted by PH, IF and NC. PH and IF wrote the first draft. All authors critically reviewed this and subsequent drafts. All authors approved the final version of the manuscript for submission. FM is the guarantor of the review. All authors accept accountability for the accuracy of the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Moini J. *Epidemiology of diabetes*. Elsevier, 2019.
2 Ozougwu O, Obimba K, Belonwu C. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J Physiol Pathophysiol* 2013;4:46–57.
3 Pambianco G, Costacou T, Ellis D, *et al*. The 30-year natural history of type 1 diabetes complications: the Pittsburgh epidemiology of diabetes complications study experience. *Diabetes* 2006;55:1463–9.
4 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4–14.
5 United Nations. World population ageing [Report], 2015. Available: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf
6 Sinclair AJ, Rodriguez-Mañas L, Diabetes R-ML. Diabetes and frailty: two converging conditions? *Can J Diabetes* 2016;40:77–83.
7 Sinclair AJ, Abdelhafiz A, Dunning T, *et al*. An international position statement on the management of frailty in diabetes mellitus: summary of recommendations 2017. *J Frailty Aging* 2018;7:10–20.
8 Clegg A, Young J, Iliffe S, *et al*. Frailty in elderly people. *Lancet* 2013;381:752–62.
9 Hoogendijk EO, Afilalo J, Ensrud KE, *et al*. Frailty: implications for clinical practice and public health. *Lancet* 2019;394:1365–75.
10 Bouillon K, Kivimaki M, Hamer M, *et al*. Measures of frailty in population-based studies: an overview. *BMC Geriatr* 2013;13:64.
11 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–57.

12 Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007;62:722–7.
13 Searle SD, Mitnitski A, Gahbauer EA, *et al*. A standard procedure for creating a frailty index. *BMC Geriatr* 2008;8:24.
14 Santos-Eggimann B, Sirven N. Screening for frailty: older populations and older individuals. *Public Health Rev* 2016;37:7.
15 Kotsani M, Chatziadamidou T, Economides D, *et al*. Higher prevalence and earlier appearance of geriatric phenotypes in old adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2018;135:206–17.
16 Thein FS, Li Y, Nyunt MSZ, *et al*. Physical frailty and cognitive impairment is associated with diabetes and adversely impact functional status and mortality. *Postgrad Med* 2018;130:561–7.
17 Castro-Rodríguez M, Carnicero JA, García-García FJ, *et al*. Frailty as a major factor in the increased risk of death and disability in older people with diabetes. *J Am Med Dir Assoc* 2016;17:949–55.
18 Hanlon P, Hannigan L, Rodriguez-Perez J, Fischbacker C, *et al*. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. *BMC Med* 2019;17:201.
19 Yoon JW, Ha YC, Kim KM, *et al*. Hyperglycemia is associated with impaired muscle quality in older men with diabetes: the Korean longitudinal study on health and aging. *Diabetes Metab J* 2016;40:140–6.
20 Maggi S, Noale M, Gallina P, *et al*. Physical disability among older Italians with diabetes. The ILSA study. *Diabetologia* 2004;47:1957–62.
21 Schernthaner G, Schernthaner-Reiter MH. Diabetes in the older patient: heterogeneity requires individualisation of therapeutic strategies. *Diabetologia* 2018;61:1503–16.
22 Formiga F, Franch-Nadal J, Rodríguez L, *et al*. Inadequate glycaemic control and therapeutic management of adults over 65 years old with type 2 diabetes mellitus in Spain. *J Nutr Health Aging* 2017;21:1365–70.
23 Braun AK, Kubiak T, Kuntsche J, *et al*. SGS: a structured treatment and teaching programme for older patients with diabetes mellitus--a prospective randomised controlled multi-centre trial. *Age Ageing* 2009;38:390–6.
24 Quartuccio M, Buta B, Kalyani RR. Comparative effectiveness for glycemic control in older adults with diabetes. *Curr Geriatr Rep* 2017;6:175–86.
25 Ida S, Kaneko R, Imataka K, *et al*. Relationship between frailty and mortality, hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2019;18:81.
26 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
27 Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
28 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
29 Mueller M, D'Addario M, Egger M, *et al*. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. *BMC Med Res Methodol* 2018;18:44.

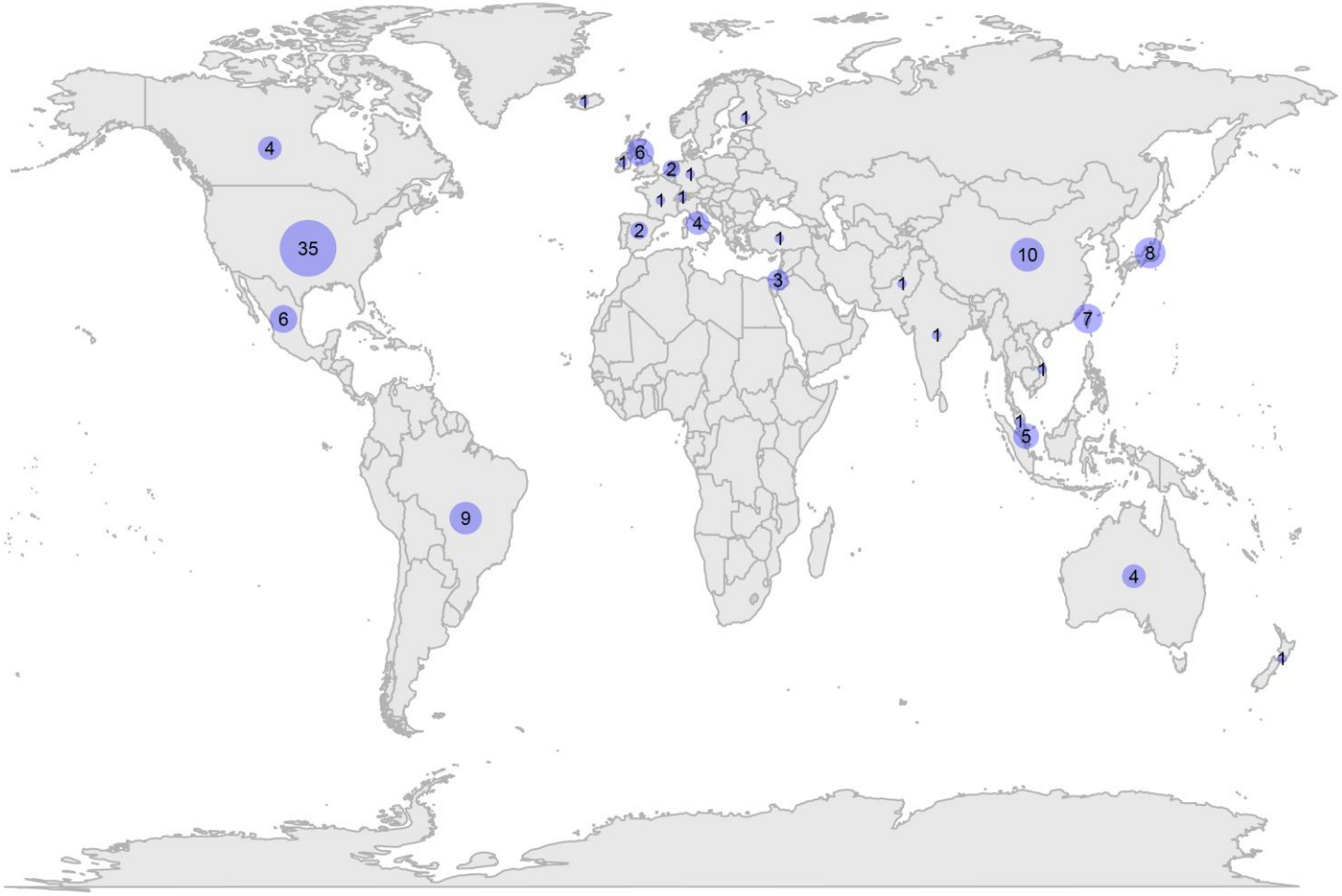
Appendix 3: Supplementary material for Chapter 4: Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis

Medline Search Strategy
Search Terms

1. Exp Frailty/
2. Exp Frail Elderly/
3. Frail*.tw
4. 1 or 2 or 3
5. Exp Diabetes Mellitus
6. Diabet*.tw
7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin ?depend).tw
9. (insulin* depend* or insulin ?depend*).tw
10. 5 or 6 or 7 or 8 or 9
11. Exp Diabetes Insipidus/
12. Diabet* insipidus.tw
13. 11 or 12
14. 10 not 13
15. 4 and 14

Language restriction
None applied to search (non-English language studies excluded at screening stage)
Years searched
2001-November 2019

Countries of included studies



The Newcastle-Ottawa Scale – Adaptation of criteria
Adaptation for studies assessing the prevalence and impact of frailty in diabetes

1 – Representativeness of the exposed (i.e. frail) cohort
a) Truly representative (one star)
b) Somewhat representative (one star)
c) Selected group
d) No description of the derivation of the cohort

2 – Selection of the non-exposed (i.e. non-frail) cohort
a) Drawn from the same community as the exposed cohort (one star)
b) Drawn from a different source
c) No description of the derivation of the non-exposed cohort

3 – Ascertainment of exposure (adapted for measurement of frailty)
a) Validated measurement tool for frailty (two stars)
b) Non-validated measurement tool, but the tool is available or described (one star)
c) No description of measurement tool

4 – Non-respondents
a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory (one star)
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory
c) No description of the response rate of the characteristics of the responders and non-responders

5 – Demonstration that outcome of interest was not present at the start of the study
a) Yes (one star)
b) No

Comparability:
1 – Comparability of the cohorts on the basis of the design or analysis being controlled for confounders
a) The study controls for age and sex (one star)
b) The study controls for other factors (one star)
c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcomes:
1 – Assessment of outcomes
a) Independent assessment (one star)
b) Record linkage (one star)
c) Self-report
d) No description
e) Other

2 – Follow-up long enough for outcomes to occur
a) Yes (one star)

b) No

3 – Adequacy of follow-up of cohorts
a) Complete follow-up: all subjects accounted for (one star)
b) Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20% or description of those lost suggested no different from those followed (one star)
c) Follow-up rate less than 80% and no description of those lost

d) No statement

Quality assessment – Adapted Newcastle Ottawa Scale

Author	Year	Representative	Selection of non frail comparison	Ascertainment of exposure frailty	Non respondents	Outcome not present at start	Controls for age and sex	Control for other factors	Outcome assessment	Length of follow up	Adequacy of follow up	Cross-sectional score	Longitudinal score
Adame Perez	2019	0	1	2	0	-	-	-	-	-	-	3/5	-
Aguilar-Navarro	2019	0	1	1	0	-	-	-	-	-	-	2/5	-
Aguayo	2019	1	1	2	0	-	-	-	-	-	-	4/5	-
Al Snih	2009	1	1	1	0	-	-	-	-	-	-	3/5	-
Almeida	2016	1	1	2	0	-	-	-	-	-	-	4/5	-
Ambagtsheer	2019	0	1	1	0	-	-	-	-	-	-	2/5	-
Anjos	2017	0	1	1	0	-	-	-	-	-	-	2/5	-
Atif	2019	0	1	2	1	-	-	-	-	-	-	4/5	-
Avila_flunes	2008	1	1	1	0	-	-	-	-	-	-	3/5	-
Azmon	2018	0	1	2	0	-	-	-	-	-	-	3/5	-
Bello-Chavolla	2017	1	1	1	0	-	-	-	-	-	-	3/5	-
Boas	2018	0	1	2	0	-	-	-	-	-	-	3/5	-
Bouillon	2013	1	1	2	0	-	-	-	-	-	-	4/5	-
Brunner	2018	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Cacciatore	2013	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Cakmur	2015	1	1	1	0	-	-	-	-	-	-	3/5	-
Calado	2016	1	1	1	0	-	-	-	-	-	-	3/5	-
Carneiro	2016	1	1	2	0	-	-	-	-	-	-	4/5	-
Castrejon-Perez	2018	1	1	2	0	-	-	-	-	-	-	4/5	-

Castrejon-Perez	2012	1	1	1	0	-	-	-	-	-	-	3/5	-
Castrejon-Perez	2017	1	1	2	0	-	-	-	-	-	-	4/5	-
Castro-Rodriguez	2016	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Cesari	2006	1	1	1	0	-	-	-	-	-	-	3/5	-
Chang	2010	1	1	1	0	-	-	-	-	-	-	3/5	-
Chang	2012	0	1	1	0	-	-	-	-	-	-	2/5	-
Chao	2018	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Chaves	2005	1	1	2	0	-	-	-	-	-	-	4/5	-
Chen	2010	1	1	2	0	-	-	-	-	-	-	4/5	-
Chen	2014	1	1	2	0	-	-	-	-	-	-	4/5	-
Cheong	2020	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Chhetri	2017	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Chiu	2019	1	1	1	1	1	1	1	1	1	1	4/5	10/11
Chode	2016	1	1	2	0	1	1	1	1	1	0	4/5	9/11
Cigolle	2009	1	1	2	1	-	-	-	-	-	-	5/5	-
Crow	2018	1	1	1	0	-	-	-	-	-	-	3/5	-
da Silva	2015	0	1	1	0	-	-	-	-	-	-	2/5	-
Danon-Hersch	2012	1	1	1	0	-	-	-	-	-	-	3/5	-
de Leon Gonzalez	2016	1	1	2	0	-	-	-	-	-	-	4/5	-
Doi	2018	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Espinoza	2010	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Espinoza	2012	1	1	2	1	1	1	1	1	1	1	5/5	11/11
Espinoza	2015	1	1	2	0	-	-	-	-	-	-	4/5	-
Ferri-Guerra	2019	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Fried	2001	1	1	2	0	-	-	-	-	-	-	4/5	-

Garcia-Esquinas	2015	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Hanlon	2018	0	1	1	0	-	-	-	-	-	-	2/5	-
Hasan	2017	0	1	2	0	-	-	-	-	-	-	3/5	-
Hippisley-Cox	2017	1	1	1	0	-	-	-	-	-	-	3/5	-
Howrey	2018	1	1	1	0	-	-	-	-	-	-	3/5	-
Hubbard	2010	0	1	2	0	1	0	0	1	1	1	3/5	7/11
Hyde	2019	1	1	2	0	-	-	-	-	-	-	4/5	-
Khan	2013	1	1	1	0	-	-	-	-	-	-	3/5	-
Khanderwal	2012	0	1	1	0	-	-	-	-	-	-	2/5	-
Kirkwood	2019	1	1	1	0	-	-	-	-	-	-	3/5	-
Kitamura	2019	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Lahousse	2014	1	1	1	0	-	-	-	-	-	-	3/5	-
Lee	2017	1	1	2	0	-	-	-	-	-	-	4/5	-
Lee	2011	1	1	1	0	-	-	-	-	-	-	3/5	-
Lee	2014	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Lekan	2018	0	1	1	0	1	1	0	1	0	1	2/5	6/11
Li	2018	1	1	1	0	0	1	1	0	0	1	3/5	6/11
Li	2019	1	1	2	0	-	-	-	-	-	-	4/5	-
Li	2019b	1	1	1	0	-	-	-	-	-	-	3/5	-
Li	2015	0	1	2	0	1	1	1	1	1	0	3/5	8/11
Li	2016	0	1	2	0	-	-	-	-	-	-	3/5	-
Liccini	2016	0	1	2	0	1	1	1	1	1	0	3/5	8/11
Lin	2015	1	1	1	0	-	-	-	-	-	-	3/5	-
MacKenzie	2019	0	1	2	0	-	-	-	-	-	-	3/5	-
Matsuzawa	2010	0	1	1	0	-	-	-	-	-	-	2/5	-
McAllister	2018	1	1	2	0	1	1	1	1	1	1	4/5	10/11
McAllister	2016	1	1	1	0	-	-	-	-	-	-	3/5	-
McAllister	2017	1	1	1	0	1	1	1	1	1	1	3/5	9/11

McClure	2019	1	1	1	0	-	-	-	-	-	-	3/5	-
Merchant	2017	1	1	2	0	-	-	-	-	-	-	4/5	-
Mohr	2007	1	1	1	0	-	-	-	-	-	-	3/5	-
Molist-Brunet	2019	0	1	1	0	-	-	-	-	-	-	2/5	-
Moreira	2017	1	1	2	0	-	-	-	-	-	-	4/5	-
Moreira	2016	1	1	1	0	-	-	-	-	-	-	3/5	-
Motokawa	2018	1	1	2	0	-	-	-	-	-	-	4/5	-
Nadruz	2017	1	1	1	0	-	-	-	-	-	-	3/5	-
Nelson	2007	0	1	1	0	-	-	-	-	-	-	2/5	-
Ng	2014	1	1	1	0	-	-	-	-	-	-	3/5	-
Nguyen	2019	1	1	1	0	-	-	-	-	-	-	3/5	-
Nguyen	2019b	0	1	1	0	-	-	-	-	-	-	2/5	-
Nishimura	2019	0	1	2	0	-	-	-	-	-	-	3/5	-
Orkaby	2019	1	1	2	0	-	-	-	-	-	-	4/5	-
Ottenbacher	2009	1	1	1	0	-	-	-	-	-	-	3/5	-
Pilotto	2014	0	1	1	0	1	1	1	1	1	0	2/5	7/11
Pollack	2017	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Presley	2019	0	1	2	0	1	1	1	1	1	1	3/5	9/11
Raji	2010	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Ricci	2014	1	1	1	0	-	-	-	-	-	-	3/5	-
Saum	2012	1	1	1	0	-	-	-	-	-	-	3/5	-
Simpson	2016	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Sirola	2011	1	1	1	0	-	-	-	-	-	-	3/5	-
Tamura	2018	0	1	1	0	-	-	-	-	-	-	2/5	-
Tang	2013	1	1	2	0	-	-	-	-	-	-	4/5	-
Tepper	2018	0	1	1	0	-	-	-	-	-	-	2/5	-
Thein	2018	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Tuttle	2018	0	1	1	0	-	-	-	-	-	-	2/5	-
Vaingankar	2017	1	1	1	0	-	-	-	-	-	-	3/5	-

van Hateren	2015	0	1	1	0	-	-	-	-	-	-	2/5	-
Vaz Fragozo	2009	1	1	1	0	-	-	-	-	-	-	3/5	-
Veronese	2017	1	1	1	0	-	-	-	-	-	-	3/5	-
Veronese	2016	1	1	1	0	-	-	-	-	-	-	3/5	-
Wang	2014	1	1	1	0	-	-	-	-	-	-	3/5	-
Wang	2017	1	1	1	0	1	1	1	1	0	0	3/5	7/11
Wata-be	2017	1	1	1	0	-	-	-	-	-	-	3/5	-
Weinstein	2018	1	1	1	0	-	-	-	-	-	-	3/5	-
Wong	2018	1	1	2	0	-	-	-	-	-	-	4/5	-
Wong	2010	1	1	1	0	-	-	-	-	-	-	3/5	-
Woo	2019	1	1	1	0	-	-	-	-	-	-	3/5	-
Woods	2005	1	1	1	0	1	1	1	1	1	1	3/5	9/11
Wu	2009	0	1	1	0	-	-	-	-	-	-	2/5	-
Wu	2018	1	1	1	0	-	-	-	-	-	-	3/5	-
Xue	2019	0	1	1	0	-	-	-	-	-	-	2/5	-
Ya-gita	2018	0	1	2	0	-	-	-	-	-	-	3/5	-
Zaslavsky	2016	1	1	1	0	-	-	-	-	-	-	3/5	-

Details of studies of frailty prevalence

Author, Year	Country	Cohort	Setting	Frailty measure	Lower age limit or specified range	Type of diabetes	Number of people with diabetes	Mean/median age*	Number (%) female
Adame Perez 2019	Canada		outpatient	Edmonton	≥65	unspecified	41	70 (65-74)	15 (36.6%)
Aguilar-Navarro 2019	Mexico	Recruited from memory clinic	outpatient	Fried	≥60	unspecified	44	73 (6.6)	NA
Aguayo 2019	UK	English Longitudinal Study of Aging	community	FI	≥50	unspecified	635	70 (65-77)	2995 (55.7%)
Al Snih 2009	USA	H-EPESE study	community	Fried	≥67	unspecified	431	75 (6)	NA
Ambagtsheer 2019	Australia	Database of 10 aged care facilities	residential_care	eFI	≥75	unspecified	120	88 (9)	394 (66.6%)
Anjos 2017	Brazil	Community diabetes clinic	outpatient	Fried	≥65	Type 2	82	71 (4.8)	82 (100%)
Atif 2019	Pakistan	Two diabetes outpatient clinics	outpatient	CFS	≥60	Type 2	400	64 (5.5)	215 (53.8%)
Avila_flunes 2008	France	Three-City study	community	Fried	≥65	unspecified	565	74.1 (5.2)	3726 (61.3%)
Azmon 2018	Israel	Specialist diabetes outpatient service	outpatient	Fried	≥60	Type 2	153	70.3	NA
Bello-Chavolla 2017	Mexico	Coyoacán Cohort Study	community	Fried	≥70	Type 2	135	77.7 (5.8)	NA
Boas 2018	Brazil		outpatient	Edmonton	≥60	unspecified	100	NA	126 (84%)
Cacciatore 2013	Italy	Osservatorio Geriatrico Regione Campania	community	Frailty staging system	≥65	unspecified	188	74.3 (6.4)	712 (55.3%)
Cakmur 2015	Turkey		community	Fried	≥65	unspecified	22	72.7 (7.7)	90 (53.6%)
Calado 2016	Brazil	FIBRA study	community	Fried	≥65	unspecified	67	73.9 (6.5)	249 (64.7%)
Carneiro 2016	Brazil		community	Edmonton	≥60	unspecified	114	74 (7.14)	327 (64%)
Castrejon-Perez 2018	Mexico	ENSANUT	community	FI	≥60	unspecified	1236	70.3 (7.8)	2943 (54.7%)
Castrejon-Perez 2012	Mexico	Mexican Study of Nutritional and Psychosocial Markers of Frailty (the Coyoacan cohort)	community	Fried	≥70	unspecified	147	77.9 (6.3)	NA
Cesari 2006	Italy	In Chianti study	community	Fried	≥65	unspecified	95	74.8 (6.8)	NA
Chang 2010	USA	WHAS I and II	community	Fried	70-79	unspecified	73	74.15 (2.8)	NA
Chang 2012	Taiwan		outpatient	Fried	≥65	unspecified	35	74.6 (6.3)	NA

Chao 2018	Taiwan	Longitudinal Cohort of Diabetes Patients database	community	FRAIL	≥20	Type 2	560795	56.4 (13.8)	258526 (46.1%)
Chaves 2005	USA	WHAS I and II	community	Fried	70-80	unspecified	90	74.3 (2.9)	NA
Chen 2010	Taiwan	Survey of Health and Living Status of the Elderly in Taiwan	community	Fried	≥65	unspecified	398	73.3 (1.5)	NA
Chen 2014	Taiwan	The Coming of the Aging Society: An Integrative Study on Social Planning in Taiwan in 2025	community	Fried	≥65	unspecified	84	73.4	239 (48.3%)
Chhetri 2017	China	BLSA-II	community	FI	≥55	unspecified	2634	70.5 (7.8)	NA
Cigolle 2009	USA	HRS	community	Fried	≥65	unspecified	260	75	NA
Crow 2018	USA	National Health and Nutrition Examination Survey	community	Fried	≥60	unspecified	1060	71.1 (0.19)	NA
da Silva 2015	Brazil		outpatient	Fried	60-79	Type 2	30	68.7 (6.92)	NA
Danon-Hersch 2012	Switzerland	Lc65+	community	Fried	65-70	unspecified	129	67 (65-70)	515 (40.1%)
de Leon Gonzalez 2016	Mexico	Mexican Health and Aging Study	community	FRAIL	≥60	unspecified	801	67	NA
Ferri-Guerra 2019	USA		community	FI	≥65	unspecified	763	72.87 (6.78)	13 (1.7%)
Fried 2001	USA	CHS	community	Fried	≥65	unspecified	840	73.6	3079 (57.9%)
Hanlon 2018	UK	UK Biobank	community	Fried	40-70	unspecified	24696	62	NA
Hasan 2017	Malaysia		residential_care	Gronigen	≥65	unspecified	69	76.8 (7.8)	126 (62.4%)
Hippisley-Cox 2017	UK	Qresearch database	community	Qmortality	≥65	Type 2	73909	75.3 (8)	274931 (55%)
Hubbard 2010	England	CSHA	community	CFS	≥70	unspecified	310	83.3	NA
Khan 2013	USA	Health ABC study	community	HABC	70-79	unspecified	404	73.6 (2.9)	1472 (52.1%)
Khanderwal 2012	India		inpatient	Fried	≥60	unpecified	51	66.4 (6.3)	NA
Kitamura 2019	Japan		community	Fried	≥65	unspecified	176	71 (5.6)	730 (57.2%)
Lahousse 2014	Netherlands	Rotterdam Study	community	Fried	≥55	unspecified	211	74 (9)	NA
Lee 2017	Japan	National Center for Geriatrics and Gerontology – Study of Geriatric Syndromes.	community	Fried	≥65	unspecified	1218	73.6 (5.5)	5037 (52.4%)

Lekan 2018	USA		inpatient	Frailty risk score	≥55	unspecified	136	70.1 (55-98)	146 (52.5%)
Li 2018	Taiwan	NHIS Taiwan	community	FRAIL	≥65	unspecified	719	NA	NA
Li 2019b	China	RuLAS	community	Fried	70-84	unspecified	121	73.3 (3.9)	937 (53.3%)
Li 2015	China		inpatient	FRAIL	≥60	Type 2	146	80 (74-84)	32 (21.9%)
Liccini 2016	USA		outpatient	FRAIL	≥50	unspecified	198	64.9 (8.7)	NA
Lin 2015	Taiwan	Taichung Community Health Study for Elders	community	Fried	≥65	unspecified	177	74 (7)	497 (48%)
MacKenzie 2019	Canada		inpatient	CFS	≥65	unspecified	141	81.4 (8.1)	228 (57%)
Matsuzawa 2010	Japan		inpatient	CGA	≥65	unspecified	288	72.8 (7.7)	164 (56.9%)
McAllister 2018	UK	United Kingdom Health Improvement Network Database	community	eFI	≥20	unspecified	292170	61.7	NA
McAllister 2016	USA	Clinformatics Data Mart	community	John Hopkins ACG	≥20	unspecified	191590	50.4 (9.9)	89151 (46.5%)
McAllister 2017	USA	Clinformatics Data Mart	community	John Hopkins ACG	≥20	unspecified	99694	53.9 (9.7)	NA
McClure 2019	Australia		community	SPPB	≥50	Type 2	87	70.2 (8.2)	29 (33.3%)
Merchant 2017	Singapore	HOPE study	community	FRAIL	≥65	unspecified	250	71.2	601 (57.2%)
Mohr 2007	USA	MMAS	community	Fried	≥50	unspecified	65	67.9 (6)	0 (0%)
Molist-Brunet 2019	Spain		inpatient	FI	≥85	Type 2	210	86.1 (4.8)	116 (55.2%)
Moreira 2017	Brazil		community	Fried	≥65	unspecified	855	74 (6)	2951 (66.3%)
Moreira 2016	Brazil	FIBRA study	community	Fried	≥65	Type 2	99	72	99 (100%)
Motokawa 2018	Japan		community	Kihon	≥65	unspecified	68	73.3 (5.8)	397 (59.7%)
Nadruz 2017	USA	ARIC	community	Fried	≥68	unspecified	1188	75.6 (5)	2355 (59%)
Nelson 2007	USA		outpatient	VES-13	≥75	unspecified	111	78	56 (50.5%)
Ng 2014	Singapore	Singapore Longitudinal Aging Study	community	Fried	≥55	unspecified	349	66.7 (7.7)	1084 (64.3%)
Nguyen 2019	Vietnam		community	Fried	≥60	unspecified	24	72.8 (8.2)	358 (68.5%)
Nguyen 2019b	New Zealand		outpatient	Fried	≥60	unspecified	158	69.5 (6.8)	98 (62%)
Nishimura 2019	Japan		outpatient	Kihon	≥60	Type 2	213	70.2 (5.5)	105 (49.3%)
Orkaby 2019	USA	Framingham Heart study	community	Fried	≥60	unspecified	350	69.7 (7)	1194 (55%)
Ottenbacher 2009	USA	H-EPESE study	community	Fried	≥65	unspecified	568	74.3 (6.4)	1195 (58.3%)
Pollack 2017	USA		community	Fried	≥65	unspecified	529	73.4 (5.8)	0 (0%)

Ricci 2014	Brazil	FIBRA study	community	Fried	≥65	unspecified	189	71.9 (5.9)	489 (64.3%)
Simpson 2016	USA		community	John Hopkins ACG	≥20	Type 2	54505	60 (52-68)	26380 (48.4%)
Sirola 2011	Finland	Helsinki Businessmen Study	community	Fried	≥65	unspecified	89	73 (73)	NA
Tamura 2018	Japan		outpatient	Fried		unspecified	185	78 (75-82)	201 (62.2%)
Tang 2013	China	BLSA-II	community	FI	≥55	unspecified	456	70.1 (9)	NA
Tepper 2018	Israel		outpatient	Fried	≥60	Type 2	117	70.6 (6.5)	46 (39.3%)
Thein 2018	Singapore	Singapore Longitudinal Ageing Study	community	Fried	≥55	Type 2	486	66 (7.6)	1693 (62.8%)
Tuttle 2018	USA		outpatient	mPPT	NA	Type 2	95	57 (12)	34 (35.8%)
Vaingankar 2017	Singapore	Well-being of the Singapore Elderly study	community	Fried	≥60	unspecified	622	69	1134 (53.9%)
van Hateren 2015	Netherlands	ZODIAC	outpatient	RAND-36	≥75	Type 2	858	72.3 (7.2)	519 (60.5%)
Vaz Fragozo 2009	USA		community	Fried	≥78	unspecified	75	84.3 (4.5)	252 (67.4%)
Veronese 2017	Iceland	Age, Gene/Environment Susceptibility (AGES)—Reykjavik Study	community	Fried	≥65	unspecified	427	76.2 (5.6)	2444 (64%)
Wang 2017	USA	Veterans Administration Electronic Medical Records	community	Frailty risk class	≥65	Type 2	41204	74.6 (5.8)	0 (0%)
Watanabe 2017	Japan	Obu Study of Health Promotion for the Elderly	community	Fried	≥60	unspecified	623	72.1 (5.6)	2446 (51.8%)
Weinstein 2018	Israel		community	Fried	45-74	unspecified	118	77.2 (6.4)	0 (0%)
Wong 2010	Canada	Montreal Unmet Needs Study	community	Fried	≥75	unspecified	125	79.6 (4)	502 (67.8%)
Woo 2019	China		community	FRAIL		unspecified	86	74.7 (7.7)	NA
Wu 2009	United States		inpatient	Fried	≥60	unspecified	14	77 (6)	NA
Wu 2018	China	Chinese Health and Retirement Longitudinal Study	community	Fried	≥65	unspecified	382	67	2618 (49.4%)
Xue 2019	China		inpatient	Fried	≥60	unspecified	36	78.5 (9)	NA
Yanagita 2018	Japan		outpatient	CFS	≥65	Type 2	132	78.3 (7.9)	NA

Outcomes of included studies
Mortality

Author	Year	Country	Setting	Frailty measure	Number with diabetes	Mean or median age (sd or IQR)	Analysis	Adjustment	Effect size
Cacciatore	2013	Italy	community	Frailty staging system	188	72.8 (5.8)	Cox model per tertile increase in frailty staging system (female)	age, BMI, waist circumference, heart rate, pulse blood pressure, Charlson comorbility index, drugs number, GDS, insulin, hypoglycemic drugs, hypertension, CAD, CHF, PAD, and CKD.	HR 1.31 (1.03-1.85)
Cacciatore	2013	Italy	community	Frailty staging system	188	72.8 (5.8)	Cox model per unit increase in frailty staging system (males)	age, BMI, waist circumference, heart rate, pulse blood pressure, Charlson comorbility index,	HR 1.99 (1.75-3.05)

								drugs number, GDS, insulin, hypoglycemic drugs, hypertension, CAD, CHF, PAD, and CKD.	
Castro-Rodriguez	2016	Spain	community	FI	363	76 (71.2-79)	Cox model per 0.1 increase in FI	age, sex, Charlson index, disability	HR 1.83 (1.49-2.26)
Castro-Rodriguez	2016	Spain	community	Frailty trait scale	363	76 (71.2-79)	Cox model per 10% increase in scale	age, sex, Charlson index, disability	HR 1.51 (1.29-1.78)
Chao	2018	Taiwan	community	FRAIL	560795	56.4 (13.8)	Cox model (categorical on 0, 1, 2, 3+ FRAIL scale indicators)	Adjusted for demographic profiles, comorbidities (including obesity, mental illnesses, hypoglycemia history), substance use (smoking and alcohol abuse), aDCSI, and medications	HR 1.25 (1.15-1.36)

Chode	2016	USA	community	FRAIL	222	57.43 (4.4)	Logistic regression 9 years follow-up	NA	1.45 (1.12-1.86)
Ferri-Guerra	2019	USA	community	FI	763	72.87 (6.78)	Cox model, frail (FI>0.21) versus non-frail (FI<0.21)	adjusted for age, race, ethnicity, BMI and Median Household Income, Charlson Comorbidity Index, diabetes complications, duration of diabetes, use of insulin or sulfonylureas, metformin and level of glycemia control.	HR 2.65 (1.52-4.64)
Hubbard	2010	England	community	CFS	310	81.3	Cox regression	Age, sex, place of residence	1.42 (1.2-1.69)
Kitamura	2019	Japan	community	Fried	176	NA	Cox model (categorical)	age, sex, hypertension, high total cholesterol, low total cholesterol, low estimated glomerular filtration rate, overweight, low	6.6 (2-22)

								body mass index, anemia, hypoalbuminemia, low Mini-Mental State Examination score, history of stroke and current smoking	
Li	2015	NA	NA	FRAIL	NA	NA	Log rank test	none	Significant assocaitio n with frailty
Liccini	2016	USA	outpatient	FRAIL	198	64.9 (8.7)	Raw numbers of deaths only	NA	NA
Presley	2019	USA	inpatient	FI	500	65 (58-75)	Cox model (continuous, with example of 0.05 point increase)	demographics, administrative, clinical EHR data	1.45 (1.32-1.6)
Thein	2018	Singapore	community	Fried	486	67.3 (7.5)	Cox (frail versus not frail)	age, gender, education level, smoking, alcohol intake, and physical exercise, diabetes duration, WC, total cholesterol,	4.37 (2.38-8.03)

								HDL cholesterol, hypertension, cardiac disease, stroke, arthritis, hip fracture, polypharmacy, and depression.	
Wang	2017	USA	community	indicator diagnoses	41204	74.6 (5.8)	Cox regression	age, race/ethnicity, Charlson comorbidity score, BMI, HbA1c, statin use	0.98 (0.89-1.07)

Hospitalisation and Emergency Department Attendance

Author	Year	Country	Setting	Frailty measure	Number with diabetes	Mean or median age (SD or IQR)	Outcome	Analysis	Covariate adjustment	Effect of frailty
Ferri-Guerra	2019	USA	community	FI	763	72.87 (6.78)	hospitalisation	CoxPH - prospective	adjusted for age, race, ethnicity, BMI and Median Household Income, Charlson Comorbidity Index, diabetes complications, duration of diabetes, use of insulin or sulfonylureas, metformin and level of glycemia control.	HR 2.36 (1.77-3.14)
Li	2018	Taiwan	community	FRAIL	719	NA	hospitalisation	Retrospective (event in past year)	Adjusted for age, sex, education, marital status, duration of diabetes, use of insulin, falls, ADl disability, and IADl disability	OR 5.31 (1.87-15.1)
Li	2015	China	inpatient	FRAIL	146	80 (74-84)	hospitalisation	prospective - logistic regression (3 or more hospitalisations in 1 year follow-up)	Adjusted for age, gender, MMSE points, BMI, duration of diabetes, HbA1c, macroangiopathy, and nephropathy	OR 5.99 (1.38-25.91)
Liccini	2016	USA	outpatient	FRAIL	198	64.9 (8.7)	hospitalisation	prospective - logistic regression (hospitalisation	adjusted for age, sex, education and HbA1c	OR 4.7 (1.67-13.19)

								at 6 month follow-up)		
Chao	2018	Taiwan	community	FRAIL	560795	56.4 (13.8)	hospitalisation	CoxPH - prospective	Adjusted for demographic profiles, comorbidities (including obesity, mental illnesses, hypoglycemia history), substance use (smoking and alcohol abuse), aDCSI, and medications	HR 1.25 (1.17-1.33)
Li	2018	Taiwan	community	FRAIL	719	NA	ED visit	Retrospective (event in past year)	Adjusted for age, sex, education, marital status, duration of diabetes, use of insulin, falls, ADl disability, and IADl disability	4.05 (1.31-12.49)

HbA1c

Author	Year	Country	Setting	Frailty measure	Number with diabetes	Mean or median age (SD or IQR)	Outcome	Analysis	Result
Atif	2019	Pakistan	outpatient	CFS	400	NA	HbA1c above target level (7%) or below)	adjusted logistic regression	No significant difference with frailty (1.11 (0.44, 2.84)
Ferri-Guerra	2019	USA	community	FI	763	72.87 (6.78)	HbA1c categorised as tight (<7%) intermediate (7-9%) and poor (>9%)	Chi squared	No significant difference with frailty
van Hateren	2015	Netherlands	outpatient	RAND-36	858	72.3 (7.2)	mean HbA1c	mean difference	No significant difference between frail and non-frail
Kitamura	2019	Japan	community	Fried	176	NA	mean HbA1c	mean difference	No significant difference between frail and non-frail

Li	2015	China	inpatient	Fried	146	80 (74-84)	mean HbA1c	mean difference	No significant difference between frail and non-frail
MacKenzie	2019	Canada	inpatient	CFS	141	80.6 (7.8)	mean HbA1c	mean difference	No significant difference between frail and non-frail
Matsuzawa	2010	Japan	inpatient	CGA	288	72.8 (7.7)	mean HbA1c	mean difference (t-test)	Higher HbA1c in frail group (7.9±1.1 vs 7.4±1.4)
McAlister	2016	NA	NA	John Hopkins ACG	NA	NA	HbA1c categorised as <7%, 7-8%, 8-9% and >9%	descriptive	no difference between health status groups
McAlister	2017	NA	NA	John Hopkins ACG	NA	NA	HbA1c categorised as <7%, 7-8%, 8-9% and >9%	Chi squared	Slightly higher proportion of frail in <7% group and in >9 group

McAlister	2018	NA	NA	eFI	NA	NA	HbA1c categorised as <6%, 6-6.5%, 6.5-7%, 7-7.5% and >7.5%	Chi squared	higher proportion of frail in <6% group, lower proportion of frail in >7.5 group
Molist-Brunet	2019	Spain	inpatient	FI	210	86.1 (4.8)	mean HbA1c	mean difference (not satistically tested by no clinically meaningful difference between frailty groups)	not satistically tested by no clinically meaningful difference between frailty groups
Nelson	2007	USA	outpatient	VES-13	111	78	mean HbA1c	mean difference	no significant difference
Nelson	2007	USA	outpatient	VES-13	111	78	HbA1c <7%	Chi squared	no significant difference
Yanagita	2018	Japan	outpatient	CFS	132	78.3 (7.9)	mean HbA1c	mean difference	lower with frailty - lowest HbA1c at most

									severe end of frailty spectrum

Diabetes complications

Author	Year	Country	Setting	Frailty_measure	N_diabetes	age	Outcome	Description	
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	cerebrovascular disease	Chi squared test for cross sectional assocation between frailty and cerebrovascular disease	Positive association
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	coronary artery disease	Chi squared test for cross sectional assocation between frailty and coronary artery disease	Positive association
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	any event in last 3 months	Logistic regression (OR 1.83 (1.17, 2.86)	Positive association
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	Hypoglycaemic hospitalisation	Logistic regression (OR 7.67 (3.32, 17.7)	Positive association

Simpson	2016	USA	community	John Hopkins ACG	54505	60 (52-68)	New macrovascular complication	Multivariate Cox Regression Analysis of New Diabetes Complication in 54 505 Patients Initiating Oral Antidiabetic Drugs. HR 0.99 (0.86-1.13)	no association
van Hateren	2015	Netherlands	outpatient	RAND-36	858	72.3 (7.2)	Macrovascular complications	Chi squared test for cross sectional assocation between frailty and macrovascular disease	Positive association
Chao	2018	Taiwan	community	FRAIL	560795	56.4 (13.8)	cardiovascular event	Cox PH model: HR 1.13 (1.02-1.25)	Positive association
Li	2015	China	inpatient	FRAIL	146	80 (74-84)	macroangiopathy	Logistic regression (OR 0.87 (0.24-3.13)	no association
Hubbard	2010	England	community	CFS	310	81.3	Complications (retinopathy, recurrent	Among older adults with diabetes,	Positive association

							infections, nephropathy and peripheral neuropathy)	those who were frail were 2.62 times more likely to have a complication of diabetes than those who were not frail (95% CI 1.36–5.06 times). This was independent of age, sex andnumber of years livingwith diabetes.	
Simpson	2016	USA	community	John Hopkins ACG	54505	50 (62-58)	New microvascular complication	Multivariate Cox Regression Analysis of New Diabetes Complication in 54 505 Patients Initiating Oral	no association

								Antidiabetic Drugs. HR 0.89 (0.70-1.13)	
Ferri-Guerra	2019	USA	community	FI	763	72.87 (6.78)	Diabetes with End organ damage: patients diagnosed with one or more of the following diagnosis: retinopathy, neuropathy and nephropathy.	Chi squared test for cross sectional assocation between frailty and microvascular disease	Positive association
Chao	2018	Taiwan	community	FRAIL	560795	56.4 (13.8)	aDCSI scores	Chi squared test for cross sectional assocation between frailty and aDCSI scores	Positive association
McAllister	2018	UK	community	eFI	292170	61.7	nephropathy	Chi squared test for cross sectional assocation between frailty and nephropathy	Positive association

Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	nephropathy	Chi squared test for cross sectional assocation between frailty and nephropathy	Positive association
Adame Perez	2019	Canada	outpatient	Edmonton	41	70 (65-74)	nephropathy	Chi squared test for cross sectional assocation between frailty and nephropathy	Positive association
Li	2015	China	inpatient	FRAIL	146	80 (74-84)	nephropathy	Logistic regression (OR 4.46 (1.24-15.97)	Positive association
Tuttle	2018	USA	outpatient	mPPT	95	57 (12)	Peripheral neuropathy	Chi squared test for cross sectional assocation between frailty and peripheral neuropathy	Positive association
McAllister	2018	UK	community	eFI	292170	61.7	neuropathy	Chi squared test for cross sectional assocation	Positive association

								between frailty and neuropathy	
Nelson	2007	USA	outpatient	VES-13	111	78	neuropathy	Chi squared test for cross sectional assocation between frailty and neuropathy	Positive association
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	neuropathy	Chi squared test for cross sectional assocation between frailty and neuropathy	Positive association
McAllister	2018	UK	community	eFI	292170	61.7	retinopathy	Chi squared test for cross sectional assocation between frailty and retinopathy	Positive association
Nelson	2007	USA	outpatient	VES-13	111	78	visual impairment	Chi squared test for cross sectional assocation between	Positive association

								frailty and retinopathy	
Pilotto	2014	Italy	Outpatient	CGA	1324	73.3 (5.6)	retinopathy	Chi squared test for cross sectional assocation between frailty and retinopathy	Positive association
Boas	2018	Brazil	outpatient	Edmonton	100	NA	foot ulcer	Increasing frailty severity assocaited with higher proportion of participants with foot ulceration	Positive association

Disability

Author	**Year**	**Country**	**Setting**	**Frailty measure**	**Number with diabetes**	**Mean or median age (SD or IQR)**	**Disability measure**	**Covariate adjustment**	**Analysis**	**Outcome**
Li	2015	China	inpatient	FRAIL	146	80 (74-84)	Physical performance was assessed by activities of daily living (ADLs) and instrumental	models adjusted for age,	logistic regression	cross sectional associatio

							activities of daily living (IADLs). ADLs included 6 items: feeding, bowels and bladder control, toileting, transfers, dressing and bathing. IADLs included 8 items: using the telephone, food preparation, shopping, managing money, house-keeping, laundry, getting to places outside of walking distance, and taking medicine. Each of the items was categorized as severely dependent, assistant living, and completely independent. ADL disability and IADL disability were defined as requiring any assistance in performing at least 1 of the items, respectively.	gender, MMSE points, BMI, duration of diabetes and HbA1c		n (OR 6.58 (1.66-26.10) for ADL)

Chode	2016	USA	community	FRAIL	222	57.43 (4.4)	ADLs included seven items (bathing, dressing, eating, transferring bed or chair, walking across a room, getting outside, and using toilet) (21). IADLs included eight items (preparing meals, shopping for groceries, managing money, making phone calls, doing light housework, doing heavy housework, getting to places outside walking distance, and managing medications)	age, sex	linear regression (number of ADL/IADL impairments)	cross sectional associations (number of impairments)

Castro-Rodriguez	2016	Spain	community	FI	363	76 (71.2-79)	Functional disability was evaluated according to the Katz Index (which ranks dependency 6six functions of daily living: bathing, dressing, toileting, transferences, continence, and feeding) obtained from each individual in the baseline and follow-up visits.24 Incident disability was ascertained by comparison of the Katz Index. People were classified as having incident disability when any worsening in the Katz Index was detected	none	Baseline FI compared between those with and without incident disability	Positive association between frailty and incident disability

Liccini	2016	USA	outpatient	FRAIL	198	64.9 (8.7)	ADLs included seven items (bathing, dressing, eating, transferring bed or chair, walking across a room, getting outside, and using toilet) (21). IADLs included eight items (preparing meals, shopping for groceries, managing money, making phone calls, doing light housework, doing heavy housework, getting to places outside walking distance, and managing medications)	age, sex, education and HbA1c	logistic regression	new disability (OR for frailty 3.57 (1.27-10.04)

Thein	2018	Singapore	community	Fried	486	67.3 (7.5)	Dependency on daily living activities was measured using self reported difficulty or needing assistance in instrumental activities of daily living (IADL) and activities of daily living (ADL), as previously validated in a local cohort	Adjusted for age, gender, education level, smoking, alcohol intake, and physical exercise, diabetes duration, WC, total cholesterol, HDL cholesterol, hypertension, cardiac disease, stroke, arthritis, hip fracture, polypharmacy, and depression.	logistic regression	cross sectional associations with ADL/IADL disability (OR 20.2 (7.74–52.6)

Cognitive impairment

Author	Year	Country	Setting	Frailty measure	Number with diabetes	Mean or median age (SD or IQR)	Measure	Cross sectional/ prospective	Analysis	Result
Bello-Chavolla	2017	Mexico	community	Fried	135	77.7 (5.8)	MMSE	cross sectional	Chi squared	positive association
Matsuzawa	2010	Japan	inpatient	CGA	288	72.8 (7.7)	MMSE	cross sectional	Chi squared	positive association
Cacciatore	2013	Italy	community	Frailty staging system	188	72.8 (5.8)	MMSE	cross sectional	multivariable logistic regression model for frailty	positive association

Quality of Life

Author	Year	Country	Setting	Frailty measure	Number with diabetes	Mean or median age (SD or IQR)	Cross sectional/ prospective	Analysis	Result
Adame Perez	2019	Canada	outpatient	Edmonton	41	70 (65-74)	cross sectional	Participants with frailty scored a median (range) of 31 (13 to 54) points lower in HRQoL scores when compared	positive association

								to nonfrail participants (p?0.05)	
Matsuzawa	2010	Japan	inpatient	CGA	288	72.8 (7.7)	cross sectional	Chi squared test comparing frail and non frailty people and QOL scores	positive association
Nguyen	2019	Vietnam	community	Fried	24	NA	cross sectional	The mean EQ-5D-5L indexes of the non-frailty, pre-frailty, and frailty groups were 0.70 (SD = 0.18), 0.70 (SD = 0.19), and 0.58 (SD = 0.20), respectively. The differences were found between non-frailty and frailty	positive association

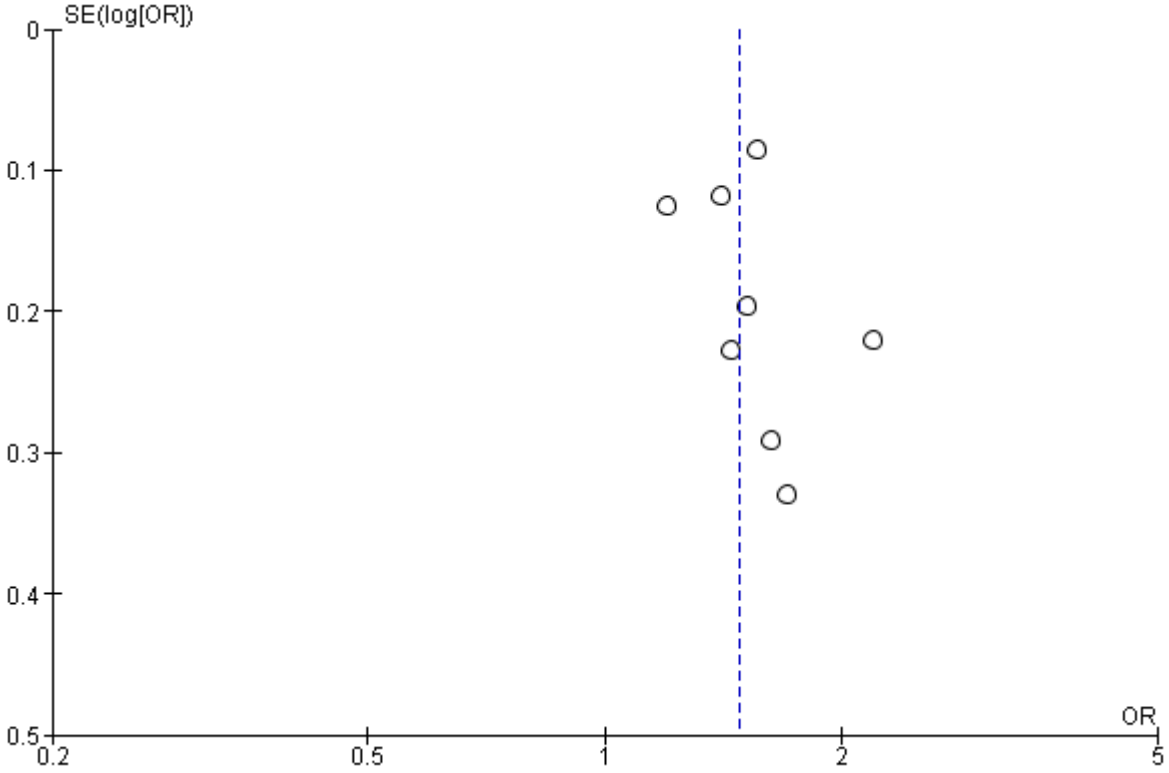
								groups (p < 0.01), as well as the pre-frailty and frailty groups (p<0.01).	

Depression

Author	**Year**	**Country**	**Setting**	**Frailty measure**	**Number with diabetes**	**Mean or median age (SD or IQR)**	**Cross sectional/ prospective**	**Analysis**	**Result**	
Almeida	2016	Australia	community	FRAIL	717	NA	Geriatric depression scale	cross sectional	OR for current depression 8.92 (7.10, 11.20)	positive association
Adame Perez	2019	Canada	outpatient	Edmonton	41	70 (65-74)	Major depression inventory	cross sectional	Frail participants had a higher incidence (83% frail vs. 6% non frail) of depression (p=0.005) than those	positive association

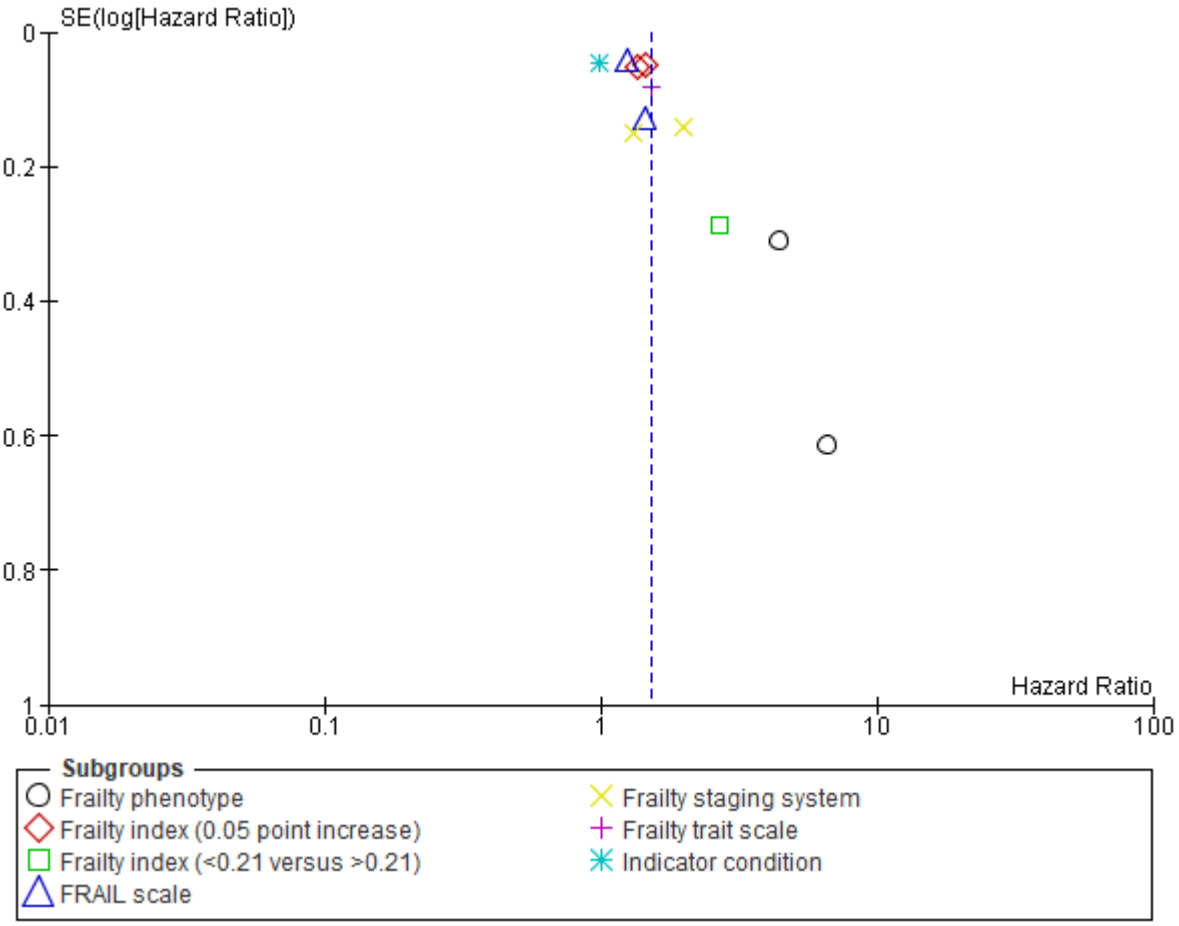
									without frailty	
Matsuzawa	2010	Japan	inpatient	CGA	288	72.8 (7.7)	Geriatric depression scale	cross sectional	No significant difference in mean score	no association

Assessment of publication bias
Funnel plot of studies assessing relationship between diabetes status and incidence of frailty



No clear evidence of publication bias. However, this should be interpreted with caution given the small number of studies included in the plot.

Funnel plot of studies assessing hazard ratio of mortality associated with frailty



Some asymmetry in this plot which may include publication bias. However this appears to be driven by the higher effect size of the frailty phenotype studies rather than true bias towards studies with higher effect sizes.

Appendix 4: Supplementary material for Chapter 5: An analysis of frailty and multimorbidity in 20,566 UK Biobank participants with type 2 diabetes

Quantification of frailty and multimorbidity

eTable1 Frailty phenotype	
Weight loss	Self-reported: "Compared with one year ago, has your weight changed?" (response: yes, lost weight=1, other=0)
Exhaustion	Self-reported: "Over the past two weeks, how often have you felt tired or had little energy?" (response: more than half the days or nearly every day=1, other=0)
Low physical activity	Self-reported: UK Biobank physical activity questionnaire. We classified the responses into: none (no physical activity in the last 4 weeks), low (light DIY activity [eg, pruning, watering the lawn] only in the past 4 weeks), medium (heavy DIY activity [eg, weeding, lawn mowing, carpentry and digging], walking for pleasure, or other exercises in the past 4 weeks), and high (strenuous sports in the past 4 weeks) (response: none or light activity with a frequency of once per week or less=1, medium or heavy activity, or light activity more than once per week=0)
Slow walking pace	Self-reported: "How would you describe your usual walking pace?" (response: slow=1, other=0)
Low grip strength	Measured grip strength (sex and body-mass index adjusted cutoffs taken from Fried et al)

Frailty index deficits were reproduced as per the supplementary material of Williams et al (https://doi.org/10.1093/gerona/gly094)

eTable2 ICD-10 codes for Charlson index		
Diagnosis	three_character	fourth_character
Congestive heart failure	I09	9
Congestive heart failure	I11	0
Congestive heart failure	I13	0
Congestive heart failure	I13	2
Congestive heart failure	I25	5
Congestive heart failure	I42	0
Congestive heart failure	I42	5
Congestive heart failure	I42	6
Congestive heart failure	I42	7
Congestive heart failure	I42	8
Congestive heart failure	I42	9
Congestive heart failure	I43	
Congestive heart failure	I50	
Congestive heart failure	P29	0
Cardiac arrhythmias	I44	1
Cardiac arrhythmias	I44	2
Cardiac arrhythmias	I44	3
Cardiac arrhythmias	I45	6
Cardiac arrhythmias	I45	9

Cardiac arrhythmias	I47	
Cardiac arrhythmias	I48	
Cardiac arrhythmias	I49	
Cardiac arrhythmias	R00	0
Cardiac arrhythmias	R00	1
Cardiac arrhythmias	R00	8
Cardiac arrhythmias	T82	1
Cardiac arrhythmias	Z45	0
Cardiac arrhythmias	Z95	0
Vascular disease	A52	0
Vascular disease	I05	
Vascular disease	I06	
Vascular disease	I07	
Vascular disease	I08	
Vascular disease	I09	1
Vascular disease	I09	8
Vascular disease	I34	
Vascular disease	I35	
Vascular disease	I36	
Vascular disease	I37	
Vascular disease	I38	
Vascular disease	I39	
Vascular disease	Q23	0
Vascular disease	Q23	1
Vascular disease	Q23	2
Vascular disease	Q23	3
Vascular disease	Z95	2
Vascular disease	Z95	3
Vascular disease	Z95	4
Pulmonary circulation disorders	I26	
Pulmonary circulation disorders	I27	
Pulmonary circulation disorders	I28	0
Pulmonary circulation disorders	I28	8
Pulmonary circulation disorders	I28	9
Peripheral vascular disorders	I70	
Peripheral vascular disorders	I71	
Peripheral vascular disorders	I73	1
Peripheral vascular disorders	I73	8
Peripheral vascular disorders	I73	9
Peripheral vascular disorders	I77	1
Peripheral vascular disorders	I79	0
Peripheral vascular disorders	I79	2
Peripheral vascular disorders	K55	1
Peripheral vascular disorders	K55	8
Peripheral vascular disorders	Z95	8
Peripheral vascular disorders	Z95	9
Hypertension, uncomplicated	I10	

Hypertension, complicated	I11	
Hypertension, complicated	I12	
Hypertension, complicated	I13	
Hypertension, complicated	I15	
Paralysis	G04	1
Paralysis	G11	4
Paralysis	G80	1
Paralysis	G80	2
Paralysis	G81	
Paralysis	G82	
Paralysis	G83	0
Paralysis	G83	1
Paralysis	G83	2
Paralysis	G83	3
Paralysis	G83	4
Paralysis	G83	9
Other neurological disorders	G10	
Other neurological disorders	G11	
Other neurological disorders	G12	
Other neurological disorders	G13	
Other neurological disorders	G20	
Other neurological disorders	G21	
Other neurological disorders	G22	
Other neurological disorders	G25	4
Other neurological disorders	G25	5
Other neurological disorders	G31	2
Other neurological disorders	G31	8
Other neurological disorders	G31	9
Other neurological disorders	G32	
Other neurological disorders	G35	
Other neurological disorders	G36	
Other neurological disorders	G37	
Other neurological disorders	G40	
Other neurological disorders	G41	
Other neurological disorders	G93	1
Other neurological disorders	G93	4
Other neurological disorders	R47	0
Other neurological disorders	R56	
Chronic pulmonary disease	I27	8
Chronic pulmonary disease	I27	9
Chronic pulmonary disease	J40	
Chronic pulmonary disease	J41	
Chronic pulmonary disease	J42	
Chronic pulmonary disease	J43	
Chronic pulmonary disease	J44	
Chronic pulmonary disease	J45	
Chronic pulmonary disease	J46	

Chronic pulmonary disease	J47	
Chronic pulmonary disease	J60	
Chronic pulmonary disease	J61	
Chronic pulmonary disease	J62	
Chronic pulmonary disease	J63	
Chronic pulmonary disease	J64	
Chronic pulmonary disease	J65	
Chronic pulmonary disease	J66	
Chronic pulmonary disease	J67	
Chronic pulmonary disease	J68	4
Chronic pulmonary disease	J70	1
Chronic pulmonary disease	J70	3
Diabetes, uncomplicated	E10	0
Diabetes, uncomplicated	E10	1
Diabetes, uncomplicated	E10	9
Diabetes, uncomplicated	E11	0
Diabetes, uncomplicated	E11	1
Diabetes, uncomplicated	E11	9
Diabetes, uncomplicated	E12	0
Diabetes, uncomplicated	E12	1
Diabetes, uncomplicated	E12	9
Diabetes, uncomplicated	E13	0
Diabetes, uncomplicated	E13	1
Diabetes, uncomplicated	E13	9
Diabetes, uncomplicated	E14	0
Diabetes, uncomplicated	E14	1
Diabetes, uncomplicated	E14	9
Diabetes, complicated	E10	2
Diabetes, complicated	E10	3
Diabetes, complicated	E10	4
Diabetes, complicated	E10	5
Diabetes, complicated	E10	6
Diabetes, complicated	E10	7
Diabetes, complicated	E10	8
Diabetes, complicated	E11	2
Diabetes, complicated	E11	3
Diabetes, complicated	E11	4
Diabetes, complicated	E11	5
Diabetes, complicated	E11	6
Diabetes, complicated	E11	7
Diabetes, complicated	E11	8
Diabetes, complicated	E12	2
Diabetes, complicated	E12	3
Diabetes, complicated	E12	4
Diabetes, complicated	E12	5
Diabetes, complicated	E12	6
Diabetes, complicated	E12	7

Diabetes, complicated	E12	8
Diabetes, complicated	E13	2
Diabetes, complicated	E13	3
Diabetes, complicated	E13	4
Diabetes, complicated	E13	5
Diabetes, complicated	E13	6
Diabetes, complicated	E13	7
Diabetes, complicated	E13	8
Diabetes, complicated	E14	2
Diabetes, complicated	E14	3
Diabetes, complicated	E14	4
Diabetes, complicated	E14	5
Diabetes, complicated	E14	6
Diabetes, complicated	E14	7
Diabetes, complicated	E14	8
Hypothyroidism	E00	
Hypothyroidism	E01	
Hypothyroidism	E02	
Hypothyroidism	E03	
Hypothyroidism	E89	0
Renal failure	I12	0
Renal failure	I13	1
Renal failure	N18	
Renal failure	N19	
Renal failure	N25	0
Renal failure	Z49	0
Renal failure	Z49	1
Renal failure	Z49	2
Renal failure	Z94	0
Renal failure	Z99	2
Liver disease	B18	
Liver disease	I85	
Liver disease	I86	4
Liver disease	I98	2
Liver disease	K70	
Liver disease	K71	1
Liver disease	K71	3
Liver disease	K71	4
Liver disease	K71	5
Liver disease	K71	7
Liver disease	K72	
Liver disease	K73	
Liver disease	K74	
Liver disease	K76	0
Liver disease	K76	2
Liver disease	K76	3
Liver disease	K76	4

Liver disease	K76	5
Liver disease	K76	6
Liver disease	K76	7
Liver disease	K76	8
Liver disease	K76	9
Liver disease	Z94	4
Peptic ulcer disease, excluding bleeding	K25	7
Peptic ulcer disease, excluding bleeding	K25	9
Peptic ulcer disease, excluding bleeding	K26	7
Peptic ulcer disease, excluding bleeding	K26	9
Peptic ulcer disease, excluding bleeding	K27	7
Peptic ulcer disease, excluding bleeding	K27	9
Peptic ulcer disease, excluding bleeding	K28	7
Peptic ulcer disease, excluding bleeding	K28	9
AIDS/HIV	B20	
AIDS/HIV	B21	
AIDS/HIV	B22	
AIDS/HIV	B24	
Lymphoma	C81	
Lymphoma	C82	
Lymphoma	C83	
Lymphoma	C84	
Lymphoma	C85	
Lymphoma	C88	
Lymphoma	C96	
Lymphoma	C90	0
Lymphoma	C90	2
Metastatic cancer	C77	
Metastatic cancer	C78	
Metastatic cancer	C79	
Metastatic cancer	C80	
Solid tumour without metastasis	C00	
Solid tumour without metastasis	C01	
Solid tumour without metastasis	C02	
Solid tumour without metastasis	C03	
Solid tumour without metastasis	C04	
Solid tumour without metastasis	C05	
Solid tumour without metastasis	C06	
Solid tumour without metastasis	C07	
Solid tumour without metastasis	C08	

Solid tumour without metastasis	C09	
Solid tumour without metastasis	C10	
Solid tumour without metastasis	C11	
Solid tumour without metastasis	C12	
Solid tumour without metastasis	C13	
Solid tumour without metastasis	C14	
Solid tumour without metastasis	C15	
Solid tumour without metastasis	C16	
Solid tumour without metastasis	C17	
Solid tumour without metastasis	C18	
Solid tumour without metastasis	C19	
Solid tumour without metastasis	C20	
Solid tumour without metastasis	C21	
Solid tumour without metastasis	C22	
Solid tumour without metastasis	C23	
Solid tumour without metastasis	C24	
Solid tumour without metastasis	C25	
Solid tumour without metastasis	C26	
Solid tumour without metastasis	C30	
Solid tumour without metastasis	C31	
Solid tumour without metastasis	C32	
Solid tumour without metastasis	C33	
Solid tumour without metastasis	C34	
Solid tumour without metastasis	C37	
Solid tumour without metastasis	C38	
Solid tumour without metastasis	C39	
Solid tumour without metastasis	C40	
Solid tumour without metastasis	C41	
Solid tumour without metastasis	C43	
Solid tumour without metastasis	C45	
Solid tumour without metastasis	C46	
Solid tumour without metastasis	C47	
Solid tumour without metastasis	C48	
Solid tumour without metastasis	C49	
Solid tumour without metastasis	C50	
Solid tumour without metastasis	C51	
Solid tumour without metastasis	C52	
Solid tumour without metastasis	C53	
Solid tumour without metastasis	C54	
Solid tumour without metastasis	C55	
Solid tumour without metastasis	C56	
Solid tumour without metastasis	C57	
Solid tumour without metastasis	C58	
Solid tumour without metastasis	C60	
Solid tumour without metastasis	C61	
Solid tumour without metastasis	C62	
Solid tumour without metastasis	C63	

Solid tumour without metastasis	C64	
Solid tumour without metastasis	C65	
Solid tumour without metastasis	C66	
Solid tumour without metastasis	C67	
Solid tumour without metastasis	C68	
Solid tumour without metastasis	C69	
Solid tumour without metastasis	C70	
Solid tumour without metastasis	C71	
Solid tumour without metastasis	C72	
Solid tumour without metastasis	C73	
Solid tumour without metastasis	C74	
Solid tumour without metastasis	C75	
Solid tumour without metastasis	C76	
Solid tumour without metastasis	C97	
Rheumatoid arthritis/collagen vascular diseases	L94	0
Rheumatoid arthritis/collagen vascular diseases	L94	1
Rheumatoid arthritis/collagen vascular diseases	L94	3
Rheumatoid arthritis/collagen vascular diseases	M05	
Rheumatoid arthritis/collagen vascular diseases	M06	
Rheumatoid arthritis/collagen vascular diseases	M08	
Rheumatoid arthritis/collagen vascular diseases	M12	0
Rheumatoid arthritis/collagen vascular diseases	M12	3
Rheumatoid arthritis/collagen vascular diseases	M30	
Rheumatoid arthritis/collagen vascular diseases	M31	0
Rheumatoid arthritis/collagen vascular diseases	M31	1
Rheumatoid arthritis/collagen vascular diseases	M31	2
Rheumatoid arthritis/collagen vascular diseases	M31	3
Rheumatoid arthritis/collagen vascular diseases	M32	
Rheumatoid arthritis/collagen vascular diseases	M33	
Rheumatoid arthritis/collagen vascular diseases	M34	
Rheumatoid arthritis/collagen vascular diseases	M35	
Rheumatoid arthritis/collagen vascular diseases	M45	

Rheumatoid arthritis/collagen vascular diseases	M46	1
Rheumatoid arthritis/collagen vascular diseases	M46	8
Rheumatoid arthritis/collagen vascular diseases	M46	9
Coagulopathy	D65	
Coagulopathy	D66	
Coagulopathy	D67	
Coagulopathy	D68	
Coagulopathy	D69	1
Coagulopathy	D69	3
Coagulopathy	D69	4
Coagulopathy	D69	5
Coagulopathy	D69	6
Obesity	E66	
Weight loss	E40	
Weight loss	E41	
Weight loss	E42	
Weight loss	E43	
Weight loss	E44	
Weight loss	E45	
Weight loss	E46	
Weight loss	R63	4
Weight loss	R64	
Fluid and electrolyte disorders	E22	2
Fluid and electrolyte disorders	E86	
Fluid and electrolyte disorders	E87	
Blood loss anaemia	D50	0
Deficiency anaemia	D50	8
Deficiency anaemia	D50	9
Deficiency anaemia	D51	
Deficiency anaemia	D52	
Deficiency anaemia	D53	
Alcohol abuse	F10	
Alcohol abuse	E52	
Alcohol abuse	G62	1
Alcohol abuse	I42	6
Alcohol abuse	K29	2
Alcohol abuse	K70	0
Alcohol abuse	K70	3
Alcohol abuse	K70	9
Alcohol abuse	T51	
Alcohol abuse	Z50	2
Alcohol abuse	Z71	4
Alcohol abuse	Z72	1
Drug abuse	F11	
Drug abuse	F12	

Drug abuse	F13	
Drug abuse	F14	
Drug abuse	F15	
Drug abuse	F16	
Drug abuse	F18	
Drug abuse	F19	
Drug abuse	Z71	5
Drug abuse	Z72	2
Psychoses	F20	
Psychoses	F22	
Psychoses	F23	
Psychoses	F24	
Psychoses	F25	
Psychoses	F28	
Psychoses	F29	
Psychoses	F30	2
Psychoses	F31	2
Psychoses	F31	5
Depression	F20	4
Depression	F31	3
Depression	F31	4
Depression	F31	5
Depression	F32	
Depression	F33	
Depression	F34	1
Depression	F41	2
Depression	F43	2

eTable3 LTC count conditions		
Long term condition grouping	**Conditions included as reported by participants**	**ICD-10 codes**
Painful conditions	Back pain	M50-54
	Joint pain	M25.5
	Back pain	R51
	Joint pain	M72.2
	Headaches (not migraine)	G56.0
	Sciatica	M79.7
	Plantar fasciitis	M15-M19, M13.9
	Carpal tunnel syndrome	G53.0
	Fibromyalgia	M45
	Arthritis	M15-M19
	Shingles	M10
	Disc problem	G50.0, G50.1
	Prolapsed disc/slipped disc	R52.1
	Spine arthritis/spondylitis	R52.2
	Ankylosing spondylitis	R52.9
	Back problem	
	Osteoarthritis	

	Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve	
Hypertension	Hypertension Essential Hypertension	
Depression	Depression Postnatal Depression	
Asthma	Asthma	J45-46
Atrial Fibrillation	Atrial Fibrillation	I48.0, I48.1, I48.2, I48.91
Coronary Heart Disease	Heart attack/Myocardial Infarction Angina	I20-25
Dyspepsia	Gastro-oesophageal reflux (GORD)/gastric reflux Oesophagitis /Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori	K20-30
Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease	
Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrotoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroiditis	E00-E07
Connective tissue disorders	Myositis/myopathy Systemic Lupus Erythematosus Connective tissue disorder Sjogrens syndrome/sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia Rheumatica Malabsorption/coeliac disease	M30-M36 M05, 06, 07, 08, 09

Chronic Obstructive Pulmonary Disease (COPD)	COPD/chronic obstructive airways disease Emphysema/chronic bronchitis Emphysema	J42, 43, 44
Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem	F40-45
Irritable bowel syndrome	Irritable bowel syndrome	K58
Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis	
Other psychoactive substance abuse	Opioid dependency Other substance abuse/dependency	
Treated constipation	Constipation	K59.0, K45.3
Stroke/Transient Ischaemic Attack (TIA)	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke	I60 61. 62, 63, 64, 69 G45
Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy	
Diverticular disease	Diverticular disease Diverticulitis	K57
Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication	
Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema	
Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy	N40, 41, 42
Glaucoma	Glaucoma	H40, H42
Epilepsy	Epilepsy	G40, G41
Dementia	Dementia Alzheimer’s disease Cognitive impairment	

Schizophrenia/bipolar disorder	Schizophrenia Mania/ Bipolar disorder Manic depression	
Psoriasis/eczema	Eczema Dermatitis Psoriasis	L40, L20, 21, 23, 24, 25, 30
Inflammatory Bowel Disease	Inflammatory Bowel Disease Crohn's disease Ulcerative colitis	K50 (Crohns), K51 (UC), K52 (non specific colitis)
Migraine	Migraine	G43
Chronic sinusitis	Chronic sinusitis	J32
Anorexia or bulimia	Anorexia Bulimia Other eating disorders	F50 (covers all eating disorders)
Bronchiectasis	Bronchiectasis	J47
Parkinson's disease	Parkinson's disease	G20
Multiple Sclerosis	Multiple Sclerosis	G35
Viral Hepatitis	Infective/viral hepatitis Hepatitis B Hepatitis C Hepatitis D Hepatitis E	B18 (chronic viral hepatitis), B19
Chronic Liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis	K70-77
Osteoporosis	Osteoporosis	M80, M81
Chronic fatigue syndrome	Chronic fatigue syndrome	R53.82 chronic fatigue syndrome, G93.3 post viral fatigue syndrome
Endometriosis	Endometriosis	N80 Endometriosis
Meniere's disease	Meniere's disease	H81.0
Pernicious Anaemia	Pernicious Anaemia	D51
Polycystic ovary	Polycystic ovary	E28.2
Cancer	Lifetime diagnosis	

Baseline sociodemographic data

eTable 4: Frailty and baseline characteristics								
	Total (n = 20566)	Frailty Phenotype			Frailty Index			
		Robust (n = 6261)	Pre-frail (n = 11026)	Frail (n = 2505)	FI <0.1 (n = 5591)	FI 0.1-0.15 (n = 5215)	FI >0.15-0.2 (n = 4196)	FI >0.2 (n = 5564)
Age								
Mean (sd)	60.2 (6.5)	60.6 (6.9)	60.1 (6.9)	59.9 (7)	59.9 (6.7)	60.4 (6.7)	60.6 (6.8)	60 (7.2)
Sex								
Female	7578 (36.8%)	1810 (28.9%)	4191 (38%)	1249 (49.9%)	1625 (29.1%)	1779 (34.1%)	1638 (39%)	2536 (45.6%)
Male	12988 (63.2%)	4451 (71.1%)	6835 (62%)	1256 (50.1%)	3966 (70.9%)	3436 (65.9%)	2558 (61%)	3028 (54.4%)
SES								
Quintile 1 (affluent)	2993 (14.6%)	1177 (18.8%)	1543 (14%)	204 (8.1%)	1013 (18.1%)	838 (16.1%)	587 (14%)	555 (10%)
Quintile 2	3314 (16.1%)	1267 (20.2%)	1724 (15.6%)	248 (9.9%)	1017 (18.2%)	949 (18.2%)	683 (16.3%)	665 (12%)
Quintile 3	3686 (17.9%)	1251 (20%)	1971 (17.9%)	355 (14.2%)	1103 (19.7%)	971 (18.6%)	733 (17.5%)	879 (15.8%)
Quintile 4	4333 (21.1%)	1277 (20.4%)	2381 (21.6%)	513 (20.5%)	1128 (20.2%)	1085 (20.8%)	915 (21.8%)	1205 (21.7%)
Quintile 5 (deprived)	6209 (30.2%)	1283 (20.5%)	3389 (30.7%)	1179 (47.1%)	1324 (23.7%)	1368 (26.2%)	1269 (30.2%)	2248 (40.4%)
NA's	31 (0.2%)	6 (0.1%)	18 (0.2%)	6 (0.2%)	6 (0.1%)	4 (0.1%)	9 (0.2%)	12 (0.2%)
Ethnicity								
White	17715 (86.1%)	5667 (90.5%)	9421 (85.4%)	2054 (82%)	4645 (83.1%)	4502 (86.3%)	3677 (87.6%)	4891 (87.9%)
Asian/Asian British	1404 (6.8%)	270 (4.3%)	808 (7.3%)	237 (9.5%)	460 (8.2%)	340 (6.5%)	260 (6.2%)	344 (6.2%)
Black/Black British	695 (3.4%)	167 (2.7%)	412 (3.7%)	92 (3.7%)	227 (4.1%)	195 (3.7%)	132 (3.1%)	141 (2.5%)
Chinese	71 (0.3%)	18 (0.3%)	50 (0.5%)	3 (0.1%)	32 (0.6%)	20 (0.4%)	13 (0.3%)	6 (0.1%)
Mixed	137 (0.7%)	48 (0.8%)	70 (0.6%)	17 (0.7%)	39 (0.7%)	34 (0.7%)	27 (0.6%)	37 (0.7%)
Other ethnic group	364 (1.8%)	66 (1.1%)	207 (1.9%)	78 (3.1%)	96 (1.7%)	95 (1.8%)	70 (1.7%)	103 (1.9%)
NA's	180 (0.9%)	25 (0.4%)	58 (0.5%)	24 (1%)	92 (1.6%)	29 (0.6%)	17 (0.4%)	42 (0.8%)
BMI								
<18.5	16 (0.1%)	6 (0.1%)	5 (0%)	2 (0.1%)	5 (0.1%)	4 (0.1%)	3 (0.1%)	4 (0.1%)
18.5-24.9	1802 (8.8%)	722 (11.5%)	911 (8.3%)	125 (5%)	695 (12.4%)	505 (9.7%)	316 (7.5%)	286 (5.1%)
25-29.9	6931 (33.7%)	2526 (40.3%)	3642 (33%)	579 (23.1%)	2297 (41.1%)	1854 (35.6%)	1387 (33.1%)	1393 (25%)

>=30	11038 (53.7%)	2932 (46.8%)	6135 (55.6%)	1606 (64.1%)	2490 (44.5%)	2710 (52%)	2324 (55.4%)	3514 (63.2%)
NA's	779 (3.8%)	75 (1.2%)	333 (3%)	193 (7.7%)	104 (1.9%)	142 (2.7%)	166 (4%)	367 (6.6%)
Smoking								
Never	9148 (44.5%)	2726 (43.5%)	5004 (45.4%)	1092 (43.6%)	2780 (49.7%)	2393 (45.9%)	1787 (42.6%)	2188 (39.3%)
Previous	8998 (43.8%)	2995 (47.8%)	4739 (43%)	1001 (40%)	2226 (39.8%)	2298 (44.1%)	1941 (46.3%)	2533 (45.5%)
Current	2197 (10.7%)	501 (8%)	1204 (10.9%)	383 (15.3%)	480 (8.6%)	478 (9.2%)	441 (10.5%)	798 (14.3%)
NA's	223 (1.1%)	39 (0.6%)	79 (0.7%)	29 (1.2%)	105 (1.9%)	46 (0.9%)	27 (0.6%)	45 (0.8%)
Alcohol								
Never or special occasions only	7151 (34.8%)	1509 (24.1%)	3935 (35.7%)	1342 (53.6%)	1635 (29.2%)	1571 (30.1%)	1453 (34.6%)	2492 (44.8%)
1-4 times/week	7851 (38.2%)	2799 (44.7%)	4182 (37.9%)	665 (26.5%)	2347 (42%)	2215 (42.5%)	1562 (37.2%)	1727 (31%)
1-3 times/month	2521 (12.3%)	708 (11.3%)	1447 (13.1%)	292 (11.7%)	645 (11.5%)	606 (11.6%)	561 (13.4%)	709 (12.7%)
Daily/almost daily	2946 (14.3%)	1242 (19.8%)	1446 (13.1%)	198 (7.9%)	899 (16.1%)	810 (15.5%)	615 (14.7%)	622 (11.2%)
NA's	97 (0.5%)	3 (0%)	16 (0.1%)	8 (0.3%)	65 (1.2%)	13 (0.2%)	5 (0.1%)	14 (0.3%)
HbA1c								
Mean (sd)	51.3 (11.3)	50.7 (13)	51.3 (14.5)	52.3 (12.6)	51.1 (12.6)	51.1 (12.6)	51.2 (13.3)	51.5 (13.3)
HbA1c categories								
< 42	4142 (20.1%)	1237 (19.8%)	2297 (20.8%)	487 (19.4%)	1155 (20.7%)	1038 (19.9%)	832 (19.8%)	1117 (20.1%)
42-48	4662 (22.7%)	1432 (22.9%)	2558 (23.2%)	540 (21.6%)	1263 (22.6%)	1186 (22.7%)	961 (22.9%)	1252 (22.5%)
48-60	6656 (32.4%)	2170 (34.7%)	3539 (32.1%)	767 (30.6%)	1784 (31.9%)	1713 (32.8%)	1393 (33.2%)	1766 (31.7%)
>60	3512 (17.1%)	1011 (16.1%)	1898 (17.2%)	489 (19.5%)	965 (17.3%)	871 (16.7%)	688 (16.4%)	988 (17.8%)
NA's	1594 (7.8%)	411 (6.6%)	734 (6.7%)	222 (8.9%)	424 (7.6%)	407 (7.8%)	322 (7.7%)	441 (7.9%)

eTable 5: Multimorbidity and baseline characteristics								
	Total (n = 20566)	**Multimorbidity count**				**Charlson comorbidity index**		
		0-1 LTCs (n = 7549)	**2 LTCs (n = 5115)**	**3 LTCs (n = 3524)**	**4 or more LTCs (n = 4378)**	**CCI = 0 (n = 12058)**	**CCI = 1 (n = 5042)**	**CCI ≥2 (n = 3466)**
Age								
Mean (sd)	60.2 (6.5)	58.8 (6.6)	60.6 (6.4)	61.1 (6.3)	61.4 (7.1)	59.6 (6.4)	60.3 (5.9)	62.2 (6.5)

Sex								
Female	7578 (36.8%)	2485 (32.9%)	1890 (37%)	1369 (38.8%)	1834 (41.9%)	4430 (36.7%)	1841 (36.5%)	1307 (37.7%)
Male	12988 (63.2%)	5064 (67.1%)	3225 (63%)	2155 (61.2%)	2544 (58.1%)	7628 (63.3%)	3201 (63.5%)	2159 (62.3%)
SES								
Quintile 1 (affluent)	2993 (14.6%)	1223 (16.2%)	793 (15.5%)	477 (13.5%)	500 (11.4%)	1825 (15.1%)	701 (13.9%)	467 (13.5%)
Quintile 2	3314 (16.1%)	1307 (17.3%)	862 (16.9%)	571 (16.2%)	574 (13.1%)	2040 (16.9%)	731 (14.5%)	543 (15.7%)
Quintile 3	3686 (17.9%)	1407 (18.6%)	963 (18.8%)	634 (18%)	682 (15.6%)	2227 (18.5%)	884 (17.5%)	575 (16.6%)
Quintile 4	4333 (21.1%)	1536 (20.3%)	1076 (21%)	739 (21%)	982 (22.4%)	2499 (20.7%)	1110 (22%)	724 (20.9%)
Quintile 5 (deprived)	6209 (30.2%)	2064 (27.3%)	1414 (27.6%)	1098 (31.2%)	1633 (37.3%)	3448 (28.6%)	1606 (31.9%)	1155 (33.3%)
NA's	31 (0.2%)	12 (0.2%)	7 (0.1%)	5 (0.1%)	7 (0.2%)	19 (0.2%)	10 (0.2%)	2 (0.1%)
Ethnicity								
White	17715 (86.1%)	6230 (82.5%)	4439 (86.8%)	3108 (88.2%)	3938 (89.9%)	10220 (84.8%)	4382 (86.9%)	3113 (89.8%)
Asian/Asian British	1404 (6.8%)	654 (8.7%)	333 (6.5%)	198 (5.6%)	219 (5%)	902 (7.5%)	346 (6.9%)	156 (4.5%)
Black/Black British	695 (3.4%)	347 (4.6%)	167 (3.3%)	101 (2.9%)	80 (1.8%)	463 (3.8%)	141 (2.8%)	91 (2.6%)
Chinese	71 (0.3%)	38 (0.5%)	19 (0.4%)	9 (0.3%)	5 (0.1%)	51 (0.4%)	16 (0.3%)	4 (0.1%)
Mixed	137 (0.7%)	54 (0.7%)	24 (0.5%)	31 (0.9%)	28 (0.6%)	87 (0.7%)	32 (0.6%)	18 (0.5%)
Other ethnic group	364 (1.8%)	159 (2.1%)	90 (1.8%)	51 (1.4%)	64 (1.5%)	231 (1.9%)	80 (1.6%)	53 (1.5%)
NA's	180 (0.9%)	67 (0.9%)	43 (0.8%)	26 (0.7%)	44 (1%)	104 (0.9%)	45 (0.9%)	31 (0.9%)
BMI								
<18.5	16 (0.1%)	9 (0.1%)	2 (0%)	0 (0%)	5 (0.1%)	10 (0.1%)	3 (0.1%)	3 (0.1%)
18.5-24.9	1802 (8.8%)	869 (11.5%)	409 (8%)	238 (6.8%)	286 (6.5%)	1100 (9.1%)	380 (7.5%)	322 (9.3%)
25-29.9	6931 (33.7%)	2864 (37.9%)	1790 (35%)	1133 (32.2%)	1144 (26.1%)	4224 (35%)	1619 (32.1%)	1088 (31.4%)
>=30	11038 (53.7%)	3624 (48%)	2728 (53.3%)	2008 (57%)	2678 (61.2%)	6336 (52.5%)	2814 (55.8%)	1888 (54.5%)
NA's	779 (3.8%)	183 (2.4%)	186 (3.6%)	145 (4.1%)	265 (6.1%)	388 (3.2%)	226 (4.5%)	165 (4.8%)
Smoking								
Never	9148 (44.5%)	3732 (49.4%)	2340 (45.7%)	1447 (41.1%)	1629 (37.2%)	5825 (48.3%)	2042 (40.5%)	1281 (37%)
Previous	8998 (43.8%)	2955 (39.1%)	2225 (43.5%)	1665 (47.2%)	2153 (49.2%)	4927 (40.9%)	2354 (46.7%)	1717 (49.5%)
Current	2197 (10.7%)	775 (10.3%)	500 (9.8%)	382 (10.8%)	540 (12.3%)	1177 (9.8%)	594 (11.8%)	426 (12.3%)
NA's	223 (1.1%)	87 (1.2%)	50 (1%)	30 (0.9%)	56 (1.3%)	129 (1.1%)	52 (1%)	42 (1.2%)

Alcohol								
Never or special occasions only	7151 (34.8%)	2347 (31.1%)	1650 (32.3%)	1289 (36.6%)	1865 (42.6%)	4046 (33.6%)	1769 (35.1%)	1336 (38.5%)
1-4 times/week	7851 (38.2%)	3095 (41%)	2042 (39.9%)	1302 (36.9%)	1412 (32.3%)	4724 (39.2%)	1888 (37.4%)	1239 (35.7%)
1-3 times/month	2521 (12.3%)	912 (12.1%)	653 (12.8%)	439 (12.5%)	517 (11.8%)	1474 (12.2%)	645 (12.8%)	402 (11.6%)
Daily/almost daily	2946 (14.3%)	1156 (15.3%)	749 (14.6%)	480 (13.6%)	561 (12.8%)	1761 (14.6%)	711 (14.1%)	474 (13.7%)
NA's	97 (0.5%)	39 (0.5%)	21 (0.4%)	14 (0.4%)	23 (0.5%)	53 (0.4%)	29 (0.6%)	15 (0.4%)
HbA1c								
Mean (sd)	51.3 (11.3)	52.1 (12.5)	50.9 (12.8)	51 (12.2)	50.4 (12.9)	51.5 (12.9)	51.1 (12.2)	50.5 (11.3)
HbA1c categories								
< 42	4142 (20.1%)	1426 (18.9%)	1054 (20.6%)	704 (20%)	958 (21.9%)	2345 (19.4%)	1032 (20.5%)	765 (22.1%)
42-48	4662 (22.7%)	1600 (21.2%)	1193 (23.3%)	852 (24.2%)	1017 (23.2%)	2753 (22.8%)	1168 (23.2%)	741 (21.4%)
48-60	6656 (32.4%)	2509 (33.2%)	1667 (32.6%)	1126 (32%)	1354 (30.9%)	3927 (32.6%)	1600 (31.7%)	1129 (32.6%)
>60	3512 (17.1%)	1416 (18.8%)	827 (16.2%)	585 (16.6%)	684 (15.6%)	2125 (17.6%)	840 (16.7%)	547 (15.8%)
NA's	1594 (7.8%)	598 (7.9%)	374 (7.3%)	257 (7.3%)	365 (8.3%)	908 (7.5%)	402 (8%)	284 (8.2%)

Relationship between frailty/multimorbidity and age

eTable 6 Frailty index			
Frailty index value	Age 40-50	Age 50-60	Age 60-72
0-0.05	163 (8.8%)	345 (5.8%)	665 (5.2%)
0.05-0.1	415 (22.3%)	1264 (21.2%)	2739 (21.5%)
0.1-0.15	422 (22.7%)	1463 (24.6%)	3330 (26.1%)
0.15-0.2	361 (19.4%)	1152 (19.4%)	2683 (21%)
>0.2	497 (26.7%)	1729 (29%)	3338 (26.2%)

eTable 7 Frailty phenotype			
Frailty phenotype	Age 40-50	Age 50-60	Age 60-72
Robust	474 (25.5%)	1713 (28.8%)	4074 (31.9%)
Pre-frail	1082 (58.2%)	3180 (53.4%)	6764 (53%)
Frail	235 (12.6%)	797 (13.4%)	1473 (11.5%)
NA	67 (3.6%)	263 (4.4%)	444 (3.5%)
Individual components			
Weight loss	672 (36.2%)	1935 (32.5%)	3455 (27.1%)
Low grip strength	370 (19.9%)	1531 (25.7%)	4070 (31.9%)
Low physical activity	379 (20.4%)	1160 (19.5%)	1968 (15.4%)
Exhaustion	543 (29.2%)	1482 (24.9%)	2051 (16.1%)
Slow walking pace	366 (19.7%)	1313 (22.1%)	3055 (24.0%)

eTable 8 Charlson Index			
Value	Age 40-50	Age 50-60	Age 60-72
0	1335 (71.9%)	3897 (65.5%)	6826 (53.5%)
1	380 (20.5%)	1365 (22.9%)	3297 (25.8%)
2-13	143 (7.7%)	691 (11.6%)	2632 (20.6%)

eTable 9 LTC count			
Count	Age 40-50	Age 50-60	Age 60-72
0	381 (20.5%)	761 (12.8%)	950 (7.4%)
1	600 (32.3%)	1726 (29%)	3131 (24.5%)
2	380 (20.5%)	1454 (24.4%)	3281 (25.7%)
3	234 (12.6%)	903 (15.2%)	2387 (18.7%)
4 or more	263 (14.2%)	1109 (18.6%)	3006 (23.6%)

Relationship between frailty/multmorbidity, age, sex, and risk of adverse events

	eTable 10 – All-cause mortality						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	1.02% (0.86-1.2)	2.09% (1.88-2.37)	4.31% (3.95-4.72)	0.6% (0.5-0.71)	1.23% (1.08-1.42)	2.53% (2.25-2.88)
	1	1.53% (1.32-1.78)	3.15% (2.84-3.5)	6.48% (5.96-7.06)	0.9% (0.77-1.06)	1.85% (1.63-2.11)	3.8% (3.39-4.31)
	2	2.09% (1.76-2.46)	4.3% (3.87-4.82)	8.85% (8.15-9.7)	1.23% (1.03-1.49)	2.53% (2.24-2.9)	5.2% (4.65-5.85)
	3	2.72% (2.32-3.22)	5.6% (5-6.32)	11.53% (10.51-12.78)	1.6% (1.32-1.92)	3.29% (2.86-3.76)	6.77% (6.01-7.68)
	4	3.43% (2.86-4.07)	7.06% (6.28-8.03)	14.54% (13.14-16.21)	2.01% (1.69-2.48)	4.15% (3.58-4.85)	8.54% (7.47-9.81)
	5	4.23% (3.55-5.13)	8.71% (7.64-9.94)	17.94% (15.93-20.2)	2.48% (2.01-3.06)	5.12% (4.39-6)	10.53% (9.2-12.18)
	6	5.13% (4.22-6.25)	10.57% (9.23-12.19)	21.76% (19-24.75)	3.01% (2.49-3.69)	6.2% (5.29-7.36)	12.78% (10.89-14.77)
	7	6.14% (5.04-7.49)	12.65% (10.73-14.91)	26.04% (22.51-29.7)	3.61% (2.94-4.48)	7.43% (6.25-8.86)	15.29% (13.13-18.07)
Frailty index	0	0.8% (0.68-0.96)	1.79% (1.6-2.05)	4% (3.57-4.48)	0.46% (0.38-0.55)	1.02% (0.86-1.19)	2.27% (1.97-2.59)
	0.05	0.92% (0.78-1.1)	2.05% (1.83-2.31)	4.58% (4.19-5.06)	0.52% (0.43-0.64)	1.17% (1.01-1.35)	2.6% (2.29-2.98)
	0.1	1.06% (0.9-1.25)	2.35% (2.12-2.63)	5.25% (4.79-5.76)	0.6% (0.5-0.71)	1.34% (1.18-1.51)	2.98% (2.66-3.34)
	0.15	1.21% (1.04-1.42)	2.7% (2.43-3.01)	6.02% (5.55-6.63)	0.69% (0.58-0.81)	1.53% (1.34-1.75)	3.41% (3.04-3.84)
	0.2	1.39% (1.2-1.62)	3.09% (2.8-3.42)	6.9% (6.34-7.54)	0.79% (0.67-0.94)	1.75% (1.55-2)	3.91% (3.49-4.37)
	0.25	1.59% (1.34-1.88)	3.55% (3.19-3.96)	7.9% (7.24-8.64)	0.9% (0.77-1.08)	2.01% (1.76-2.32)	4.48% (3.99-5.07)
	0.3	1.82% (1.53-2.15)	4.06% (3.58-4.6)	9.06% (8.23-10.13)	1.03% (0.88-1.23)	2.31% (1.98-2.69)	5.14% (4.54-5.87)
	0.35	2.09% (1.75-2.52)	4.66% (4.08-5.38)	10.39% (9.26-11.69)	1.19% (0.98-1.43)	2.64% (2.29-3.08)	5.89% (5.14-6.88)
	0.4	2.4% (1.98-2.94)	5.34% (4.6-6.23)	11.9% (10.33-13.71)	1.36% (1.11-1.66)	3.03% (2.56-3.65)	6.75% (5.79-7.91)
	0.45	2.75% (2.27-3.37)	6.12% (5.23-7.18)	13.64% (11.72-16.06)	1.56% (1.26-1.9)	3.47% (2.94-4.22)	7.74% (6.66-9.06)
	0.5	3.15% (2.5-3.93)	7.02% (5.91-8.42)	15.64% (13.09-18.65)	1.79% (1.46-2.26)	3.98% (3.25-4.82)	8.87% (7.4-10.72)
Frailty [illegible]	Robust	0.92% (0.78-1.08)	2.08% (1.84-2.34)	4.72% (4.21-5.25)	0.51% (0.42-0.62)	1.16% (1.01-1.35)	2.64% (2.31-3.07)
	Pre-frail	1.21% (1.04-1.42)	2.73% (2.45-3.05)	6.2% (5.69-6.8)	0.67% (0.55-0.81)	1.53% (1.33-1.75)	3.46% (3.08-3.94)
	Frail	1.92% (1.6-2.32)	4.36% (3.8-4.98)	9.87% (8.71-11.24)	1.07% (0.89-1.31)	2.43% (2.06-2.84)	5.52% (4.81-6.33)
LTC count	0	0.85% (0.73-1)	1.75% (1.57-1.97)	3.61% (3.26-3.99)	0.48% (0.41-0.58)	1% (0.87-1.13)	2.06% (1.81-2.34)
	1	1.03% (0.88-1.2)	2.12% (1.9-2.37)	4.38% (4.01-4.81)	0.59% (0.5-0.7)	1.21% (1.06-1.37)	2.5% (2.21-2.85)
	2	1.25% (1.08-1.47)	2.58% (2.32-2.85)	5.31% (4.89-5.83)	0.71% (0.61-0.84)	1.47% (1.31-1.69)	3.03% (2.71-3.43)
	3	1.52% (1.31-1.77)	3.13% (2.83-3.49)	6.44% (5.93-7.02)	0.87% (0.73-1.03)	1.78% (1.56-2.03)	3.68% (3.28-4.15)
	4	1.84% (1.57-2.15)	3.79% (3.42-4.24)	7.81% (7.22-8.5)	1.05% (0.89-1.25)	2.16% (1.91-2.47)	4.46% (3.99-5.04)
	5	2.23% (1.92-2.66)	4.6% (4.12-5.13)	9.48% (8.69-10.39)	1.27% (1.08-1.53)	2.62% (2.3-3.01)	5.41% (4.8-6.1)
	6	2.71% (2.3-3.18)	5.58% (5-6.31)	11.5% (10.49-12.7)	1.54% (1.27-1.85)	3.18% (2.77-3.66)	6.56% (5.85-7.4)
	7	3.28% (2.72-3.92)	6.77% (5.97-7.73)	13.95% (12.52-15.61)	1.87% (1.56-2.29)	3.86% (3.36-4.55)	7.96% (6.97-9.17)

	8	3.98% (3.32-4.82)	8.21% (7.21-9.6)	16.92% (15.04-19.2)	2.27% (1.87-2.75)	4.68% (4.04-5.51)	9.66% (8.42-11.1)
	9	4.83% (3.92-6.02)	9.96% (8.6-11.61)	20.52% (18.12-23.67)	2.76% (2.25-3.42)	5.68% (4.77-6.78)	11.71% (10.05-13.7)
	10	5.86% (4.78-7.2)	12.08% (10.25-14.18)	24.89% (21.55-28.92)	3.34% (2.71-4.23)	6.89% (5.72-8.23)	14.21% (12.17-17.03)

	eTable 11 – Cardiovascular mortality						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	0.27% (0.21-0.36)	0.59% (0.48-0.73)	1.25% (1.07-1.49)	0.11% (0.08-0.16)	0.24% (0.19-0.32)	0.52% (0.42-0.66)
	1	0.51% (0.39-0.68)	1.1% (0.91-1.35)	2.35% (2.06-2.74)	0.21% (0.16-0.3)	0.46% (0.36-0.59)	0.98% (0.78-1.23)
	2	0.68% (0.5-0.9)	1.45% (1.18-1.8)	3.1% (2.65-3.69)	0.28% (0.2-0.4)	0.6% (0.47-0.79)	1.29% (1.04-1.63)
	3	0.8% (0.58-1.09)	1.71% (1.41-2.15)	3.66% (3.1-4.41)	0.33% (0.24-0.47)	0.71% (0.55-0.92)	1.52% (1.2-1.99)
	4	0.89% (0.67-1.26)	1.91% (1.58-2.43)	4.1% (3.47-5)	0.37% (0.27-0.53)	0.8% (0.6-1.04)	1.71% (1.35-2.19)
	5	0.97% (0.72-1.34)	2.08% (1.65-2.6)	4.45% (3.71-5.4)	0.4% (0.28-0.59)	0.87% (0.66-1.15)	1.86% (1.48-2.44)
	6	1.04% (0.78-1.44)	2.22% (1.74-2.84)	4.75% (3.94-5.93)	0.43% (0.3-0.61)	0.92% (0.7-1.24)	1.98% (1.55-2.57)
	7	1.09% (0.8-1.48)	2.34% (1.86-2.98)	5.01% (4.18-6.2)	0.45% (0.32-0.68)	0.97% (0.74-1.29)	2.09% (1.65-2.7)
Frailty index	0	0.22% (0.16-0.3)	0.52% (0.42-0.66)	1.21% (1-1.49)	0.09% (0.06-0.13)	0.21% (0.16-0.28)	0.48% (0.37-0.64)
	0.05	0.26% (0.2-0.35)	0.6% (0.49-0.76)	1.41% (1.18-1.68)	0.1% (0.07-0.14)	0.24% (0.19-0.32)	0.56% (0.44-0.71)
	0.1	0.3% (0.22-0.42)	0.7% (0.59-0.87)	1.64% (1.39-1.93)	0.12% (0.09-0.17)	0.28% (0.22-0.37)	0.66% (0.52-0.83)
	0.15	0.35% (0.27-0.47)	0.82% (0.68-1)	1.91% (1.66-2.24)	0.14% (0.1-0.2)	0.33% (0.26-0.42)	0.76% (0.63-0.95)
	0.2	0.41% (0.3-0.55)	0.95% (0.8-1.18)	2.23% (1.92-2.64)	0.16% (0.12-0.23)	0.38% (0.3-0.5)	0.89% (0.73-1.12)
	0.25	0.48% (0.35-0.64)	1.11% (0.93-1.38)	2.59% (2.23-3.1)	0.19% (0.13-0.27)	0.44% (0.34-0.58)	1.04% (0.83-1.32)
	0.3	0.56% (0.41-0.76)	1.3% (1.06-1.63)	3.02% (2.55-3.63)	0.22% (0.16-0.32)	0.52% (0.39-0.68)	1.21% (0.98-1.56)
	0.35	0.65% (0.47-0.89)	1.51% (1.18-1.94)	3.52% (2.89-4.4)	0.26% (0.18-0.37)	0.6% (0.45-0.81)	1.41% (1.1-1.81)
	0.4	0.75% (0.55-1.07)	1.76% (1.37-2.33)	4.1% (3.2-5.26)	0.3% (0.21-0.45)	0.7% (0.53-0.95)	1.64% (1.23-2.16)
	0.45	0.88% (0.62-1.26)	2.05% (1.55-2.83)	4.78% (3.59-6.28)	0.35% (0.24-0.53)	0.82% (0.59-1.15)	1.91% (1.41-2.58)
	0.5	1.02% (0.68-1.53)	2.39% (1.72-3.3)	5.57% (4.18-7.57)	0.41% (0.28-0.65)	0.96% (0.67-1.39)	2.23% (1.54-3.14)
Frailty phenotype	Robust	0.26% (0.19-0.36)	0.6% (0.48-0.76)	1.4% (1.17-1.73)	0.11% (0.07-0.15)	0.25% (0.18-0.33)	0.57% (0.45-0.73)
	Pre-frail	0.36% (0.27-0.5)	0.85% (0.69-1.04)	1.97% (1.69-2.33)	0.15% (0.11-0.21)	0.34% (0.27-0.45)	0.8% (0.64-1.02)
	Frail	0.63% (0.45-0.91)	1.46% (1.15-1.9)	3.39% (2.78-4.2)	0.26% (0.18-0.37)	0.59% (0.44-0.81)	1.38% (1.06-1.81)
LTC count	0	0.18% (0.13-0.25)	0.38% (0.3-0.48)	0.78% (0.63-0.97)	0.07% (0.05-0.1)	0.15% (0.12-0.2)	0.31% (0.25-0.41)
	1	0.27% (0.21-0.37)	0.57% (0.48-0.7)	1.19% (1-1.43)	0.11% (0.08-0.15)	0.23% (0.18-0.3)	0.48% (0.38-0.62)
	2	0.38% (0.29-0.51)	0.79% (0.65-0.96)	1.64% (1.41-1.93)	0.15% (0.11-0.21)	0.32% (0.25-0.42)	0.66% (0.53-0.82)
	3	0.5% (0.38-0.66)	1.03% (0.86-1.26)	2.16% (1.87-2.53)	0.2% (0.14-0.28)	0.41% (0.33-0.53)	0.86% (0.69-1.09)
	4	0.63% (0.48-0.85)	1.31% (1.09-1.62)	2.74% (2.39-3.26)	0.25% (0.18-0.35)	0.53% (0.41-0.68)	1.1% (0.89-1.38)
	5	0.78% (0.59-1.04)	1.63% (1.33-2.04)	3.4% (2.93-4.05)	0.31% (0.22-0.45)	0.65% (0.52-0.85)	1.36% (1.1-1.71)
	6	0.95% (0.71-1.34)	1.99% (1.64-2.5)	4.15% (3.54-5.04)	0.38% (0.28-0.56)	0.8% (0.61-1.05)	1.66% (1.33-2.1)
	7	1.15% (0.84-1.61)	2.39% (1.9-3.1)	4.99% (4.2-6.07)	0.46% (0.32-0.66)	0.96% (0.73-1.28)	2% (1.6-2.57)
	8	1.36% (1-1.94)	2.85% (2.24-3.68)	5.94% (4.87-7.44)	0.55% (0.38-0.78)	1.14% (0.85-1.53)	2.38% (1.87-3.16)

	9	1.61% (1.16-2.31)	3.36% (2.62-4.47)	7% (5.56-9)	0.64% (0.44-0.95)	1.34% (0.99-1.84)	2.8% (2.19-3.75)
	10	1.88% (1.28-2.69)	3.92% (2.97-5.26)	8.19% (6.61-10.49)	0.75% (0.51-1.13)	1.57% (1.16-2.21)	3.28% (2.46-4.36)

	eTable 12 – Cancer mortality						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	0.47% (0.37-0.6)	0.95% (0.8-1.11)	1.92% (1.68-2.21)	0.35% (0.28-0.47)	0.72% (0.58-0.88)	1.45% (1.24-1.74)
	1	0.64% (0.51-0.82)	1.3% (1.13-1.53)	2.64% (2.32-3.01)	0.49% (0.38-0.65)	0.99% (0.82-1.24)	2% (1.7-2.4)
	2	0.88% (0.7-1.13)	1.79% (1.52-2.12)	3.63% (3.25-4.2)	0.67% (0.51-0.88)	1.36% (1.13-1.66)	2.75% (2.34-3.29)
	3	1.22% (0.95-1.56)	2.47% (2.07-2.93)	4.99% (4.34-5.77)	0.92% (0.7-1.24)	1.87% (1.5-2.27)	3.79% (3.21-4.51)
	4	1.68% (1.31-2.19)	3.39% (2.85-4.07)	6.87% (5.96-8.14)	1.27% (0.96-1.68)	2.57% (2.06-3.2)	5.21% (4.29-6.32)
	5	2.31% (1.75-3.08)	4.67% (3.81-5.69)	9.45% (7.94-11.31)	1.75% (1.28-2.39)	3.54% (2.82-4.46)	7.17% (5.97-8.85)
	6	3.17% (2.35-4.45)	6.42% (5.16-7.97)	13.01% (10.72-16.02)	2.41% (1.77-3.32)	4.88% (3.79-6.29)	9.87% (7.95-12.29)
	7	4.37% (3.17-5.99)	8.84% (6.77-11.5)	17.9% (14.2-22.76)	3.31% (2.41-4.69)	6.71% (5.06-8.74)	13.59% (10.72-17.38)
Frailty index	0	0.4% (0.31-0.53)	0.87% (0.73-1.07)	1.9% (1.59-2.3)	0.29% (0.22-0.41)	0.65% (0.51-0.8)	1.41% (1.16-1.77)
	0.05	0.44% (0.35-0.57)	0.97% (0.82-1.18)	2.13% (1.84-2.51)	0.33% (0.24-0.44)	0.72% (0.59-0.9)	1.58% (1.3-1.95)
	0.1	0.5% (0.39-0.63)	1.08% (0.92-1.3)	2.37% (2.09-2.77)	0.37% (0.28-0.49)	0.81% (0.66-1)	1.76% (1.49-2.13)
	0.15	0.55% (0.44-0.7)	1.21% (1.04-1.44)	2.65% (2.33-3.03)	0.41% (0.31-0.53)	0.9% (0.76-1.09)	1.97% (1.65-2.33)
	0.2	0.62% (0.48-0.78)	1.35% (1.15-1.58)	2.96% (2.6-3.38)	0.46% (0.36-0.6)	1% (0.83-1.23)	2.2% (1.87-2.62)
	0.25	0.69% (0.53-0.89)	1.51% (1.29-1.81)	3.31% (2.89-3.86)	0.51% (0.4-0.67)	1.12% (0.92-1.4)	2.45% (2.06-2.94)
	0.3	0.77% (0.6-1.03)	1.69% (1.41-2.03)	3.69% (3.18-4.33)	0.57% (0.43-0.75)	1.25% (1.02-1.55)	2.74% (2.29-3.29)
	0.35	0.86% (0.66-1.15)	1.88% (1.53-2.31)	4.12% (3.44-5.04)	0.64% (0.48-0.87)	1.4% (1.12-1.79)	3.06% (2.5-3.79)
	0.4	0.96% (0.73-1.29)	2.1% (1.68-2.71)	4.61% (3.74-5.78)	0.71% (0.52-0.99)	1.56% (1.21-2.02)	3.42% (2.75-4.36)
	0.45	1.07% (0.78-1.5)	2.35% (1.83-3.19)	5.14% (3.99-6.58)	0.8% (0.57-1.13)	1.74% (1.37-2.33)	3.82% (3.02-4.94)
	0.5	1.2% (0.85-1.71)	2.62% (1.92-3.44)	5.74% (4.38-7.51)	0.89% (0.62-1.3)	1.95% (1.43-2.71)	4.26% (3.2-5.72)
Frailty phenotype	Robust	0.48% (0.36-0.63)	1.06% (0.89-1.3)	2.34% (2.01-2.79)	0.35% (0.26-0.47)	0.78% (0.62-0.98)	1.72% (1.42-2.13)
	Pre-frail	0.56% (0.43-0.71)	1.23% (1.05-1.48)	2.73% (2.39-3.15)	0.41% (0.31-0.55)	0.9% (0.74-1.12)	2% (1.67-2.41)
	Frail	0.72% (0.53-0.98)	1.6% (1.28-2.02)	3.54% (2.9-4.34)	0.53% (0.39-0.73)	1.17% (0.91-1.5)	2.6% (2.11-3.29)
LTC count	0	0.44% (0.34-0.57)	0.91% (0.77-1.1)	1.88% (1.62-2.21)	0.33% (0.25-0.44)	0.68% (0.55-0.84)	1.41% (1.18-1.73)
	1	0.5% (0.4-0.64)	1.04% (0.89-1.23)	2.15% (1.9-2.51)	0.37% (0.29-0.51)	0.78% (0.64-0.94)	1.61% (1.36-1.96)
	2	0.57% (0.46-0.73)	1.19% (1.02-1.4)	2.46% (2.17-2.83)	0.43% (0.34-0.57)	0.89% (0.74-1.1)	1.85% (1.55-2.19)
	3	0.65% (0.52-0.85)	1.36% (1.16-1.6)	2.82% (2.51-3.22)	0.49% (0.37-0.64)	1.02% (0.84-1.25)	2.11% (1.79-2.53)
	4	0.75% (0.59-0.96)	1.55% (1.32-1.84)	3.22% (2.84-3.71)	0.56% (0.44-0.75)	1.16% (0.96-1.42)	2.41% (2.06-2.86)
	5	0.85% (0.66-1.14)	1.77% (1.5-2.16)	3.68% (3.25-4.26)	0.64% (0.49-0.85)	1.33% (1.08-1.64)	2.76% (2.32-3.32)
	6	0.98% (0.75-1.28)	2.03% (1.67-2.46)	4.21% (3.58-4.98)	0.73% (0.55-0.98)	1.52% (1.22-1.89)	3.16% (2.63-3.85)
	7	1.12% (0.85-1.51)	2.32% (1.86-2.91)	4.82% (4.1-5.84)	0.84% (0.62-1.14)	1.74% (1.4-2.21)	3.61% (2.92-4.5)
	8	1.28% (0.93-1.74)	2.65% (2.11-3.35)	5.51% (4.51-6.74)	0.96% (0.71-1.33)	1.99% (1.55-2.58)	4.13% (3.33-5.28)

	9	1.46% (1.05-2.02)	3.03% (2.36-3.98)	6.3% (4.97-7.79)	1.09% (0.79-1.53)	2.27% (1.75-3.08)	4.72% (3.66-6.06)
	10	1.67% (1.2-2.32)	3.47% (2.63-4.55)	7.2% (5.63-9.44)	1.25% (0.89-1.78)	2.6% (1.94-3.55)	5.4% (4.14-7.22)

	eTable 13 – MACE						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	0.93% (0.73-1.18)	1.76% (1.5-2.05)	3.35% (2.92-3.86)	0.44% (0.33-0.59)	0.83% (0.68-1.04)	1.59% (1.31-1.92)
	1	1.3% (1.03-1.63)	2.46% (2.12-2.92)	4.68% (4.13-5.34)	0.61% (0.46-0.83)	1.17% (0.95-1.45)	2.21% (1.84-2.65)
	2	1.58% (1.23-2.06)	2.99% (2.52-3.57)	5.69% (5.06-6.48)	0.75% (0.55-1)	1.42% (1.14-1.75)	2.69% (2.24-3.29)
	3	1.81% (1.39-2.32)	3.44% (2.86-4.18)	6.54% (5.56-7.68)	0.86% (0.62-1.2)	1.63% (1.29-2.04)	3.09% (2.52-3.85)
	4	2.02% (1.53-2.66)	3.83% (3.15-4.7)	7.28% (6.15-8.7)	0.95% (0.7-1.33)	1.81% (1.4-2.3)	3.45% (2.78-4.23)
	5	2.2% (1.64-2.97)	4.18% (3.41-5.19)	7.95% (6.6-9.57)	1.04% (0.75-1.42)	1.98% (1.51-2.61)	3.76% (3.07-4.81)
	6	2.37% (1.75-3.16)	4.51% (3.55-5.68)	8.56% (7.07-10.58)	1.12% (0.79-1.58)	2.13% (1.63-2.76)	4.05% (3.19-5.11)
	7	2.53% (1.84-3.45)	4.81% (3.75-6.11)	9.13% (7.18-11.36)	1.2% (0.86-1.67)	2.27% (1.71-2.97)	4.32% (3.35-5.57)
Frailty index	0	0.69% (0.53-0.91)	1.38% (1.14-1.68)	2.75% (2.32-3.24)	0.32% (0.23-0.44)	0.63% (0.49-0.82)	1.25% (0.99-1.58)
	0.05	0.8% (0.61-1.04)	1.59% (1.33-1.91)	3.16% (2.73-3.69)	0.36% (0.27-0.49)	0.72% (0.56-0.91)	1.43% (1.17-1.75)
	0.1	0.92% (0.73-1.19)	1.82% (1.54-2.14)	3.62% (3.17-4.13)	0.42% (0.31-0.56)	0.83% (0.66-1.04)	1.64% (1.35-1.99)
	0.15	1.05% (0.83-1.34)	2.09% (1.78-2.46)	4.16% (3.7-4.75)	0.48% (0.36-0.62)	0.95% (0.76-1.18)	1.89% (1.56-2.28)
	0.2	1.21% (0.95-1.55)	2.4% (2.07-2.81)	4.77% (4.18-5.41)	0.55% (0.42-0.72)	1.09% (0.89-1.35)	2.17% (1.77-2.59)
	0.25	1.38% (1.08-1.76)	2.75% (2.34-3.32)	5.48% (4.75-6.3)	0.63% (0.47-0.85)	1.25% (1.01-1.56)	2.49% (2.05-3.05)
	0.3	1.59% (1.22-2.08)	3.16% (2.63-3.79)	6.29% (5.36-7.4)	0.72% (0.54-0.97)	1.43% (1.15-1.82)	2.85% (2.38-3.57)
	0.35	1.82% (1.39-2.41)	3.63% (2.92-4.54)	7.22% (6.05-8.8)	0.83% (0.61-1.13)	1.65% (1.29-2.11)	3.28% (2.65-4.15)
	0.4	2.09% (1.55-2.81)	4.16% (3.27-5.26)	8.29% (6.71-10.34)	0.95% (0.7-1.35)	1.89% (1.43-2.46)	3.76% (2.96-4.78)
	0.45	2.4% (1.74-3.38)	4.78% (3.71-6.24)	9.51% (7.41-11.99)	1.09% (0.77-1.58)	2.17% (1.64-2.85)	4.32% (3.33-5.66)
	0.5	2.76% (1.94-4.1)	5.49% (4.18-7.6)	10.92% (8.42-14.76)	1.25% (0.87-1.86)	2.49% (1.77-3.43)	4.95% (3.67-6.65)
Frailty phenotype	Robust	0.89% (0.68-1.16)	1.74% (1.45-2.09)	3.41% (2.91-3.98)	0.41% (0.3-0.57)	0.8% (0.64-1.03)	1.56% (1.26-1.96)
	Pre-frail	1.19% (0.94-1.55)	2.33% (1.97-2.75)	4.56% (3.98-5.24)	0.54% (0.4-0.73)	1.06% (0.86-1.31)	2.08% (1.71-2.53)
	Frail	1.7% (1.28-2.29)	3.32% (2.69-4.13)	6.5% (5.31-7.98)	0.77% (0.57-1.07)	1.52% (1.16-1.97)	2.97% (2.35-3.82)
LTC count	0	0.79% (0.62-1.01)	1.47% (1.23-1.77)	2.73% (2.35-3.19)	0.36% (0.27-0.49)	0.68% (0.54-0.84)	1.26% (1.02-1.55)
	1	0.93% (0.73-1.2)	1.73% (1.47-2.04)	3.22% (2.81-3.68)	0.43% (0.33-0.57)	0.8% (0.65-0.99)	1.48% (1.22-1.8)
	2	1.1% (0.87-1.38)	2.04% (1.76-2.38)	3.79% (3.36-4.34)	0.5% (0.38-0.69)	0.94% (0.76-1.17)	1.75% (1.45-2.13)
	3	1.29% (1.01-1.64)	2.4% (2.06-2.82)	4.47% (4-5.1)	0.59% (0.44-0.78)	1.11% (0.9-1.38)	2.06% (1.73-2.45)
	4	1.52% (1.19-1.98)	2.83% (2.43-3.31)	5.27% (4.63-6.07)	0.7% (0.53-0.93)	1.3% (1.05-1.6)	2.43% (2.03-2.95)
	5	1.79% (1.43-2.29)	3.34% (2.84-4)	6.21% (5.47-7.15)	0.83% (0.62-1.11)	1.54% (1.23-1.94)	2.86% (2.36-3.48)
	6	2.12% (1.63-2.75)	3.94% (3.3-4.79)	7.33% (6.32-8.57)	0.97% (0.74-1.33)	1.81% (1.44-2.28)	3.37% (2.71-4.13)
	7	2.49% (1.92-3.33)	4.64% (3.72-5.65)	8.64% (7.24-10.36)	1.15% (0.82-1.63)	2.14% (1.68-2.77)	3.97% (3.19-4.89)
	8	2.94% (2.2-4.04)	5.47% (4.29-6.85)	10.18% (8.37-12.45)	1.35% (0.98-1.87)	2.52% (1.93-3.33)	4.69% (3.77-5.95)

	9	3.47% (2.48-4.91)	6.45% (5.02-8.23)	12% (9.55-15.37)	1.6% (1.09-2.25)	2.97% (2.18-3.89)	5.52% (4.29-7.16)
	10	4.09% (2.87-5.77)	7.6% (5.69-10.08)	14.15% (10.98-18.4)	1.88% (1.29-2.7)	3.5% (2.58-4.8)	6.51% (4.91-8.47)

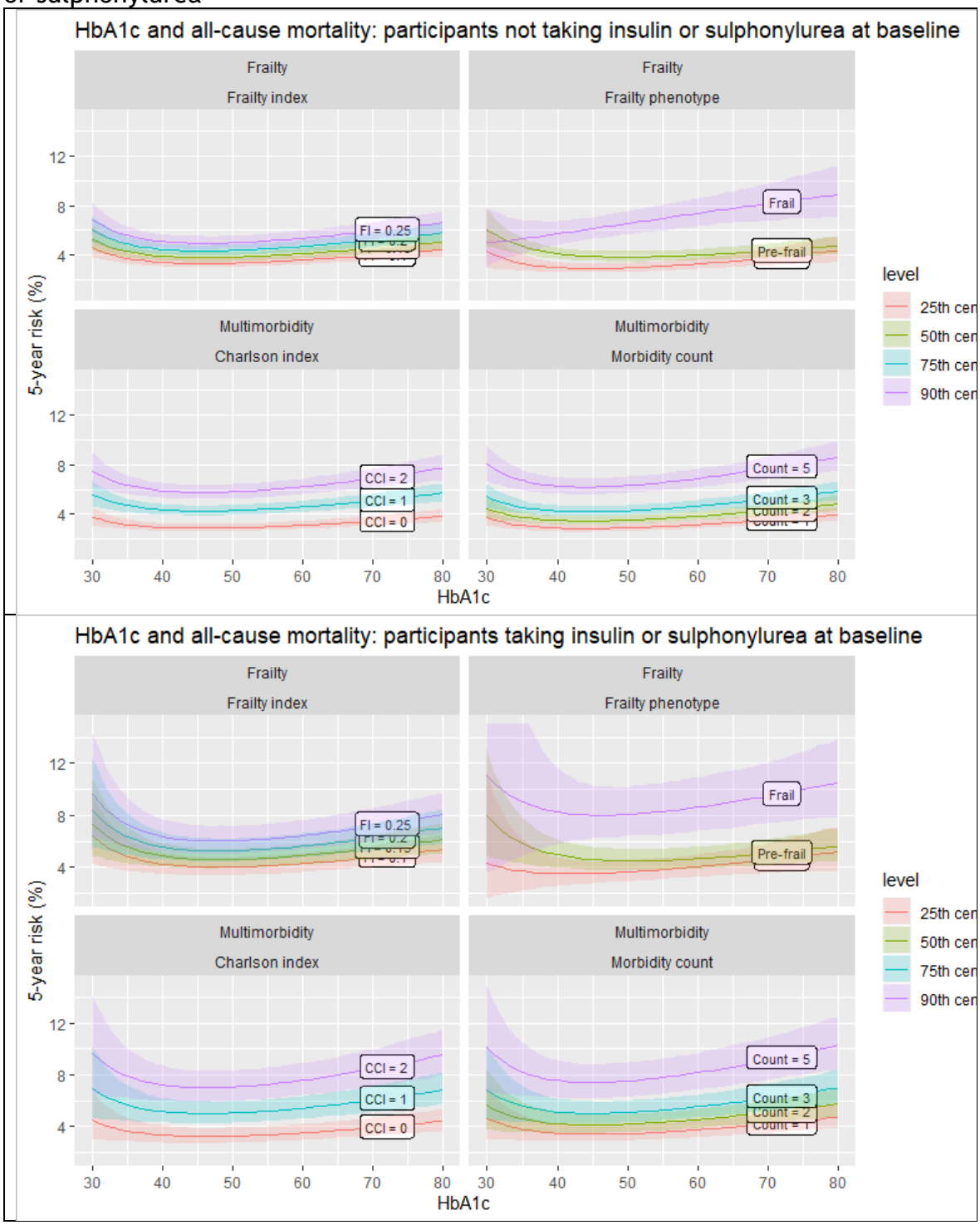
	eTable 14 – Hospitalisation with hypoglycaemia						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	0.27% (0.19-0.4)	0.46% (0.36-0.61)	0.78% (0.62-0.99)	0.19% (0.12-0.29)	0.31% (0.22-0.44)	0.53% (0.4-0.74)
	1	0.37% (0.26-0.54)	0.62% (0.48-0.8)	1.05% (0.86-1.32)	0.25% (0.17-0.39)	0.42% (0.31-0.58)	0.71% (0.55-0.97)
	2	0.5% (0.34-0.73)	0.84% (0.66-1.1)	1.42% (1.14-1.79)	0.34% (0.22-0.53)	0.57% (0.41-0.79)	0.96% (0.72-1.3)
	3	0.67% (0.45-1)	1.13% (0.85-1.52)	1.91% (1.53-2.47)	0.45% (0.28-0.7)	0.77% (0.55-1.09)	1.3% (0.96-1.78)
	4	0.9% (0.59-1.41)	1.52% (1.13-2.16)	2.57% (1.95-3.38)	0.61% (0.38-0.99)	1.04% (0.73-1.49)	1.75% (1.28-2.41)
	5	1.22% (0.79-1.94)	2.05% (1.48-2.94)	3.47% (2.6-4.69)	0.83% (0.51-1.32)	1.4% (0.93-2.08)	2.36% (1.64-3.5)
	6	1.64% (1.01-2.75)	2.77% (1.89-4.2)	4.68% (3.37-6.54)	1.11% (0.67-1.93)	1.88% (1.22-2.91)	3.18% (2.17-4.82)
	7	2.21% (1.29-3.74)	3.73% (2.37-5.9)	6.31% (4.34-9.45)	1.5% (0.84-2.69)	2.54% (1.58-4.14)	4.29% (2.77-6.89)
Frailty index	0	0.16% (0.11-0.26)	0.3% (0.21-0.42)	0.53% (0.4-0.73)	0.1% (0.06-0.18)	0.19% (0.13-0.28)	0.34% (0.24-0.5)
	0.05	0.2% (0.14-0.31)	0.36% (0.28-0.5)	0.66% (0.51-0.86)	0.13% (0.08-0.21)	0.23% (0.16-0.35)	0.42% (0.31-0.61)
	0.1	0.25% (0.17-0.38)	0.45% (0.35-0.61)	0.81% (0.64-1.04)	0.16% (0.1-0.25)	0.29% (0.2-0.41)	0.52% (0.38-0.72)
	0.15	0.31% (0.22-0.44)	0.55% (0.43-0.74)	1% (0.82-1.25)	0.2% (0.13-0.31)	0.35% (0.25-0.49)	0.64% (0.48-0.87)
	0.2	0.38% (0.26-0.56)	0.68% (0.54-0.9)	1.24% (1.02-1.55)	0.24% (0.16-0.38)	0.44% (0.32-0.62)	0.79% (0.6-1.07)
	0.25	0.47% (0.33-0.69)	0.84% (0.65-1.12)	1.53% (1.21-1.98)	0.3% (0.19-0.48)	0.54% (0.39-0.76)	0.98% (0.73-1.33)
	0.3	0.58% (0.37-0.84)	1.04% (0.78-1.38)	1.88% (1.45-2.5)	0.37% (0.24-0.59)	0.67% (0.48-0.97)	1.2% (0.87-1.67)
	0.35	0.71% (0.46-1.11)	1.28% (0.93-1.8)	2.32% (1.7-3.15)	0.45% (0.29-0.74)	0.82% (0.58-1.22)	1.48% (1.06-2.12)
	0.4	0.87% (0.55-1.42)	1.58% (1.07-2.26)	2.86% (2.05-4.13)	0.56% (0.35-0.96)	1.01% (0.67-1.58)	1.83% (1.28-2.68)
	0.45	1.08% (0.66-1.74)	1.95% (1.29-3.05)	3.53% (2.43-5.18)	0.69% (0.4-1.2)	1.25% (0.81-1.99)	2.26% (1.48-3.47)
	0.5	1.33% (0.75-2.33)	2.41% (1.51-3.94)	4.35% (2.78-6.79)	0.85% (0.45-1.58)	1.54% (0.93-2.59)	2.79% (1.76-4.55)
Frailty phenotype	Robust	0.19% (0.13-0.32)	0.35% (0.24-0.49)	0.62% (0.46-0.88)	0.12% (0.07-0.21)	0.22% (0.15-0.33)	0.4% (0.28-0.57)
	Pre-frail	0.36% (0.24-0.54)	0.64% (0.49-0.85)	1.14% (0.9-1.46)	0.23% (0.15-0.36)	0.41% (0.3-0.58)	0.73% (0.54-0.99)
	Frail	0.62% (0.41-0.99)	1.12% (0.79-1.64)	2% (1.49-2.79)	0.4% (0.25-0.68)	0.71% (0.46-1.05)	1.27% (0.9-1.86)
LTC count	0	0.19% (0.13-0.29)	0.32% (0.24-0.43)	0.52% (0.4-0.68)	0.13% (0.08-0.19)	0.21% (0.14-0.3)	0.34% (0.24-0.47)
	1	0.25% (0.17-0.37)	0.41% (0.31-0.54)	0.66% (0.52-0.85)	0.16% (0.1-0.25)	0.26% (0.19-0.38)	0.43% (0.32-0.59)
	2	0.32% (0.22-0.47)	0.52% (0.41-0.68)	0.85% (0.7-1.08)	0.21% (0.14-0.32)	0.34% (0.24-0.47)	0.56% (0.42-0.75)
	3	0.41% (0.29-0.6)	0.67% (0.52-0.87)	1.1% (0.9-1.37)	0.27% (0.17-0.4)	0.44% (0.32-0.62)	0.71% (0.53-0.97)
	4	0.53% (0.36-0.75)	0.86% (0.67-1.13)	1.41% (1.16-1.82)	0.34% (0.22-0.54)	0.56% (0.42-0.78)	0.92% (0.71-1.26)
	5	0.67% (0.46-0.98)	1.11% (0.86-1.48)	1.81% (1.46-2.27)	0.44% (0.27-0.7)	0.72% (0.52-1.05)	1.18% (0.86-1.59)
	6	0.87% (0.58-1.32)	1.42% (1.09-1.94)	2.33% (1.83-3.02)	0.56% (0.36-0.89)	0.93% (0.67-1.34)	1.52% (1.14-2.1)
	7	1.11% (0.71-1.75)	1.83% (1.33-2.51)	3% (2.31-3.96)	0.73% (0.45-1.18)	1.19% (0.83-1.77)	1.95% (1.4-2.7)
	8	1.43% (0.91-2.27)	2.35% (1.65-3.41)	3.85% (2.91-5.32)	0.93% (0.57-1.56)	1.53% (1-2.28)	2.51% (1.76-3.66)

	9	1.84% (1.13-3.17)	3.02% (2.07-4.52)	4.95% (3.55-6.97)	1.2% (0.71-1.97)	1.96% (1.29-2.97)	3.22% (2.27-4.8)
	10	2.37% (1.43-3.96)	3.88% (2.55-5.98)	6.36% (4.48-9.51)	1.54% (0.88-2.71)	2.52% (1.59-4.03)	4.14% (2.83-6.62)

	eTable 15 – Hospitalisation with fall or fracture						
	Level	Predicted 5-year risk of event					
		Males			Females		
		45 years	55 years	65 years	45 years	55 years	65 years
Charlson Index	0	1.3% (1.06-1.61)	1.91% (1.65-2.21)	2.8% (2.45-3.22)	1.6% (1.28-2)	2.35% (1.97-2.8)	3.44% (2.96-4.02)
	1	1.81% (1.48-2.23)	2.65% (2.32-3.06)	3.88% (3.44-4.4)	2.22% (1.76-2.75)	3.26% (2.77-3.86)	4.78% (4.16-5.56)
	2	2.19% (1.75-2.72)	3.21% (2.76-3.75)	4.7% (4.14-5.41)	2.69% (2.08-3.41)	3.95% (3.3-4.68)	5.79% (4.98-6.74)
	3	2.51% (1.97-3.11)	3.68% (3.15-4.34)	5.39% (4.65-6.31)	3.08% (2.44-3.98)	4.52% (3.71-5.5)	6.63% (5.56-7.93)
	4	2.79% (2.16-3.53)	4.08% (3.44-4.97)	5.99% (5.15-7.05)	3.43% (2.7-4.53)	5.03% (4.12-6.14)	7.37% (6.1-8.78)
	5	3.04% (2.33-3.96)	4.45% (3.65-5.5)	6.53% (5.46-7.81)	3.74% (2.85-4.86)	5.48% (4.43-6.84)	8.03% (6.65-9.83)
	6	3.27% (2.51-4.2)	4.79% (3.91-5.93)	7.02% (5.9-8.49)	4.02% (3.08-5.37)	5.89% (4.73-7.4)	8.64% (7.17-10.61)
	7	3.48% (2.69-4.56)	5.1% (4.18-6.46)	7.48% (6.17-9.13)	4.28% (3.23-5.69)	6.28% (4.93-7.99)	9.2% (7.52-11.66)
Frailty index	0	0.81% (0.65-1.03)	1.23% (1.03-1.48)	1.87% (1.57-2.21)	0.94% (0.74-1.23)	1.43% (1.16-1.76)	2.18% (1.79-2.65)
	0.05	0.99% (0.8-1.23)	1.5% (1.28-1.75)	2.28% (1.98-2.62)	1.15% (0.9-1.45)	1.74% (1.44-2.07)	2.65% (2.23-3.13)
	0.1	1.2% (0.98-1.49)	1.82% (1.59-2.12)	2.77% (2.45-3.18)	1.39% (1.11-1.79)	2.12% (1.78-2.52)	3.22% (2.73-3.76)
	0.15	1.46% (1.2-1.82)	2.22% (1.94-2.55)	3.37% (3-3.83)	1.7% (1.35-2.13)	2.58% (2.17-3.04)	3.92% (3.35-4.57)
	0.2	1.78% (1.45-2.18)	2.7% (2.35-3.1)	4.1% (3.63-4.63)	2.06% (1.65-2.61)	3.14% (2.67-3.72)	4.77% (4.11-5.61)
	0.25	2.16% (1.75-2.66)	3.28% (2.8-3.79)	4.99% (4.42-5.73)	2.51% (2.02-3.19)	3.81% (3.26-4.5)	5.8% (4.97-6.79)
	0.3	2.63% (2.08-3.31)	4% (3.41-4.69)	6.07% (5.24-7)	3.05% (2.39-3.92)	4.64% (3.9-5.6)	7.06% (6.02-8.36)
	0.35	3.2% (2.5-4.15)	4.86% (4.05-5.87)	7.39% (6.27-8.8)	3.71% (2.88-4.79)	5.65% (4.61-6.82)	8.59% (7.24-10.28)
	0.4	3.89% (2.97-5.02)	5.91% (4.81-7.39)	8.99% (7.47-10.88)	4.52% (3.49-5.89)	6.87% (5.61-8.64)	10.45% (8.6-12.78)
	0.45	4.73% (3.64-6.3)	7.2% (5.65-9.13)	10.94% (8.7-13.57)	5.5% (4.18-7.14)	8.36% (6.61-10.9)	12.71% (10.03-16.1)
	0.5	5.76% (4.34-7.74)	8.75% (6.76-11.38)	13.31% (10.52-16.94)	6.69% (5.01-9.35)	10.17% (7.8-13.59)	15.46% (12.09-19.9)
Frailty phenotype	Robust	1.13% (0.91-1.44)	1.73% (1.46-2.07)	2.66% (2.27-3.13)	1.39% (1.07-1.8)	2.13% (1.76-2.58)	3.27% (2.73-3.97)
	Pre-frail	1.54% (1.24-1.9)	2.36% (2.04-2.77)	3.62% (3.17-4.15)	1.9% (1.51-2.41)	2.91% (2.45-3.46)	4.45% (3.79-5.2)
	Frail	2.46% (1.92-3.14)	3.77% (3.14-4.65)	5.79% (4.88-6.95)	3.03% (2.35-3.95)	4.65% (3.8-5.71)	7.12% (5.95-8.6)
LTC count	0	1% (0.82-1.24)	1.41% (1.22-1.65)	1.98% (1.71-2.29)	1.2% (0.95-1.52)	1.68% (1.4-2.03)	2.35% (1.99-2.78)
	1	1.24% (1.02-1.55)	1.74% (1.51-2.01)	2.44% (2.13-2.79)	1.47% (1.17-1.84)	2.07% (1.75-2.45)	2.9% (2.49-3.39)
	2	1.53% (1.26-1.88)	2.14% (1.87-2.45)	3% (2.64-3.39)	1.82% (1.47-2.28)	2.55% (2.14-3.02)	3.58% (3.12-4.15)
	3	1.88% (1.51-2.3)	2.64% (2.32-3.02)	3.7% (3.26-4.19)	2.24% (1.77-2.85)	3.14% (2.65-3.71)	4.41% (3.81-5.09)
	4	2.32% (1.88-2.82)	3.25% (2.86-3.79)	4.57% (4-5.13)	2.76% (2.22-3.47)	3.88% (3.34-4.54)	5.44% (4.74-6.35)
	5	2.86% (2.26-3.58)	4.01% (3.43-4.7)	5.63% (4.93-6.46)	3.41% (2.75-4.36)	4.78% (4.03-5.72)	6.7% (5.75-7.82)
	6	3.53% (2.83-4.47)	4.95% (4.15-5.83)	6.94% (6.03-7.99)	4.2% (3.27-5.38)	5.89% (4.87-7.06)	8.26% (6.99-9.74)
	7	4.35% (3.4-5.41)	6.1% (5.09-7.29)	8.56% (7.33-10.02)	5.18% (4.07-6.69)	7.26% (5.97-8.93)	10.19% (8.51-12.12)
	8	5.36% (4.16-7.03)	7.52% (6.1-9.04)	10.55% (8.73-12.6)	6.38% (4.87-8.55)	8.95% (7.15-11.18)	12.56% (10.36-15.3)

	9	6.61% (4.96-8.76)	9.27% (7.4-11.73)	13% (10.66-16)	7.87% (5.96-10.65)	11.04% (8.84-14.06)	15.48% (12.48-19.06)
	10	8.15% (6-10.85)	11.43% (9.05-14.51)	16.03% (13.05-19.99)	9.7% (7.2-13.04)	13.61% (10.69-17.64)	19.09% (15.13-24.55)

Relationship between HbA1c and mortality, stratified by baseline use of insulin or sulphonylurea



Appendix 5:Supplementary material for chapter 7: Frailty in rheumatoid arthritis and its relationship with disease activity, hospitalisation and mortality: a longitudinal analysis of the Scottish Early Rheumatoid Arthritis cohort and UK Biobank

SERA frailty index deficits

Deficit	**Source**	**Coding**
Alcohol problems	Medical history	Present = 1, absent = 0
Anxiety	Medical history	Present = 1, absent = 0
Asthma	Medical history	Present = 1, absent = 0
Atrial fibrillation	Medical history	Present = 1, absent = 0
Bronchiectasis	Medical history	Present = 1, absent = 0
Cancer	Medical history	Present = 1, absent = 0
Coronary heart disease	Medical history	Present = 1, absent = 0
Chronic kidney disease	Medical history	Present = 1, absent = 0
Chronic liver disease	Medical history	Present = 1, absent = 0
COPD	Medical history	Present = 1, absent = 0
Depression	Medical history	Present = 1, absent = 0
Diabetes	Medical history	Present = 1, absent = 0
Diverticular disease	Medical history	Present = 1, absent = 0
Dyspepsia	Medical history	Present = 1, absent = 0
Epilepsy	Medical history	Present = 1, absent = 0
Glaucoma	Medical history	Present = 1, absent = 0
Heart failure	Medical history	Present = 1, absent = 0
Hypertension	Medical history	Present = 1, absent = 0
Osteoporosis	Medical history	Present = 1, absent = 0
Chronic pain	Medical history	Present = 1, absent = 0
Parkinson’s disease	Medical history	Present = 1, absent = 0
Pernicious anaemia	Medical history	Present = 1, absent = 0
Peripheral vascular disease	Medical history	Present = 1, absent = 0
Schizophrenia	Medical history	Present = 1, absent = 0
Stroke or TIA	Medical history	Present = 1, absent = 0
Thyroid disease	Medical history	Present = 1, absent = 0
Difficulty getting out of bed	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with household chores	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty climbing stairs	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with shopping (groceries)	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficult standing	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with toilet	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0

Limited mobility	EQ5D-1	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with self-care	EQ5D-2	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited in usual activities	EQ5D-3	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety	EQ5D-5	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoblobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Platelets	baseline laboratory measures	<150 = 1, >150 = 0

UK Biobank frailty index deficits

Deficit	**Coding**
Glaucoma	Categorised 0/1
Cataracts	Categorised 0/1
Hearing difficulty	Categorised 0/1
Migraine	Categorised 0/1
Dental problems	Categorised 0/1 for none vs. any
Self-rated health	0 – excellent; 0.25 – good; 0.5 - fair, 1 - poor
Fatigue: frequency of tiredness / lethargy in last two weeks	0, 0.25, 0.5, 1, respectively
Sleep: experience of sleeplessness/insomnia	Categorised 0, 0.5, 1, respectively
Depressed feelings: frequency in last two weeks	0 – not at all, 0.5 – several days, 0.75 -- more than half, 1 – nearly every day
Self-described nervous personality	Categorised 0/1
Severe anxiety/ panic attacks	Categorised 0/1
Common to feel loneliness	Categorised 0/1
Sense of misery (ever/never)	Categorised 0/1
Infirmity: long-standing illness or disability	Categorised 0/1
Falls in last year	0 - no fall, 0.5 - one fall, 1 - more than one fall
Fractures/broken bones in last five years	Categorised 0/1
Diabetes	Categorised 0/1

Myocardial infarction	Categorised 0/1
Angina	Categorised 0/1
Stroke	Categorised 0/1
High blood pressure	Categorised 0/1
Hypothyroidism	Categorised 0/1
Deep-vein thrombosis	Categorised 0/1
High cholesterol	Categorised 0/1
Breathing: wheeze in last year	Categorised 0/1
Pneumonia	Categorised 0/1
Chronic bronchitis/emphysema	Categorised 0/1
Asthma	Categorised 0/1
Rheumatoid arthritis	Categorised 0/1
Osteoarthritis	Categorised 0/1
Gout	Categorised 0/1
Osteoporosis	Categorised 0/1
Hayfever, allergic rhinitis or eczema	Categorised 0/1
Psoriasis	Categorised 0/1
Any cancer diagnosis	Categorised 0/1
Multiple cancers diagnosed (number reported)	Categorised 0/1
Chest pain	Categorised 0/1
Head and/or neck pain	Categorised 0/1
Back pain	Categorised 0/1
Stomach/abdominal pain	Categorised 0/1
Hip pain	Categorised 0/1
Knee pain	Categorised 0/1
Whole-body pain	Categorised 0/1
Facial pain	Categorised 0/1
Sciatica	Categorised 0/1
Gastric reflux	Categorised 0/1
Hiatus hernia	Categorised 0/1
Gall stones	Categorised 0/1
Diverticulitis	Categorised 0/1

UK Biobank frailty phenotype – comparison of participants with and without missing data

	Complete data (frailty phenotype)	Missing data (frailty phenotype)
Total	3344	262
Mean age (sd)	59.4 (7.1)	60.4 (6.7)
Male (%)	998 (29.8%)	65 (24.8%)
Female (%)	2346 (70.2%)	196 (74.8%)
Mean frailty index (sd)	0.18 (0.08)	0.20 (0.08)

Appendix 6: Supplementary material for Chapter 9: Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank

UK Biobank: Comparison of participants with linked GP data versus those without GP data available

	Whole cohort (n=502,533)	GP data available (n=211,597)	No GP data available (n=290,936)
Mean age (sd)	56.5 (8.1)	56.5 (8.1)	56.5 (8.1)
Sex (%)			
Male	229,132 (45.6%)	96,060 (45.4%)	133,072 (45.7%)
Female	273,401 (54.4%)	115,537 (54.6%)	157,864 (54.3%)
Socioeconomic status			
Quintile 1 (most affluent)	100,663 (20.1%)	42,155 (20.0%)	58,508 (20.1%)
2	100,096 (19.9%)	41,628 (19.7%)	58,468 (20.1%)
3	100,398 (20.0%)	43,378 (20.5%)	57,020 (19.6%)
4	100,375 (20.0%)	42,531 (20.1%)	57,844 (19.9%)
Quintile 5 (most deprived)	100,378 (20.0%)	41,581 (19.7%)	58,797 (20.2%)
Self-reported LTC count*			
0	172,565 (34.5%)	71,572 (34.0%)	100,993 (34.8%)
1	163,680 (32.7%)	68,987 (32.7%)	94,693 (32.7%)
2	95,211 (19.0%)	40,353 (19.1%)	54,858 (18.9%)
3	43,113 (8.6%)	18,702 (8.9%)	24,411 (8.4%)
4	16,732 (3.3%)	7,175 (3.4%)	9,557 (3.3%)
5	6,056 (1.2%)	2,580 (1.2%)	3,476 (1.2%)
6 or more	3,331 (0.7%)	1,428 (0.7%)	1,903 (0.7%)
Note that the LTC count displayed here is based on baseline assessment centre self-report of LTCs, with conditions based on the original list of conditions used in the main analysis, adapted for UK Biobank baseline self-reported data. These definitions were not used in the main analysis as equivalent (self-reported) data are not available for SAIL.			

Quantification of frailty index

Frailty index deficits taken from Williams DM, Jylhävä J, Pedersen NL, Hägg S. A frailty index for UK Biobank participants. The Journals of Gerontology: Series A. 2019 Mar 14;74(4):582-7.
https://doi.org/10.1093/gerona/gly094

Deficit	**Coding**
Glaucoma *	Categorised 0/1
Cataracts *	Categorised 0/1
Hearing difficulty	Categorised 0/1
Migraine *	Categorised 0/1
Dental problems	Categorised 0/1 for none vs. any
Self-rated health	0 – excellent; 0.25 – good; 0.5 - fair, 1 - poor
Fatigue: frequency of tiredness / lethargy in last two weeks	0, 0.25, 0.5, 1, respectively
Sleep: experience of sleeplessness/insomnia	Categorised 0, 0.5, 1, respectively

Depressed feelings: frequency in last two weeks	0 – not at all, 0.5 – several days, 0.75 -- more than half, 1 – nearly every day
Self-described nervous personality	Categorised 0/1
Severe anxiety/ panic attacks *	Categorised 0/1
Common to feel loneliness	Categorised 0/1
Sense of misery (ever/never)	Categorised 0/1
Infirmity: long-standing illness or disability	Categorised 0/1
Falls in last year	0 - no fall, 0.5 - one fall, 1 - more than one fall
Fractures/broken bones in last five years	Categorised 0/1
Diabetes *	Categorised 0/1
Myocardial infarction *	Categorised 0/1
Angina *	Categorised 0/1
Stroke *	Categorised 0/1
High blood pressure *	Categorised 0/1
Hypothyroidism *	Categorised 0/1
Deep-vein thrombosis *	Categorised 0/1
High cholesterol *	Categorised 0/1
Breathing: wheeze in last year	Categorised 0/1
Pneumonia *	Categorised 0/1
Chronic bronchitis/emphysema *	Categorised 0/1
Asthma *	Categorised 0/1
Rheumatoid arthritis *	Categorised 0/1
Osteoarthritis *	Categorised 0/1
Gout *	Categorised 0/1
Osteoporosis *	Categorised 0/1
Hayfever, allergic rhinitis or eczema *	Categorised 0/1
Psoriasis *	Categorised 0/1
Any cancer diagnosis *	Categorised 0/1
Multiple cancers diagnosed (number reported)	Categorised 0/1
Chest pain	Categorised 0/1
Head and/or neck pain	Categorised 0/1
Back pain	Categorised 0/1
Stomach/abdominal pain	Categorised 0/1
Hip pain	Categorised 0/1
Knee pain	Categorised 0/1
Whole-body pain	Categorised 0/1
Facial pain	Categorised 0/1
Sciatica *	Categorised 0/1
Gastric reflux *	Categorised 0/1
Hiatus hernia *	Categorised 0/1
Gall stones *	Categorised 0/1
Diverticulitis *	Categorised 0/1

Quantification of the frailty phenotype

Taken from Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. The Lancet Public Health. 2018 Jul 1;3(7):e323-32. https://doi.org/10.1016/S2468-2667(18)30091-4

Frailty phenotype variable definitions adapted for UK Biobank	
Weight loss	Self-reported: "Compared with one year ago, has your weight changed?" (response: yes, lost weight=1, other=0)
Exhaustion	Self-reported: "Over the past two weeks, how often have you felt tired or had little energy?" (response: more than half the days or nearly every day=1, other=0)
Low physical activity	Self-reported: UK Biobank physical activity questionnaire. We classified the responses into: none (no physical activity in the last 4 weeks), low (light DIY activity [eg, pruning, watering the lawn] only in the past 4 weeks), medium (heavy DIY activity [eg, weeding, lawn mowing, carpentry and digging], walking for pleasure, or other exercises in the past 4 weeks), and high (strenuous sports in the past 4 weeks) (response: none or light activity with a frequency of once per week or less=1, medium or heavy activity, or light activity more than once per week=0)
Slow walking pace	Self-reported: "How would you describe your usual walking pace?" (response: slow=1, other=0)
Low grip strength	Measured grip strength (sex and body-mass index adjusted cutoffs taken from Fried et al)

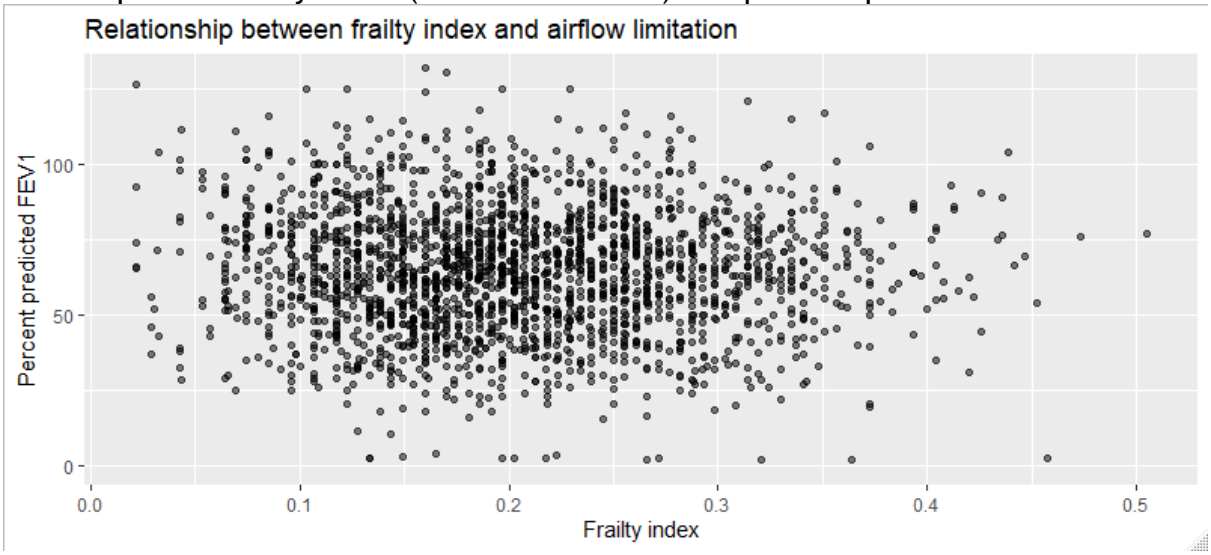
Comparison of frailty prevalence with full cohort

	COPD	No COPD
Total	3132	215439
Frailty phenotype		
Robust	979 (31.3%)	125207 (58.1%)
Pre-frail	1518 (48.5%)	79484 (36.9%)
Frail	514 (16.4%)	7319 (3.4%)
Missing	121	3429
Frailty index		
Robust	467 (14.9%)	112289 (52.1%)
Mild	1671 (53.4%)	88142 (40.9%)
Moderate	872 (27.9%)	13919 (6.5%)
Severe	121 (3.9%)	1089 (0.5%)
Missing	1	349

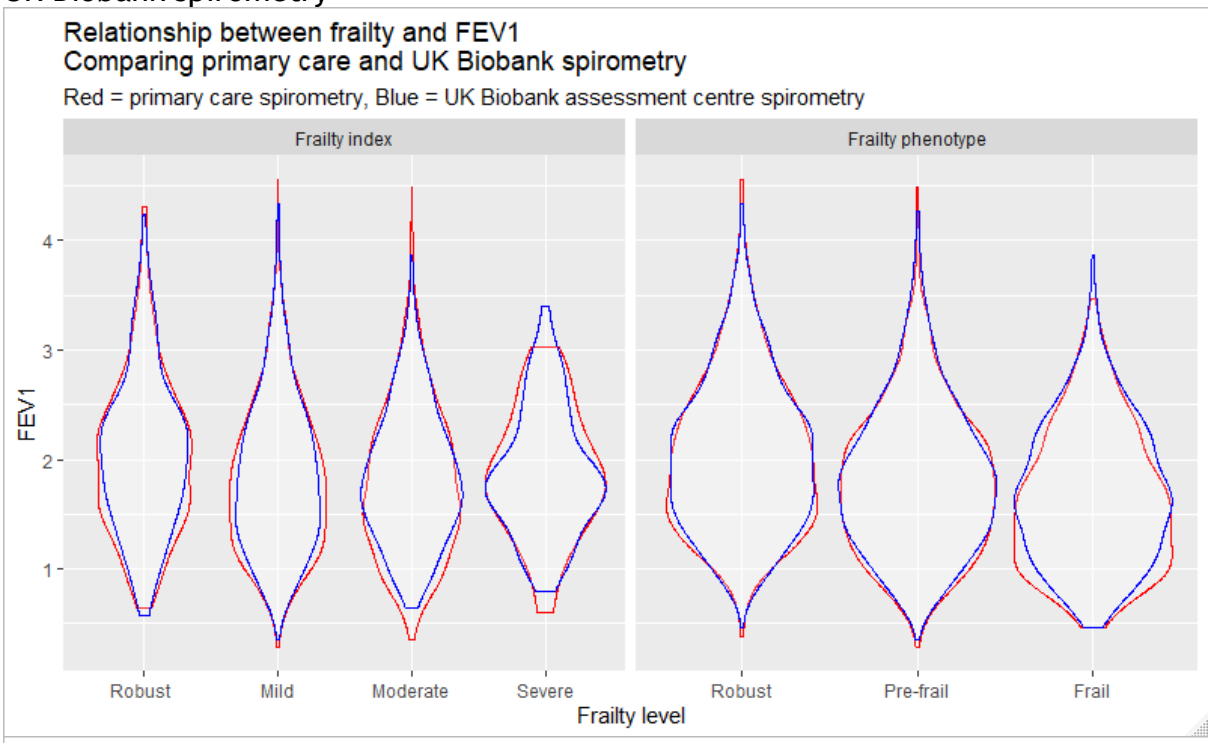
Prevalence of domains of frailty phenotype

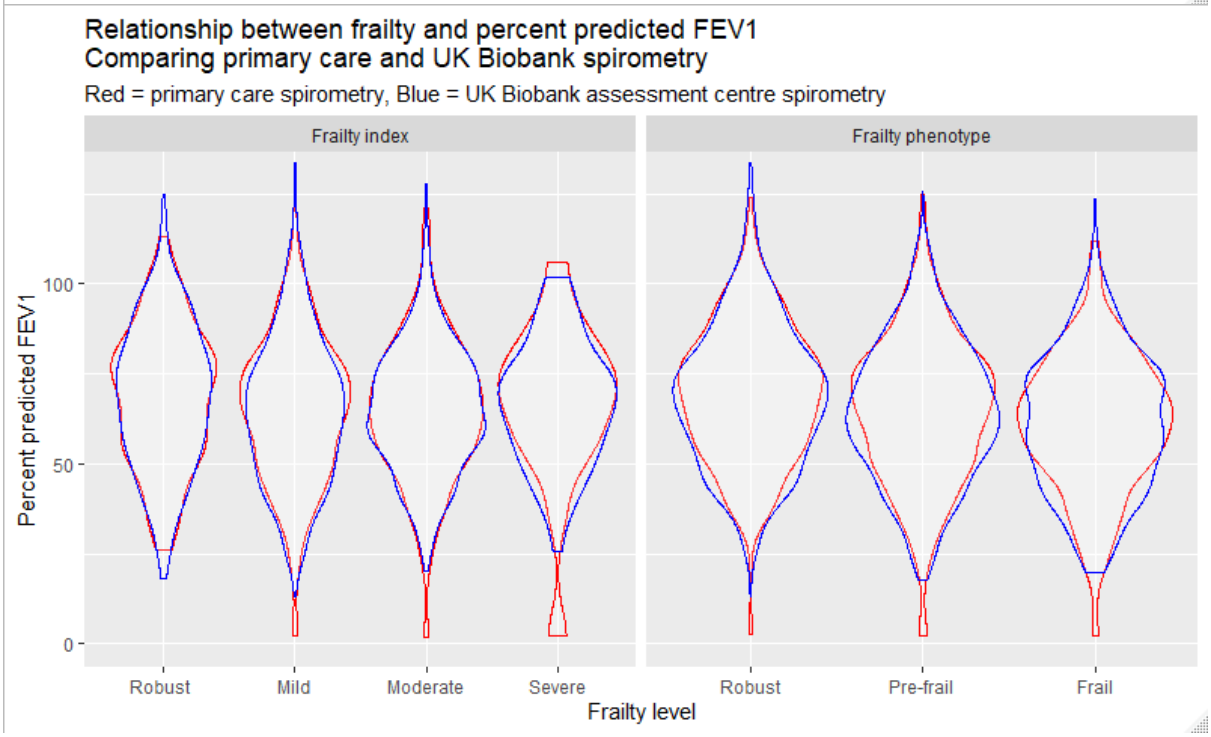
Domain	Total with deficit (%)	Total missing
Low grip strength	870 (28.3%)	55
Weight loss	547 (17.5%)	9
Exhaustion	748 (23.9%)	8
Slow walking speed	1098 (35.8%)	62
Low physical activity	709 (23.2%)	71

Scatter plot of frailty index (numerical values) and percent predicted FEV1

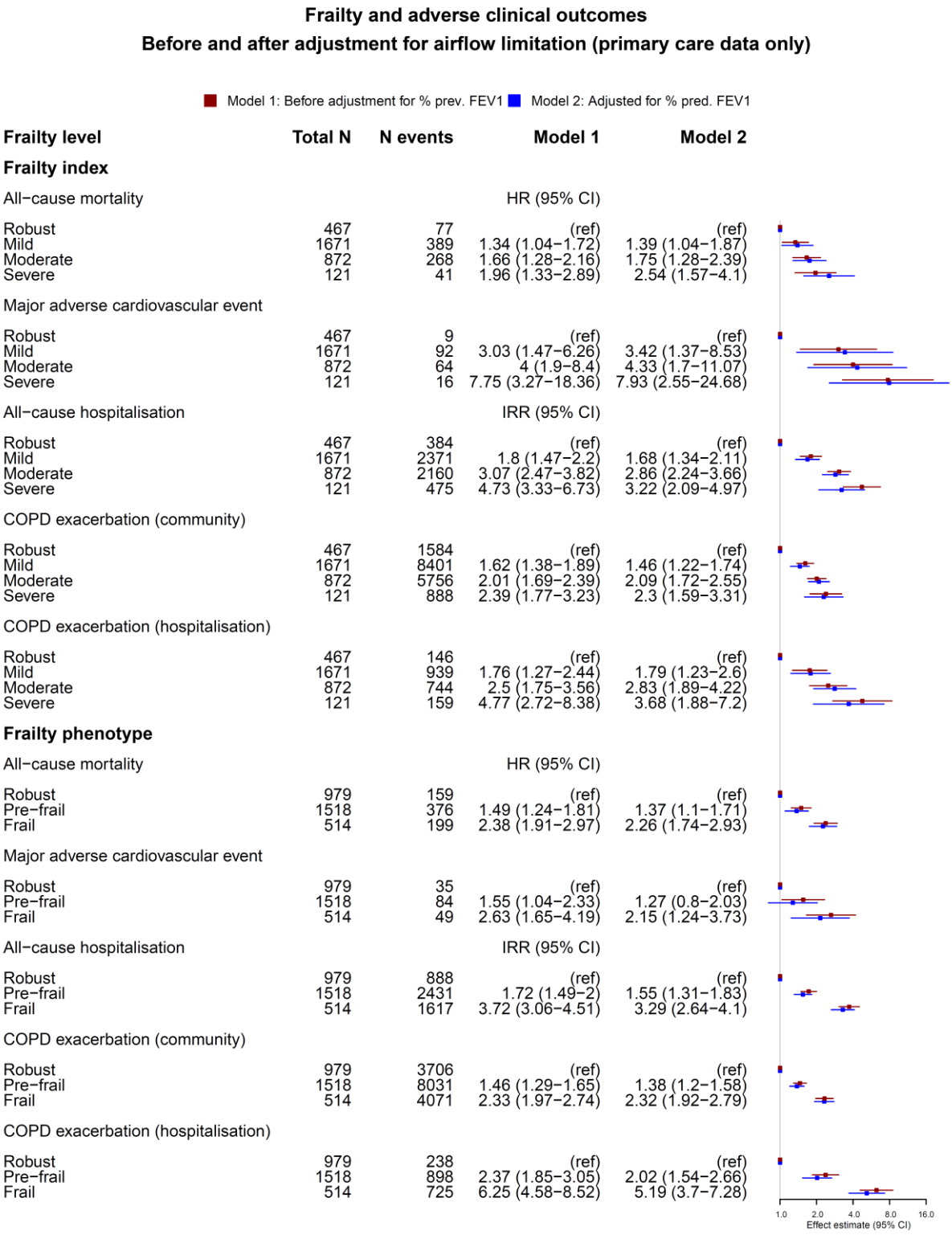


Comparing distribution of airflow limitation using primary care spirometry and UK Biobank spirometry



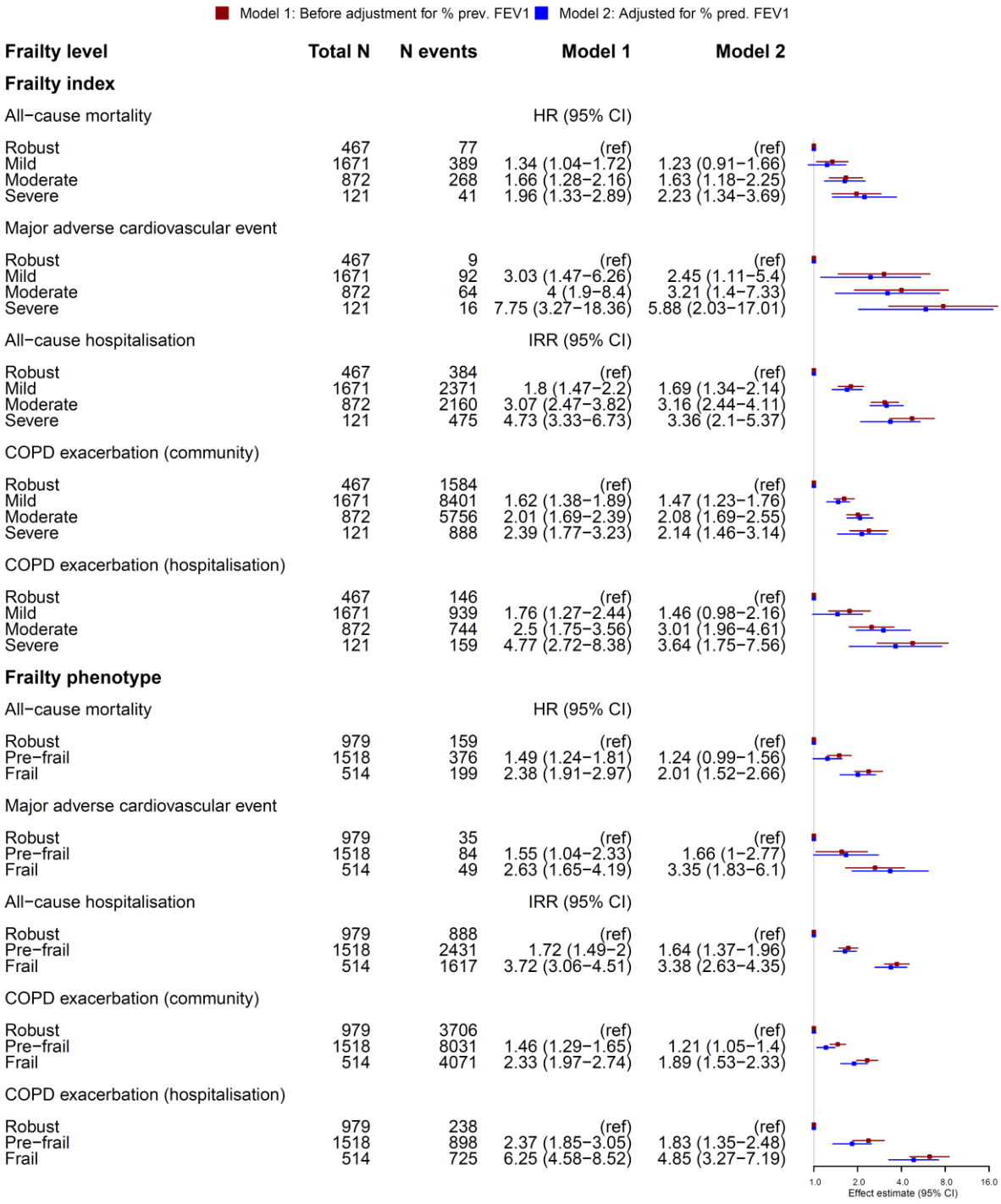


Relationship between frailty and clinical outcomes, adjusting for primary care spirometry only



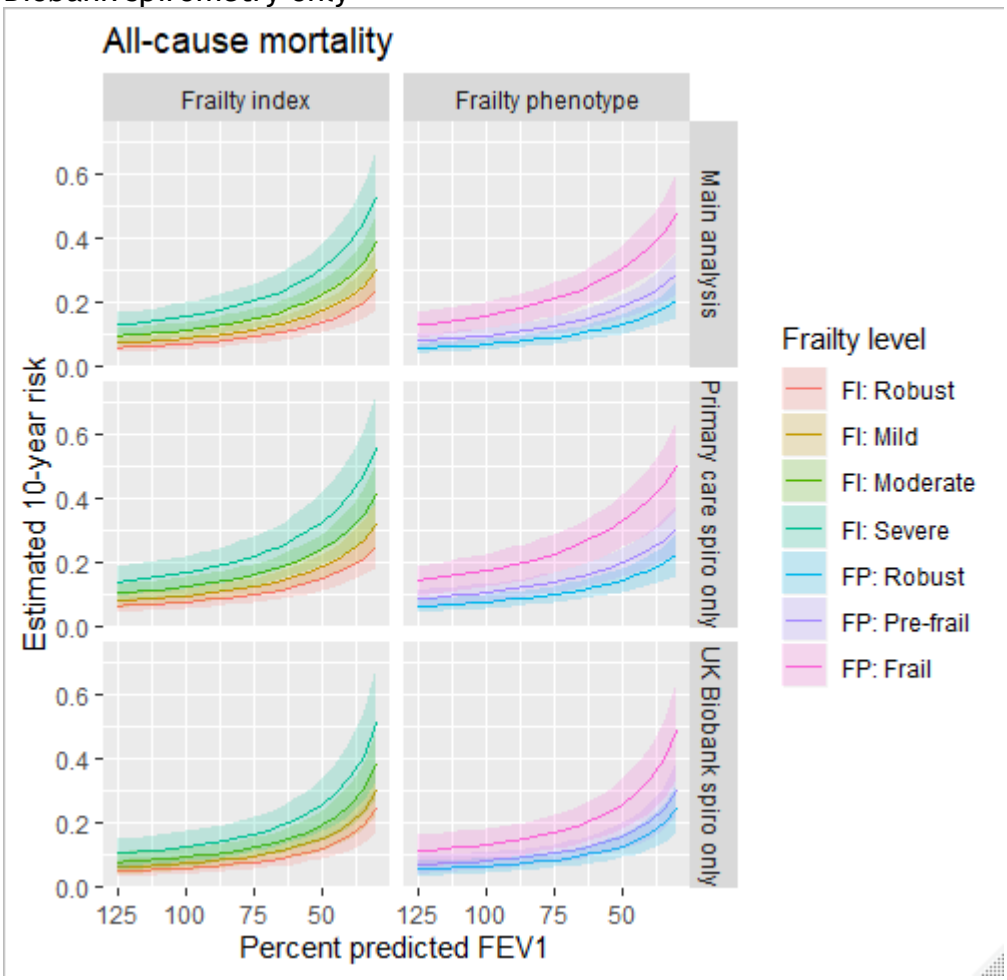
Relationship between frailty and clinical outcomes, adjusting for UK Biobank spirometry only

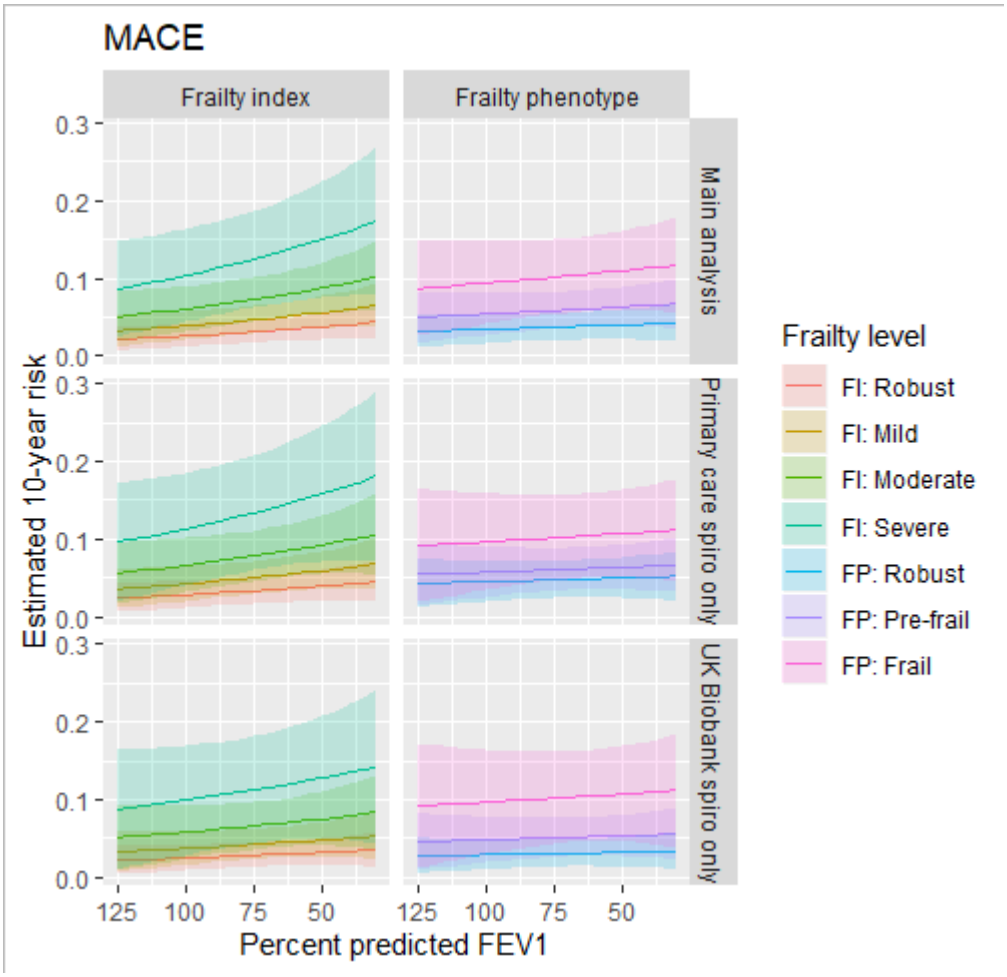
Frailty and adverse clinical outcomes
Before and after adjustment for airflow limitation (UK Biobank spirometry data only)

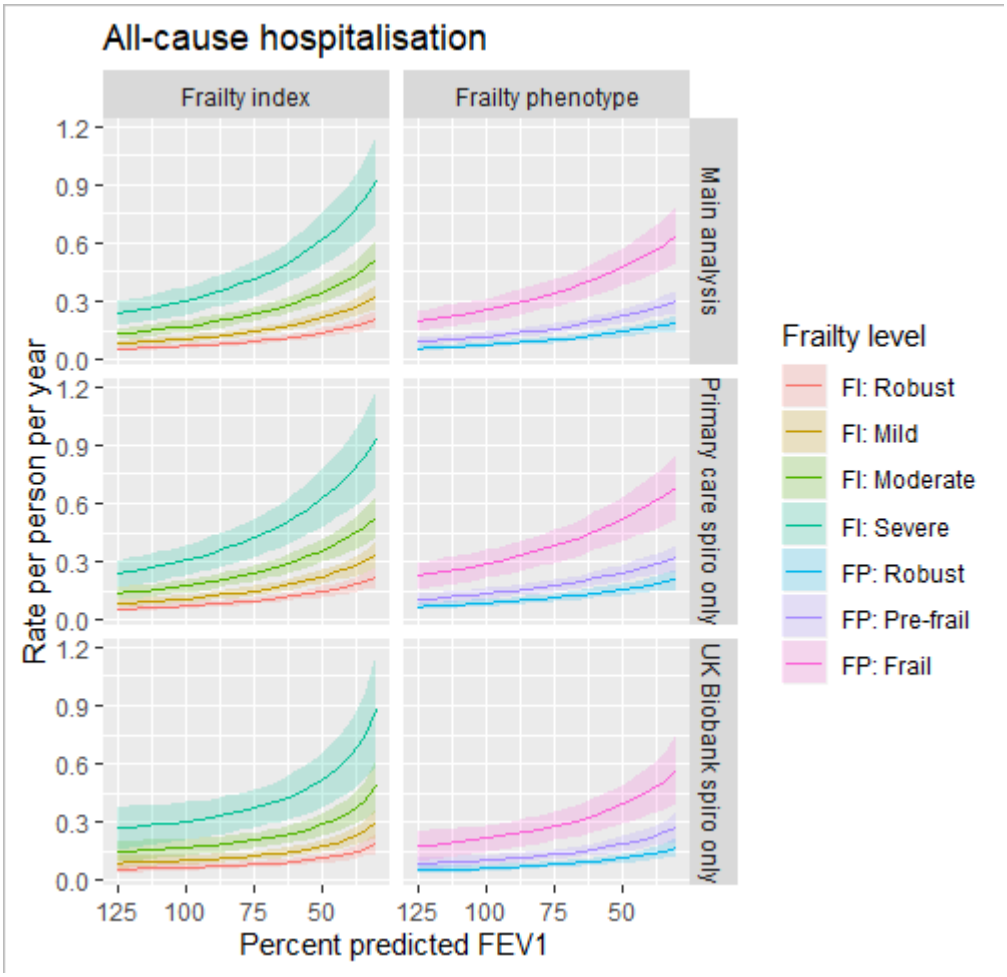


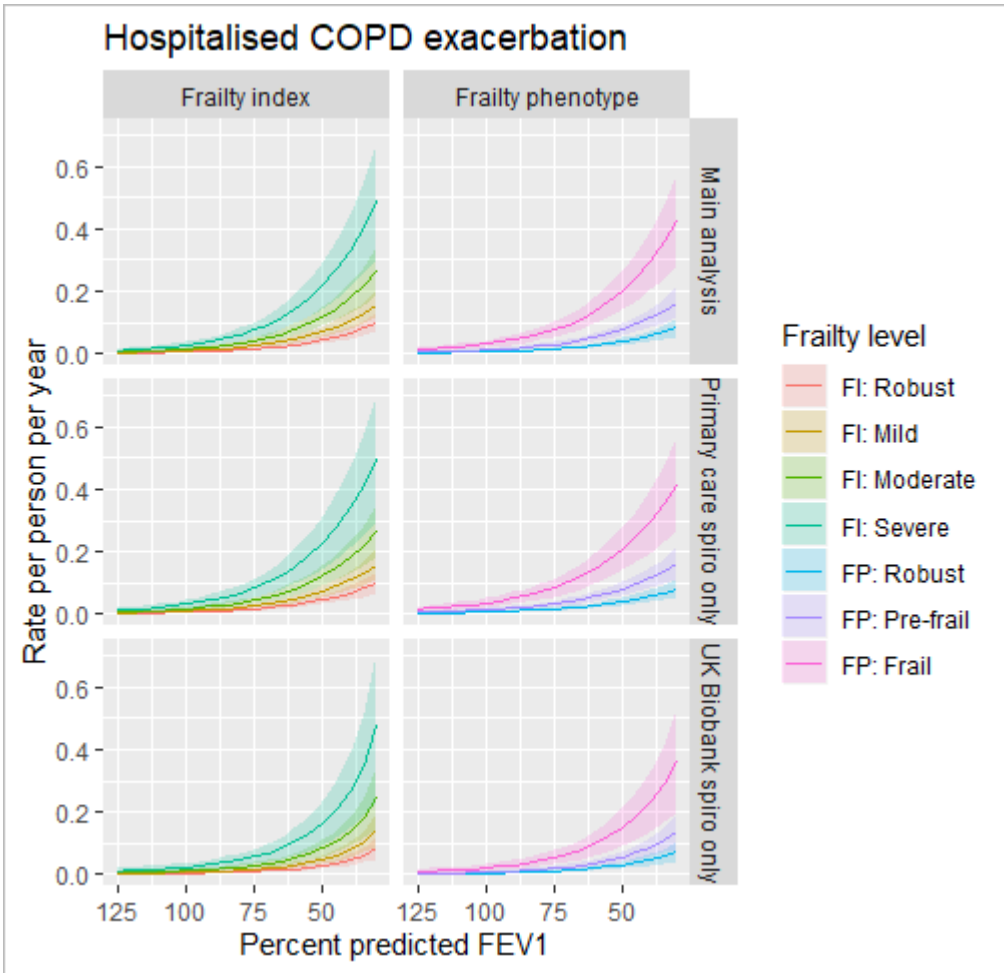
Frailty level	Total N	N events	Model 1	Model 2
Frailty index				
All−cause mortality			HR (95% CI)	
Robust	467	77	(ref)	(ref)
Mild	1671	389	1.34 (1.04−1.72)	1.23 (0.91−1.66)
Moderate	872	268	1.66 (1.28−2.16)	1.63 (1.18−2.25)
Severe	121	41	1.96 (1.33−2.89)	2.23 (1.34−3.69)
Major adverse cardiovascular event				
Robust	467	9	(ref)	(ref)
Mild	1671	92	3.03 (1.47−6.26)	2.45 (1.11−5.4)
Moderate	872	64	4 (1.9−8.4)	3.21 (1.4−7.33)
Severe	121	16	7.75 (3.27−18.36)	5.88 (2.03−17.01)
All−cause hospitalisation			IRR (95% CI)	
Robust	467	384	(ref)	(ref)
Mild	1671	2371	1.8 (1.47−2.2)	1.69 (1.34−2.14)
Moderate	872	2160	3.07 (2.47−3.82)	3.16 (2.44−4.11)
Severe	121	475	4.73 (3.33−6.73)	3.36 (2.1−5.37)
COPD exacerbation (community)				
Robust	467	1584	(ref)	(ref)
Mild	1671	8401	1.62 (1.38−1.89)	1.47 (1.23−1.76)
Moderate	872	5756	2.01 (1.69−2.39)	2.08 (1.69−2.55)
Severe	121	888	2.39 (1.77−3.23)	2.14 (1.46−3.14)
COPD exacerbation (hospitalisation)				
Robust	467	146	(ref)	(ref)
Mild	1671	939	1.76 (1.27−2.44)	1.46 (0.98−2.16)
Moderate	872	744	2.5 (1.75−3.56)	3.01 (1.96−4.61)
Severe	121	159	4.77 (2.72−8.38)	3.64 (1.75−7.56)
Frailty phenotype				
All−cause mortality			HR (95% CI)	
Robust	979	159	(ref)	(ref)
Pre−frail	1518	376	1.49 (1.24−1.81)	1.24 (0.99−1.56)
Frail	514	199	2.38 (1.91−2.97)	2.01 (1.52−2.66)
Major adverse cardiovascular event				
Robust	979	35	(ref)	(ref)
Pre−frail	1518	84	1.55 (1.04−2.33)	1.66 (1−2.77)
Frail	514	49	2.63 (1.65−4.19)	3.35 (1.83−6.1)
All−cause hospitalisation			IRR (95% CI)	
Robust	979	888	(ref)	(ref)
Pre−frail	1518	2431	1.72 (1.49−2)	1.64 (1.37−1.96)
Frail	514	1617	3.72 (3.06−4.51)	3.38 (2.63−4.35)
COPD exacerbation (community)				
Robust	979	3706	(ref)	(ref)
Pre−frail	1518	8031	1.46 (1.29−1.65)	1.21 (1.05−1.4)
Frail	514	4071	2.33 (1.97−2.74)	1.89 (1.53−2.33)
COPD exacerbation (hospitalisation)				
Robust	979	238	(ref)	(ref)
Pre−frail	1518	898	2.37 (1.85−3.05)	1.83 (1.35−2.48)
Frail	514	725	6.25 (4.58−8.52)	4.85 (3.27−7.19)

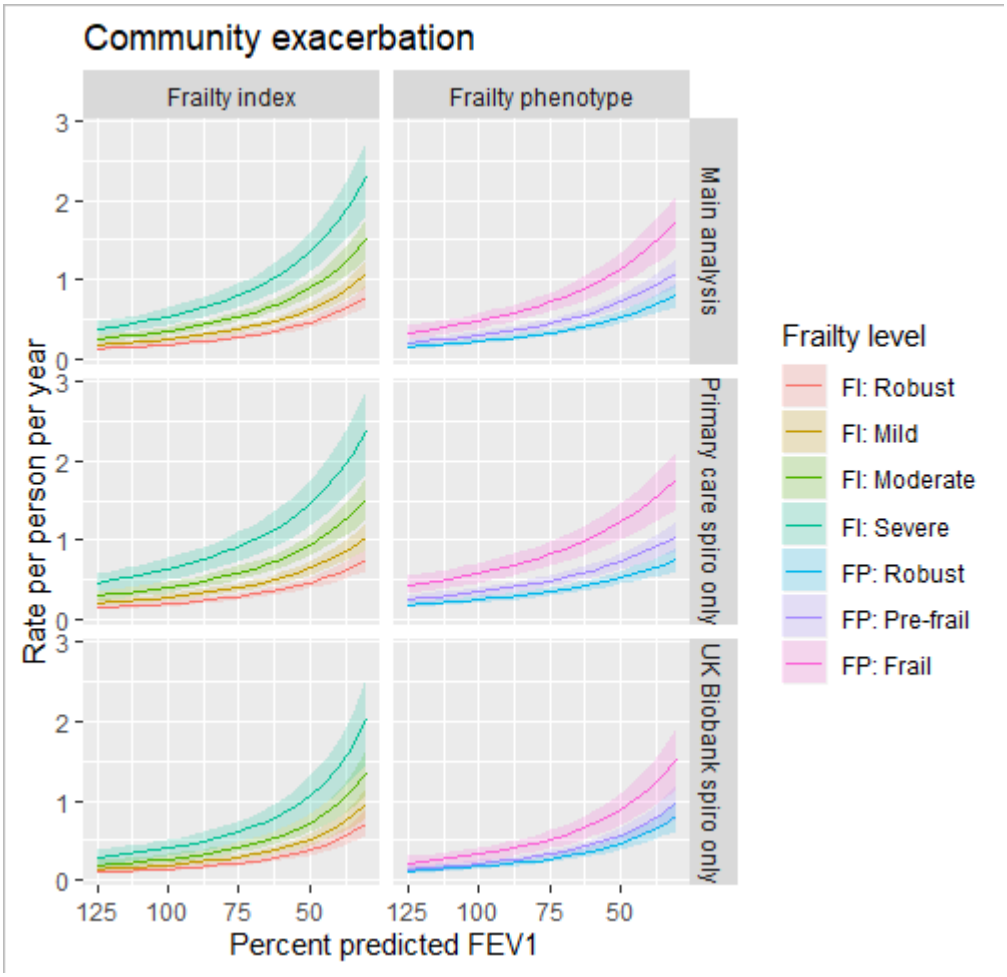
Relationship between frailty, FEV1 and outcomes, comparing main analysis to UK Biobank spirometry only




MACE
Frailty index
Frailty phenotype
Main analysis
Primary care spiro only
UK Biobank spiro only
Estimated 10-year risk
0.0
0.1
0.2
0.3
125
100
75
50
Percent predicted FEV1
Frailty level
FI: Robust
FI: Mild
FI: Moderate
FI: Severe
FP: Robust
FP: Pre-frail
FP: Frail


All-cause hospitalisation
Frailty index
Frailty phenotype
Main analysis
Primary care spiro only
UK Biobank spiro only
Rate per person per year
1.2
0.9
0.6
0.3
0.0
125
100
75
50
Percent predicted FEV1
Frailty level
FI: Robust
FI: Mild
FI: Moderate
FI: Severe
FP: Robust
FP: Pre-frail
FP: Frail


Hospitalised COPD exacerbation
Frailty index
Frailty phenotype
Main analysis
Primary care spiro only
UK Biobank spiro only
Rate per person per year
0.0
0.2
0.4
0.6
125
100
75
50
Percent predicted FEV1
Frailty level
FI: Robust
FI: Mild
FI: Moderate
FI: Severe
FP: Robust
FP: Pre-frail
FP: Frail


Community exacerbation
Frailty index
Frailty phenotype
Main analysis
Primary care spiro only
UK Biobank spiro only
Rate per person per year
0
1
2
3
125
100
75
50
Percent predicted FEV1
Frailty level
FI: Robust
FI: Mild
FI: Moderate
FI: Severe
FP: Robust
FP: Pre-frail
FP: Frail

Appendix 7: Supplementary material for Chapter 10: Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions

Deficits included in frailty index for each condition

Diabetes trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboemolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Arthritis and arthralgia	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthopathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional dosirders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0
Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parksinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty picking up objects	IWQOL1	Present = 1, absent = 0
Difficulty getting up from chairs	IWQOL3	Present = 1, absent = 0
Trouble with stairs	IWQOL4	Present = 1, absent = 0
Difficulty dressing	IWQOL5	Present = 1, absent = 0
Difficulty with mobility	IWQOL6	Present = 1, absent = 0
Short of breath on mild exertion	IWQOL8	Present = 1, absent = 0
Self-rated health	EQ5D/SF36-1	((Total out of 100)-100)/100
Limited mobility/difficulty walking several blocks	EQ5D-1/SF36-10	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0

Difficulty with self-care	EQ5D-2/SF36-12	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited in usual activities	EQ5D-3/SF25-32	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4/SF36-21	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety or Down in dumps	EQ5D-5/SF36-25	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoblobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0
Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Cholesterol	baseline laboratory measures	>6.2 mmol/L = 1, <6.2 = 0
Systolic blood pressure	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

Rheumatoid arthritis trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboemolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthopathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional dosirders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0

Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parksinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty getting out of bed	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with household chores	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty climbing stairs	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with shopping (groceries)	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficult standing	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with toilet	HAQ-DI	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Self-rated health	EQ5D/SF36-1	((Total out of 100)-100)/100
Limited mobility	EQ5D-1/SF36-10	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Difficulty with self-care	EQ5D-2/SF36-12	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Limited in usual activities	EQ5D-3/SF25-32	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Pain	EQ5D-4/SF36-21	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
Anxiety	EQ5D-5/SF36-25	Severe difficulty/unable = 1, some difficulty = 0.5, no difficulty = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoblobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0

Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Glucose	baseline laboratory measures	>11 mmol/L = 1, >7 = 0.5, <7 = 0
Cholesterol	baseline laboratory measures	>6.2 mmol/L = 1, <6.2 = 0
Systolic blood pressure	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

COPD trials frailty index deficits		
Deficit	**Source**	**Coding**
Acid-related disorders	Concomitant medications	Present = 1, absent = 0
Diabetes mellitus	Concomitant medications	Present = 1, absent = 0
Thromboemolic disease/AF	Concomitant medications	Present = 1, absent = 0
Cardiovascular disease	Concomitant medications	Present = 1, absent = 0
Urinary tract disorder/incontinence	Concomitant medications	Present = 1, absent = 0
Glaucoma	Concomitant medications	Present = 1, absent = 0
Arthritis and arthralgia	Concomitant medications	Present = 1, absent = 0
Osteoporosis	Concomitant medications	Present = 1, absent = 0
Gout	Concomitant medications	Present = 1, absent = 0
Inflammatory conditions (arthopathies, IBD, connective tissue diseases)	Concomitant medications	Present = 1, absent = 0
Migraine	Concomitant medications	Present = 1, absent = 0
Chronic pain	Concomitant medications	Present = 1, absent = 0
Schizophrenia and delusional dosirders	Concomitant medications	Present = 1, absent = 0
Affective disorders/sleep disorders	Concomitant medications	Present = 1, absent = 0
Epilepsy	Concomitant medications	Present = 1, absent = 0
Parkinson's disease/parksinsonism	Concomitant medications	Present = 1, absent = 0
Dementia	Concomitant medications	Present = 1, absent = 0
Chronic lower respiratory disease	Concomitant medications	Present = 1, absent = 0
Thyroid disorders	Concomitant medications	Present = 1, absent = 0
Skin disorders	Concomitant medications	Present = 1, absent = 0
Difficulty with Stairs	SGRQ	Present = 1, absent = 0
Difficulty with Dressing	SGRQ	Present = 1, absent = 0
Difficulty with Housework	SGRQ	Present = 1, absent = 0
Difficulty with Shopping	SGRQ	Present = 1, absent = 0
Difficulty with Sports	SGRQ	Present = 1, absent = 0
Bath/shower long time	SGRQ	Present = 1, absent = 0

Everything too much effort	SGRQ	Present = 1, absent = 0
Feel that exercise not safe for me	SGRQ	Present = 1, absent = 0
Feel frail because of chest	SGRQ	Present = 1, absent = 0
Panic	SGRQ	Present = 1, absent = 0
Exhausted easily	SGRQ	Present = 1, absent = 0
eGFR	baseline laboratory measures	<30 = 1, <60 = 0.5, >60 = 0
Haemoglobin	baseline laboratory measures	<115 = 1 (men), <110 = 1 (women)
Fib4	baseline laboratory measures	>2.67 = 1, >2 = 0.5, <2 = 0
Sodium	baseline laboratory measures	<133 = 1
Calcium	baseline laboratory measures	>2.7 mmol/L = 1, <2.7 = 0
Glucose	baseline laboratory measures	>11 mmol/L = 1, >7 = 0.5, <7 = 0
Systolic BP	baseline assessment	>150 = 1
Body mass index	baseline assessment	<18.5 or >30 = 1, >25 = 0.5, 18.5-25 = 0

Parameters for the distributions of the frailty index for each trial

Generalised gamma distribution. P-value for fit (Kolmogorov Smirnov test) – p>0.05 indicated good fit.

Trial	Mu	Sigma	Q	P-value
NCT00734474	-2.1384099	0.5184630	0.2126836	0.6536614
NCT01064687	-1.8686473	0.4334530	-0.0911457	0.3841132
NCT01075282	-1.9262997	0.4534190	-0.0070541	0.1537916
NCT01191268	-1.7281470	0.4233779	0.2312597	0.1205054
NCT01624259	-1.9900970	0.4453075	-0.2423449	0.3977397
NCT01106625	-1.7845810	0.4249601	0.6854553	0.7535057
NCT01106677	-1.8141929	0.4008267	0.4329018	0.0994761
NCT00106535	-1.3622950	0.3178938	1.2024470	0.1125004
NCT01007435	-1.4211607	0.3644020	1.3289993	0.1304014
NCT01119859	-1.3239383	0.3311765	0.9893788	0.6863576
NCT01232569	-1.3903390	0.3191592	1.0485768	0.5766842
NCT00236028	-1.2671025	0.2418719	0.9600227	0.2527657
NCT00264537	-1.1828921	0.2272744	0.8935029	0.7031388
NCT00264550	-1.2542247	0.2725728	0.7223240	0.0897029
NCT00361335	-1.2060284	0.2486708	0.8211526	0.4014494
NCT01316900	-1.5972347	0.3817339	1.1277266	0.1655973
NCT01316913	-1.5434427	0.3536005	1.2548760	0.0574210
NCT01957163	-1.7122818	0.4290410	0.7032241	0.0350085
NCT02119286	-1.6826762	0.4197403	1.0602738	0.2451722

Generalised gamma model coefficients and variance covariance matrices

Each of these describes a generalised gamma model for FI values on age (centred at 60 years), sex (male = 1, female = 0) and disease severity

NCT00734474: generalised gamma model coefficients	
Mu	-1.99992
Sigma	-0.70364
Q	0.203893
Age	0.007928
Sex	-0.21326
HbA1c	0.023292

NCT00734474: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.000813	-9.8E-05	0.001435	1.13E-05	-0.00039	-4.4E-05
Sigma	-9.8E-05	0.000439	-0.00031	3E-07	4E-07	3.9E-06
Q	0.001435	-0.00031	0.005856	-4.9E-06	-5.8E-06	-5.7E-05
Age	1.13E-05	3E-07	-4.9E-06	2.1E-06	0	-2E-07
Sex	-0.00039	4E-07	-5.8E-06	0	0.000823	1.31E-05
HbA1c	-4.4E-05	3.9E-06	-5.7E-05	-2E-07	1.31E-05	0.000176

NCT01064687: generalised gamma model coefficients	
Mu	-1.73457
Sigma	-0.86705
Q	-0.0698
Age	0.007821
Sex	-0.16049
HbA1c	0.000813

NCT01064687: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.000826	3.61E-05	0.001552	8.5E-06	-0.00049	1.77E-05
Sigma	3.61E-05	0.000514	0.000127	-1E-07	-4E-06	6E-07
Q	0.001552	0.000127	0.006997	-3.9E-06	-0.00017	2.45E-05
Age	8.5E-06	-1E-07	-3.9E-06	1.9E-06	-1.9E-06	1E-07
Sex	-0.00049	-4E-06	-0.00017	-1.9E-06	0.00076	-3.5E-05
HbA1c	1.77E-05	6E-07	2.45E-05	1E-07	-3.5E-05	0.000106

NCT01075282: generalised gamma model coefficients	
Mu	-1.74062
Sigma	-0.86522
Q	0.080101
Age	0.011933
Sex	-0.25352

HbA1c	0.024706

NCT01075282: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.00093	-5.3E-05	0.002002	8.1E-06	-0.00051	-4.3E-05
Sigma	-5.3E-05	0.000608	-0.00019	2E-07	8.4E-06	0.000002
Q	0.002002	-0.00019	0.008797	-6.1E-06	-0.00031	-7.6E-05
Age	8.1E-06	2E-07	-6.1E-06	2.4E-06	-2.2E-06	3E-07
Sex	-0.00051	8.4E-06	-0.00031	-2.2E-06	0.000869	-4.6E-06
HbA1c	-4.3E-05	0.000002	-7.6E-05	3E-07	-4.6E-06	0.000217

NCT01191268: generalised gamma model coefficients	
Mu	-1.63563
Sigma	-0.9037
Q	0.163278
Age	0.009778
Sex	-0.19765
HbA1c	0.008889

NCT01191268: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.000747	-8.7E-05	0.001595	-2.2E-06	-0.00037	-9E-05
Sigma	-8.7E-05	0.00058	-0.00035	0.000001	-6.9E-06	2.7E-06
Q	0.001595	-0.00035	0.008136	-1.9E-05	0.000126	-5E-05
Age	-2.2E-06	0.000001	-1.9E-05	2.3E-06	-2E-06	0.000002
Sex	-0.00037	-6.9E-06	0.000126	-2E-06	0.000743	4.9E-06
HbA1c	-9E-05	2.7E-06	-5E-05	0.000002	4.9E-06	0.00017

NCT01624259: generalised gamma model coefficients	
Mu	-1.87022
Sigma	-0.83679
Q	-0.09601
Age	0.01037
Sex	-0.10408
HbA1c	-0.03629

NCT01624259: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.001502	0.000112	0.003486	2.07E-05	-0.00075	-4.4E-05
Sigma	0.000112	0.000847	0.000372	1.2E-06	-1.9E-05	-3.5E-06
Q	0.003486	0.000372	0.014139	3.75E-05	-0.0006	-0.00011
Age	2.07E-05	1.2E-06	3.75E-05	3.5E-06	-2.2E-06	5.5E-06
Sex	-0.00075	-1.9E-05	-0.0006	-2.2E-06	0.001282	2.58E-05
HbA1c	-4.4E-05	-3.5E-06	-0.00011	5.5E-06	2.58E-05	0.000502

NCT01106625: generalised gamma model coefficients	
Mu	-1.80232
Sigma	-1.1759
Q	-0.37176
Age	-0.00021
Sex	-0.1019
HbA1c	0.023065

NCT01106625: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.001582	0.000589	0.004772	0.000024	-0.00083	-1.9E-05
Sigma	0.000589	0.00194	0.002561	0.000007	-0.00013	-1.7E-05
Q	0.004772	0.002561	0.025632	5.71E-05	-0.00103	-0.00014
Age	0.000024	0.000007	5.71E-05	3.6E-06	-3.3E-06	3.1E-06
Sex	-0.00083	-0.00013	-0.00103	-3.3E-06	0.001296	-7.4E-05
HbA1c	-1.9E-05	-1.7E-05	-0.00014	3.1E-06	-7.4E-05	0.000379

NCT01106677: generalised gamma model coefficients	
Mu	-1.84125
Sigma	-1.12867
Q	-0.34734
Age	-0.00236
Sex	-0.10274
HbA1c	0.015572

NCT01106677: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	HbA1c
Mu	0.000447	0.000154	0.001337	5.9E-06	-0.00021	1.56E-05
Sigma	0.000154	0.000584	0.000738	4E-07	-8.4E-06	-5.2E-06
Q	0.001337	0.000738	0.007892	3.3E-06	-7.3E-05	-4.5E-05
Age	5.9E-06	4E-07	3.3E-06	1.2E-06	-1E-07	1.1E-06
Sex	-0.00021	-8.4E-06	-7.3E-05	-1E-07	0.000425	-2.1E-05
HbA1c	1.56E-05	-5.2E-06	-4.5E-05	1.1E-06	-2.1E-05	0.000134

NCT00106535: generalised gamma model coefficients	
Mu	-1.7998
Sigma	-1.17989
Q	1.089106
Age	0.004992
Sex	-0.10346
DAS-28	0.072516

NCT00106535: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.002681	-0.00057	0.001884	2.3E-06	-0.00017	-0.00035
Sigma	-0.00057	0.000838	-0.00132	2.3E-06	-4.7E-05	4.99E-05

Q	0.001884	-0.00132	0.005923	-7.5E-06	0.000156	-0.00016
Age	2.3E-06	2.3E-06	-7.5E-06	6E-07	6E-07	2E-07
Sex	-0.00017	-4.7E-05	0.000156	6E-07	0.000606	1.64E-05
DAS-28	-0.00035	4.99E-05	-0.00016	2E-07	1.64E-05	5.11E-05

NCT01007435: generalised gamma model coefficients	
Mu	-2.74094
Sigma	-1.05458
Q	0.839224
Age	0.002688
Sex	-0.06333
DAS-28	0.193328

NCT01007435: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.004236	-0.00081	0.003118	1.6E-06	-4.6E-05	-0.00056
Sigma	-0.00081	0.000639	-0.00109	1.9E-06	-2.4E-05	9.16E-05
Q	0.003118	-0.00109	0.00537	-7.2E-06	9.28E-05	-0.00035
Age	1.6E-06	1.9E-06	-7.2E-06	5E-07	-8E-07	4E-07
Sex	-4.6E-05	-2.4E-05	9.28E-05	-8E-07	0.000529	-8.8E-06
DAS-28	-0.00056	9.16E-05	-0.00035	4E-07	-8.8E-06	0.000079

NCT01119859: generalised gamma model coefficients	
Mu	-2.15833
Sigma	-1.18086
Q	0.958357
Age	0.004792
Sex	-0.05208
DAS-28	0.125889

NCT01119859: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.018213	-0.00252	0.008921	-1.2E-05	-0.00068	-0.00243
Sigma	-0.00252	0.003155	-0.00572	8E-07	-0.00028	0.000212
Q	0.008921	-0.00572	0.025457	-2.7E-06	0.000997	-0.00075
Age	-1.2E-05	8E-07	-2.7E-06	1.9E-06	-6.3E-06	3.6E-06
Sex	-0.00068	-0.00028	0.000997	-6.3E-06	0.001953	6.36E-05
DAS-28	-0.00243	0.000212	-0.00075	3.6E-06	6.36E-05	0.000343

NCT01232569: generalised gamma model coefficients	
Mu	-2.22043
Sigma	-1.23044
Q	0.982978
Age	0.005164
Sex	-0.11025
DAS-28	0.128846

NCT01232569: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.007379	-0.00117	0.004063	-2.4E-06	7.23E-05	-0.00099
Sigma	-0.00117	0.001415	-0.00225	5.4E-06	-0.00006	0.000115
Q	0.004063	-0.00225	0.010483	-1.9E-05	0.000209	-0.0004
Age	-2.4E-06	5.4E-06	-1.9E-05	1.2E-06	-2.6E-06	1.4E-06
Sex	7.23E-05	-0.00006	0.000209	-2.6E-06	0.001021	-3.2E-05
DAS-28	-0.00099	0.000115	-0.0004	1.4E-06	-3.2E-05	0.000142

NCT00236028: generalised gamma model coefficients	
Mu	-1.94368
Sigma	-1.51325
Q	0.804074
Age	0.00327
Sex	-0.0831
DAS-28	0.096618

NCT00236028: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.002321	-0.00046	0.001825	-9E-07	-2.5E-05	-0.00028
Sigma	-0.00046	0.000828	-0.0013	1.6E-06	-3.3E-05	3.97E-05
Q	0.001825	-0.0013	0.006823	-6.5E-06	0.000132	-0.00016
Age	-9E-07	1.6E-06	-6.5E-06	3E-07	-1.4E-06	5E-07
Sex	-2.5E-05	-3.3E-05	0.000132	-1.4E-06	0.000246	-6E-06
DAS-28	-0.00028	3.97E-05	-0.00016	5E-07	-6E-06	3.75E-05

NCT00264537: generalised gamma model coefficients	
Mu	-1.57697
Sigma	-1.51704
Q	0.556751
Age	0.003795
Sex	-0.06288
DAS-28	0.062217

NCT00264537: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.003785	-0.00067	0.003663	4.2E-06	-0.00011	-0.00049
Sigma	-0.00067	0.00129	-0.00189	3.3E-06	-3.9E-05	0.000066
Q	0.003663	-0.00189	0.013283	-1.8E-05	0.000212	-0.00036
Age	4.2E-06	3.3E-06	-1.8E-05	6E-07	-1E-06	0
Sex	-0.00011	-3.9E-05	0.000212	-1E-06	0.000638	1.8E-06
DAS-28	-0.00049	0.000066	-0.00036	0	1.8E-06	6.75E-05

NCT00264550: generalised gamma model coefficients

Mu	-1.89756
Sigma	-1.39654
Q	0.526478
Age	0.004579
Sex	-0.05166
DAS-28	0.096635

NCT00264550: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.00744	-0.00102	0.005915	1.41E-05	-0.00038	-0.00091
Sigma	-0.00102	0.001821	-0.00304	-2.2E-06	-4.3E-05	7.78E-05
Q	0.005915	-0.00304	0.021535	1.25E-05	0.000245	-0.00045
Age	1.41E-05	-2.2E-06	1.25E-05	1.3E-06	-4E-06	0
Sex	-0.00038	-4.3E-05	0.000245	-4E-06	0.001009	2.46E-05
DAS-28	-0.00091	7.78E-05	-0.00045	0	2.46E-05	0.000123

NCT00361335: generalised gamma model coefficients	
Mu	-2.02391
Sigma	-1.46475
Q	0.602766
Age	0.004842
Sex	-0.07576
DAS-28	0.085114

NCT00361335: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	DAS-28
Mu	0.006429	-0.00076	0.00388	-3.6E-05	1.24E-05	-0.00061
Sigma	-0.00076	0.001408	-0.00239	-3.3E-06	-2.4E-05	8.55E-05
Q	0.00388	-0.00239	0.015101	1.57E-05	0.000134	-0.00043
Age	-3.6E-05	-3.3E-06	1.57E-05	8E-07	-2.6E-06	0
Sex	1.24E-05	-2.4E-05	0.000134	-2.6E-06	0.00064	5E-07
DAS-28	-0.00061	8.55E-05	-0.00043	0	5E-07	8.38E-05

NCT01316900: generalised gamma model coefficients	
Mu	-1.38005
Sigma	-0.95181
Q	1.148042
Age	-0.00065
Sex	-0.13994
FEV1 (% predicted)	-0.00288

NCT01316900: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	FEV1 (% predicted)
Mu	0.003355	-0.00033	0.001079	-9E-07	-0.00078	-5.1E-05
Sigma	-0.00033	0.00128	-0.0022	1.6E-06	-8.6E-05	-3.9E-06
Q	0.001079	-0.0022	0.009302	-5.5E-06	0.000276	1.22E-05

Age	-9E-07	1.6E-06	-5.5E-06	2.2E-06	-6.1E-06	-1E-07
Sex	-0.00078	-8.6E-05	0.000276	-6.1E-06	0.000878	5.2E-06
FEV1 (% predicted)	-5.1E-05	-3.9E-06	1.22E-05	-1E-07	5.2E-06	0.000001

NCT01316913: generalised gamma model coefficients	
Mu	-1.35748
Sigma	-1.05067
Q	1.255863
Age	-0.00199
Sex	-0.12404
FEV1 (% predicted)	-0.00219

NCT01316913: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	FEV1 (% predicted)
Mu	0.002384	-0.00023	0.000707	-6.3E-06	-0.00051	-3.7E-05
Sigma	-0.00023	0.001323	-0.00233	-9E-07	-5.4E-05	-5.8E-06
Q	0.000707	-0.00233	0.009506	2.6E-06	0.000171	1.81E-05
Age	-6.3E-06	-9E-07	2.6E-06	0.000002	-3.7E-06	0
Sex	-0.00051	-5.4E-05	0.000171	-3.7E-06	0.000663	2.4E-06
FEV1 (% predicted)	-3.7E-05	-5.8E-06	1.81E-05	0	2.4E-06	8E-07

NCT01957163: generalised gamma model coefficients	
Mu	-1.49634
Sigma	-0.86352
Q	0.71645
Age	-0.00257
Sex	-0.11424
FEV1 (% predicted)	-0.00284

NCT01957163: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	FEV1 (% predicted)
Mu	0.004403	-0.00033	0.001445	-1.2E-05	-0.00084	-7E-05
Sigma	-0.00033	0.001269	-0.00201	0.000004	-7.8E-06	-5.5E-06
Q	0.001445	-0.00201	0.011348	-1.8E-05	3.84E-05	2.38E-05
Age	-1.2E-05	0.000004	-1.8E-05	4.6E-06	-1.9E-06	-3E-07
Sex	-0.00084	-7.8E-06	3.84E-05	-1.9E-06	0.001276	4E-07
FEV1 (% predicted)	-7E-05	-5.5E-06	2.38E-05	-3E-07	4E-07	1.7E-06

NCT02119286: generalised gamma model coefficients	
Mu	-1.49243
Sigma	-0.88122
Q	1.07303
Age	-0.00321

Sex	-0.04148
FEV1 (% predicted)	-0.00326

NCT02119286: variance covariance matrix from generalised gamma model						
	Mu	sigma	Q	Age (centred)	Sex	FEV1 (% predicted)
Mu	0.00484	-0.00051	0.001709	-2.2E-06	-0.0009	-7.6E-05
Sigma	-0.00051	0.001849	-0.00346	2.8E-06	2.91E-05	-9.5E-06
Q	0.001709	-0.00346	0.014391	-9.2E-06	-9.6E-05	3.13E-05
Age	-2.2E-06	2.8E-06	-9.2E-06	0.000004	-8.6E-06	-1E-07
Sex	-0.0009	2.91E-05	-9.6E-05	-8.6E-06	0.001214	2.8E-06
FEV1 (% predicted)	-7.6E-05	-9.5E-06	3.13E-05	-1E-07	2.8E-06	1.7E-06