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EPIDEMIOLOGICAL STUDIES ON FRAILTY AND ITS ASSOCIATIONS WITH MORTALITY, DEMENTIA, AND POLYPHARMACY

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To my family

ABSTRACT

Frailty describes the status of decreased physiological reserves and increased vulnerability to adverse outcomes. As the aging population increases, frailty has become an important public health concern. However, longitudinal studies disclosing the associations of frailty with adverse outcomes over the life course are limited. In the thesis, we aimed at investigating the associations of frailty with mortality, dementia, and polypharmacy using three Swedish longitudinal studies of aging and comparing the characteristics of frailty between young and old adults using Swedish and UK data. Frailty was measured using the frailty index (FI).

In **Study I**, we assessed how frailty trajectories look by age at death and compared the predictive values of the level of frailty and the changes of frailty on mortality. We found that individuals who died before the age of 70 years had a steadily increasing trajectory, whereas in those individuals who died at older ages, frailty only increased after 75 years. The level of FI was a stronger predictor of mortality than the rate of change in FI in a longitudinal setting.

In **Study II**, we examined the association between baseline FI and the risk of subsequent dementia using a multivariate Cox model. Familial effects on frailty-dementia association were analyzed using a within-pair analysis. The age-varying effects of FI on dementia were also assessed. We found that the FI was associated with an increased risk of dementia independent of the *Apolipoprotein E* (*APOE*) ε4 carrier status. After adjusting for familial factors, no attenuation was found in dizygotic (DZ) and monozygotic (MZ) twins, indicating that shared environmental and genetic factors had no influence on the frailty-dementia association. The effect of the FI on dementia was constant after age 50.

In **Study III,** we investigated the differences in the prevalence, characteristics, and risk factors of early-life (aged <65) and late-life (aged ≥65) frailty using data from Sweden and UK. Comparison of the characteristics of early-life and late-life frailty was performed by collating the FI items (deficits) into domains and comparing the domain scores. We found that frailty is prevalent also in younger age groups, with pooled prevalence rates of 10.3% and 14.4% in individuals aged ≤ 55 and 55-65 years, respectively. Younger frail adults had higher scores in immunological, mental wellbeing, and pain-related domains, whereas older frail adults had higher scores in cardiometabolic, cancer, musculoskeletal, and sensory-related domains. Higher age, female sex, smoking, lower alcohol consumption, lower education, obesity, overweight, low income, and maternal smoking were similarly associated with the risk of early-life and late-life frailty.

In **Study IV**, we focused on visualizing FI trajectories by polypharmacy and assessing the longitudinal associations between frailty and polypharmacy using a linear mixed model. We found that the long-term polypharmacy group had a higher FI trajectory than the transient and non-polypharmacy group. Polypharmacy was significantly associated with a higher risk of frailty, and the risk of being frail conferred by polypharmacy increased with age.

In conclusion, frailty is a strong and independent predictor of adverse outcomes. Monitoring frailty and frailty progression is of great importance in middle-aged and older adults. Also, appropriate prescribing should be considered for middle-aged and old adults to prevent later frailty.

LIST OF SCIENTIFIC PAPERS

I. **Bai G**, Szwajda A, Wang Y, Li X, Bower H, Karlsson IK, Johansson B, Aslan AKD, Pedersen NL, Hägg S, Jylhävä J. Frailty trajectories in three longitudinal studies of aging: Is the level or the rate of change more predictive of mortality? Age Ageing. 2021;50

II. **Bai G**, Wang Y, Kuja-Halkola R, Li X, Tomata Y, Karlsson IK, Pedersen NL, Hägg S, Jylhävä J. Frailty and the risk of dementia: is the association explained by shared environmental and genetic factors? BMC Med. 2021;19(1):248.

III. **Bai G**, Wang Y, Mak JKL, Ericsson M, Hägg S, Jylhävä J. Is frailty different in younger adults compared to old? Prevalence, characteristics and risk factors of early-life and late-life frailty in samples from Sweden and UK. *Manuscript*.

IV. **Bai G**, Wang Y, Mak JKL, Oliveira TLD, Pedersen NL, Jylhävä J, Hägg S. Frailty, polypharmacy, and associations with age in three longitudinal population-based studies of ageing in Sweden. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
APOE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDR	Cause of Death Register
CI	Confidence Interval
DZ	Dizygotic
eFI	Electronic frailty index
FI	Frailty index
FP	Frailty phenotype
HLA	Human leukocyte antigen
HR	Hazard ratio
ICD	International Classification of Diseases
IPT	In-person testing
IQR	Interquartile range
MZ	Monozygotic
NPR	National Patient Register
OCTO-Twin	Origin of Variances in the Oldest-Old: Octogenarian Twins
PDR	Prescribed Drug Register
SD	Standard deviation
SATSA	Swedish Adoption/Twin Study of Aging
SALT	Screening Across the Life Span Twin study
STR	Swedish Twin Registry
TELE	Telephone cognitive screening instrument

1 INTRODUCTION

Population aging increases rapidly. World Health Organization has reported that the proportion of individuals over 60 years will double from 12% (2015) to 22% (2050) [1]. This dramatic demographic shift in population and increasing life expectancy is likely to lead in challenges in health and social systems. Due to the substantial complexity and heterogeneity of health status between individuals, chronological age alone cannot be used to define the population in need of prompt and effective health care. In the meantime, the present care for older adults should not be limited in curing one disease by traditional medicine, but a broad and comprehensive understanding in assessing the health status deterioration is needed in the aged care [2]. The concept of frailty provides the possibility to assess the general health status of older adults.

Frailty is defined as a geriatric syndrome characterized by reduced psychological reserves to a stressor event and increased vulnerability to adverse outcomes. Frailty can be described as an umbrella term including different components, such as physical health, mental health, psychological factors, social factors, physical environment, and economic factors [3]. These components influence each other, which leads to the increased susceptibility to mortality, hospitalization and falls. Due to the lack of a universal definition of frailty, there is currently no "gold standard" measurement tool. Although several tools have been used to measure frailty, the two most frequently used measurements in aging research are frailty phenotype (FP) and frailty index (FI). The population-level frailty prevalence is around 12% -24% [4]. In addition, the pooled prevalence of frailty and pre-frailty among geriatric hospital inpatients is 47.4% and 25.8%, respectively [5]. Therefore, investigating the mechanisms behind the associations of frailty with mortality and other geriatric symptoms is of great importance.

Frailty is progressive and often irreversible with time [6]. Therefore, long-term associations of frailty and its changes on mortality and polypharmacy are essential to be explored. Different FI trajectories or transition patterns and their associations with adverse outcomes have been reported [6-8]. Investigating the changes of frailty is imperative to learn about the development of frailty, making us able to identify the target population having a progressive frailty status, and identifying the individuals amenable for frailty intervention in clinical settings.

In this thesis, to explore the trajectories of frailty and its associations with adverse outcomes, we used three longitudinal samples from Swedish Twin Registry (STR) to assess FI trajectories by age at death and polypharmacy and assess the longitudinal associations of frailty or the rate of frailty change with mortality or polypharmacy. We assessed the association of baseline frailty with later dementia risk in twin individuals and estimate familial effects on the frailty-dementia association. We also compared the prevalence, characteristics, and risk factors of frailty in younger and older individuals.

2 BACKGROUND

2.1 Frailty and its measurement tools

Frailty is a common geriatric syndrome characterized by a cumulative decline in functional and physiological systems and a vulnerability to stressors, leading to a high risk of hospitalizations, falls, disability and mortality [9, 10]. Frailty occurs and increases in prevalence with age [11], which leads to lower life quality [12] and increase in health care burden [13]. However, the mechanisms underlying its relationship with the adverse outcomes are still unclear. Frailty is measured by different measurement tools [14], representing a transition phase between healthy aging and disability [15]. Frailty overcame the limitation of focusing on a single disease of the old adults, capturing the substantial heterogeneity and complexity of the health problems in aging individuals [16].

To identify the individuals living with frailty, two main approaches are commonly employed. The Fried frailty phenotype (FP) [17] classifies the person as frail if three or more of the five components – weakness, slowness, unintentional weight loss, exhaustion, and low physical activity – are present, pre-frail with one or two items and robust (or non-frail) if none of the components are present. The Rockwood frailty index (FI) [18] is based on the ratio of deficits present in an individual, calculated by dividing the deficits present by the total number of deficits considered. The deficits included in the FI should be health-related items representing medical conditions, signs, symptoms, functioning and psychosocial well-being and covering a range of systems/health domains [18]. Because the FI is a continuous measure, it is more sensitive in catching the dynamic change of frailty [19]. However, the crucial advantage of the FP is its clear phenotypic definition and efficiency in clinical management of patients, such as following the response to interventions [20]. One of the biggest challenges of these two approaches is the differences they yield in evaluating the prevalence of frailty. The pooled prevalence of frailty using physical frailty was 12%, whereas the prevalence was 24% using frailty index [4]. Other screening tools, such as the electronic frailty index (eFI) is constructed and validated based on the FI framework [21]. The frailty items of eFI are extracted from routine electronic health records and the eFI is convenient for clinicians to monitor frailty in older adult inpatients. As the measurement tools are various, comprehensive exploration of the components of these measurements and standardized evaluation of the prevalence of frailty are needed in the future.

2.2 Epidemiological characteristics of frailty

The prevalence of frailty increases with age, reaching 15.7% in people aged 80 to 84 years and 26.1% in those aged 85 or above [16]. The prevalence of frailty also varies according to the assessment tools, settings and geographic regions. A systematic review reported that the prevalence of frailty in those aged 50 and older across 62 countries was 12% using FP and 24% using the FI. Moreover, the prevalence of pre-frailty was 46% using FP and 49% using the FI [4]. In terms of sex-stratified prevalence, studies have reported that the prevalence of frailty was higher in women than men using both FI and FP [4], whereas women tolerated frailty better than men as seen in a lower mortality risk in women at any given level of frailty [22]. One study

explained this sex-frailty paradox using 'chronic disease hypothesis', so that men suffer more 'life-threatening' diseases but women are more likely to experience more 'non-life-threatening' and 'disabling' diseases [23]. At present, the exact causes of this phenomenon are unclear, and sex-stratified analysis should be considered in frailty-related studies to explore the potential mechanisms underlying this paradox.

Risk factors of frailty have been studied frequently in older adults. Systematic reviews have outlined that increasing age, female sex, malnutrition, lower levels of physical exercise, Activities of Daily Living (ADL) disability, living in lower income countries, and lower socioeconomic status are risk factors of frailty [24-26]. Age-related symptoms, such as persistent pain and sensory loss have also been reported as risk factors of frailty in meta-analyses [27, 28]. Poor oral status can also increase the risk of frailty, probably due to malnutrition or weight loss [29]. Consumption of low-fat milk and yogurt [30], fruits and vegetables [31] are instead associated with a lower risk of frailty. Although specific mechanisms underlying the associations are complex, risk factor analysis of frailty is needed to provide evidence to support tailored interventions on frailty.

2.3 Transitions and progression of frailty

Frailty changes dynamically with aging. A meta-analysis on frailty transitions demonstrated that more than 50% of older individuals remained at the same frailty status, 3% of frail older people returned to robust, about 10% improved and about 40% worsened in their frailty status over ~4 years [8]. In five longitudinal studies, the annual increase in FI ranged from 0.002 to 0.009 and women had higher frail status than men in all cohorts [32]. Women had a faster rate of accumulated health deficits than men in a study by Stolz et al [33], however, sex did not affect the FI change rate in a study by Hoogendijk [34]. Overall, the trajectories of frailty are heterogeneous between individuals and sex influences the rate of frailty change differently across studies [32, 35].

Reversal of frailty is possible [36]. Meta-analyses on a spontaneous (i.e., without an intervention) reversal of frailty showed that 23.3% of surviving pre-frail individuals returned to a robust state and 35.2% of surviving frail individuals reversed to a pre-frail or robust state in a median follow-up of 3.0 years [37]. A systematic review [8] has reported that one quarter of pre-frail older adults, and only 3% of frail older adults, improved to robust during a 3.9-year follow-up.

The risk factors of frailty trajectories have varied across studies. A meta-analysis summarized that the rate of frailty progression has been associated with age, socioeconomic status, physical exercise, and brain pathologies [35]. Peek et al [38] found that older ages were associated with significantly increased risk of being in the progressive high frailty and progressive moderate frailty trajectories compared to the stable low frailty trajectory. Brain pathology related with Alzheimer's disease and cognitive impairment were also related with higher frailty trajectories [39]. Physical activity, diseases, and injuries have been less frequently reported but nevertheless regarded as potential factors influencing the progression of frailty [17]. A number of studies have provided evidence for a psychological and functional decline and the vulnerability to adverse

outcomes on frailty, nevertheless, how frailty changes over the lifespan, and the key factors contributing to the change, remain uncertain.

2.4 Genetic determinants of frailty

A heritability study using a cohort of UK Twins showed that 45% of the variance in FI was heritable and 52% originated from the individual's environment, indicating that frailty is both genetically and environmentally determined [40]. The single nucleotide polymorphism heritability (i.e., an estimate that does not capture non-additive and interaction effects) of the FI has been reported to be 11% [41]. A sex-specific heritability study in twins demonstrated that genetic and individual-specific environmental factors equally contribute to the FI variance, with the heritability of FI being 52% in women and 45% in men [42]. A genome-wide association study (GWAS) of frailty have been conducted to explain potential pathways and mechanism underlying frailty. Several genetic variants linked to smoking, cardiovascular disease, BMI, and HLA proteins, depression, and neuroticism were associated with the FI, with a functional annotation analyses showing that these variants were enriched for neurological pathways and brain function [41]. Another GWAS and an epigenome-wide association study showed that variants associated with neurological pathways are common to both chronic widespread musculoskeletal pain and FI [43]. In terms of the role of *apolipoprotein E* (*APOE*) ε4 and ε2 alleles on frailty, although these alleles have been shown to have an impact on longevity, a recent UK Biobank study found no association between *APOE* and frailty [41].

2.5 Frailty, frailty trajectories, and the risk of death

A systematic review [44] has shown that frailty is significantly associated with a higher mortality risk with the pooled Hazard Ratio (HR) per 0.01 FI increase being 1.039 (95% confidence interval [CI] 1.033-1.044) and pooled HR per 0.1 FI increase being 1.282 (95% CI 1.258-1.307). Frailty is also associated with other adverse outcomes, but with different HRs compared to mortality. A meta-analysis has shown that higher frailty is a risk factor of mortality from all causes (HR 2.40; 95% CI 2.17-2.65), cardiovascular disease (HR 2.64; 95% CI 2.20-3.17), respiratory illness (HR 4.91; 95% CI 2.97-8.12), and cancer (HR 1.97; 95% CI 1.50-2.57) [45]. In addition, studies have shown that the effects of frailty on mortality were similar in men and women [46, 47]. Williams *et al* [48] showed that a 0.1 increment of the FI was associated with an HR of 1.94 (95% CI 1.60-2.35) in men and 2.06 (95% CI 1.58-2.69) in women. Li *et al* [49] demonstrated that increased FI was associated with higher risks of all-cause, CVD, and respiratory-related mortality, with the corresponding hazard ratios of 1.28 (95% CI 1.24-1.32), 1.31 (95% CI 1.23-1.40), and 1.23 (1.11-1.38) associated with a 10% increase in FI in men, and 1.21 (95% CI 1.18-1.25), 1.27 (95% CI 1.15-1.34), and 1.26 (95% CI 1.15-1.39) in women. In terms of the frailty instruments to predict mortality, a systematic review indicated that FI might be superior to FP in predicting all-cause mortality [46]. Several studies [48-50] have shown that higher HRs were seen in middle-aged individuals than in older individuals. Williams *et al* [48] showed that the FI-mortality associations were stronger in younger participants than in older participants. Similarly, Li *et al* [49] showed relatively greater HRs at younger ages compared to

old, and the effect sizes decreased with age for all the causes of death. Fan *et al* [51] also showed that the associations were stronger among younger adults than among older adults with HRs per 0.1 increment of the FI of 1.95 (95% CI 1.87-2.03) for those younger than 50 years, 1.80 (1.76-1.83) for those aged 50-64 years, and 1.56 (1.53-1.59) for those aged 65 years and older.

Since frailty is a strong predictor of mortality, understanding the progression of frailty in later life or prior to death using longitudinal studies provides ways of identifying and intervening those at the highest risk of health decline. Ward *et al* [52] found nine distinct trajectories including stable, progressing and recovering frailty trajectories in the 5 years prior to death. Similar to the level of frailty, the heterogeneity of frailty trajectories over 12 years in individuals aged 70 years at baseline has been reported [53]. Although individuals with a distinct frailty trajectory with a rapid initial rise from a low baseline in the last 12 months of life were found at the highest risk of death [54], evidence from other longer-term longitudinal studies is still lacking to support such a result. However, whether the age at death is associated with distinct frailty trajectories remains unknown.

2.6 Frailty and dementia

Frailty and dementia are among the main geriatric topics that need attention in research and clinical settings due to their high prevalence, influence on the individual's quality of life and health care systems. Frailty and dementia are closely linked, but the mechanisms remain unclear. The relationship between frailty and dementia is complex. One study suggested that a potential mechanism could be that worsening frailty accompanies with reduced cognition [39]. This study also showed that neuropathologies influenced the rate of frailty and cognitive status, simultaneously [39]. Wallace *et.al* [55] confirmed that the presence of frailty aggravated the development from a low level of Alzheimer's disease (AD) pathology to dementia. On the other hand, evidence also suggests that older adults are at a higher risk of cognitive decline, which, in turn, increases the possibility of being frail [56]. This indicated that the co-occurrence of frailty and declined cognition are risk factors for incident dementia and that each condition exerts an effect on the other [57]. Several studies [58-61] have also shown that the components of FP (slow gait speed or grip strength or muscle strength) were related with specific cognitive domains (motor skills, memory, verbal skills, spatial skills, and processing speed), suggesting that prevention or mitigation of dementia might be possible by intervening the aforementioned FP components.

Dementia is a neurodegenerative disease, which significantly affects the ADL through impairing cognition and behavior [62]. Since frailty shares most common risk factors with dementia, studies [56, 63] have investigated the potential biological and pathological mechanisms underlying the association between frailty and dementia. Wallace *et al* [55] confirmed a strong link of frailty with AD and other dementia, and also suggested that frailty may be a moderator between Alzheimer's pathology and dementia. A life course model of dementia development [64] illustrated that genetic and environmental factors simultaneously interact and trigger pathological changes, which ultimately results in the development and onset of dementia. A study [63] has shown that frailty, assessed by FP and FI, is predictive of dementia probably due to dysfunction in biological processes related to aging. Since frailty is a reversible syndrome

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but dementia is not, reducing the burden of dementia-related morbidity might be possible by mitigating frailty.

Environmental and genetic factors influence both frailty and dementia. It has been reported that less education, chronic diseases, depression, low social contacts, hearing impairment, physical activity, smoking and alcohol drinking are risk factors of dementia [65]. Frailty and dementia share similar and common risk factors, such as lifestyle factors, sociodemographic factors and morbidities. AD, the most common form of dementia, is also highly heritable [66], with the *APOE* ε4 allele being the strongest genetic risk factor [67]. Ward *et al* [68] found that frailty was not only associated with dementia independent of genetic risk, but also moderated the expression of the genetic risk on dementia. In order to better explore genetic and environmental factors behind the association between frailty and dementia, twin or sibling comparison method becomes a good way to assess how shared familial factors influence frailty [69]. Siblings and twins are both automatically matched on cultural background, parental characteristics and child-rearing practices but share different proportions of their segregating genes (100% for monozygotic [MZ] twins and 50% for dizygotic [DZ] twins). Therefore, twin or sibling design is a way to control for both shared environmental and genetic factors to elucidate the association of frailty with dementia and also compare the differences between MZ and DZ twins to assess whether and to what degree genetic and shared environmental factors explain the associations between frailty and outcomes, such as dementia [70].

2.7 Frailty in younger adults

Studies on the predictive value of frailty on adverse outcomes have been performed most frequently in old adults above 65 years and less is known about younger adults and frailty. It has been shown that antecedents of frailty appear before old age, but whether frailty confers the same risk in younger adults as in older adults, and to what extent the risk varies with age remains unclear [71, 72]. The prevalence of frailty in adults younger than 65 has been reported to be lower than the prevalence in those older than 65. The prevalence rates of frailty in the 18-34 and 35-49 age groups have been reported to be 1.8% and 3.4%, respectively in the Canadian Health Measures Survey study [73]. Meanwhile, a large cohort study from China [51] showed that the prevalences of frailty were 0.8% in those aged <50 years and 3.5% in those aged 50–64 years using FI≥0.25 as the cut-off for frailty. This study also illustrated that the association between frailty and mortality was stronger among younger adults than among older adults [51], which corresponded to the conclusion of the UK Biobank study [48] that the risk of mortality in relation to frailty was highest for younger people. Moreover, Li *et al* [49] demonstrated that attenuation of the FI-mortality association was found in older adults compared to younger adults. Ferrucci *et al* [74] suggested that this phenomenon might be biased by the 'healthy survivor' effect in the older age groups. More cohort studies are needed to evaluate this phenomenon and explore the characteristics and possible reasons of the early onset of frailty.

Risk factors of frailty in sociodemographic, clinical, lifestyle, and biological domains have been extensively assessed in older adults with relatively consistent findings across studies. Among the most robust findings are those on increasing age, female sex, and socioeconomic

deprivation that have been shown to increase the risk of late-life frailty [75]. Early life exposures, such as childhood stress, have also been regarded as risk factors for late-life frailty [75-77]. Risk factors for early-life frailty are however unstudied. Understanding on this matter is urgently needed to be able to tackle frailty early on.

2.8   Frailty and polypharmacy

Polypharmacy is generally defined as the concurrent use of five or more medications, although there is no consensus regarding the number of medications [78, 79]. People reaching old age commonly encounter chronic diseases, such as hypertension and diabetes. Hence, the number of prescribed medications increases naturally with the accumulation of diseases with age, and the prescribed medication is rarely discontinued unless the disease is cured [78]. However, polypharmacy, especially the inappropriate number of prescribed drugs in older adults, presents a substantial burden of adverse drug events, ill health, disability, hospitalization, and even death [80]. Hence, polypharmacy may lead to increased vulnerability in multimorbid old adults, and frailty status of the patients might play a role in this association [81]. A study [82] showed that frail older adults are more vulnerable to the influence of fall-risk-increasing drugs than the robust ones. Bonaga *et al* [79] reported that polypharmacy was associated with mortality, incident disability, hospitalization, and emergency department visits in frail and pre-frail older adults, but not in non-frail adults.

In terms of whether patients with frailty take more prescribed medications, both cross-sectional and longitudinal studies have shown that the number of medications is higher in older individuals with frailty [83, 84] and patients with frailty are more inclined to take seven or more drugs [84, 85]. On the other hand, several studies have also suggested that patients with polypharmacy develop high levels of frailty [86, 87]. Moreover, the evidence suggests that polypharmacy is significantly associated with frailty, independent of comorbidities, which implies that polypharmacy is a risk factor of frailty [78]. Despite the existing evidence, it is still difficult to address the causality of the relationship between polypharmacy and frailty. More studies are needed to better understand the complex interplay.

3 AIMS

The overarching aim of the thesis is to assess frailty trajectories stratified by age at death and polypharmacy and also assess the association of frailty with mortality, dementia, and polypharmacy. More specifically, the aim of each study is as follows.

Study I aimed to explore the frailty trajectories by age at death, compare the predictive ability of frailty and the change in frailty on mortality and test whether the associations vary with age.

Study II aimed to analyze the association between frailty and the risk of dementia in a large twin cohort and test whether familial factors influence the association.

Study III aimed to compare the prevalence, characteristics, and risk factors of frailty for early-life and late-life frailty, as well as looking at FI domain distribution differences between early-life and late-life frailty.

Study IV aimed to assess frailty trajectories by polypharmacy and analyze the longitudinal association between frailty and polypharmacy.

4   MATERIALS AND METHODS

4.1   Data sources

All data analyzed in this thesis came from two large-scale population resources, the Swedish Twin Registry (STR) and UK Biobank. The STR was established in the 1950s, being one of the largest twin resources in the world [70]. In the latest updates till 2019 [88], 216,258 twins born between 1886-2015 have been enrolled in the STR. The STR collects genetic information, molecular biomarkers, lifestyle behaviors, and disease diagnoses through in-person testing (IPT), questionnaires (Qs), and linkages to the national and quality registers [89]. Due to abundant data and broad interest, the STR comprises several substudies of aging, of which SATSA, GENDER, and OCTO-Twin were used in this study.

4.1.1   SATSA

The Swedish Adoption/Twin Study of Aging (SATSA) is a longitudinal cohort aimed at understanding individual differences in aging, consisting of data from mailed 10 questionnaires and nine IPTs [90, 91]. The first Q was sent out in 1984, after which the Qs were sent again at three-year intervals in 1987, 1990, and 1993, and after a break in 2004, 2007, 2010, 2012, and 2014. The Qs include information on rearing, socioeconomic environment, health status, and health-related behaviors (e.g., alcohol, tobacco, and dietary habits). The first IPT (IPT1) started in 1986-1988, and the follow up IPTs were conducted in 1989-1991 (IPT2), 1992-1994 (IPT3), 1995-1997 (IPT4), 1999-2001 (IPT5), 2002-2004 (IPT6), 2005-2007 (IPT7), 2008- 2010 (IPT8), 2010-2012 (IPT9), and 2012-2014 (IPT10). The IPTs include a health assessment, structured interviews, tests of functional capacity, and memory and cognitive abilities. In **Study 1**, all waves except Q1, IPT1, IPT4, and Q6 were included (Q2 was regarded as the baseline wave), with 1,637 individuals aged between 29 and 96. In **Study 4**, only IPT 2, 3, and 5-10 with available FI and drug data across 26 years were included, with 709 individuals aged between 44.9 and 91 years at baseline (Figure 4.1.5).

4.1.2   GENDER

A Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly (GENDER) is a population-based cohort to study sex differences in health and aging. GENDER recruited opposite-sex twin pairs born between 1906 and 1925 [92]. The first Q (Q1) was sent in 1994 and 1,843 opposite-sex twins (605 complete pairs) born 1906-1925 responded. After that, 498 twins (249 pairs) participated in three IPTs at a four-year intervals (1995-1997, 1999-2001, and 2003-2005) have been collected. The second questionnaire (Q2) was sent out in 2007. The **Study 1** included all five waves with 1,210 individuals aged between 68 and 88 years at baseline. The **Study 4** only included three IPTs with available FI items and drug data, with 495 individuals aged between 68 and 79 at baseline (Figure 4.1.5).

4.1.3   OCTO-Twin

The Origin of Variances in the Oldest-Old: Octogenarian Twins (OCTO-Twin) was designed similarly to the SATSA study but aimed at studying the etiology of individual differences for twins aged ≥80 [93]. Among 549 twin pairs, 351 participated in the first IPT that included cognitive tests, health measurements, and tests of physical function and well-being between

1991 and 1994. The OCTO-Twin included five IPTs, with the four subsequent IPT waves conducted every two years from the first wave. All five IPTs were included in **Studies 1 and 4** (Figure 4.1.5).

4.1.4 SALT

The Screening Across the Life Span Twin study (SALT) was designed for all STR twins born in 1958 and earlier (aged between 41 and 97 years), and used a computer-assisted telephone interview to assess diseases, symptoms, lifestyle factors, and medication use [70, 89, 94, 95]. In **Study 2**, a total of 44,919 twin individuals participated in the comprehensive health screening between 1998 and 2002, and those aged ≥65 further received a cognitive assessment. Data on dementia diagnoses was linked to National Patient Register (NPR), the Cause of Death Register (CDR), and the Prescribed Drug Register (PDR) using personal identification numbers. After excluding individuals with an onset of dementia before baseline or who had severe cognitive impairment at baseline, 41,550 SALT participants ('full sample') were included in the study 2 analysis. Further, 10,487 twin individuals aged 65 and older from the full sample with cognitive assessments available were included to a 'cognitive sample' to assess whether baseline cognitive level affects the associations. From the full and cognitive samples, 11,502 and 3,156 participants with available *APOE* genotype data status were extracted, denoted as genotyped samples I and II, respectively. Among 41,550 and 10,487 twin participants, 11,031 DZ twin pairs and 4,055 MZ twin pairs in the full sample, and 2,176 DZ twin pairs and 766 MZ twin pairs in the cognitive sample were extracted for a within-pair analysis. In **Study 3**, 43,641 SALT twin individuals with available FI (created based on 44 FI items) were included (Figure 4.1.5).

4.1.5 UK Biobank

The UK Biobank is a large multicenter cohort study. The UK Biobank recruited participants from 22 assessment sites in England, Scotland, and Wales in 2006-2010. A total of 502,640 participants aged 37–73 undertook in-person interviews and a self-completed touch-screen questionnaire that collected physical measurements, demographics, socioeconomics, lifestyle, environmental exposures, health factors, and medical history [96, 97]. In **Study 3**, 405,123 UK Biobank individuals with complete data on the 49 FI items were included (Figure 4.1.5).

An overview of the timelines for each cohort is presented in Figure 4.1.5.
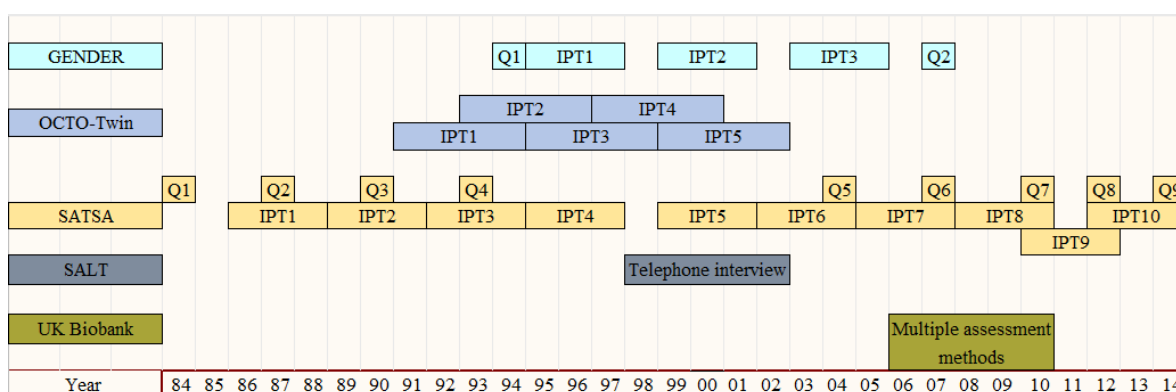
Abbreviations: IPT, in-person testing; Q, questionnaire.

Figure 4.1.5 Timelines of each cohort.

4.2 Measurements

4.2.1 Frailty

The FI was created to operationalize frailty based on the Rockwood accumulation of deficits model in all four studies [18, 98]. More than 40 health deficits, including function, diseases, co-morbidity, mental health, general health status, and physical performance measures were chosen as the FI items. Due to multiple domains considered in the FI, FI is a sensitive measure to catch minor changes of frailty also at the lower and middle ends of the frailty continuum. Therefore, FI is suitable for adverse outcome prediction and a good tool to track changes in frailty also in younger individuals.

The FIs were constructed based on self-reported data on symptoms, signs, disabilities, and diseases covering a wide range of biological systems. In all the samples, the deficits included in the FI had to have a prevalence of at least 1% in the cohort and at most 10% missingness across the participants. For maximum utility of the data, imputation was used to replace missing values in those participants who had ≤20% missing data across the FI items. Participants having >20% missing data across the FI items were excluded. The multiple imputation based on chained equations, logistic regression for binary variables and predictive mean matching for categorical and continuous variables, was used to replace missing values. When a certain frailty item was imputed, the other FI items, age, sex, BMI, smoking status and mortality data were used as predictors in the imputation model. Ten rounds of imputations were performed and the pooled mean from the simulations was used as the final value. The FI value for each individual was calculated as the number of deficits present divided by the total number of deficits considered. Each item was recoded between 0 and 1, 0 denoting absence of a given deficit and 1 presence of a deficit. An FI value is calculated as the sum of the deficits present in an individual divided by the total number of deficits considered, with the final FI value ranging between 0 and 1. For example, an individual having 7 deficits of 43 has an FI of $7/43 = 0.16$. A similar procedure has been previously applied and described for the construction of the FIs in all datasets of the thesis. Finally, the SATSA, GENDER FIs consisted of 42 items, the OCTO-Twin of 41 items, the SALT of 44 items, the UK Biobank of 49 items (Table 4.2.1.1). In **Studies 1 and 4**, the level of FI was multiplied by 10 and 100, respectively to facilitate interpretation, so that the HRs and the coefficients associated with the FI level represent increments of 10% and 1% in the FI. In **Study 3**, to assess the differences in the characteristics of frailty, the items used to construct FI were assigned into 11 and 12 domains in the UK Biobank and SALT, respectively (Table 4.2.1.2). Each FI domain score was then calculated. For example, glaucoma, cataracts, and hearing difficulty were included in the sensory domain, and the sensory domain score of an individual with glaucoma, hearing difficulty but no cataracts is (1+1+0)/3=0.67.

The list of items used to create the frailty indexes for each cohort is presented in Table 4.2.1.1.

The list of FI domains in the UK Biobank and SALT is presented in Table 4.2.1.2

Table 4.2.1.1 Items used to calculate the Rockwood frailty index in each cohort.

Item	SATSA	GENDER	OCTO-Twin	SALT	UK Biobank
Health limits activities	X	X	X	X	
Self-reported general health	X	X	X	X	X
Cancer or leukemia	X	X		X	X
Rheumatoid arthritis	X	X	X	X	X
Arthritis	X		X	X	
Chronic bronchitis or emphysema	X		X	X	X
Cataracts	X	X	X		X
Chest pain	X	X	X		X
Circulation problems in arms or legs	X	X	X	X	
Persistent cough	X			X	
Diabetes	X	X	X	X	X
Goiter or other gland problems	X	X	X	X	
Heart failure	X	X	X	X	
Hypertension	X	X	X	X	X
Kidney disease	X	X	X	X	
Osteoporosis	X	X	X	X	X
Sciatica	X	X	X	X	X
Anemia	X		X		
Cerebral hemorrhage or blood clot in brain	X		X	X	
Dizziness	X		X	X	
Gastric ulcer	X	X	X	X	X
Allergies/allergic manifestations	X		X	X	
Asthma	X		X	X	X
Shower and bathe	X	X	X		
Get in and out of bed	X	X			
Dress and undress	X	X			
Self-grooming	X				
Walking	X	X	X		

Trouble getting to toilet in time	X	X	X		
Travel further distances	X	X			
Housework	X	X			
Prepare meals	X				
Manage medications	X	X			
Manage money	X				
Use telephone	X	X			
Grocery shopping	X	X			
Buzzing in ears				X	
Hearing acuity	X		X	X	X
Vision acuity	X		X	X	
Loneliness	X	X	X	X	X
Depressions	X	X		X	X
Feel happy	X			X	
Feel tired	X				X
Keep body fit			X		
Heart attack		X	X	X	
Vascular spasm in leg		X	X	X	
Herpes			X		
Migraine		X	X	X	X
Glaucoma		X	X		X
Speech impairment		X	X		
Eczema		X	X		X
Hip joint impairment		X	X	X	X
Neck pain			X	X	X
Shoulder pain			X		
Gall bladder		X	X	X	X
Insomnia		X	X		X
Psychological problems			X		
Stroke		X		X	X
Epilepsy		X			
Liver disease		X		X	

Gout		X		X	X
Picking something up from the floor		X			
Handle small things with your fingers		X			
Dental problems					X
Self-described nervous personality					X
Severe anxiety/panic attacks					X
Sense of misery					X
Long-standing illness or disability				X	X
Falls in last year					X
Fractures in last five years					X
Myocardial infarction					X
Angina				X	X
Hypothyroidism					X
Deep-vein thrombosis				X	X
High cholesterol				X	X
Breathing: wheeze in last year					X
Pneumonia					X
Osteoarthritis					X
Psoriasis					X
Multiple cancers diagnosed					X
Back pain				X	X
Stomach/abdominal pain				X	X
Irregular cardiac rhythm				X	
Knee pain					X
Whole-body pain					X
Facial pain					X
Hiatus hernia					X
Diverticulitis					X
Total number of items	42	42	41	44	49

Table 4.2.1.2 FI domains in the UK Biobank and SALT.

UK Biobank FI items	UK Biobank FI domains	SALT FI items	SALT FI domains
Glaucoma	Sensory	Buzzing in ears	Sensory
Cataracts		Vision status	
Hearing difficulty		Hearing status	
Migraine	Cranial	Dizziness	Cranial
Dental problems		Migraine	
Poor or fair self-rated health	Mental wellbeing	Poor or fair self-rated health	Mental wellbeing
Fatigue		Health prevent activities	
Sleeplessness/insomnia		Feeling depressed	
Depressed feelings		Feeling happy	
Nervous personality		Feeling lonely	
Severe anxiety		Intermittent claudication	
Loneliness		Mobility disability	Infirmity
Sense of misery		Angina pectoris	
Infirmity	Infirmity	Heart attack	Cardiometabolic
Falls in last year		Heart failure	
Fractures		High blood pressure	
Diabetes	Cardiometabolic	Dyslipidemia	
Myocardial infarction		Stroke	
Angina pectoris		Transient ischemic attack	
Stroke		Irregular heart rhythm	
High blood pressure		Venous thrombosis	

Hypothyroidism		Diabetes	
Deep-vein thrombosis		Asthma	Respiratory
High cholesterol		Chronic bronchitis	
Wheezing in last year	Respiratory	Recurrent cough	
Pneumonia		Rheumatoid arthritis	Musculoskeletal
Chronic Bronchitis		Knee joint problem	
Asthma		Osteoporosis	
Rheumatoid arthritis	Musculoskeletal	Hip joint problem	
Osteoarthritis		Gout	
Gout		Number of infections (/year)	Immunological
Osteoporosis		Allergic manifestations	
Allergies	Immunological	Inflammatory bowel disease	
Psoriasis		Cancer	Cancer
Multiple cancers diagnosed	Cancer		
Any cancer diagnosed		Sciatica	Pain
Chest pain	Pain	Back pain	
Head and/or neck pain		Neck pain	
Back pain		Gall bladder trouble	Gastrointestinal
Stomach pain		Abdominal problems	
Hip pain		Goiter	Other
Knee pain		Glandular disease	
Whole-body pain		Liver disease	
Facial pain		Kidney disease	

Sciatica		Recurring urinary tract infection	
Gastric reflux	Gastrointestinal		
Hiatus hernia			
Gall stones			
Diverticulitis			

4.2.2 Health outcomes

All-cause mortality

In **Studies 1 and 2**, the dates of death for all-cause mortality were derived from the Swedish National Death Registry on 15 June 2019 and 31 December 2016, respectively.

Dementia ascertainment

Incident dementia diagnoses were linked with national register data during the follow-up time. Registers used in this study were the NPR, the CDR, and the PDR [99]. Both the NPR (with nationwide coverage since 1987) and the CDR (with national coverage since 1961) contain disease information based on the International Classification of Diseases (ICD) system. The PDR includes dispensed dementia medication according to Anatomical Therapeutic Chemical (ATC) codes (regarded as a proxy for dementia diagnosis) [99]. ATC codes for anti-dementia drugs in the N06D group were considered. For all STR studies of aging, including SALT for participants aged 65 or older (the cognitive sample), dementia diagnoses were set at multidisciplinary consensus conferences based on Diagnostic and Statistical Manual of Mental Disorders-third version (DSM-III-R) and the fifth version (DSM-IV) criteria [100]. The primary dementia diagnosis or death was followed up from baseline until 31 December 2016, yielding up to 19 years of follow-up.

Polypharmacy

Medication use was collected through self-reported questionnaires in each wave and recoded to the ATC code. The classification of individual drugs was conducted according to the 3rd ATC level, and the number of drugs at each observation was counted. Polypharmacy was defined as using five or more drugs in the same individual. In longitudinal analysis, an individual belonged to the polypharmacy group if using five or more drugs at all occasions. Similarly, an individual belonged to the non-polypharmacy group if taking four or fewer drugs at all occasions. If neither, the individual belonged to the transient group.

4.2.3 Covariates

Socio-demographic and health-related variables

Age, sex, smoking status, and BMI were common covariates in four studies. Smoking status was assessed as a three-category variable (non-smoker=1, ex-smoker=2, and current-smoker=3) in **Studies 1, 3, and 4**, whereas it was classified as a binary variable (non-user or user) in **Study 2**. BMI was assessed as self-reported weight in kilograms divided by height in meters squared and used as a continuous variable in **Studies 1, 2, and 4**, whereas it was categorized into normal weight (≥18.5-25; reference category), underweight (≤18.5), overweight (≥25-30), and obese (≥30) in **Study 3**. Years of education were assessed in **Study 2**. Educational attainment was classified into low, intermediate, and high education levels in **Study 3**, whereas it was classified into primary education, lower secondary or vocational education, upper secondary education, and tertiary education in **Study 4**. Other covariates, such as living alone in **Study 2** was a binary variable with "not living alone" as the reference category. Physical activity in **Study 2** was assessed based on two questions: 1) "Of these seven alternatives, which fits your annual exercise pattern?" assessed for those who were born after 1926 (N=37,218). The alternatives were ranging from 0-6, corresponding with "almost never exercise", "much less exercise than average", "less exercise than average", "average amount of exercise", "more exercise than average", "much more exercise than average", and "maximum amount of exercise", respectively. 2) "How much do you exercise?" assessed for those who were born before 1926 (N=4,046). The alternatives were ranging from 0 to 3, corresponding with "almost no exercise, 1 (light exercise), 2 (regular median exercise), and 3 (hard physical exercise). These two covariates were calculated into z scores (each unit representing one standard deviation from the mean) and merged into the physical activity for the analysis. Alcohol consumption frequency in **Study 3** was categorized as less than weekly if the individual never drank or drank on special occasions only or one or three times a week, and weekly if the individual drank more than once a week. Also, in **Study 3** for UK Biobank individuals, annual household income was self-reported and categorized into <£18 000, £18 000–30 999, £31 000–51 999 and ≥£52 000 and regarded as a continuous variable [101]. Maternal smoking in **Study 3** was included as the early life factor of frailty (coded as 0=No and 1=Yes) for UK Biobank. The occupation in **Study 3** was only available in SALT and categorized into low (unskilled manual employees; reference category), medium (skilled manual workers, lower non-manual employees, farmers, self-employed [not including professionals], intermediate non-manuals), and high level (higher non-manuals [including professionals]) [102, 103].

Genetic variable

In **Study 2**, the *APOE* ε4 carrier status was adjusted to test its influence on the association between frailty and dementia in the genotyped sample I (N=11,502) and genotyped sample II (N=3,156). The individuals were classified into non-carriers (carrying the genotypes ε2/ε2, ε2/ε3, or ε3/ε3), heterozygous (carrying the genotypes ε2/ε4 or ε3/ε4), and homozygous (the genotype ε4/ε4). The *APOE* ε4 genotypes were either directly genotyped or determined from Illumina OmniExpress imputed to 1000 Genomes Project using a pipeline with a high accuracy [104, 105].

Cognitive impairment screening

In **Study 2**, those aged 65 and older in SALT received baseline cognitive assessment through a cognitive screening instrument (TELE). The TELE score is assessed by a 10-item mental status questionnaire, three-word recall, a word similarities task, and questions about health and daily functioning [100]. The range of the TELE score is from 0 to 19. Those who scored less than 13.5 points were informed to take the Blessed Dementia Rating Scale interview to assess the individual's cognitive levels interfered with daily functioning. The cognitive status of each individual was classified into 0-4 to represent cognitively intact, minor errors, performed poorly, and cognitive dysfunction, respectively.

Charlson Comorbidity index

The Charlson Comorbidity index (CCI) is defined as a disease index to predict short-term mortality and an index presenting comorbidity burden [106]. The CCI was created based on ICD 7, 8, 9, and 10 using longitudinal data across 25 years [106]. The ICD codes for the diagnoses of both inpatient and outpatient were extracted from the NPR. The CCI was used as a continuous covariate variable to adjust for the effect of comorbidity in **Study 4**.

4.3 Statistical analysis

4.3.1 Descriptive analysis and identifying a cut-off age for early-life and late-life frailty

Descriptive analyses of the cohort characteristics were conducted in each study. In **Study 1**, to assess whether age at death was associated with distinct frailty trajectories, we estimated the frailty trajectories by four age-at-death groups (<70, 70–80, 80–90, and >90 years). In **Study 3**, domain scores were assessed by dividing the number of deficits one individual had in a given domain by the total number of deficits considered in this domain. To analyze differences in the FI domain scores between younger and older frail adults (frailty demarcated by FI$\geq$0.21), the means of the FI domains scores were compared using linear regression. In SALT, the non-independence of twin pairs was accounted for by using robust standard errors. In the analyses, we used the Benjamini-Hochberg false discovery rate method to adjust for multiple testing [107]. The age cut-off for stratifying the participants into the younger and older adults was identified based on the highest significant estimate of the principal component score with age groups. Six principal component scores were firstly generated from the 49 FI items in the UK Biobank using principal component analysis and their linear associations with baseline age were assessed. The principal component score with the highest significant estimate was then introduced to another linear model with age groups stratified by 40, 45, 50, 55, 60, 65, 70 years as the explanatory variables. The age cut-off was determined in the age group with the highest significant estimate.

In **Study 4**, to assess whether long-term polypharmacy associates with frailty trajectories, we estimated the FI trajectories by long-term-, transient-, and non-polypharmacy groups. Several

models, including the generalized survival model, Cox regression model, logistic regression model, and linear mixed model, were applied in the thesis. A two-sided P-value < 0.05 was considered statistically significant in all the studies. Both estimates and 95% CIs were reported. All analyses were performed using Stata 14 and R 4.1.2.

4.3.2 Generalized survival model

In **Study 1**, we used the generalized survival model to estimate the association of the FI level and the rate of FI change with mortality during the follow-up. One of the aims in this study was to assess the predictive values of FI and the rate of change in FI on mortality using longitudinal data. Firstly, we assessed the effect of the FI adjusted by sex alone and then further adjusted by age interaction, BMI, and smoking. Then, the association of the rate of change in FI on mortality was assessed first adjusting by sex alone and then further adjusting by the current FI level to compare the predictive abilities of the current FI and the rate of FI change. The model estimating the FI and the rate of FI change was also adjusted by age interaction, BMI, and smoking. To verify whether the effects of the current (most recent) FI level and FI change on mortality vary across age at measurement or time since measurement, we also added an interaction between age (centered at 74 years based on cohort mean at baseline) and these two variables. We used the *rstpm2* package in R to assess these estimates [108].

4.3.3 Cox regression model

In **Study 2**, we applied Cox regression models with time since the FI measurement as the time scale to assess the population-based effect of baseline FI with dementia risk. In consideration of the potential impacts of baseline cognitive status and *APOE ε4* carrier status on dementia, those aged ≥65 with baseline cognitive assessment (cognitive sample) and with *APOE* genotype data (genotyped sample) were included. The FI effects were also estimated in the model after being further adjusted by the baseline cognitive status or *APOE ε4* carrier status. The proportional hazard assumption was tested using an interaction term between the covariates and time in the model, and no violations of proportionality were detected. Robust standard errors were introduced to adjust for the clustering of twins within a pair. Models were also adjusted by age at FI assessment, sex, BMI, tobacco use, and years of education.

The between-within (BW) model was applied in the framework of the Cox regression model, by decomposing the effects into the between and within pair effect for each variable in the model. The BW model was conducted in DZ and MZ twins and the within-pair effect of each variable was reported. As DZ and MZ twin pairs share 50% and 100% of their segregating genes, respectively, dissimilar associations between frailty and dementia within twin pairs may indicate the involvement of genetic and/or shared environmental factors in the association [69]. Also, if the within-pair effect of FI in the within-pair analysis in DZ and MZ twins remains similar to the corresponding population-based effect, it would suggest no influences from genetic and shared environmental factors in the FI-dementia association.

Moreover, if a similar attenuation of the effect relative to the population-level estimate is seen in both DZ and MZ twin pairs, shared environmental factors, including but not limited to early life exposures and lifestyle-related factors are likely underlying the association. Lastly, the attenuation of the effect in MZ twins relative to DZ twins would imply genetic factors influencing the frailty-dementia association as genetic influences are fully adjusted for in the within-MZ pair analysis. The age-varying effects of the FI were assessed by adding interaction terms between FI and zygosity and FI and age at FI measurement, a statistical interaction between FI and age was modeled based on as a natural cubic spline function (the standard interaction model). Based on the standard interaction model, the age-varying within-pair effects were assessed after further controlling for familial factors.

To further explore the genetic effects in the association between frailty and dementia, the difference in the estimates of the MZ and DZ twin pairs across the age range in the within-pair interaction model was assessed by deriving the ratio of the HR between DZ and MZ (HRDZ/HRMZ) as a function of age. To remove the impact of risk factors of dementia in constructing the FI items in this study, a sensitivity analysis was performed by dividing the FI into those items that are traditional risk factors for dementia (FI-TRF) and those that are not (FI-NTRF) and analyzing them separately using Cox regression.

4.3.4 Logistic regression model

In **Study 3**, age 65 was identified as the most appropriate age cut-off to stratify the sample into younger and older individuals (the analysis described in paragraph 4.3.1). We then performed multivariable logistic regression models separately in younger (<65) and older (≥65) individuals to estimate the risk factors of early-life and late-life frailty. All potential variables including sex, age, tobacco use, alcohol consumption, education, BMI, occupation, income, and maternal smoking in SALT and UK Biobank were included to the model. FI level ≥0.21 was used to indicate frailty and considered as a dichotomous outcome variable in the models. Robust standard errors were also introduced to account for the non-independence of the twin pairs in SALT.

4.3.5 Linear mixed model

In **Study 4**, we conducted linear mixed models to assess the longitudinal association between polypharmacy and frailty. The crude model (model 1) included fixed effects of age, sex, study and random intercepts and slopes between individuals nested in twin pairs. The second model (model 2) added the fixed effects of smoking status and BMI based on model 1. To verify whether the risk of frailty by polypharmacy is age-varying, we added a fixed effect of an interaction term between age (centered at 74 years based on cohort mean at baseline) and polypharmacy based on model 2 (model 3).

5 RESULTS

5.1 STUDY 1

5.1.1 Population characteristics

Among 2,677 individuals aged 29-98 from three cohorts at baseline, 1,560 (58.3%) were women (Table 5.1.1). The median levels of FI were 0.08, 0.07, and 0.10 in the full, male and female samples, respectively. The level of FI change was 0.003/year. During the follow-ups, of the 2,677 individuals, 83 (4%), 284 (13.6%), 946 (45.2%), and 781 (37.3%) died aged <70, 70-80, 80-90, and ≥90, respectively (Table 5.1.1).

Table 5.1.1. Sample characteristics at baseline (i.e., when 2,677 individuals were analyzed in models).

	GENDER	OCTO-Twin	SATSA	Full sample
N waves	5	5	15	15
N individuals	611	525	1,541	2,677
Female (%)	310 (50.7)	344 (65.5)	906 (58.8)	1,560 (58.3)
Age range	68-83	79-98	29-89	29-98
Age (SD)	72.9 (2.8)	83.2 (2.9)	60.1 (13.1)	67.6 (13.7)
Age male (SD)	72.7 (2.7)	82.7 (2.5)	59.3 (12.4)	66.7 (13.1)
Age female (SD)	73.1 (2.9)	83.5 (3.0)	60.7 (13.5)	68.2 (14.1)
FI, median (min, max)	0.06 (0, 0.52)	0.20 (0, 0.57)	0.07 (0, 0.57)	0.08 (0, 0.57)
FI, median male (min, max)	0.06 (0, 0.52)	0.17 (0.02, 0.56)	0.07 (0, 0.54)	0.07 (0, 0.56)
FI, median female (min, max)	0.06 (0, 0.46)	0.22 (0, 0.57)	0.08 (0, 0.57)	0.10 (0, 0.57)
FI change, median (min, max)	0.01 (-0.14, 0.19)	0.00 (-0.16, 0.10)	0.00 (-0.06, 0.10)	0.003 (-0.16, 0.19)
BMI (SD)	25.2 (3.2)	24.7 (3.7)	24.9 (3.6)	24.9 (3.6)
Smoking status				
Non-smoker (%)	374 (61.6)	350 (67.0)	1,078 (70.7)	1,802 (67.9)
Ex-smoker (%)	178 (29.3)	128 (24.5)	84 (5.5)	390 (14.7)
Current smoker (%)	55 (9.1)	44 (8.4)	363 (23.8)	462 (17.4)
N deaths (%)	557 (91.2)	525 (100)	1,012 (65.7)	2,094 (78.2)
By age at death				
<70 years (%)	0	0	83 (8.1)	83 (4.0)
70-80 years (%)	65 (11.7)	0	219 (21.4)	284 (13.6)
80-90 years (%)	265 (47.6)	229 (43.6)	452 (44.3)	946 (45.2)
>90 years (%)	227 (40.8)	296 (56.4)	258 (25.3)	781 (37.3)
*Time to follow-up, median (min, max)	16.4 (1.9, 24.6)	7.5 (1.9, 23.4)	22.9 (1.9,31.6)	17.0 (1.9,31.6)

*Time to mortality follow-up in years since the last FI assessment. Abbreviations: BMI, body mass index; FI, frailty index; SD, standard deviation. The table is reproduced from Bai et al. Age ageing 2021 [109].

5.1.2 Frailty trajectories by age at death

Among 3,689 individuals with up to 25-year follow-up, we plotted FI trajectory lines stratified by four age-at-death groups (Figure 5.1.2). A steadily increasing trajectory throughout the ~40 years before death was found in those who died <70 years old. However, those who died at ages 80-90 and >90 only accrued deficits after 65 or 75 years old, respectively. Furthermore, a difference was seen across the four age-at-death groups, with distinct FI trajectories in individuals who died before vs. after 80 years old.
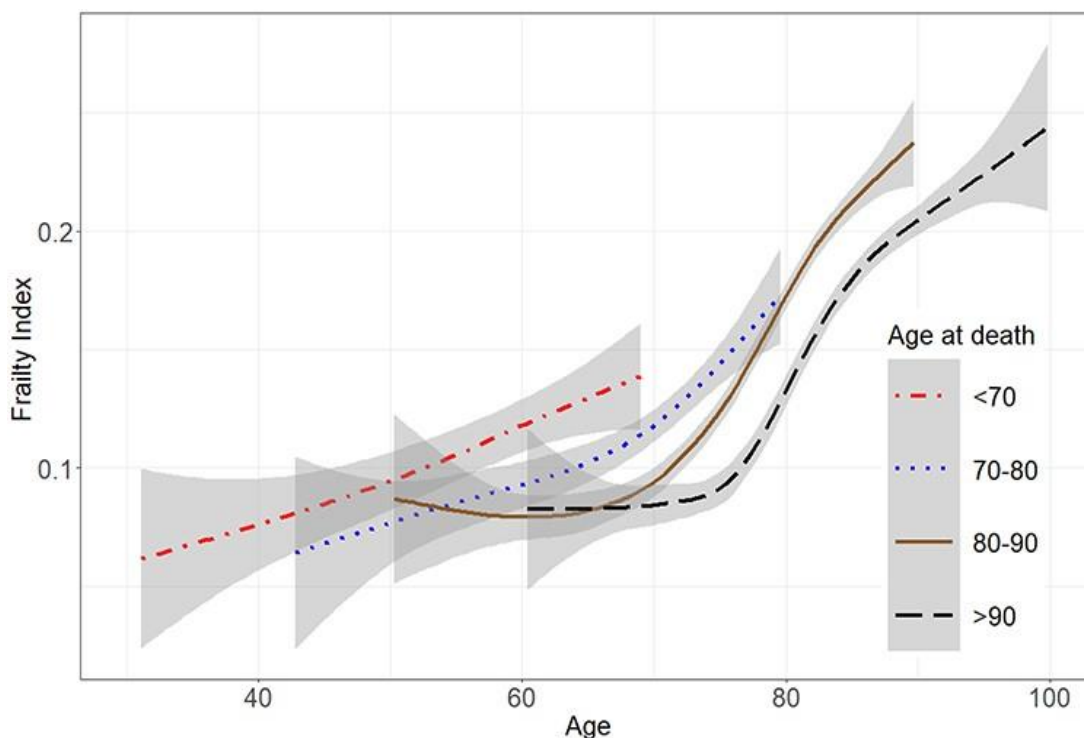

Figure 5.1.2. Frailty trajectories by age at death in 3,689 individuals. Middle parts of the trajectories suggest significant differences in frailty trajectories. The grey-shaded areas represent 95% confidence intervals. The figure is reproduced from Bai et al. Age ageing 2021 [109].

5.1.3 Associations of the FI and FI change with mortality

Higher FI was associated with all-cause mortality when adjusted only for sex (Model 1, Table 5.1.3A). This association remained after being further adjusted by age interaction, BMI, and smoking (Model 3, Table 5.1.3A). In addition, a higher rate of FI change was associated with the risk of mortality after the adjustment of sex, age interaction, smoking, and BMI (Model 2, Table 5.1.3B). The effect of FI change attenuated to null after being further adjusted by the current FI level, but the association with the current FI level remained significant (Model 3, Table 5.1.3B). Moreover, the risk carried by the FI was significantly higher at younger-old ages, decreasing by 3% every year after age 74 (the centering age). In contrast, no age interaction was found for FI change (Model 4, Table 5.1.3B). The risks carried by the FI level or FI change were not affected by time elapsed since their measurement (Model 4, Table 5.1.3B).

Table 5.1.3. Associations between a 10% increase in the level of FI and all-cause mortality (A) and between 10% increase in the rate of change in FI and all-cause mortality (B) in the full sample of 2,677 individuals.

A

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
FI	1.29 (1.24, 1.34)*	1.68 (1.59, 1.78)*	1.69 (1.59, 1.79)*
Sex	0.57 (0.53, 0.63)*	0.57 (0.53, 0.63)*	0.60 (0.54, 0.66)*
FI × age at measurement		0.78 (0.75, 0.81)*	0.97 (0.97, 0.98)*
BMI			0.98 (0.97, 0.99)*
Smoking			1.16 (1.08, 1.25)*

*p<0.05. Age at measurement refers to attained age at the FI assessment, centered at 74 years. The FI level is based on the current FI i.e., the most recent measurement at any given time. Abbreviations: BMI, body mass index; CI, confidence interval; FI, frailty index; HR, hazard ratio

B

	Model 1	Model 2	Model 3	Model 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
FI change	1.63 (1.27, 2.10)*	1.90 (1.37, 2.65)*	0.97 (0.72, 1.31)	1.16 (0.34, 3.95)
Sex	0.63 (0.57, 0.69)*	0.65 (0.59, 0.72)*	0.62 (0.56, 0.68)*	0.60 (0.54, 0.66)*
FI change × age at measurement		0.98 (0.94, 1.02)		1.00 (0.95, 1.04)
BMI		0.99 (0.98, 1.00)	0.99 (0.98, 0.99)*	0.98 (0.96, 0.99)*
Smoking		1.22 (1.13, 1.31)*	1.21 (1.12, 1.30)*	1.16 (1.08, 1.25)*
FI			1.27 (1.21, 1.33)*	1.68 (1.47, 1.91)*
FI × age at measurement				0.97 (0.97, 0.97)*
FI × time since measurement				1.00 (0.99, 1.01)
FI change × time since measurement				0.97 (0.89, 1.05)

The table is reproduced from Bai et al. Age ageing 2021 [109].

5.2   STUDY 2

5.2.1   Population characteristics

Of 41,550 participants, 22,193 (53.4%) were women and 30,172 (72.6%) were twins in complete pairs (11,031 DZ and 4,055 MZ twin pairs). The baseline median FI levels were

0.108, 0.102, and 0.102 in full, DZ pairs, and MZ pairs, respectively (Table 5.2.1.1). Among 10,487 individuals with cognitive function assessment, 5,872 (56%) were women, and 5,923 (56.55) were twins in complete pairs (2,176 DZ and 766 MZ twin pairs).

Table 5.2.1.1. Descriptive statistics of the full sample and the within-pair sample I.

	Full sample	Within-pair sample I	
	N=41,550	DZ twin individuals N=22,062	MZ twin individuals N=8,110
Age at baseline	58.0 (10.1)	56.7 (9.1)	56.6 (9.1)
Age range at baseline	41-97	41-91	41-88
Women, N (%)	22,193 (53.4)	11,621 (52.7)	4,606 (56.8)
BMI	25.0 (3.5)	25.0 (3.5)	24.9 (3.5)
Tobacco user, N (%)	24,491 (58.9)	13,282 (60.2)	4,549 (56.1)
Years of education	10.6 (3.2)	10.7 (3.2)	11.0 (3.2)
§Physical activity, median (IQR)			
Born before 1926	1(1)	1(1)	1(1)
Born after 1926	3(2)	3(2)	3(2)
Living alone, N (%)	9,005 (21.7)	4,395 (19.9)	1,558 (19.2)
FI, median (IQR)	0.108 (0.108)	0.102 (0.108)	0.102 (0.108)
Categorized FI			
Non-frail, N (%)	15,464 (37.2)	8,557 (38.8)	3,133 (38.6)
Pre-frail, N (%)	22,354 (53.8)	11,757 (53.3)	4,298 (53.0)
Frail, N (%)	3,732 (9.0)	1,748 (7.9)	679 (8.4)
Dementia diagnosis during follow-up, N (%)	3,183 (7.7)	1,364 (6.2)	494 (6.1)
Time to diagnosis, median (IQR)	16.0 (2.4)	16.1 (2.3)	16.1 (2.2)
Died during follow-up, N (%)	9,932 (23.9)	2,012 (9.1)	756 (9.3)

Data presented for the dizygotic (DZ) and monozygotic (MZ) twins includes those individuals who were available for the within-pair analysis. Values are mean (standard deviation, SD) unless otherwise indicated. Note. Participants who used tobacco products include current smokers, ex-smokers, and snuff users at baseline. §Physical activity was assessed using a different questionnaire for those born before 1926 vs after 1926. Abbreviations: BMI body mass index; DZ dizygotic; FI frailty index; IQR interquartile range; MZ monozygotic; N number. The table is reproduced from Bai et al. BMC Medicine 2021.[110]

5.2.2 Frailty-dementia association and the *APOE* ε4 effect on the association

The multivariate Cox models in the full sample showed a 10% higher FI (i.e., increment of 0.1) was associated with a 19% (HR 1.19; 95% CI 1.14, 1.24) increase in the risk of incident dementia (Table 5.2.2.1). In the genotyped sample I (i.e. individuals with the *APOE* genotypes available in the full sample), the effect remained the same after further adjusting for the *APOE* ε4 carrier status (Table 5.2.2.1). In the cognitive sample (i.e., individuals with cognitive function assessment available), the effect of FI on a higher risk of dementia was observed and remained similar after adjusting for the baseline cognitive score (Table 5.2.2.2). Meanwhile, in the genotyped sample II (i.e. individuals with the *APOE* genotypes available in the cognitive sample), the effect of FI on the risk of dementia remained when adding the cognitive score to the multivariate Cox model and remained significant also after further adjusting for the *APOE* ε4 carrier status.

Table 5.2.2.1. Association of the frailty index (FI) with the risk of dementia in the full sample (left panel) and in the genotyped sample I adjusting for the *APOE* ε4 carrier status (right panel).

	Multivariate Cox models		Multivariate Cox models adjusting for the *APOE* ε4 carrier status	
	Full sample (N=41,550)		Genotyped sample I (N=11,502)	
	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
FI	1.19 (1.14, 1.24)*	1.17 (1.13, 1.23)*	1.13 (1.04, 1.23)*	1.13 (1.03, 1.23)*
Age at FI measurement	1.15 (1.14, 1.16)*	1.15 (1.14, 1.16)*	1.15 (1.14, 1.16)*	1.16 (1.15, 1.17)*
Male sex	0.85 (0.78, 0.91)*	0.87 (0.80, 0.94)*	0.83 (0.72, 0.97)	0.82 (0.71, 0.96)*
Education years		0.97 (0.96, 0.98)*	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Tobacco user		1.19 (1.10, 1.29)*	1.17 (1.01,1.35)*	1.16 (1.00, 1.34)*
APOE ε4 status (ref. non-carrier)				
Heterozygous (ε2/ε4 or ε3/ε4)				2.04 (1.75, 2.37)*
Homozygous (ε4/ε4)				7.02 (5.21, 9.46)*

Hazard ratios (HR) from the Cox regression and 95% confidence intervals (CI) are presented for a 10% increase in FI. Note. Model 1 in each sample adjusts for age and sex and model 2 adjusts additionally for education and tobacco use. Model 1 for the genotyped sample represents the FI-dementia association in this sample without adjusting for the *APOE* ε4 status and model 2 adjusts for the *APOE* ε4 status. *P<0.05. The table is reproduced from Bai et al. BMC medicine 2021. [110]

Table 5.2.2.2. Association of the frailty index (FI) with the risk of dementia using Cox regression in the cognitive sample (left panel) and in the genotyped samples II adjusting for the *APOE ε4* carrier status (right panel).

	Multivariate Cox model		Multivariate Cox models adjusting for	
	Cognitive sample (N=10,487)		Genotyped sample II (N=3,156)	
	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
FI	1.15 (1.09, 1.20)*	1.13 (1.07, 1.18)*	1.16 (1.05, 1.27)*	1.15 (1.04, 1.27)*
Age at FI measurement	1.14 (1.13, 1.15)*	1.13 (1.12, 1.14)*	1.13 (1.11, 1.15)*	1.14 (1.12, 1.16)*
Sex	0.86 (0.78, 0.94)*	0.84 (0.76, 0.92)*	0.81 (0.68, 0.97)*	0.80 (0.67, 0.96)*
Education years	0.97 (0.95, 0.98)*	0.99 (0.98, 1.01)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Tobacco use	1.17 (1.06, 1.28)*	1.20 (1.09, 1.31)*	1.14 (0.96, 1.35)	1.14 (0.96, 1.35)
Cognitive function score		0.79 (0.77, 0.81)*	0.88 (0.83, 0.92)*	0.88 (0.84, 0.93)*
APOE ε4 status (ref. non-carrier)				
Heterozygous (ε2/ε4 or ε3/ε4)				1.79 (1.50, 2.13)*
Homozygous (ε4/ε4)				5.04 (3.44, 7.38)*

Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for a 10% increase in the FI. Note. Model 1 in the right panel presents associations in the genotyped sample (that is a subsample of the Cognitive sample) without adjusting for the *APOE* ε4 status whereas Model 2 additionally adjusts for the *APOE* ε4 status. *P<0.05. The table is reproduced from Bai et al. BMC medicine 2021 [110].

5.2.3 Within-pair analysis and the age-varying effect of FI-dementia associations

Compared to the population-level effect of the FI on dementia in the multivariate Cox model, we found that the effect of the FI on dementia remained similar in the within-pair model for the DZ twin pairs (HR 1.23; 95% CI 1.15, 1.31 vs HR 1.24; 95% CI 1.12, 1.37) (Table 5.2.3, DZ twins, left vs. right panel). The effects of FI in the multivariate Cox model and within-pair model were similar in the MZ twin pairs (HR 1.12; 95% CI 1.00, 1.25 vs HR 1.13; 95% CI 0.91, 1.42). However, the significance was attenuated in the within-pair model for the MZ twin pairs (Table 5.2.3, MZ twins, left vs. right panel). The plot on age-varying FI effects in MZ and DZ twins showed a similar pattern of risk across age at FI assessment in both the standard interaction and within-pair interaction models, testing for interaction terms between FI and zygosity and FI and age at FI measurement, respectively (Figure 5.2.3.1). Otherwise, the effect sizes of FI in DZ twins decreased between 40 and 50 years, after which the risk was seemingly constant across age. Since the DZ estimate was found to be higher than the MZ estimate across most of the age range, the HR_{DZ}/HR_{MZ} (varying over age at FI assessment) in the within-pair interaction model was assessed (Figure 5.2.3.2). However, the effect sizes did not differ significantly between MZ and DZ twin pairs.

Table 5.2.3. Association of the frailty index (FI) with the risk of dementia in complete DZ and MZ twin pairs in the within-pair sample in multivariate Cox model (left panel) and the within-pair model (right panel).

	Within-pair sample I			
	Multivariate Cox model		**Within-pair model**	
	DZ twins	MZ twins	DZ twins	MZ twins
	N=11,031 pairs	N=4,055 pairs	N=2,176 pairs	N=766 pairs
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
FI	1.23 (1.15, 1.31)*	1.12 (1.00, 1.25)*	1.24 (1.12, 1.37)*	1.13 (0.91, 1.42)
Age at FI measurement	1.15 (1.14, 1.16)*	1.14 (1.12, 1.15)*	1.17 (1.16, 1.18)*	1.18 (1.16, 1.20)*
Male sex	0.83 (0.74, 0.94)*	0.87 (0.70, 1.08)	0.77 (0.65, 0.92)*	0.89 (0.68, 1.17)
Education years	0.97 (0.95, 0.99)*	0.96 (0.93, 0.99)*	0.97 (0.93, 1.00)	0.97 (0.89, 1.04)
Tobacco user	1.13 (1.00, 1.27)*	1.28 (1.04, 1.57)*	1.17 (0.96, 1.41)	0.78 (0.51, 1.18)

Hazard ratios (HR) and 95% confidence intervals (CI) are presented for a 10% increase in FI.*P<0.05. The table is reproduced from Bai et al. BMC medicine 2021 [110].
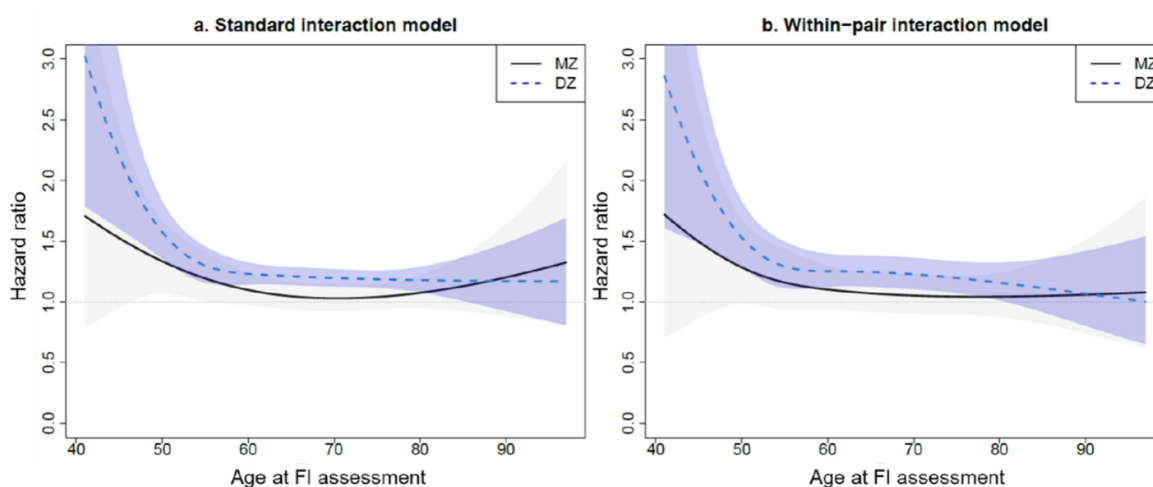

Figure 5.2.3.1. Age-varying effects of the frailty index (FI) on dementia in dizygotic (DZ) and monozygotic (MZ) twin pairs in the within-pair sample I. Age refers to age at FI assessment. The standard interaction model (a) represents the Cox model adjusted for sex, age at FI measurement, years of education, tobacco use and interaction terms between FI and zygosity and FI and age at FI measurement. The within-pair interaction model (b) additionally controls for familial factors. The dashed line represents the age-varying estimates in DZ twins and the solid line in MZ twins. The figure is reproduced from Bai et al. BMC medicine 2021 [110].

Difference in HR between MZ and DZ twins

Figure 5.2.3.2. The ratio of the hazard ratios (HRs; HR_{DZ}/HR_{MZ}) in the within-pair interaction model in the within-pair sample I adjusted for age at frailty index measurement, sex, education years and tobacco use. The figure is reproduced from Bai et al. BMC medicine 2021 [110].

5.3   STUDY 3

5.3.1   Population characteristics

Of 307,568 participants in the UK Biobank and 38,381 participants in SALT, 161,295 (52.4%) in the UK Biobank and 19,732 (51.4%) in SALT were women. In the UK Biobank and SALT, the mean baseline ages were 56.0 (SD 8.1) and 57.6 (SD 10.0) years. The age cut-off with the highest discrimination to stratify the sample into younger and older adults was found to be 65 as earlier described. 254,955 participants (82.9%) in the UK Biobank and 29,164 (76.0%) in SALT were "younger", aged <65. The characteristics of the study samples by age group (younger adults aged <65 and older adults aged ≥65) and the differences across the study variables between the younger and older adults are presented in Table 5.3.1.1 and Table 5.3.1.2. The prevalence rates of frailty (those with the FI value ≥0.21) in the UK Biobank were 8.4%, 12.1%, and 14.9% in individuals aged ≤55, 55-65, and 65-75, respectively, whereas the prevalence rates in SALT were 11.8%, 15.8%, 22.1%, 27.5%, and 33.5% in individuals aged ≤55, 55-65, 65-75, 75-85, and >85, respectively (Figure 5.3.1). The pooled prevalence rates of frailty were 10.3 % (95% CI 2.7%-32.7%), 14.4 % (95% CI 4.5%-37.2%), 19.2 % (95% CI 2.5%-68.5%) in individuals aged ≤55, 55-65, 65-75 based on the UK Biobank and SALT data, respectively. In SATL, the prevalence rates of frailty in individuals aged 75-85, and >85 were 27.5%, and 33.5%, respectively.

Table 5.3.1.1. Characteristics of the study population in the UK Biobank.

	UK Biobank			
	All N=307,568	Younger adults N=254,955	Older adults N=52,613	P-value
Frailty, N (%)				
Relatively fit (FI<0.03)	20,994 (6.8%)	18,960 (7.4%)	2,034 (3.9%)	<0.01
Less fit (0.1>FI≥0.03)	121,794 (39.6%)	104,229 (40.9%)	17,565 (33.4%)	
Least fit (0.21>FI≥0.1)	131,466 (42.7%)	106,152 (41.6%)	25,314 (48.1%)	
Frail (FI≥0.21)	33,314 (10.8%)	25,614 (10.0%)	7,700 (14.6%)	
Age, mean (SD)	56.0 (8.1)	53.8 (7.0)	66.9 (1.5)	<0.01
Sex, N (%)				
Women	161,295 (52.4%)	137,063 (53.8%)	24,232 (46.1%)	<0.01
Men	146,273 (47.6%)	117,892 (46.2%)	28,381 (53.9%)	
Tobacco use status, N (%)				
Never	171,637 (55.8%)	145,799 (57.2%)	25,838 (49.1%)	<0.01
Previous	106,004 (34.5%)	82,925 (32.5%)	23,079 (43.9%)	
Current	29,927 (9.7%)	26,231 (10.3%)	3696 (7.0%)	
Alcohol consumption, N (%)				
Less than weekly	86,699 (28.2%)	71,127 (27.9%)	15,572 (29.6%)	<0.01
Weekly	220,869 (71.8%)	183,828 (72.1%)	37,041 (70.4%)	
Education, N (%)				
Low	40,773 (13.3%)	26,387 (10.3%)	14,386 (27.3%)	<0.01
Intermediate	152,288 (49.5%)	128,343 (50.3%)	23,945 (45.5%)	
High	114,507 (37.2%)	100,225 (39.3%)	14,282 (27.1%)	
BMI, N (%)				
Underweight	1,513 (0.5%)	1,283 (0.5%)	230 (0.4%)	<0.01
Normal weight	102 752 (33.4%)	87,535 (34.3%)	15,217 (28.9%)	
Overweight	131,467 (42.7%)	106,721 (41.9%)	24,746 (47.0%)	
Obese	71,836 (23.4%)	59,416 (23.3%)	12,420 (23.6%)	
Income, mean (SD)	2.69 (1.20)	2.83 (1.18)	1.99 (1.00)	<0.01
Maternal smoking				
No	215,722 (70.1%)	175,714 (68.9%)	40,008 (76.0%)	<0.01
Yes	91,846 (29.9%)	79,241 (31.1%)	12,605 (24.0%)	

Notes. Abbreviations: BMI, body mass index; FI, frailty index; IQR, Interquartile range; SALT, Screening Across the Lifespan Twin Study; SD, standard deviation. * The categories of income in the UK Biobank are: 1=<£18 000; 2=£18 000 to £30 999; 3=£31 000 to £51 999; 4=£52 000 to £100 000; 5=>£100 000. P-values for comparison between younger and older individuals with and without sufficient data for FI, based on t-tests for continuous variables, and χ2 tests for categorical variables.

Table 5.3.1.2. Characteristics of the study population in SALT

	SALT			
	All **N=38,381**	**Younger adults** **N=29,164**	**Older adults** **N=9,217**	**P-value**
Frailty, N (%)				
Relatively fit (FI<0.03)	3,677 (9.6%)	3,181 (10.9%)	496 (5.4%)	<0.01
Less fit (0.1>FI≥0.03)	14,129	11,470 (39.3%)	2,659 (28.8%)	
Least fit (0.21>FI≥0.1)	14,594	10,666 (36.6%)	3,928 (42.6%)	
Frail (FI≥0.21)	5,981 (15.6%)	3,847 (13.2%)	2,134 (23.2%)	
Age, mean (SD)	57.6 (10)	53.0 (5.7)	72.1 (5.8)	<0.01
Sex, N (%)				
Women	19,732	15,229 (52.2%)	4,503 (48.9%)	<0.01
Men	18,649	13,935 (47.8%)	4,714 (51.1%)	
Tobacco use status, N (%)				
Never	14,446	10,327 (35.4%)	4,119 (44.7%)	<0.01
Previous	15,621	11,747 (40.3%)	3,874 (42.0%)	
Current	8,314 (21.7%)	7,090 (24.3%)	1,224 (13.3%)	
Alcohol consumption, N (%)				
Less than weekly	12,406	7,850 (26.9%)	4,556 (49.4%)	<0.01
Weekly	25,975	21,314 (73.1%)	4,661 (50.6%)	
Education, N (%)				
Low	9,985 (26.0%)	5,280 (18.1%)	4,705 (51.0%)	<0.01
Intermediate	21,922	18,279 (62.7%)	3,643 (39.5%)	
High	6,474 (16.9%)	5,605 (19.2%)	869 (9.4%)	
BMI, N (%)				
Underweight	468 (1.2%)	332 (1.1%)	136 (1.5%)	<0.01
Normal weight	20,381	15,712 (53.9%)	4,669 (50.7%)	
Overweight	14,496	10,797 (37.0%)	3,699 (40.1%)	
Obese	3,036 (7.9%)	2,323 (8.0%)	713 (7.7%)	
Occupation, N (%)				
Low	10,292	7,435 (25.5%)	2,857 (31.0%)	<0.01
Medium	23,555	17,926 (61.5%)	5,629 (61.1%)	
High	4,534 (11.8%)	3,803 (13.0%)	731 (7.9%)	

Notes. Abbreviations: BMI, body mass index; FI, frailty index; IQR, Interquartile range; SALT, Screening Across the Lifespan Twin Study; SD, standard deviation.
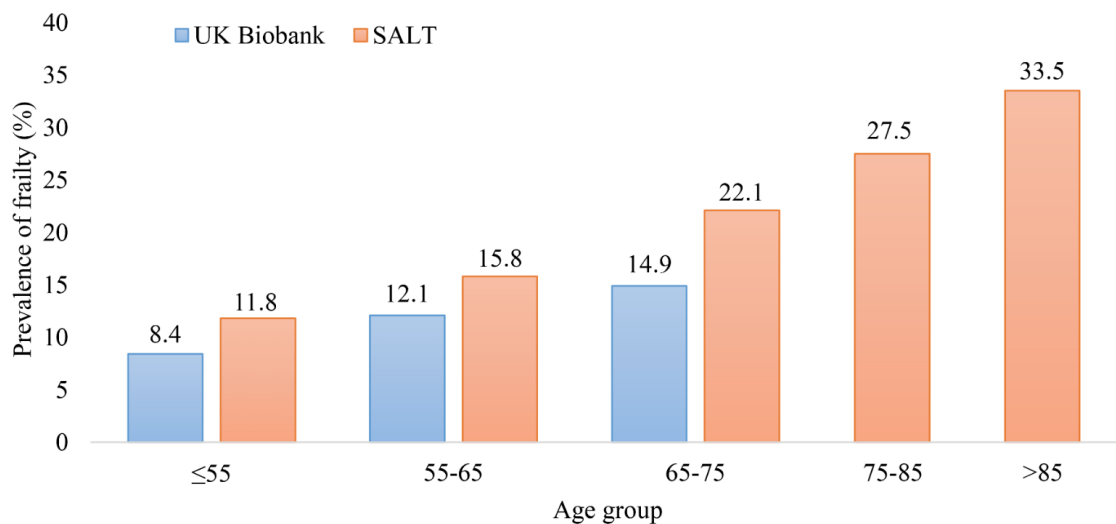
Figure 5.3.1. Prevalence of frailty across age categories in the UK Biobank and SALT. Abbreviations: SALT, Screening Across the Lifespan Twin Study.

5.3.2 Differences in frailty domains between younger and older frail adults

Comparing the mean FI domain scores between younger and older frail adults (FI ≥ 0.21) revealed statistically significant differences across most of the domains, yet the effect sizes of the differences were generally small (Figure 5.3.2). The greatest differences with consistent findings in both samples were seen in pain, immunological, and mental wellbeing domains, with younger frail adults having higher domain scores compared to older frail adults, whereas older frail adults had higher mean scores in sensory, cardiometabolic, musculoskeletal, and cancer domains (Figure 5.3.2).
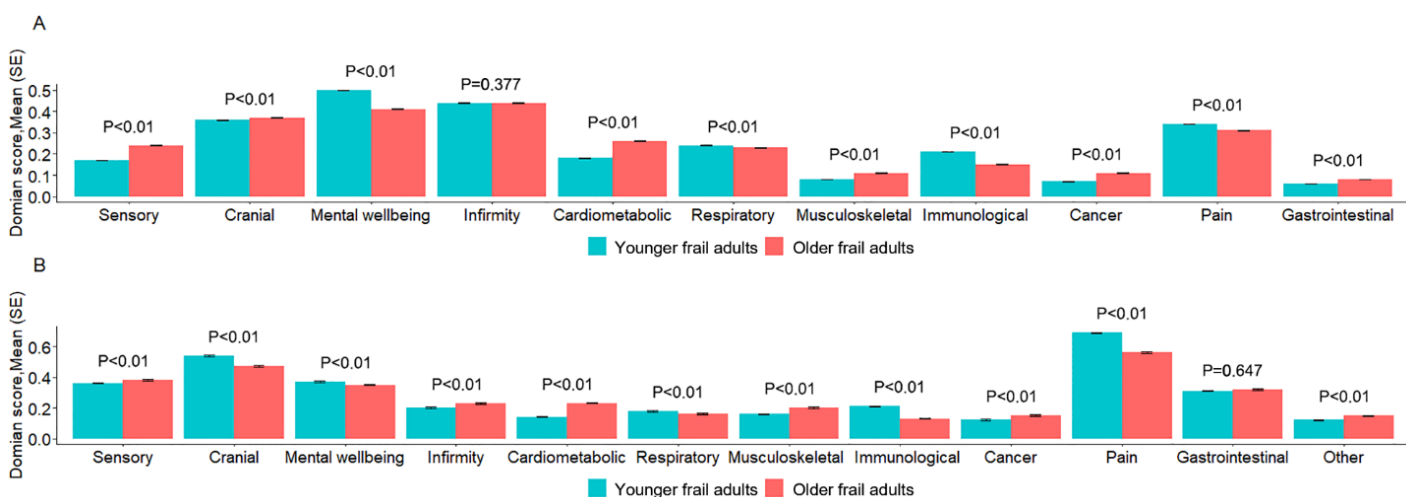
Figure 5.3.2. The mean of domain score of frailty in younger and older frail adults of UK Biobank (A) and SALT (B). Younger frail adults= individuals aged $\leq$ 65, old frail adults = individuals aged >65. The p-values are for the comparison between younger and older frail individuals. The p-value threshold level is corrected to 0.045 based on Benjamini-Hochberg false discovery rate method.

5.3.3 Risk factors of early-life and late-life frailty

Higher age, female sex, being a previous or current smoker, consuming alcohol less than weekly, overweight, and obesity were similarly associated with early-life and late-life frailty in both samples (Figure 5.3.3). Underweight was associated with early-life frailty in UK Biobank, and with late-life frailty in SALT. Low education, low income, and maternal smoking history were associated with both early-life and late-life frailty in the UK Biobank. In SALT, low education and low occupation level were associated with early-life frailty but not with late-life frailty (Figure 5.3.3).
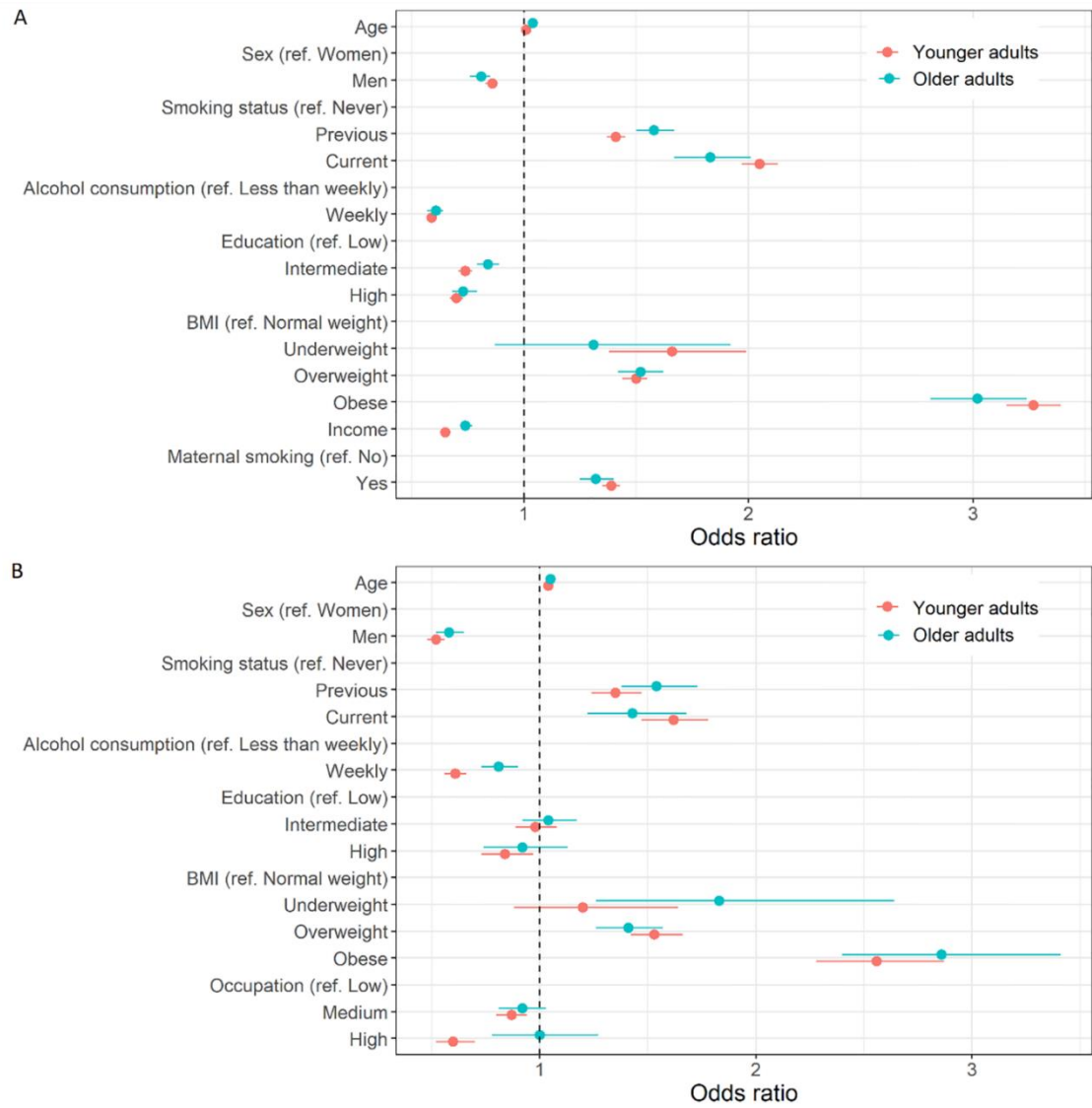
Figure 5.3.3. Associations of the common risk factors with frailty in younger and older adults in the UK Biobank (A) and SALT (B) in a multivariable logistic regression model. The whiskers present 95% confidence intervals for the estimates. Abbreviations: BMI, Body mass index.

5.4 STUDY 4

5.4.1 Population characteristics

Among 1,858 individuals aged 44-98 from three cohorts at baseline, 1,101 (59.3%) were women (Table 5.4.1). The median levels of FI were 0.09, 0.06, 0.20, and 0.11 in SATSA,

GENDER, OCTO-Twin, and the full sample, respectively. The prevalence rates of polypharmacy were 3.5%, 19.6%, 25.1%, and 15.4% in SATSA, GENDER, OCTO-Twin, and full sample, respectively. In addition, 179 (9.6%) participants had long-term polypharmacy use, whereas 666 (35.8%) and 1,030 (55.4%) participants had transient and non-polypharmacy use across the whole study period, respectively. (Table 5.4.1).

Table 5.4.1. Sample characteristics at baseline.

	SATSA (N=709)	GENDER (N=495)	OCTO-Twin (N=654)	Full sample (N=1,858)
Age				
Mean (SD)	66.9 (9.16)	73.0 (2.60)	83.4 (3.06)	74.3 (9.38)
Median [Min, Max]	66.6 [44.9, 91.0]	72.7 [68.8, 78.6]	82.5 [79.4, 97.9]	74.7 [44.9, 97.9]
Sex				
Men	288 (40.6%)	248 (50.1%)	221 (33.8%)	757 (40.7%)
Women	421 (59.4%)	247 (49.9%)	433 (66.2%)	1,101 (59.3%)
FI				
Median [Min, Max]	0.09 [0, 0.55]	0.06 [0, 0.52]	0.20 [0, 0.63]	0.11 [0, 0.63]
Frailty				
Non-frail (FI<0.21)	648 (91.4%)	470 (94.9%)	353 (54.0%)	1471 (79.2%)
Frail (FI>=0.21)	61 (8.6%)	25 (5.1%)	301 (46.0%)	387 (20.8%)
Frailty group				
Relatively fit (FI<0.03)	92 (13.0%)	131 (26.5%)	5 (0.8%)	228 (12.3%)
Less fit (FI=0.03-0.1)	304 (42.9%)	231 (46.7%)	107 (16.4%)	642 (34.6%)
Least fit (FI=0.1-0.21)	252 (35.5%)	108 (21.8%)	241 (36.9%)	601 (32.3%)
Frail (FI>=0.21)	61 (8.6%)	25 (5.1%)	301 (46.0%)	387 (20.8%)
Drugs (N)				
Median [Min, Max]	1.00 [0, 13.0]	2.00 [0, 11.0]	3.00 [0, 12.0]	2.00 [0, 13.0]
Polypharmacy				
No	684 (96.5%)	398 (80.4%)	490 (74.9%)	1,572 (84.6%)
Yes	25 (3.5%)	97 (19.6%)	164 (25.1%)	286 (15.4%)
Polypharmacy use				
Long-term use	17 (2.4%)	30 (6.1%)	132 (20.2%)	179 (9.6%)
Transient use	227 (32%)	194 (39.2%)	245 (37.4%)	666 (35.8%)
Non-polypharmacy use	465 (65.6%)	271 (54.7%)	277 (42.4%)	1,030 (55.4%)
CCI				
Median [Min, Max]	0 [0, 7.00]	0 [0, 8.00]	0 [0, 8.00]	0 [0, 8.00]
BMI				
Mean (SD)	25.7 (4.01)	25.3 (3.31)	24.5 (3.74)	25.2 (3.77)

Missing	5 (0.7%)	11 (2.2%)	86 (13.1%)	102 (5.5%)
Smoking status				
Non-smoker	550 (77.6%)	288 (58.2%)	438 (67.0%)	1,276 (68.7%)
Current-smoker	110 (15.5%)	55 (11.1%)	53 (8.1%)	218 (11.7%)
Ex-smoker	41 (5.8%)	148 (29.9%)	157 (24.0%)	346 (18.6%)
Missing	8 (1.1%)	4 (0.8%)	6 (0.9%)	18 (1.0%)
Education				
Primary education	397 (56.0%)	401 (81.0%)	485 (74.2%)	1,283 (69.1%)
Lower secondary or vocational education	198 (27.9%)	37 (7.5%)	128 (19.6%)	363 (19.5%)
Upper secondary education	46 (6.5%)	41 (8.3%)	30 (4.6%)	117 (6.3%)
Tertiary education	44 (6.2%)	15 (3.0%)	11 (1.7%)	70 (3.8%)
Missing	24 (3.4%)	1 (0.2%)	0 (0%)	25 (1.3%)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; FI, frailty index; SD, standard deviation.

5.4.2   FI trajectories by polypharmacy

Assessments of the FI trajectories by polypharmacy group illustrated differences between long-term, transient, and non-polypharmacy use (Figure 5.4.2). The FI values in the long-term polypharmacy use group were higher overall than in the non-polypharmacy use group across the whole study period, both in the full sample (Figure 5.4.2A) and in the individual cohorts (Figure 5.4.2B-D). In SATSA (Figure 5.4.2B), the FI of the long-term polypharmacy use group increased rapidly after 65 years, and was less steep in the other polypharmacy groups, indicating that polypharmacy might lead to the increasing accumulation of health deficits of the individuals. A similar increasing trend in the long-term polypharmacy use group was seen in GENDER (Figure 5.4.2C) but not in OCTO-Twin (Figure 5.4.2D). The FI levels in the transient polypharmacy group were generally found in between the polypharmacy and the non-polypharmacy groups, except for in GENDER (Figure 5.4.2C). The differences in the trajectories might depend on the general FI level of each cohort and also some other potential factors influencing the accelerating rate of increase. Overall, the FI increase was stable in all individuals in the non-polypharmacy groups.
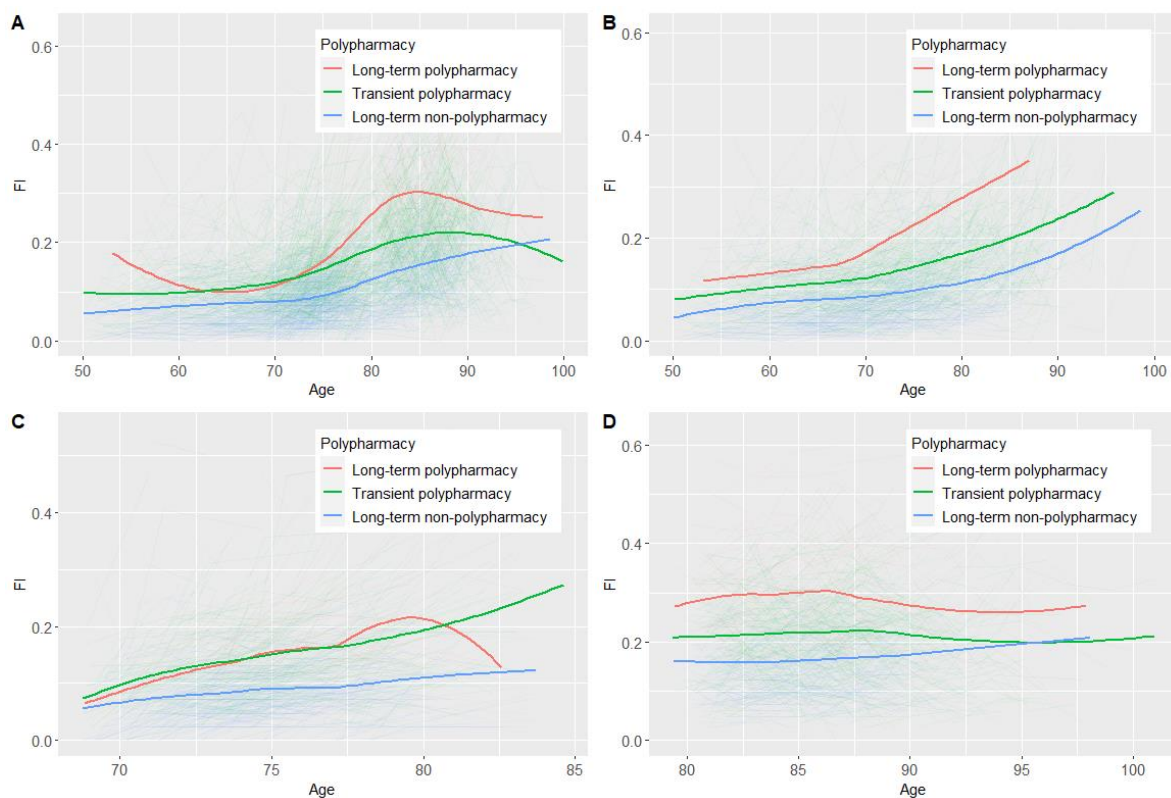
Figure 5.4.2. FI trajectories stratified by polypharmacy in the full sample (A), SATSA (B), GENDER (C), and OCTO-Twin (D). The lines represent the fitted locally estimated scatterplot smoothing curves (LOESS). The red, green and blue lines in each plot represent the changes of FI with age in long-term-, transient-, and non-polypharmacy use groups, respectively. Abbreviations: FI, frailty index.

5.4.3 The association of polypharmacy with frailty

The crude (model 1) and multivariate (model 2) models showed that the polypharmacy group had 2.29% (95% CI 1.86%–2.72%) and 2.35% (95% CI 1.92%–2.79%) increases in the FI, respectively, compared to the non-polypharmacy group (Table 5.4.3). In addition, being a woman, having a lower education, and more frequent smoking (ex-smoker and current smoker), higher CCI as well as having higher age were associated with a higher FI level.

The individual studies also had an effect on the FI levels such that OCTO-Twin participants had a higher frailty levels, whereas GENDER participants had a lower frailty risk compared to SATSA. BMI did not influence FI levels. The interaction term of polypharmacy with age (centered at 74 years) in model 3 indicated that the effect of polypharmacy on frailty was increasing with age (Table 5.4.3). Overall, in the longitudinal mixed models, polypharmacy was statistically significantly associated with increased FI (Table 5.4.3).

Table 5.4.3. Associations of polypharmacy with the FI adjusted by age, sex, CCI, BMI, smoking status, education based on linear mixed model in the full sample (n=1,858).

	Model 1	Model 2	Model 3
Fixed Effects			
Polypharmacy (ref. non-polypharmacy)	2.29 (1.86 – 2.72)	2.35 (1.92 – 2.79)	1.95 (1.43 – 2.48)
Age	0.35 (0.32 – 0.38)	0.35 (0.31 – 0.38)	
Sex (ref. men)	1.83 (1.06 – 2.59)	2.43 (1.64 – 3.21)	2.42 (1.63 – 3.21)
Study (ref. SATSA)			
GENDER	-1.42 (-2.42 – -0.42)	-1.83 (-2.82 – -0.84)	-1.77 (-2.77 – -0.78)
OCTO-Twin	3.26 (2.26 – 4.27)	3.27 (2.24 – 4.29)	3.21 (2.18 – 4.23)
CCI		0.37 (0.22 – 0.53)	0.37 (0.22 – 0.52)
BMI		0.00 (-0.07 – 0.08)	0.01 (-0.06 – 0.09)
Smoking status (ref. non-smoker)			
Current-smoker		1.42 (0.54 – 2.30)	1.39 (0.51 – 2.27)
Ex-smoker		1.22 (0.42 – 2.01)	1.21 (0.41 – 2.00)
Education (ref. primary education)			
Lower secondary or vocational education		-0.71(-1.68 – 0.25)	-0.69 (-1.66 – 0.27)
Upper secondary education		-1.63(-3.12 – -0.14)	-1.61 (-3.11 – -0.12)
Tertiary education		-0.60 (-2.54 – 1.34)	-0.58 (-2.52 – 1.36)
Age-74			0.34 (0.31 – 0.37)
(Age-74) * Polypharmacy (ref. non-polypharmacy)			0.07 (0.02 – 0.11)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; FI, frailty index. (Age-74) * Polypharmacy represents the interaction term of polypharmacy with age (centered at 74 years)

6 DISCUSSION

6.1 The association between frailty and mortality

In Study 1, we first found that age at death is associated with distinct FI trajectories. Generally, those who died at age 80 or younger experienced a steady increase in frailty throughout the 40 years of follow-up before death. In contrast, those dying older than 80 or 90 years started to accumulate deficits only after age 70. A distinct terminal health deficit accumulation, measured using the FI, was found three years before death in a US sample with a median baseline age of 78.9 [111]. In other words, besides the calendar age driving the progression of frailty, time to death also explains the FI progression from midlife onwards. A systematic review demonstrated the necessity of assessing frailty for those at the end of life [112]. Considering that a large proportion of older adults are frail or advancing to frail towards the end of life, it would be helpful to assess frailty when adults approach the end of life to identify those individuals who would need more attention and/or comprehensive care [113]. In this study, those who died at an earlier age experienced an accelerated accumulation of health deficits during midlife, which suggests that a rapid increase of frailty during midlife can be harmful to survival. Therefore, it is essential to pay close attention to the change of FI already during midlife and find ways to mitigate accelerating frailty during midlife and late life.

Second, the significant FI-mortality association found in this study is in line with the previous findings [44]. A similar significant association was also found between the rate of FI change and mortality when assessing the rate of FI change in the model alone. However, after adding the current FI level into the model, the association of the FI change attenuated to null. This implies that the predictive ability of the current FI on mortality is stronger than that of the rate of FI change. Few previous studies have also observed an association of the rate of frailty change with mortality, independent of baseline frailty [54]. A study on FI trajectories indicated that those in the highest frailty trajectory experienced worse survival independent of baseline frailty [7]. Another longitudinal study has also found that the level and the rate of change in frailty measured using a composite measure of physical frailty were independently associated with mortality [6]. Another study combining four longitudinal cohorts demonstrated that a higher rate of increase in the FI predicted mortality independent of the baseline FI [114]. Although most studies found that baseline FI was a potential predictor of mortality, it might lose its strength especially with long-term follow-ups. Thompson *et al* [115] demonstrated that both FI and FP at a follow-up was a stronger predictor of mortality compared to baseline FI in an up to 10 years follow-up study. Therefore, when comparing the predictive abilities of FI and the rate of FI change, the current FI might be more appropriate for a long-term data than the baseline frailty scores. However, a recent short-term follow-up study found the opposite result that the significance of the FI level was attenuated after adjusting for within-person FI change, and showed that the rate of FI change was regarded as a better approach to predict mortality [54]. This contradictory result might be explained by the high level of FI in most of the oldest old sample in this study, which may lead to within-person frailty change becoming a more significant variable to predict the mortality than the younger sample in our study. Due to the different frailty measurement tools and follow-up times as well as differences in the numbers and time intervals between the measurement occasions, the results might vary across studies.

6.2 FI-dementia association

Our study investigated the association of baseline FI with incident dementia among middle-aged and older individuals during a 19-year follow-up in a large cohort of twins. A significant association of the FI with incident dementia was found in our study. A previous meta-analysis on frailty and dementia demonstrated the same finding [116]. The estimates of the FI-dementia association remained stable after adjusting for *APOE* ε4 carrier status, which is in line with a recent finding that the frailty-dementia effects were similar in both carriers and non-carriers of the *APOE* ε4 allele [117]. Our study also suggests that accounting for baseline cognitive score does not significantly attenuate the FI-dementia associations, indicating that the FI predicts the risk of dementia independent of cognitive functioning.

Due to the potentially common risk factors shared by FI and dementia, our study used a novel method to analyze familial factors (shared environmental and genetic factors) underlying this association. We used a within-pair design to assess the within-pair effect of FI on mortality separately in DZ and MZ twin pairs, and found that the within-pair effects were similar to the effect size in the multivariate Cox model (the population-level analysis). The difference between the DZ and MZ twin estimates in the within-pair analysis was not significant, even though the DZ estimate appeared higher in the full sample and the age-varying analysis, indicating that familial factors are not likely involved in the frailty-dementia association. In addition, when comparing the within-MZ twin estimate with the population estimate, the estimates were very similar and not statistically significantly different. This implies that familial factors have no influence on the FI-dementia association even across age. In addition, the FI stripped from traditional dementia risk factors was associated with a later dementia risk, indicating that risk factors of dementia used in the construction of FI are unlikely to drive the association between frailty and dementia. A novel result of this study is thus that the FI is independent of familial factors in its association with dementia and is perhaps a potential target to prevent future dementia.

Preventive strategies for frailty, such as medication reviews and fall prevention measures, might decrease the odds of escalating frailty and its negative sequelae that further pave the way for dementia. Moreover, we observed that the risk conferred by a higher level of frailty was constant from age 50 to 90. The result suggests that even though the risk of dementia increases with age, the risk conferred by increased frailty is similar in magnitude from midlife into old age. Therefore, screening for frailty before or at midlife might provide benefits in identifying at-risk individuals. However, specific approaches targeting frailty are still challenging to design, and studies on how to target frailty to prevent later dementia are needed.

6.3 Differences between early-life and late-life frailty

Using FI≥0.21 to demarcate frailty, we found that the pooled prevalence rates of frailty were 10.3% (95% CI 2.7-32.7), 14.4% (95% CI 4.5-37.2), 19.2% (95% CI 2.5-68.5) in individuals aged ≤55, 55-65, 65-75, respectively. Overall, previous prevalence estimates of frailty in individuals aged 18-65 have ranged widely from 3.9% to 63%, the variation arising from different inclusion criteria and scales to measure frailty [4]. When limiting to studies using the FI to measured frailty, the prevalence of frailty in the Canadian Health Measures Study was 1.8% in the 18–34 age group, 4.3% in the 35–49 age group, and 11.6% in the 50–64 age group [73]. A Chinese Kadoorie Biobank study found somewhat lower prevalence estimates: 0.8% in individuals aged <50 years and 3.5% in individuals aged 50–64 years [51]. The prevalence of early-life frailty in our study was relatively higher than the previous findings, possibly due to the lower FI cut-off value [118]. The presence of frailty in younger adults suggests that frailty screening could be extended to younger age groups to facilitate the early identification of at-risk individuals.

Notably, when comparing the characteristics of frailty between young and old adults using FI domain scores, we found that younger frail adults had higher scores in mental well-being, pain-related, and immunological domains, and older frail adults had higher scores in cardiometabolic, cancer, musculoskeletal, and sensory-related domains. Our result is similar to the finding of a higher prevalence of diabetes, cancer, and arthritis (as FI items) in older individuals, and a higher prevalence of persistent cough and asthma in younger individuals as reported in the Canadian Health Measures Study [73]. These findings suggest that younger individuals presenting with a clustering of such health issues should receive close attention in healthcare. Although our findings indicate that frailty is statistically significantly different in younger and older adults in some of its characteristics, the differences in most domains were very small. Therefore, our results would support a hypothesis that early-life and late-life frailty are not totally different entities. More studies are nevertheless needed into the characteristics of early-life and late-life frailty as the current evidence is limited to the Canadian Health Measures Study [73] and our study.

Secondly, we observed that a higher age, female sex, smoking, consuming alcohol less than weekly (in reference to a weekly use), overweight, obesity, lower income, and maternal smoking were similarly associated with increased risk of early-life and late-life frailty. However, there were differences in some of the associations between the two cohorts used in the study. In specific, high occupation level was associated with a lower risk of early-life frailty but not with late-life frailty in SALT, whereas underweight was associated with early-life frailty in the UK Biobank and late-life frailty in SALT. The reason for this remains unclear; however, our previous longitudinal study in Swedish twins found that being underweight might be a greater risk factor in later life [77]. For the socioeconomic variables, the overall protective effects of education and income level in the UK Biobank might be stronger than education and occupation level in SALT. Previous studies also found lower alcohol consumption was associated with a higher risk of frailty [119, 120]. At present, no longitudinal study has provided evidence to indicate that higher alcohol consumption is associated with lower odds of incident frailty, with the possible explanations for the "protective" effect of alcohol including social bonding as alcohol is often consumed socially when it can reinforce social networks and

prevent social isolation, a "sick quitter" effect, and survival bias [120]. As available analyses on the risk factors of frailty is limited for older adults, more research is needed to confirm the difference and the associations especially in younger adults.

6.4 Polypharmacy-frailty association

We observed that individuals with long-term polypharmacy use had higher frailty trajectories than transient- and non-polypharmacy individuals. Due to the long-term multimorbidity and multiple medication use, the pharmacological burden from adverse drug reactions, drug-drug interactions, drug-disease interactions, and medication errors might accelerate frailty. Further, in SATSA, the FI in the long-term polypharmacy use group increased rapidly after 65 years, but was less steep in the other polypharmacy groups. The rapid increase of FI after age 65 in the polypharmacy group in SATSA could be partly explained by the higher prevalence of multimorbidity in individuals aged ≥65 [121]. Despite the fact that both frailty and polypharmacy might be influenced by multimorbidity, the lower frailty trajectory in non-polypharmacy supports the role of polypharmacy in accelerating the accruement of health deficits.

We found a significant longitudinal association of polypharmacy with a higher risk of frailty, independent of comorbidity. Although we cannot disentangle causal effects in the longitudinal polypharmacy-frailty association in our study, our result is in line with several short-term follow-up studies showing that using multiple prescriptions is significantly associated with a later development of frailty [86]; however, results to the other way around have also been presented, showing that polypharmacy is not a predictor of adverse outcome but frailty could be used as risk classification [81]. In addition, we observed a higher risk of frailty in individuals having both frailty and polypharmacy. Based on the risk of mortality that was found to be six times higher for individuals having both frailty and excessive polypharmacy (10 drugs or more) in a previous study [122], a recommendation of lower doses of medications for frail older individuals has been proposed to minimize the risk of adverse drug reactions [86]. Therefore, clinical assessment of polypharmacy and frailty status is vital to avoid adverse events. We further observed that the risk of frailty conferred by polypharmacy increased slightly with age. The finding suggests that age plays a role in the polypharmacy-frailty association. The age-varying effect on the polypharmacy-frailty association demonstrated the need for a closer monitoring of frailty levels and polypharmacy especially in older adults.

6.5 Methodological considerations

Misclassification bias

Any measurement error easily generates misclassification bias. A limitation across the four studies is the self-reported variables used to create the FI and covariates, such as BMI, smoking status, and alcohol consumption. In addition, the identification of cases of dementia in **Study 2** relies on register-based data. However, the combined sensitivity of dementia diagnoses in

both the NPR and CDR data is low (63%) [123]. Moreover, no validity studies have been conducted on the PDR. Therefore, the harmonization and use of three register data sources is likely to increase the sensitivity but decrease the specificity due to the prescription of dementia drugs to patients with mild cognitive impairment. Also, since the diagnosis time for the onset of dementia obtained from the NPR is uncertain, the diagnoses in the NPR are recorded approximately five years after the age at onset [124]. In **Study 4**, self-reported drug use data might also lead to misclassification and recall bias.

Selection bias

The common selection bias in aging studies is caused by the established population cohorts, as those who are healthier and live longer are more likely to be included in the studies. As participation in SATSA, GENDER, OCTO-Twin, SALT, and UK Biobank is volunteer-based, such a setting may create more health-conscious samples. A previous study has in fact shown that UK Biobank is not representative of the sampling population [125].

Missing data can also lead to selection bias, especially in the longitudinal data analysis. Attrition due to dropout during the follow-up time might have affected the frailty trajectories, especially when including the participants with only one observation, such individuals contributing only to the intercept but not the slopes. The bias may result in an underestimation of the rate of FI change. The censored data due to death and drop out will likely generate bias in longitudinal aging studies. In **Study 2**, the number of informative MZ twin pairs – a pair of twins who are discordant for the outcome – was limited in SALT, which resulted in imprecise within-pair estimates and increases the risk of non-representative population-based estimates.

In SALT, comorbidities and other medical conditions were somewhat overrepresented in the FI, skewing the FI towards medical conditions, which might limit the generalizability of "exposure-outcome associations". Also, a study has also reported that chronic conditions and multimorbidity might accelerate frailty with time [126], such that the effect of the FI might be driven by multimorbidity. However, Voshaar *et al* showed that the association between multimorbidity and mortality attenuated to null after adding the FI in the multivariate Cox model, suggesting that frailty explains the variance in mortality better than a mere number of diseases [127]. Regarding **Study 2**, comorbidities that are known risk factors of dementia might drive the FI-dementia association beyond frailty itself. Nevertheless, the estimates of FI constructed with or without dementia-related items remained similar indicating that the comorbidities used in the construction of the FI did not drive the association between frailty and dementia.

In **Study 3**, although 65 was the most appropriate cut-off age to define early-life and late-life frailty based on the principal component analysis (i.e. greatest differences in frailty could be seen when using this age cut-off), using any cut-off is always somewhat arbitrary and might result in diluting the effect in comparison to using age as a continuous variable. However, since we aimed at doing a crude comparative analysis on the characteristics of early-life and late-life frailty, determining an age cut-off was needed to achieve the research aim.

6.6 Ethical Considerations

The primary aim of this thesis was to investigate the role of frailty and frailty trajectories on mortality, dementia, and polypharmacy. To achieve this, observational data from population-based data were analyzed. The whole study process including data collection, data analyzing, and data publishing, might generate risks. Therefore, several risk-benefit balances are considered as follows.

The first consideration of the ethical requirements is an informed consent from participants when collecting data including demographic and socioeconomic status, height, weight, smoking and drinking status, diseases, functional and cognitive tests, mental health, and other information by in-person testing and questionnaires. Moreover, the participants should be informed about the aims, procedures, and potential results for the study, and researchers should receive the consents or permits before performing this study. The studies should follow the guidelines of the Declaration of Helsinki [128].

Secondly, sensitive personal data should be handled with caution in the analysis. Sensitive personal data containing various physical, cognitive and genetic variables as well as register-based data on diseases and vital status should be treated without breaching participants' privacy. To protect the privacy of the participants, the data analyzed in this thesis are pseudonymized and unidentifiable, such as the STR data, using twin serial numbers instead of personal identity numbers.

Thirdly, another consideration of ethics is the study methods and data analysis applied to the studies. Before conducting each study, we have referred to several books and papers in this research field and discussed with statisticians to find the most suitable epidemiological methods to answer the research questions properly. Moreover, the analysis plans were selected based on solid scientific justification rather than an expected result.

Ethical permits of each study:

All individuals included in these four studies provided informed consent, and the four studies have ethical approvals. The diary numbers for each study permits are as follows,

Study I: 2015/1729-31/5

Study II&III: 97-051 and 00-132; 2016/1888-31/1

Study IV: 2016/1888-31/1

Ethical approvals 2015/1729-31/5 and 2016/1888-31/1 were issued by the Regional Ethical Review Board in Stockholm. Ethical approvals 97-051 and 00-132 were issued by the Ethical Review Board of Karolinska Institutet.

7 CONCLUSIONS

I. Those who died at age <70 had higher FI levels and rates of change from age 50 onwards compared to those dying at older ages. Although the rate of FI change was associated with mortality, the association disappeared after considering the current FI level. Also, a slight decrease in the FI effect size with age was found. The current status of FI is therefore a stronger marker for risk stratification than the rate of change. A middle-aged individual presenting with a high level of frailty should be considered for monitoring their frailty progression in clinical practices.

II. Increased frailty is associated with a higher risk of dementia and the effect remains after considering familial factors. The risk was also constant after age 50 until very old age. The FI-dementia association was independent of cognitive functioning and *APOE* ε4 carrier status. Timely management of frailty might provide a means to decrease or delay incident dementia.

III. Frailty is also prevalent in younger adults. Early-life frailty differs from late-life frailty in some of its characteristics, yet the overall differences were not sizeable enough to consider early-life and late-life frailty as different entities. The risk factors of frailty were nevertheless largely similar for early-life and late-life frailty. Similar frailty interventions may thus be applicable in both younger and older adults.

IV. Long-term polypharmacy use is associated with a trend of a higher frailty risk across age compared to transient or no polypharmacy use. Polypharmacy is significantly associated with frailty also longitudinally. Adults with polypharmacy may also have a higher risk of frailty with age. Appropriate drug prescribing should be considered for middle-aged and older adults to reduce the risk of later frailty.

8 FUTURE PERSPECTIVES

Longitudinal results of this thesis elucidated different frailty trajectory types and the longitudinal associations of frailty with adverse outcomes. However, causalities of the frailty-outcome associations could not be addressed in this thesis. Further studies regarding the causal relationships are thus needed.

The frailty measurement tools have been diverse across studies. Due to the limitation of frailty measurements in the data included in this thesis, only FI was used to disclose the role of frailty on adverse outcomes and the prevalence of frailty in younger adults. More frailty measurement tools should be considered in similar analyses to support the results generated in the thesis.

The thesis found that frailty is a strong and independent predictor of adverse outcomes. Therefore, regular monitoring of frailty might be helpful in risk evaluation. Frailty is also prevalent in younger adults. Age-varying estimates in the thesis emphasized that escalating frailty in middle-aged individuals needs special attention. Therefore, studies assessing the effects on the interventions on frailty are required to support further clinical applications.

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