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Measuring Multimorbidity

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Abstract

Introduction

Multimorbidity is common. The gaps in multimorbidity research are in the measurement of the prevalence, the levels of multimorbidity and its associated outcomes.

Objectives

This thesis aimed to provide a uniform definition for multimorbidity, identify instruments for measuring the level of multimorbidity, and describe patient-reported outcomes for different levels of multimorbidity.

Methods

Three studies were conducted. The first determined the prevalence rates of multimorbidity and explored whether there were differences among the different age, sex and ethnic groups in the primary care population. Common dyads and triads of conditions were described. The systematic review updated the list of instruments for measuring the level of multimorbidity for community-dwelling adults. The third study determined the association of different levels of multimorbidity with depression, anxiety and quality of life. The agreement between patients' self-reported conditions and conditions recorded in their electronic medical records (EMR) were reported.

Results

Increasing age was associated with a higher prevalence of multimorbidity. The commonest dyad was hyperlipidaemia/hypertension, and triad was hyperlipidaemia/hypertension/diabetes. Disease count and weighted indices were the most commonly used instruments for measuring the level of multimorbidity. Self-reported disease count was positively associated with depression and anxiety, and negatively associated with quality of life. Stroke was the only condition that showed substantial agreement between patients' self-reported medical conditions and the EMR.

Conclusion

We identified a practical definition of multimorbidity in the Singapore primary care population, described the commonly used instruments for measuring the level of multimorbidity, and reported the disparity of multimorbidity outcomes between patients' self-reported chronic conditions and EMR.

(249 words)

Keywords

Anxiety, chronic condition, concordance, depression, level of multimorbidity, measurement of multimorbidity, patterns of multimorbidity, patient-reported outcomes, prevalence, quality of life.

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Western University

CHAPTER ONE

Multimorbidity

1 Introduction

Epidemiologically, we are in the age of degenerative and human-made diseases whereby overall mortality continues to decline[1]. This is mainly due to demographic changes in many developed societies and public health improvement. During this transition, a long-term shift occurs in mortality and disease patterns whereby degenerative diseases gradually displace pandemic infections as the chief form of morbidity and primary death.

In 2015, the Global Burden of Disease study reported that chronic conditions like heart disease, stroke, diabetes, chronic kidney disease and Alzheimer's disease caused seven out of every ten deaths in 2014[2]. This occurred at the same time that death rates from communicable diseases like HIV/AIDS and malaria were falling.

The report also revealed that people's average life spans had risen by 6.1 years over the last 15 years steadily in 191 countries, resulting in a significant overall increase in life expectancy. Not only does a longer life expectancy increase the chance of developing a chronic condition, but the likelihood of having multiple chronic conditions (i.e., multimorbidity) also increases. As the population ages in many societies worldwide, an increasing number of people are living with multimorbidity.

Multimorbidity was an important but often ignored medical phenomenon until recently. Until ten years ago, the disease-centred approach to research has led to a predominant focus on the index disease and resulted in a dearth of information about multimorbidity and its complexity[3]. In this chapter, we discussed the salient issues on what is currently known on the subject matter and highlighted the gaps in the body of knowledge. We provided the context of multimorbidity in Singapore next as the accompanying research activities were all conducted in the country. Finally, we described the research studies we had undertaken to help close this gap and add to the body of knowledge on the subject matter.

2 What is multimorbidity?

The concept of multimorbidity was first published in 1976 in Germany, and since the 1990s, the concept has spread widely and has been researched by many worldwide[4]. The World Health

Organization (WHO) defines multimorbidity as the co-occurrence of two or more chronic medical conditions in one person[5].

However, the term 'comorbidity' has been used interchangeably with the term 'multimorbidity' for a long time even up to now. Comorbidity was described in a seminal paper in 1970 by Feinstein[6] for 'any distinct additional clinical entity that has existed, or that may occur during the clinical course of a patient who has the index disease under study'. Since 1996, van den Akker et al. has addressed the conceptual confusion between the two terms[7,8]. The consensus is that comorbidity describes the simultaneous presence of multiple health conditions when there is an index condition and other unrelated conditions whereas multimorbidity describes the co-occurrence of two or more chronic medical conditions without specifying which is the index condition. For comorbidity, health outcomes are evaluated in the context of the index condition. For multimorbidity, health outcomes are interpreted in the context of the interaction and burden of all the co-existing chronic conditions.

Although comorbidity is not a comprehensive way to design research interventions and care delivery programs for the whole person, it is a concept commonly used by secondary and tertiary care clinicians. Advocates of the concept of multimorbidity tend to focus on primary care where the identification of an index disease is often neither obvious nor useful[9].

There is an explosion of interest in multimorbidity in the last decade[10,11]. In 2013, the European General Practice Research Network (EGPRN) defined multimorbidity as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or physical risk factor. Any biopsychosocial factor, any physical risk factor, the social network, the burden of diseases, the healthcare consumption and the patient's coping strategies may function as modifiers (of the effects of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty[12].

PubMed, the free search engine provided by the United States National Library of Medicine at the National Institutes of Health, adopted multimorbidity as a medical subject heading (MeSH) term in January 2018 and defined it as 'the complex interactions of several co-existing diseases'. These complex interactions have profound implications on individuals with

multimorbidity, their health care providers, and accounts for most of the expenditures of the healthcare system, putting pressure on its sustainability[13].

3 Epidemiology of multimorbidity

A chronic disease does not occur in isolation[14]. A study on multimorbidity in the primary care setting reported that more than half of individuals with a chronic condition had at least two, and frequently more, other conditions[15]. The overall estimates of the prevalence of multimorbidity varied widely in the literature and ranged from 12.9% in participants aged 18 years and older to 95.1% in those aged 65 years and older[16]. Public health studies tend to use hospital validated definition of chronic diseases to estimate population prevalence of multimorbidity. There are very few validated conditions and in one such studies, there were only five conditions[17].

Age and lower socioeconomic status are consistently associated with multimorbidity[10,16,18]. Sex and the presence of mental health problems also show associations with multimorbidity, but the evidence is less consistent across studies[16]. Other risk factors for multimorbidity include health behaviours such as smoking, obesity, and inactivity[10].

Two types of patterns of multimorbidity are reported in prevalence studies[14]. The first pattern is the most frequent combinations of specific conditions based on the frequency of all possible combinations of two or three conditions (dyads and triads). Descriptive statistics showed that the commonest dyad was the combination of hypertension and osteoarthritis followed by different combinations of cardiovascular conditions[16]. The combination of hyperlipidaemia, hypertension and diabetes was the commonest triad[19,20].

The second pattern is to identify groups of conditions with the highest degree of non-random associations using analytical statistics such as cluster or factor analysis[10,16]. Three distinct patterns were commonly reported[21]. The first being a combination of cardiovascular and metabolic conditions, the second pattern included mental health conditions, and the third pattern included musculoskeletal conditions.

Kanesarajah et al.[22] suggested that from an epidemiological and health planning perspective, using disease count to describe multimorbidity is useful to establish the prevalence of multimorbidity. However, for clinical practice and health policy, patterns of conditions that tend to co-occur are more useful. Public health studies tend to use hospital validated definition of chronic diseases to estimate population prevalence of multimorbidity. There are very few validated conditions and in one such studies, there were only five conditions.

4 Problems of multimorbidity

4.1 From the patients' perspective

Multimorbidity affects individuals to varying degrees. Living with multimorbidity is a state of complexity that goes beyond counts of conditions and symptom burden[23]. Patient's perspectives of living with multimorbidity speak more to psychological and functional challenges leading to poorer quality of life than to disease-specific issues[24].

The risk of psychological distress increased five times for individuals with a high level of multimorbidity compared to those with no multimorbidity, after controlling for age, sex, social support and economic status[25]. Clinical depression was two to three times more likely in people with multimorbidity compared to people without multimorbidity or those who had no chronic physical condition[26]. However, clinically depressed patients with chronic physical conditions were inconsistently picked up in primary care[27].

The functional challenges of individuals with multimorbidity included coping with managing the complexity of multiple chronic conditions, physical limitations experienced such as pain or fatigue, financial constraints, complexity of communication with healthcare providers, inadequate or inappropriate family and social support, logistical challenges in managing the scheduling of different appointments or coordination of medications, lifestyle changes, and the burden of treatment imposed[28,29].

4.2 From the care providers' perspective

Generally, medical and public health programs targeting commonly defined chronic conditions have been fixated on individual chronic conditions without considering the broader context of

co-occurring chronic conditions. Clinical practice guidelines are written by committees dominated by specialists, mainly drawing on research in selected individuals without other co-occurring medical conditions[30]. The applicability of existing disease management guidelines to individuals with multimorbidity is limited, particularly for those with discordant* combinations[31,32]. Medical interventions may be less effective in individuals with multimorbidity than in individuals with no other comorbidities included in clinical trials. Even if treatments were effective, older individuals with multimorbidity might have less to gain because of their reduced life expectancy[33].

Basing standards for quality of care and pay for performance on existing practice guidelines could lead to inappropriate management and create perverse incentives that emphasise the wrong aspects of care for individuals with multimorbidity and diminish the quality of their care[33]. The struggle most family physicians experience is in finding the balance of promoting autonomy for individuals with multimorbidity in self-management and for professional autonomy in straying away safely from clinical guidelines to provide individualised care[34]. In an attempt to achieve this patient-centred care, this can lead to potential conflicts with specialist services and confuse patients.

4.3 From the health system's perspective

There is a global consensus that multimorbidity is a growing concern for healthcare policymakers trying to provide optimal healthcare services within resource-constrained environments[11]. Multimorbidity is associated with higher levels of utilisation across almost all resource types including medications, primary care, specialist outpatient consultations, emergency department presentations and hospitalizations[11,35]. Moreover, it appears that spending more money is not always better for health in healthcare[36]. This puts into doubt the sustainability of healthcare services for managing the complexity of multimorbidity using the current model of care. A revamped and better model of care will need to be developed and implemented for managing the inevitable increase in the number of patients with multimorbidity. More thoughtful care for individuals with multimorbidity and shifting the

* Conditions that are not directly related in either their pathogenesis or management and do not share an underlying predisposing factor (31. Lugtenberg M, Burgers JS, Clancy C, et al. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. *PLoS ONE* 2011;6(10):e25987. doi: 10.1371/journal.pone.0025987)

goals towards medical care that is less disruptive to their lives may be the solution to the ever-increasing health care spending and achieve better patient/provider satisfaction[37].

5 Multimorbidity interventions and their outcomes

Most of the interventional studies for multimorbidity are relatively recent, reflecting the fact that research to date has focused on description and impact rather than the evaluation of the effectiveness of the intervention. Many of these studies were not robust methodologically and most had no control groups for comparison[38-40]. In general, none of the intervention studies fully supported the implementation of the following modes of interventions – chronic care model[41], promotion of self-management[39], comprehensive care management[38], nurse-led case management[40], and general case-management[42].

Interventions that targeted well-defined conditions like depression and diabetes or focused on specific problems experienced by individuals such as functional status were more effective than interventions with a broader focus[43]. Therefore, attention to particular issues, risk factors or practical difficulties using a nuanced management approach rather than a one-size-fits-all general approach may be superior[39].

6 Gaps in knowledge – prevalence, levels, and outcomes of multimorbidity

Measurements are the foundation of medical research and clinical practice[44,45]. The major gaps in multimorbidity research are in the measurement of the prevalence of multimorbidity, the measurement of the different levels of multimorbidity, and the measurement of outcomes associated with multimorbidity. And the fundamental reason for these gaps is in the contentious issues related to the definition of multimorbidity. Even though the World Health Organization (WHO) defines multimorbidity as the co-occurrence of two or more chronic medical conditions in one person[5], many other different definitions of multimorbidity exist as described in Section 2 *(p2-4*).

6.1 Prevalence and definition of multimorbidity

Disease count is the most typical approach to measure the prevalence of multimorbidity[46]. However, even using the simple count of chronic conditions resulted in a wide range of prevalence estimates being reported in epidemiological studies. Estimates of multimorbidity prevalence vary widely from 12.9% to 95.1% internationally[16].

Using disease count to determine prevalence estimates is greatly influenced by five components in the definition of multimorbidity : a) the types of conditions selected to form the multimorbidity list; b) the total number of conditions considered in the multimorbidity list; c) the data sources of the conditions; d) the cut-points used to define multimorbidity; and e) the reference population being measured[47-49].

6.1.1 The type of conditions selected to form the multimorbidity list of conditions

There is a lot of controversy in the types of conditions that are selected to form the list of conditions used in multimorbidity research. Primarily, the conditions included in the list of conditions are chronic diseases or noncommunicable diseases as defined by the World Health Organisation, i.e., they are not passed from person to person, of long duration and generally slow in progression[50]. However, it is not so apparent what a 'chronic disease' is.

Bernell and Howard[51] described many variations in the diseases that are included under the umbrella term 'chronic disease' and also the variation in the time a disease must be present for it to be referred to as chronic from different professional and academic bodies. To add to the confusion, the European professional body included both acute and chronic medical conditions and also social conditions like poverty[12], the National Institute for Health and Care Excellence (NICE) guideline on multimorbidity included symptoms experienced by individuals like frailty[52], and a multimorbidity study in Ghana excluded mental health conditions[53].

While it is idealistic to bring into focus all the possible needs of individuals with multimorbidity, there are concerns of including acute conditions in the primary care context and operationalisation of social factors[10,54]. Concerning the inclusion of mental health conditions, Fortin et al.[55] emphasised that excluding psychiatric diagnoses in primary care for

counting towards multimorbidity is unacceptable. Two recommendations were suggested for the progress of research in multimorbidity - either unrestricted eligibility of health conditions or an agreement on a defined list of key conditions[43].

6.1.2 The total number of conditions considered in the multimorbidity list

The number of conditions used in multimorbidity prevalence studies ranged from 4 to 147[54]. It has been reported that studies that included a higher number of conditions would report a higher prevalence rate of multimorbidity compared to studies using a lower number of conditions[47,48].

6.1.3 The data sources of chronic conditions

Data sources could be from chart reviews, administrative data, or self-reports from patients[49]. Fortin et al.[56] reported that health administrative data based on the billing system underestimated the prevalence of multimorbidity when compared to self-reported chronic conditions. However, other studies have raised concerns about the reliability of self-reporting of medical conditions due to biases, including respondent recall and poor respondent understanding[57,58].

6.1.4 The cut-points used to define multimorbidity

Holzer et al.[59] reported that the cut-points of two or three chronic conditions provide essentially the same information on prevalence. However, Fortin et al.[47] reported that 'three or more' conditions better identify patients with higher needs that is more meaningful for primary care physicians.

6.1.5 The reference population

Generally, prevalence estimates of multimorbidity for the family practice-based population were higher than those for the general population[48]. The prevalence estimates of multimorbidity also increase with age with the prevalence in older persons almost reaching 100%[10].

Although the prevalence of multimorbidity increases with age, the absolute number of individuals with multimorbidity is higher in those aged less than 65 years old[15,60]. Multimorbidity is not uniquely an ageing-related phenomenon as one would expect. Research emphasis should also be on understanding the optimal health systems for younger people with multimorbidity[49].

In summary, there is no common lexicon amongst stakeholders in the definition, and therefore the measurement of the prevalence of multimorbidity. The definition of multimorbidity needs further clarification and consensus. Most researchers agree that a precise definition of multimorbidity to allow for generalisability or applicability of studies is lacking. While waiting for the broad consensus of the definition and measurement of multimorbidity to materialise, Fortin et al.[47] suggested that future studies should include two operational definitions of multimorbidity, i.e., for two or more and three or more chronic conditions. The authors also urged researchers to carefully consider the specific diagnoses included in the list of chronic conditions and to state the recruitment and data collection methods clearly.

Comparing different definitions of multimorbidity and determining the prevalence of multimorbidity are key goals of the thesis described later in this chapter.

6.2 Measurement of the different levels of multimorbidity

For measurement of the level of multimorbidity, Lefevre et al.[14] listed four common methods. They are: by simple counts of chronic diseases from a list of individual conditions (i.e., disease count), by grouping chronic diseases into dyads or triads (i.e., dyad and triad patterns), by identifying groups of people with common disease and characteristics that occur more often than by chance, and by using an index of variable complexity (i.e., weighted indices). However, this does not clearly explain the different purposes of measuring multimorbidity[45]. According to de Vet et al.[61], the three main purposes of measurement in medicine are for diagnosis, evaluation of intervention, and prediction of outcome. The instrument for each of the above purpose is called a discriminant measurement, an evaluation measurement, aobjectivesnd a prediction measurement respectively. Each of these four measurement methods described by Lefevre et al.[14] can be used for any of the three different purposes described by de Vet et al.[61]

The first three methods described by Lefevre et al.[14] are usually used for measuring the prevalence or patterns of multimorbidity (consistent with the purpose of diagnosis described above). All three methods have already been described in Section 3 *(p4*). The three methods of measurements help to differentiate between those who have multimorbidity and those without multimorbidity, or those with a certain pattern of multimorbidity from those without. One major criticism of these three methods is that the severity of individual conditions is not usually specified[47]. Only 23% of multimorbidity studies reported the severity of individual conditions and they were reported in many different ways[54]. A concern on the lack of reporting on severity is that common conditions in the population like hypertension and hyperlipidaemia are not necessarily those with the most significant impact on individuals' functional status or quality of life[54]. Relying too much on these conditions without indicating their severity when describing the prevalence of multimorbidity will shift the focus to awareness of future illness rather than the actual disease burden and functional status of individuals with multimorbidity.

The fourth method described by Lefevre et al.[14] of using indices of variable complexity (i.e., weighted indices) is usually used for measuring the different levels of multimorbidity in association with specific outcomes either for evaluation of intervention or for prediction of an outcome. Disease count[†], which is the first method described by Lefevre et al.[14], is also commonly used for the same purpose. When a group of individuals with multimorbidity has already been identified, these two methods help to categorise these individuals into different levels of the overall multimorbidity. The systematic review by Huntley et al.[46] described theses two methods as indices for the measurement of the morbidity burden of multimorbidity.

In this same systematic review, seventeen different indices used for measuring the morbidity burden for multimorbidity in the primary care and the general population were found. The most common index was 'disease count'. Other common indices for measuring multimorbidity in relation to a particular outcome include the Charlson Index, Adjusted Clinical Groups System, and Cumulative Illness Rating Scale[46]. In general, these indices weighted individual conditions differently and then added the scores up to provide a total score. Even though most of these indices were initially developed and validated in the hospital setting, many of them have been adapted for use in the primary care and the community populations.

[†] 'Disease count' as a measuring instrument has two purposes here. One is for measuring the prevalence of multimorbidity, and the other is for measuring the different levels of multimorbidity.

The systematic review by Huntley et al.[46] included original articles only till the end of 2009, and there has not been any update on the use of the existing measurement indices or new measurement indices created since then. Getting a summary update of the measurement instruments used for measuring the different levels of multimorbidity for specific outcomes for community-dwelling individuals is the next key goal of the thesis described later in this chapter.

6.3 Measurement of the outcomes associated with multimorbidity

The use of clinical outcomes has always been the norm in medical research. However, there is increasing recognition of involving patients in clinical research, evaluation of health care service delivery, and quality improvement[62]. Good clinical care requires patients to provide information regarding how they are feeling, their symptoms, and any effects of treatment.

A patient-reported outcome is directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment[62]. However, heterogeneity in the choice of outcome measures in multimorbidity research has led to a lack of consistent evidence for multimorbidity intervention research[63].

Sasseville et al.[64] compiled a list of patient-reported outcomes used in multimorbidity intervention research into six domains including general health, psycho-social health, disease management, health-associated behaviours, functional, and health services. The most universal three outcomes reported in their scoping review were depression under psychosocial health, quality of life under general health, and self-efficacy under disease management. However, these outcomes were rarely reported together. Care satisfaction, goal assessment, social health and communication with the providers were the least frequently reported patient-reported outcomes.

Core outcome sets (COS) represent the minimum that should be measured and reported in all clinical trials of a specific condition or conditions[65]. This is in relation to the recognition that outcomes measured in clinical trials were not always relevant to health service users and policymakers[66]. The widespread adoption of COS can help improve the uniformity in outcome measurement and reduce outcome reporting bias[67]. In accordance with the above, the long-

awaited set of core outcomes of multimorbidity (COSmm) was recently published in 2017 by Smith et al.[68] after consulting a Delphi panel of experts. Seventeen core outcomes were identified, and the three essential core outcomes were quality of life, mental health outcomes, and mortality.

Obtaining patient-reported outcomes and relating them to the different levels of multimorbidity is another key goal of the thesis described later in this chapter.

7 Conceptual frameworks

Theories are integral to healthcare practice and research[69]. Making explicit the theoretical assumptions is vital as they can offer a generalisable framework for engaging with the concept of multimorbidity, a concept that is still unclear and inconsistent as shown in the previous sections. More theory-driven research should help us decide on the best approaches to provide solutions to the challenges generated by multimobidity[70].

Realistically, it is impossible to pile on the recommendations from the Clinical Practice Guidelines of each of the single chronic diseases for patients with multimorbidity as doing so would overburden them and render the health system unsustainable. As such, we adopted two conceptual frameworks for the research work done for this thesis. One is the Patient Centred Clinical Method[71] (PCCM) that focuses on building a positive interaction between clinicians and their patients at both the personal and practice level.

"Patient-centred care is the willingness to become involved in the full range of difficulties individuals bring to their doctors, and not just their biomedical problems."[72]

The PCCM framework outlines four components for the clinician to combine medical science with knowledge of patients as people, their experiences, their values and their beliefs within their context, with an ongoing and affirmative relationship.

The other framework is applicable at the personal, practice and policy levels. Minimally disruptive medicine (MDM) draws attention to the impact of treatment burden, imposed by the

clinician and the health care system, on patients' capacity to cope with their medical conditions on top of their other life demands[73].

"*Minimally disruptive medicine is a patient-centred approach to care that focuses on achieving patient goals for life and health while imposing the smallest possible treatment burden on patients' lives. It is particularly appropriate for patients who are at risk of being (or who already are) overwhelmed by the demands of life, illness, and health care. Such patients include the expanding group of vulnerable individuals with multiple chronic conditions."*[74]

The MDM framework is a theory-based, patient-centred, and context-sensitive approach to care that focuses on achieving patients' goals while imposing the smallest possible burden on their lives[74]. The four principles for MDM are to establish the weight of the burden, encourage coordination in clinical practice, acknowledge multimorbidity in clinical evidence, and prioritise treatment from the patient perspective[73].

The two theories work in tandem at the personal, practice and policy levels. PCCM will promote the holistic patient-centred care tailored to the overall needs of individuals with multimorbidity in an ongoing, positive relationship over the long term. MDM is designed to provide comprehensive, evidence-based, supportive care that fits into the patient's life. Both PCCM and MDM are approaches used in the intervention and management of multimorbidity and will be used in interpreting the results of the proposed studies which are non-interventional.

8 Family medicine and multimorbidity

There is debate in the medical community as to who should coordinate all the medical conditions an individual with multimorbidity faces. Articles and editorials in the specialty literature advocate shifting the care of chronically ill persons from primary to specialty care[75]. The argument for such a shift can be found in the growing body of evidence demonstrating that specialists are more knowledgeable on the specific condition and are more likely to follow disease-specific guidelines[76]. Arguments opposing the shift of chronic illness care from generalists to specialists include concerns about the receipt of preventive care, the care of comorbid conditions outside of the specialty focus, and cost[75].

In 2009, Stange and Ferrer[77] described the paradox of primary care. They observed that primary care is associated with low levels of evidence-based care for individual diseases. However, healthcare systems based on primary care have healthier populations, use fewer resources, and have less health inequality. Homa et al.[78] explored the above observation further by developing an agent-based computer simulation model with a participatory group model-building process. Primary care in the model is less effective than specialty care in treating single diseases, but it has the ability to manage multiple diseases at once[78]. Primary care also can provide disease prevention, help improve individuals' health behaviours and lower their threshold for seeking care. In a model simulation with primary care features turned off, individuals have poorer health. In a model simulation with all primary care features turned on, better population health was observed, with significant improvements in individuals who are disadvantaged or those with multimorbidity.

However, Rothman and Wagner reasoned that most studies of the quality of chronic disease care had not differentiated the sources of care or the specialty of the primary clinician[75]. The few available comparative studies of primary and specialty care made it clear that the quality gap pertains to both. They suggested that the practice environment and system determine the quality of chronic disease care far more prominently than whether the care provider is a specialist or a generalist.

Primary care practices offer an ideal setting to study individuals with diverse patterns of multimorbidity[79]. It is the best setting for studying the causality of seemingly unrelated chronic diseases and including individuals with multimorbidity into clinical trials. Family medicine is more patient-centred and less disease-focused. The rationale for the discipline is based on the health of people and populations, not the one-by-one counting of diseases, their diagnoses, and their management[80]. In concordance with the way multimorbidity is described in PubMed as 'the complex interactions of several co-existing diseases', the goal is not to manage each disease separately but to provide holistic care and to improve both clinical and patient-reported outcomes instead. Family physicians who adopt the patient centred clinical method (PCCM) will be the most likely professionals to lead collaborative work with other professionals in primary, secondary and tertiary healthcare; together with policymakers, the patients themselves and their caregivers to achieve the above aims. Afterall, the patients they serve traverse through the whole health care system, and it is myopic to make the artificial divide between primary and specialty care for individuals with multimorbidity. The crux is in the formation of a

practice environment and system that allows coordination and continuity of healthcare to happen with minimal disruption to the patients.

9 Multimorbidity in Singapore

Singapore is a city-state country in southeast Asia with a population of 5.6 million, of which close to 4.0 million are Singapore residents[81]. The rest comprises permanent residents and non-residents, including foreign workers, their dependants and international students. Singapore is a multi-ethnic society where the Chinese formed 74% of the resident population, the Malay at 13% and the Indian at 9.2% according to the 2010 Census[82]. According to the Bloomberg Healthiest Country Index which ranks 169 economies according to factors that contribute to overall health, Singapore was ranked fourth position in 2017 and eighth position in 2019.

One in four Singaporeans aged 40 years and older have at least one chronic condition and the risk increases with age. By 2030, one in four adults will be 65 and above, up from one in eight today and many of them will have multimorbidity[83]. Total life expectancy at birth rose from 65.8 years in 1970 to 82.5 years in 2013. Life expectancy at age 65 rose from 8.4 years to 20.6 years over the same period. Therefore, not only has the elderly population grown but the elderly, as a group, are themselves getting older with longer life expectancy, many of them with multimorbidity[84]. Longevity is not equivalent to good health. A local study projected that the number of seniors who require assistance with daily activities would increase from 31,738 in 2010 to 82,968 in 2030, and more women than men will require assistance[85].

Unfortunately, only four studies could be found in Singapore looking at multimorbidity specifically[86-89]. Subramaniam et al.[86] reported that 16.3% of the Singapore general population has two or more chronic conditions. Those who were older, economically inactive, unemployed, overweight or obese had higher odds of having multimorbidity. Individuals from the Malay ethnic group had significantly lower odds of multimorbidity as compared to the Chinese ethnic group. Picco et al.[87] reported that the prevalence of multimorbidity was 51.5% for those aged 60 years and above in the general population of Singapore. The authors also found that the total societal cost of multimorbidity equated to SGD‡15,148 per person annually for those with multimorbidity while those with one or no chronic conditions, the total annual

‡ SGD – Singapore Dollar (1.00 SGD is equivalent to 0.99 Canadian dollar)

societal costs per person were SGD5,610 and SGD2,806 respectively. Quah et al.[88] conducted a study on older adults in the primary care setting and found that the prevalence of multimorbidity was 89.4% for those above 65 years old and was associated with poorer quality of life. Ge et al.[89] interviewed community-dwelling adults aged 21 years and above and reported that the prevalence of multimorbidity was 35.0%. They also reported that there was no difference in the prevalence rates between the two sexes.

Among the four multimorbidity studies conducted in Singapore, different lists of chronic medical conditions were used. Subramaniam et al.[86] used eight conditions, Picco et al.[87] used ten, Quah et al.[88] used fourteen, and Ge et al.[89] used seventeen. None of the studies described clearly how and why they chose the list of chronic conditions in their study. All four studies used data sources from patients' self-report. All the studies used two or more chronic conditions as the cut-point to define multimorbidity. Three of the reference populations were from the general population, and one was from a practice-based population. Two of the studies were for all adults while the other two were for older adults. Only one out of the four studies measured the levels of multimorbidity using disease count and drug count. The different characteristics of the four studies are summarised in Table 1-1.

Table 1-1. A summary of the different characteristics of measuring prevalence, levels, and outcomes of multimorbidity of studies conducted in Singapore

	Subramaniam et al.[86] (Published in 2014)	**Picco et al.[87] (Published in 2016)**	**Quah et al.[88] (Published in 2016)**	**Ge et al.[89] (Published in 2018)**
Definition of chronic disease ***(Section 6.1.1)***	No	No	No	Diseases that are irreversible and persistent throughout adulthood
No. of conditions ***(Section 6.1.2)***	8	10	14	17
Source of list of chronic conditions ***(Section 6.1.2)***	Modified Composite International Diagnostic Interview (CIDI)	Not mentioned	Conditions from the Singapore Mental Health Study 2011	Not mentioned
Sources of data ***(Section 6.1.3)***	Self-reported	Self-reported	Self-reported	At least one of the sources from self-reported or from chronic disease management system database
Cut-point ***(Section 6.1.4)***	2 conditions	2 conditions	2 conditions	2 conditions
Reference population ***(Section 6.1.5)***	General population	General population	Practice-based population	General population
Age group ***(Section 6.1.5)***	≥ 18 years old	≥ 60 years old	≥ 65 years old	≥ 21 years old
Measured levels of multimorbidity ***(Section 6.2)***	No	No	Yes 1. Disease Count 2. Drug Count	No
Patient-reported Outcomes ***(Section 6.3)***	Yes Health-related quality of life	No Health care utilisation and costs	Yes 1. Health-related quality of life 2. Functional disability 3. Chronic musculoskeletal pain	Yes Physical function

10 Proposed studies

In 2015, Le Reste et al.[4] established a research agenda for multimorbidity and suggested that the highest priorities should be given to the measurement of multimorbidity and the impact of multimorbidity on the different stakeholders. This agenda has been supported by many

investigators. However, the unintended consequence was a marked variation among studies of the prevalence of multimorbidity concerning both methodologies and findings[90]. Furthermore, observational studies of multimorbidity were generally not done well with questionable generalisability relating to issues of sampling, attrition and non-response[91].

The key message for this chapter is the immaturity of the different measurements of multimorbidity: prevalence, levels of morbidity burden, and outcomes. This thesis aimed to provide a uniform definition for multimorbidity, identify a list of instruments to measure the levels of multimorbidity and explore some patient-reported outcomes for different levels of multimorbidity.

As primary care practices offer an ideal setting to study individuals with diverse patterns of multimorbidity[79], the following three studies for this thesis were all conducted in the primary care setting. The research activities were focused on clarifying the definitions, measurements and the impact of multimorbidity. No attempt was made to conduct intervention trials for the current management of multimorbidity in this thesis.

As with most research in multimorbidity, acute, social and non-medical conditions were not included in the list of conditions for multimorbidity in this thesis. Only chronic conditions were used. Frailty is interrelated with multimorbidity as they are both age-related and highly correlated but they are two different concepts or clinical conditions[92]. Frailty will not be considered and discussed further in this thesis. However, as described in Section 6.1.1 *(p8)*, defining what constitutes a chronic condition is not simple[51]. N'Goran et al.[93] described a four-step study in family medicine in Switzerland to define the list of conditions family doctors coded in their medical records which were deemed to be considered 'chronic'. A similar approach, on a smaller scale, was conducted to emulate their study to create a master list of chronic conditions in Singapore.

The three studies are briefly described below.

10.1 The prevalence and the common patterns of multimorbidity in Singapore: An epidemiology study based on administrative data

This was a cross-sectional epidemiology study looking at the prevalence of multimorbidity in the primary care setting by using administrative data. We used two multimorbidity lists (one local source and the other from an international source) and compared two different cut-offs of 'two or more' or 'three or more' chronic conditions to define multimorbidity. We used the full age range for the study to look at the changes from early adulthood to the older age group. We hypothesised that the standardised prevalence rate of multimorbidity might differ between the different sex and among different age and ethnic groups.

Violan et al.[16] encouraged studying the patterns of the clustering of chronic diseases because it helps to identify what makes certain conditions co-occur from the aetiological perspective; tailors special care to a stratified stratum of people who are at high risks with a familiar pattern from the clinical perspective; and prevent multimorbidity and its associated risks from the policy perspective. As such, we also described the most common dyads and triads of multimorbidity for those ages 45 years old and above and reported the crude prevalence rates of the dyads and triads for the different ethnic groups and sex.

The study aimed to describe the epidemiology of chronic conditions in primary care, establish the standardised prevalence rates of multimorbidity in the primary care population, compare the standardised prevalence rates among different age, sex and ethnic groups, and describe the most common dyads and triads for those 45 years and older by each sex/ethnic groups. We explicitly reported all the definitions of the variables so that the study could be easily replicated.

10.2 A systematic review of the instruments used for measuring the level of multimorbidity

This was a systematic review that used three electronic databases to provide an update from Huntley et al.'s [46] review on the current instruments used for measuring the level of multimorbidity in the primary care or general population setting. The other objectives were to report the advantages and disadvantages of using selected instruments, provide the details of the data sources and resources required to use the instruments, and compile a list of

corresponding instruments for measuring the level of multimorbidity for the three essential core outcomes identified for multimorbidity (COSmm)[68].

The study aimed to provide a useful and handy resource for researchers and clinicians who can easily choose an instrument for measuring the level of multimorbidity for a specific outcome.

10.3 A cross-sectional study on the level of multimorbidity and its association with depression, anxiety and quality of life

Based on the common triads of multimorbidity noted in the polyclinics, we targeted the group of patients with the most common triad of chronic conditions in Singapore and looked at how the levels of multimorbidity were associated with depressive symptoms, anxiety symptoms, and quality of life. We also looked at what other sociodemographic factors were associated with the same outcomes. The outcomes were chosen as they were part of the patient-centred COSmm outcomes. This was a cross-sectional study using interviewer-administered questionnaires where we took into account the rigour for research design, population and sampling, data definition, and outcome measures used in cross-sectional studies as suggested by Stewart et al.[90] A concordance study on patient self-report of the presence or absence of chronic condition with those recorded in the clinical notes was also conducted.

The main study aim was to describe the baseline patient-reported outcomes of patients with the most common triad of chronic conditions seen in primary care for different levels of multimorbidity.

11 References

1. Omran AR. The epidemiologic transition. A theory of the epidemiology of population change. *Milbank Mem Fund Q* 1971;49(4):509-38.
2. Collaborators GMaCoD. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 2016:1459-544.
3. Salive ME. Multimorbidity in older adults. *Epidemiol Rev* 2013;35:75-83. doi: 10.1093/epirev/mxs009
4. Le Reste JY, Nabbe P, Lingner H, et al. What research agenda could be generated from the European General Practice Research Network concept of Multimorbidity in Family Practice? *BMC Fam Pract* 2015;16:125. doi: 10.1186/s12875-015-0337-3
5. WHO. The World Health Report 2008. Primary Care - Now more than ever. 2008.
6. Feinstein AR. The Pre-Therapeutic Classification of Co-Morbidity in Chronic Disease. *J Chronic Dis* 1970;23(7):455-68.
7. van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity. *Eur J Gen Pract* 1996;2(2):65-70. doi: 10.3109/13814789609162146
8. Nicholson K, Makovski TT, Griffith LE, et al. Multimorbidity and comorbidity revisited: refining the concepts for international health research. *J Clin Epidemiol* 2019;105:142-46. doi: 10.1016/j.jclinepi.2018.09.008 [published Online First: 2018/09/27]
9. van den Akker M, Buntinx F, Metsemakers JF, et al. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *Journal of clinical epidemiology* 1998;51(5):367-75.
10. Xu X, Mishra GD, Jones M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. *Ageing research reviews* 2017;37:53-68. doi: 10.1016/j.arr.2017.05.003
11. McPhail SM. Multimorbidity in chronic disease: Impact on health care resources and costs. *Risk Management and Healthcare Policy* 2016;9:143-56. doi: http://dx.doi.org/10.2147/RMHP.S97248
12. Le Reste JY, Nabbe P, Manceau B, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc* 2013;14(5):319-25. doi: 10.1016/j.jamda.2013.01.001
13. Huber M, Knottnerus JA, Green L, et al. How should we define health? *Bmj* 2011;343:d4163. doi: 10.1136/bmj.d4163
14. Lefevre T, d'Ivernois JF, De Andrade V, et al. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. *Rev Epidemiol Sante Publique* 2014;62(5):305-14. doi: 10.1016/j.respe.2014.09.002
15. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2
16. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PloS one* 2014;9(7):e102149. doi: 10.1371/journal.pone.0102149
17. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Health Promot Chronic Dis Prev Can* 2017;37(7):215-22. doi: 10.24095/hpcdp.37.7.02

18. Fabbri E, Zoli M, Gonzalez-Freire M, et al. Aging and Multimorbidity: New Tasks, Priorities, and Frontiers for Integrated Gerontological and Clinical Research. *J Am Med Dir Assoc* 2015;16(8):640-7. doi: 10.1016/j.jamda.2015.03.013
19. Ashman JJ, Beresovsky V. Multiple chronic conditions among US adults who visited physician offices: data from the National Ambulatory Medical Care Survey, 2009. *Prev Chronic Dis* 2013;10:E64. doi: 10.5888/pcd10.120308
20. Laux G, Kuehlein T, Rosemann T, et al. Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project. *BMC Health Serv Res* 2008;8:14. doi: 10.1186/1472-6963-8-14
21. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, et al. Multimorbidity patterns: a systematic review. *Journal of clinical epidemiology* 2014;67(3):254-66. doi: https://dx.doi.org/10.1016/j.jclinepi.2013.09.021
22. Kanesarajah J, Waller M, Whitty JA, et al. Multimorbidity and quality of life at mid-life: A systematic review of general population studies. *Maturitas* 2018;109:53-62. doi: http://dx.doi.org/10.1016/j.maturitas.2017.12.004
23. Coventry PA, Small N, Panagioti M, et al. Living with complexity; marshalling resources: a systematic review and qualitative meta-synthesis of lived experience of mental and physical multimorbidity. *BMC family practice* 2015;16:171. doi: 10.1186/s12875-015-0345-3
24. Liddy C, Blazkho V, Mill K. Challenges of self-management when living with multiple chronic conditions: systematic review of the qualitative literature. *Canadian family physician Medecin de famille canadien* 2014;60(12):1123-33.
25. Fortin M, Hudon C, Bayliss EA, et al. Caring for body and soul: the importance of recognizing and managing psychological distress in persons with multimorbidity. *International journal of psychiatry in medicine* 2007;37(1):1-9.
26. Read JR, Sharpe L, Modini M, et al. Multimorbidity and depression: A systematic review and meta-analysis. *J Affect Disord* 2017;221:36-46. doi: 10.1016/j.jad.2017.06.009
27. Menear M, Dore I, Cloutier AM, et al. The influence of comorbid chronic physical conditions on depression recognition in primary care: a systematic review. *Journal of psychosomatic research* 2015;78(4):304-13. doi: 10.1016/j.jpsychores.2014.11.016
28. Rosbach M, Andersen JS. Patient-experienced burden of treatment in patients with multimorbidity - A systematic review of qualitative data. *PloS one* 2017;12(6):e0179916. doi: 10.1371/journal.pone.0179916
29. Koch G, Wakefield BJ, Wakefield DS. Barriers and facilitators to managing multiple chronic conditions: a systematic literature review. *West J Nurs Res* 2015;37(4):498-516. doi: 10.1177/0193945914549058
30. Fortin M, Dionne J, Pinho G, et al. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? *Ann Fam Med* 2006;4(2):104-8. doi: 10.1370/afm.516
31. Lugtenberg M, Burgers JS, Clancy C, et al. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. *PLoS ONE* 2011;6(10):e25987. doi: 10.1371/journal.pone.0025987
32. Tinetti ME, Fried T. The end of the disease era. *The American journal of medicine* 2004;116(3):179-85.
33. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. *Journal of the American Medical Association* 2005;294(6):716-24. doi: http://dx.doi.org/10.1001/jama.294.6.716

34. Cottrell E, Yardley S. Lived experiences of multimorbidity: An interpretative meta-synthesis of patients', general practitioners' and trainees' perceptions. *Chronic illness* 2015;11(4):279-303. doi: 10.1177/1742395315574764
35. Sum G, Hone T, Atun R, et al. Multimorbidity and out-of-pocket expenditure on medicines: a systematic review. *BMJ Glob Health* 2018;3:e00505. doi: 10.1136/bmjgh-2017-000505
36. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. *Annals of internal medicine* 2003;138(4):288-98.
37. Abu Dabrh AM, Gallacher K, Boehmer KR, et al. Minimally disruptive medicine: the evidence and conceptual progress supporting a new era of healthcare. *J R Coll Physicians Edinb* 2015;45(2):114-7. doi: 10.4997/JRCPE.2015.205
38. Hopman P, de Bruin SR, Forjaz MJ, et al. Effectiveness of comprehensive care programs for patients with multiple chronic conditions or frailty: A systematic literature review. *Health policy* 2016;120(7):818-32. doi: https://dx.doi.org/10.1016/j.healthpol.2016.04.002
39. Crowe M, Jordan J, Burrell B, et al. Clinical effectiveness of transdiagnostic health management interventions for older people with multimorbidity: a quantitative systematic review. *Journal of advanced nursing* 2016;72(10):2315-29. doi: 10.1111/jan.13011
40. Lupari M, Coates V, Adamson G, et al. 'We're just not getting it right'- how should we provide care to the older person with multi-morbid chronic conditions? *Journal of clinical nursing* 2011;20(9-10):1225-35. doi: http://dx.doi.org/10.1111/j.1365-2702.2010.03620.x
41. Boehmer KR, Abu Dabrh AM, Gionfriddo MR, et al. Does the chronic care model meet the emerging needs of people living with multimorbidity? A systematic review and thematic synthesis. *PLoS ONE [Electronic Resource]* 2018;13(2):e0190852. doi: https://dx.doi.org/10.1371/journal.pone.0190852
42. Stokes J, Panagioti M, Alam R, et al. Effectiveness of Case Management for 'At Risk' Patients in Primary Care: A Systematic Review and Meta-Analysis. *PLoS ONE [Electronic Resource]* 2015;10(7):e0132340. doi: https://dx.doi.org/10.1371/journal.pone.0132340
43. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *The Cochrane database of systematic reviews* 2016;3:CD006560. doi: 10.1002/14651858.CD006560.pub3
44. Lassere MN. A users guide to measurement in medicine. *Osteoarthritis Cartilage* 2006;14 Suppl A:A10-3. doi: 10.1016/j.joca.2006.02.021
45. de Vet HCW, Terwee CB, Mokkink LB, et al. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
46. Huntley AL, Johnson R, Purdy S, et al. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Annals of family medicine* 2012;10(2):134-41. doi: 10.1370/afm.1363
47. Fortin M, Stewart M, Poitras ME, et al. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10(2):142-51. doi: 10.1370/afm.1337
48. Fortin M, Hudon C, Haggerty J, et al. Prevalence estimates of multimorbidity: a comparative study of two sources. *BMC Health Serv Res* 2010;10:111. doi: 10.1186/1472-6963-10-111 [published Online First: 2010/05/13]

49. Boyd CM, Fortin M. Future of multimorbidity research: How should understanding of multimorbidity inform health system design? *Public Health Reviews* 2010;32(2):451-74.
50. WHO. Noncommunicable Diseases. 2016. http://www.who.int/topics/noncommunicable_diseases/en/ accessed on 30 Jun 2018.
51. Bernell S, Howard SW. Use Your Words Carefully: What Is a Chronic Disease? *Front Public Health* 2016;4:159. doi: 10.3389/fpubh.2016.00159
52. NICE. Multimorbidity: clinical assessment and management. 21 Sep 2016 ed: NICE guideline, 2016.
53. Nimako BA, Baiden F, Sackey SO, et al. Multimorbidity of chronic diseases among adult patients presenting to an inner-city clinic in Ghana. *Global Health* 2013;9:61. doi: 10.1186/1744-8603-9-61
54. Willadsen TG, Bebe A, Koster-Rasmussen R, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scandinavian journal of primary health care* 2016;34(2):112-21. doi: 10.3109/02813432.2016.1153242
55. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity and quality of life in primary care: a systematic review. *Health and quality of life outcomes* 2004;2:51. doi: 10.1186/1477-7525-2-51
56. Fortin M, Haggerty J, Sanche S, et al. Self-reported versus health administrative data: implications for assessing chronic illness burden in populations. A cross-sectional study. *CMAJ Open* 2017;5(3):E729-E33. doi: 10.9778/cmajo.20170029
57. Wu CS, Lai MS, Gau SS, et al. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. *PLoS ONE* 2014;9(12):e112257. doi: 10.1371/journal.pone.0112257
58. Jiang L, Zhang B, Smith ML, et al. Concordance between Self-Reports and Medicare Claims among Participants in a National Study of Chronic Disease Self-Management Program. *Front Public Health* 2015;3:222. doi: 10.3389/fpubh.2015.00222
59. Holzer BM, Siebenhuener K, Bopp M, et al. Overcoming cut-off restrictions in multimorbidity prevalence estimates. *BMC Public Health* 2014;14(780)
60. Ryan BL, Bray Jenkyn K, Shariff SZ, et al. Beyond the grey tsunami: a cross-sectional population-based study of multimorbidity in Ontario. *Can J Public Health* 2018 doi: 10.17269/s41997-018-0103-0
61. de Vet HCW, Terwee CB, Mokkink LB, et al. Chapter 3 - Development of a measurement instrument. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
62. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health Serv Insights* 2013;6:61-8. doi: 10.4137/HSI.S11093
63. Pillay M, Dennis S, Harris MF. Quality of care measures in Multimorbidity. *Aust Fam Physician* 2014;43(3):132-6.
64. Sasseville M, Chouinard MC, Fortin M. Patient-reported outcomes in multimorbidity intervention research: A scoping review. *International journal of nursing studies* 2018;77:145-53. doi: 10.1016/j.ijnurstu.2017.09.016
65. Kirkham JJ, Gorst S, Altman DG, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLoS Med* 2016;13(10):e1002148. doi: 10.1371/journal.pmed.1002148
66. Williamson P, Altman D, Blazeby J, et al. Driving up the quality and relevance of research through the use of agreed core outcomes. *J Health Serv Res Policy* 2012;17(1):1-2. doi: 10.1258/jhsrp.2011.011131

67. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132. doi: 10.1186/1745-6215-13-132
68. Smith SM, Wallace E, Salisbury C, et al. A Core Outcome Set for Multimorbidity Research (COSmm). *Ann Fam Med* 2018;16(2):132-38. doi: 10.1370/afm.2178
69. Alderson P. The importance of theories in health care. *BMJ (Clinical research ed)* 1998;317(7164):1007-10.
70. Eccles M, Grimshaw J, Walker A, et al. Changing the behavior of healthcare professionals: the use of theory in promoting the uptake of research findings. *Journal of clinical epidemiology* 2005;58(2):107-12. doi: 10.1016/j.jclinepi.2004.09.002
71. LaPierre D. Patient-Centred Clinical Method. 2013. http://www.sharinginhealth.ca/health_care/characteristics/pccm.html (accessed 28 Jul 2018).
72. Stewart M, Brown JB, Weston WW, et al. Patient-Centered Medicine: Transforming the Clinical Method. Third ed. Oxford, UK: Radcliffe Publishing 2014.
73. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *Bmj* 2009;339:b2803. doi: 10.1136/bmj.b2803
74. Leppin AL, Montori VM, Gionfriddo MR. Minimally Disruptive Medicine: A Pragmatically Comprehensive Model for Delivering Care to Patients with Multiple Chronic Conditions. *Healthcare (Basel)* 2015;3(1):50-63. doi: 10.3390/healthcare3010050
75. Rothman AA, Wagner EH. Chronic illness management: What is the role of primary care? *Ann Intern Med* 2003;138(3):256-61.
76. Harrold LR, Field TS, Gurwitz JH. Knowledge, patterns of care, and outcomes of care for generalists and specialists. *Journal of general internal medicine* 1999;14(8):499-511.
77. Stange KC, Ferrer RL. The paradox of primary care. *Annals of family medicine* 2009;7(4):293-9. doi: 10.1370/afm.1023
78. Homa L, Rose J, Hovmand PS, et al. A participatory model of the paradox of primary care. *Annals of family medicine* 2015;13(5):456-65. doi: 10.1370/afm.1841
79. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity is common to family practice: is it commonly researched? *Canadian family physician Medecin de famille canadien* 2005;51:244-5.
80. Starfield B. Family medicine should shape reform, not vice versa. *Fam Pract Manag* 2009;16(4):6-7.
81. Population Trends 2017. In: Singapore DoS, ed. Singapore, 2017.
82. Census of Population 2010 Advance Census Release. In: Statistics SDo, ed. Singapore, 2010.
83. Older Singaporeans to double by 2030: Health Promotion Board; 2016 [Available from: https://www.population.sg/articles/older-singaporeans-to-double-by-2030 accessed 10 Apr 2019.
84. Yap MT, Gee C. Ageing in Singapore: Social Issues and Policy Challenges. In: Chan D, ed. 50 years of social issues in Singapore. Singapore: World Scientific Publishing Co. Pte Ltd 2015:3-30.
85. Picco L, Lau YW, Pang S, et al. Predictors of General Functioning and Correlates of Quality of Life: A Cross-Sectional Study among Psychiatric Outpatients. *Annals of the Academy of Medicine, Singapore* 2018;47(1):3-12. [published Online First: 2018/03/02]
86. Subramaniam M, Abdin E, Picco L, et al. Multiple chronic medical conditions: prevalence and risk factors--results from the Singapore Mental Health Study. *General hospital psychiatry* 2014;36(4):375-81. doi: 10.1016/j.genhosppsych.2014.03.002

87. Picco L, Achilla E, Abdin E, et al. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res* 2016;16:173. doi: 10.1186/s12913-016-1421-7
88. Quah JH, Wang P, Ng RR, et al. Health-related quality of life of older Asian patients with multimorbidity in primary care in a developed nation. *Geriatr Gerontol Int* 2016 doi: 10.1111/ggi.12881
89. Ge L, Yap CW, Heng BH. Sex differences in associations between multimorbidity and physical function domains among community-dwelling adults in Singapore. *PLoS ONE* 2018;13(5):e0197443. doi: 10.1371/journal.pone.0197443
90. Stewart M, Fortin M, Britt HC, et al. Comparisons of multi-morbidity in family practice--issues and biases. *Fam Pract* 2013;30(4):473-80. doi: https://dx.doi.org/10.1093/fampra/cmt012
91. France EF, Wyke S, Gunn JM, et al. Multimorbidity in primary care: a systematic review of prospective cohort studies. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2012;62(597):e297-307. doi: 10.3399/bjgp12X636146 [published Online First: 2012/04/24]
92. Villacampa-Fernandez P, Navarro-Pardo E, Tarin JJ, et al. Frailty and multimorbidity: Two related yet different concepts. *Maturitas* 2017;95:31-35. doi: 10.1016/j.maturitas.2016.10.008
93. N'Goran AA, Blaser J, Deruaz-Luyet A, et al. From chronic conditions to relevance in multimorbidity: A four-step study in family medicine. *Family practice* 2016;33(4):439-44. doi: http://dx.doi.org/10.1093/fampra/cmw030

Western University

CHAPTER TWO

The *P*revalence and the common patterns of multimorbidity in Singapore: An *E*pidemiology *S*tudy based on *A*dministrative *D*ata (PESAD)

1 Introduction

Chapter One has clearly demonstrated that individuals with multimorbidity are the rule in primary care[1]. The overall estimates of the prevalence of multimorbidity varied widely in the literature and ranged from 12.9% in participants aged 18 years and older to 95.1% in those aged 65 years and older[2].

Even though multimorbidity is a common phenomenon, there were only four studies[3-6] done in Singapore that looked at it so far. The prevalence rates of multimorbidity in these four studies ranged from 16.3% to 89.4%, which was not too different from the range reported in the literature. The reason for the wide range is due to varying standards of measuring multimorbidity[7].

Issues with multimorbidity studies in Singapore included the the lack of proper definition of chronic disease, the total number of conditions considered in the multimorbidity list, the data source, and the reference population (*Chapter One Table 1-1 p18*). Subramaniam et al.[3] used a list of eight chronic conditions, Picco et al.[4] used ten, Quah et al.[5] used fourteen, and Ge et al.[6] used seventeen conditions. Out of the four studies, only Ge et al.[6] gave a brief description of what chronic disease was while the other three did not provide any definition. The data source for the chronic conditions was self-reported in three of the studies while the data source for the fourth study was from a combination of self-report and administrative data. The reference population for three of the studies was from the general population[3,4,6] whereas the reference population for Quah et al.[5] was from the primary care population. Two of the studies included younger adults (≥18 years old[3] and ≥21 years old[6]) whereas the other two studies only targeted older adults (≥60 years old[4] and ≥65 years old[5]).

Subramaniam et al.[3] reported that the prevalence of multimorbidity was 16.3% in the Singapore general population. Her team also reported that individuals from the Malay ethnic group had significantly lower odds of multimorbidity as compared to the Chinese ethnic group. Picco et al.[4] reported that the prevalence of multimorbidity was 51.5% in those aged 60 years and above in the general population of Singapore. Quah et al.[5] conducted a study on older adults aged 65 years and above in the primary care setting and reported that 89.4% of them had two or more chronic conditions. Ge et al.[6] interviewed community-dwelling adults aged 21 years and above

and reported that the prevalence of multimorbidity was 35.0%. They also reported that there was no difference in the prevalence rates between the two sexes. The only similarity in these four studies was that multimorbidity was defined by the unweighted count of two or more chronic conditions.

Primary care practices offer an ideal setting to study individuals with diverse patterns of multimorbidity[8]. Studies using primary care as their source population can provide insights on the optimal intervention of care for individuals with multimorbidity as compared to using information from the general population which are more desirable for surveillance and public health analysis[9].

An increased understanding of the epidemiology of multimorbidity is needed to inform how health care in Singapore should be organised and delivered to patients with multimorbidity. However, efforts to manage and study multimorbidity in Singapore are hampered by a lack of basic, up-to-date, and consistent epidemiologic data. The lack of consensus on the definition of multimorbidity makes it difficult to compare the magnitude of the problem internationally and among different health care settings in Singapore.

We proposed to measure the prevalence of multimorbidity in the primary care setting by using a local list of chronic conditions for defining multimorbidity and an internationally-recommended list from the literature. We also adopted Fortin et al.'s[10] suggestion to include two operational definitions of multimorbidity, that is, multimorbidity defined as a cut-off of 'two or more' and 'three or more' chronic conditions. As the prevalence of multimorbidity is dependent on the prevalence of each of the individual chronic conditions that made up the list, the epidemiology of the chronic conditions belonging to each list were also described.

Most studies found that the proportion of individuals with multimorbidity tended to increase rapidly in the fourth decade of life[10]. As such, we described the most common patterns of multimorbidity (i.e., dyads and triads) stratified by sex and ethnicity for patients who were 45 years and older that visited primary care. This would provide evidence for primary care physicians to create meaningful multimorbidity guidelines for the common patterns of multimorbidity seen in primary care that occur at high frequency.

The objectives of the study were to: (1) describe the epidemiology of chronic conditions depicted in the two lists for the sample population; (2) determine the overall prevalence rates of multimorbidity (crude and standardised) in the National Healthcare Group polyclinics based on two different lists of chronic conditions and two different definitions of multimorbidity in terms of cut-points; (3) determine whether there were differences in standardised prevalence rates among the different age, sex and ethnic groups; and (4) describe the common dyads and triads of chronic conditions, stratified by ethnicity and sex in primary care patients who were 45 years and above with multimorbidity. We hypothesised that there were differences in sex[2], ethnicity[3] and age[11] based on existing literature.

2 Methods

This was a cross-sectional study determining the prevalence and common patterns of multimorbidity amongst all patients who consulted a doctor in the National Healthcare Group Polyclinics (NHGP) between 1st Jul 2015 and 30th Jun 2016. We received approval from the ethics review board (National Healthcare Group Domain Specific Review Board Reference number 2018/00466) on 18 June 2018. We followed the reporting of studies conducted using observational routinely-collected health data (RECORD) statement as a guideline in preparing the report[12]. There was no funding for this project.

2.1 Setting and study population

There are eighteen polyclinics spread over the island of Singapore. Each polyclinic serves as a primary care safety net providing government-funded subsidised primary care. Each polyclinic offers a one-stop health centre for chronic disease management, National Childhood Immunisation program, children development assessment, women's cancer screening, antenatal care, health promotion, education and disease prevention, medical education and training, and National emergency planning and mobilisation.

The primary health care services in Singapore underwent a major restructuring on 1st October 2000 and was reorganised into two clusters – National Healthcare Group Polyclinics (NHGP) and SingHealth Polyclinics (SHP)[13]. This clustering and reorganisation provided a platform for consolidation and integration in order to bring about better health outcomes and greater

efficiency while maintaining some competition. NHGP consisted of nine polyclinics and they were located geographically in the central, western and northern parts of Singapore. SHP also consisted of nine polyclinics and they were located geographically in the central and eastern parts of Singapore.

About 300 primary care doctors work in the eighteen polyclinics (public primary care) compared to another 2,700 primary care doctors who work in 1,700 private general practitioner clinics[14,15]. Although the private clinics provided about 80% of the total primary care clinical load, they only provided about 55% of the demand for primary care chronic disease management. As such, the 10% of primary care doctors in the eighteen polyclinics managed 45% of all the patients with chronic diseases in primary care.

This study included all the patients who visited the nine polyclinics of NHGP.

2.2 Data Source

The source population of this study were all patients who visited National Healthcare Group Polyclinics (NHGP). Data were collected from the National Healthcare Group Polyclinics (NHGP) Business Informatics (BI) system that is an administrative database that captures all the consultation episodes, clinical parameters from structured data fields within the electronic medical records (EMR) e.g., blood pressure readings, body mass index, diagnoses codes, pharmacy data, laboratory data, and billing[16]. All the data collected were linked using patients' National Registration Identity Card (NRIC) number. We de-identified all patient information according to the personal data protection act (PDPA). A separate 'patient key' was created for each patient for de-identification by the Office of Clinical Informatics (OCI). Subsequently, NRICs were removed from the dataset prior to being made available to the research team. OCI cut the data for this research study on 14th September 2018. Data cleaning was then conducted by the research team based on the de-identified list before the analysis was performed.

The National Healthcare Group Polyclinics (NHGP) BI system is used for generating reports to the Singapore Ministry of Health regularly. System integration and user acceptance tests were implemented before any new information request from the NHGP BI system to ensure

completeness and accuracy of data. Regular surveillance is also scheduled by the OCI to rectify any anomalies detected.

For this study, the study population was the total unique number of patients of age ranging from 0 to 99 years old who had consulted a family physician at least once in NHGP between 1st Jul 2015 and 30th Jun 2016 for any reason documented with an ICD-10 diagnosis code. We excluded all patient encounters in the polyclinic that did not include an ICD-10 diagnosis code by a physician, for example, well-child visit and vaccination.

2.3 Determining the denominator and numerator for the prevalence rate

2.3.1 Denominator

Epidemiology is the study of disease about populations[17]. The 'population at risk' (PAR) is a basic concept of epidemiology and denotes the 'denominator' used for calculating the prevalence of a condition where the cases with the condition observed are used as the numerator.

In the 1970-80s, there was a lot of discussion in the family medicine literature on the ascertainment of the PAR, i.e., the denominator problem. Six methods have been proposed, each with its limitations[18]. These include the: (1) *Census method* where a single medically isolated practice serving a well-defined community could estimate its denominator by obtaining the community census; (2) *Registration by intent method* where every patient informs the practice about which members of their family considers the practice to be their regular source of care; (3) *De facto registration method* where the denominator is determined by the number of individuals who have visited a practice one or more times during a specified time period; (4) *Indicator disease method* where a disease of relatively constant frequency across all patient populations is identified, and the number of patients seen with that disease annually is then used to extrapolate the total population (i.e., the denominator); (5) *Episodes of illness method* where the frequency of episodes of illness was assumed to follow a negative binomial distribution. Hence, if the practice was able to determine the annual number of episodes of illness for each of their patients, the practice denominator could be derived from that number; and (6) *Utilisation correction factor method* where the denominator is estimated by assuming

that relatively constant proportions of the populations served will visit the practice during a particular time period. Only the 'de facto registration' and 'Utilisation correction factor' methods are the widely acceptable ascertainment methods[18].

Bass[19] argued that, although the 'de facto registration' method was useful in describing the workload of the practice, the method resulted in too many sources of variability to allow adequate comparisons of incidence and prevalence rates across practices. He suggested that the most acceptable denominator for office morbidity studies was best done by the 'utilisation correction factor' which could be determined by a separate study or through analysis of health insurance statistics[19].

However, not many investigators have used the 'utilisation correction factor' as a denominator. Recent examples included a Belgium primary care database that consisted of 43 practices[20] and a research team in Australia that has consistently used this method to adjust for the PAR from publications dating from 2008 to 2017 on the prevalence of chronic disease or multimorbidity[21-24].

For those using a capitation model, investigators used the register list[25,26] for their primary care service. For those in a fee-for-service model, many investigators used the 'de facto registration' method by using the number of patients seen over a pre-defined time-frame in a health-care setting and excluded disease-free persons who were not seeking health care[9]. , . The pre-defined time-frame ranged from at least once a year for three consecutive years[27], one visit within a time-frame of six months[28], to as short as one visit in three weeks[29]. Most studies used unique patients seen in one year as their denominators[21,23,24,30,31].

Perusing the Singapore National Health Survey 2010[32], the percentage of the general population who visited the polyclinic was not captured and therefore the 'utilisation correction factor' is unknown. A separate study needs to be conducted in the general population to derive the PAR by including both groups of persons who visited and did not visit the polyclinics. This is not permissible in the timeline for the PhD study and is not within the scope of work of the thesis.

This study was conducted in a fee-for-service primary care environment in the polyclinic setting. As such, no listing or practice register can be used. Therefore, the study team decided

to use the ‘de facto registration’ method by including all patients who had consulted a doctor in National Healthcare Group Polyclinics (NHGP) at least once between 1st Jul 2015 and 30th Jun 2016 as the denominator.

2.3.2 Numerator

Four senior family physicians in the National Healthcare Group Polyclinics (NHGP) worked together to provide a full list of chronic conditions based on our local clinical practice and doctors’ coding practices that fulfilled the criteria of the definition of chronicity. We simplified and adopted the steps used by N’Goran et al.[33] to create a master list of chronic conditions used in the local context that were deemed suitable for a study of multimorbidity in Singapore. We used O’Halloran and colleagues’ definition of chronicity of a disease as lasting at least six months, having a documented pattern of recurrence or deterioration, and having an impact on an individual’s quality of life[34].

As there was no consensus among the four senior family physicians on which multimorbidity list of chronic conditions to use, the study team adopted two lists where one was readily available locally, and another was from an international source. The local list, which consisted of 20 conditions, was the Chronic Disease Management Programme (CDMP) list[35] from the Ministry of Health whereby the government subsidised medical costs for Singaporeans with these conditions. The international list, which also consisted of 20 conditions, was recommended by Fortin et al.[36] These two lists will hereafter be referred to as the CDMP list and the Fortin list respectively. Using the International Statistical Classification of Diseases and Related Health Problems revision 10 (ICD-10), we subsequently matched all NHGP chronic conditions diagnosis codes with the CDMP list (*Appendix 2-1*) and Fortin list (*Appendix 2-2*) to determine the number of patients with any of those conditions in the NHGP database.

The study team was also unable to come to a consensus on which cut-point to select for the definition of multimorbidity. We followed the recommendation of Fortin et al.[10] of using two operational definitions of multimorbidity. Therefore, we included both cut-offs of ‘two or more’ chronic conditions (hereafter referred to as MM2+) and ‘three or more’ chronic conditions (hereafter referred to as MM3+).

The numerator was therefore, the number of patients who consulted a family physician in the specified period who had ‘two or more’ or ‘three or more’ chronic conditions based on the CDMP and Fortin lists.

This resulted in four numerators used with the same denominator:

a. The number of patients who visited the polyclinic with at least one doctor visit and at least two chronic conditions based on the CDMP list
b. The number of patients who visited the polyclinic with at least one doctor visit and at least two chronic conditions based on the Fortin list
c. The number of patients who visited the polyclinic with at least one doctor visit and at least three chronic conditions based on the CDMP list
d. The number of patients who visited the polyclinic with at least one doctor visit and at least three chronic conditions based on the Fortin list

2.4 Outcome variables

For objective 1 *(p31)*, the outcomes for the epidemiology of chronic conditions were the crude prevalence rates of single chronic conditions or single categories as described by the CDMP and Fortin lists. The outcomes for objective 2 were the crude prevalence rates and standardised prevalence rates of multimorbidity. For objective 3, the standardised prevalence rates of different age, sex and ethnic groups were compared. Finally, objective 4 described the most common dyads and triads for patients age 45 years and older. The most common dyads and triads of each sex and ethnic groups were determined by the crude prevalence rates.

2.4.1 Crude prevalence rate

The crude prevalence rate was expressed as a numeral with the numerator as the number of patients with multimorbidity and the denominator as the total number of unique patients who had consulted a doctor in National Healthcare Group Polyclinics (NHGP) at least once between 1st Jul 2015 and 30th Jun 2016. There were four crude prevalence rates due to four numerators as described in Section 2.3.2 above.

2.4.2 Standardised prevalence rate

As it was likely that different prevalence rates may occur in different sub-populations, a comparison of crude prevalence rates would be misleading since it would not be reflective of the population. Therefore, we used the standardised prevalence rate as a summary measure. We used the direct standardisation method as detailed by Bains[38]. Confidence intervals of 95% were calculated using the Poisson approximation around the standardised rates[39]. To determine whether prevalence rates of multimorbidity differ among age, sex and ethnic groups, the standardised prevalence rates were altered to 1) age-stratified, sex-and-ethnicity standardised prevalence rate; 2) sex-stratified, age-and-ethnicity standardised prevalence rate; and 3) ethnicity-stratified, age-and-sex standardised prevalence rate respectively.

We used superscripts 'a' for age-stratified, sex-and-ethnicity standardised prevalence rate, 'g' for sex-stratified, age-and-ethnicity standardised prevalence rate, and 'e' for ethnicity-stratified, age-and-sex standardised prevalence rate attached to the phrase 'standardised prevalence rate' in the results section to clearly describe the different rates used. The standardised prevalence rate with a superscript 't' attached provides the weighted average of the prevalence rate where the weights were the proportions of persons in the corresponding age/sex/ethnic groups according to the 2016 Singapore population[37] (*Appendix 2-3*). It will be termed age-sex-ethnicity standardised prevalence rate for short.

2.4.3 Dyads and Triads

Dyads were created by summing every combination of two chronic conditions separately from the CDMP and Fortin lists respectively. Triads were created by summing every combination of three chronic conditions.

For the most common dyads and triads of the total population, the number of unique patients age 45 years and above with the specified dyad (or triad) of each list was denoted the numerator. The denominator was all patients age 45 years and above who had consulted a doctor in National Healthcare Group Polyclinics (NHGP) at least once between 1st Jul 2015 and 30th Jun 2016. We chose '45 years old and above' as the 45-49 years old age group was found to be the age group with the steepest rise of multimorbidity shown in Fig 2-2 (p44).

For the most common dyads and triads of a specific sub-population, the numerator and denominator would be altered accordingly. For example, for the most common dyads of the Chinese male population within the study population, the numerator would be the number of unique Chinese male patients age 45 years and above with the specified dyads of each list; and the denominator would be all Chinese male patients age 45 years and above who had consulted a doctor in NHGP at least once between 1st Jul 2015 and 30th Jun 2016. For all cases, the most common dyads and triads were defined as a crude prevalence of 1.0% or more.

2.5 Independent variables

The independent variables (with no implication of causation) were age, sex and ethnicity. Age was divided into four categories – '0-24','25-44', '45-64', '65-99' following similar age groups used by Ashman et al.[40] and Fortin et al.[26]. Sex was classified into male and female. Ethnicity was categorised into Chinese, Malay, Indians, and Others.

2.6 Analysis

The sample size was determined by the number of patients aged 0 to 99 who visited the National Healthcare Group Polyclinics (NHGP) for at least one doctor consultation between 1st Jul 2015 and 30th Jun 2016. We used listwise deletion method for missing data[41].

For descriptive statistics, we described the mean for continuous variables and their respective standard deviation. For categorical variables, we described proportions and their respective confidence intervals where appropriate.

In objective 1 *(p31)* for describing the epidemiology of chronic conditions, the age group of patients (x-axis) was plotted against the proportion of patients with different number of chronic conditions (y-axis) in a line graph. We calculated the gradient between consecutive age groups using the formula as follows:

$$\text{Gradient}_i = (y_{i+1} - y_i) / (x_{i+1} - x_i)^{\S}$$

§ Gradient_i = gradient of age group i,
y_i = prevalence of age grp i
x_i = lower limit of age grp i

The highest gradient value indicated the sharpest rise in the percentage of patients with a specific number of chronic conditions within that specified age group.

For the third objective *(p31)*, we considered no overlap of the 95% confidence intervals for the standardised prevalence rates among the different age, sex and ethnic groups as statistically significant. For multiple comparisons, we adjusted with Bonferroni adjustment by taking the statistically significant p value as less than 0.05 divided by the number of comparisons. However, we considered only an absolute difference between the different groups of 5.0% for clinical significance.

For the fourth objective *(p31)*, we used the crude prevalence rate to rank the most common dyads and triads of co-occurring chronic conditions for primary care patients who were 45 years and above for the same population. We listed only the common dyads and triads with an overall crude prevalence rate of at least 1.0% and above. We next compared the dyads and triads among different sex and ethnic groups. For multiple comparisons, we adjusted with Bonferroni adjustment by taking the statistically significant p value as less than 0.05 divided by the number of comparisons. We considered an absolute difference between the subgroups of 10.0% or a relative difference of 300% for clinical significance.

IBM SPSS version 21 and Microsoft Office Excel 2016 were used for all statistical calculations and analyses.

2.7 Sub-group analysis

As the crude prevalence rates of the common dyads and triads would likely be determined in a large part by the majority Chinese ethnic group for the overall population, a sub-group analysis was made by determining the common dyads and triads for each of the three major ethnic groups stratified by sex. This sub-group analysis was performed using the multimorbidity list that gave a higher standardised prevalence rate between the two lists. We listed only the common dyads and triads with crude prevalence rates of at least 1.0% and above.

3 Results

3.1 Demographics of the study population

This study included 787,447 unique patients who consulted a doctor in the National Healthcare Group Polyclinics (NHGP) at least once between 1st Jul 2015 and 30th Jun 2016. We excluded one individual whose sex was not recorded. The final sample size was 787,446.

Within this study population, there were more adults aged between 65-99 years and fewer adults aged 0-44 years who visited a family physician over the one-year period when compared to the national population (*Table 2-1*). Using the CDMP list of conditions, the average number of chronic conditions increased from 0.1 for the '0-24' year age group to 0.2 for the '25-44' year age group to 1.3 for the '45-64' year age group and to 2.4 for the '65-99' year age group. Using the Fortin list, the average number of chronic conditions increased from 0.1 for the '0-24' year age group to 0.4 for the '25-44' year age group to 1.7 for the '45-64' year age group to 3.0 for the '65-99' year age group.

Patients under 25 years old had very low rates of chronic conditions for both the CDMP and Fortin lists. The increase from the '25-44' year age group to the '45-64' year age group was 6.5 times for CDMP list and 4.3 times for the Fortin list. The average number of chronic conditions almost doubled from the '45-64' year age group to the '65-99' year age group for both lists.

In terms of ethnicity, there were fewer Chinese, more Malays, Indians, and patients of other ethnicity[**] in this study population who visited a family physician over the one-year period compared to the national population. The mean age of the different ethnic groups was very different compared to each other. The Chinese were the oldest at 47.1 years old, followed by the Indians at 39.7 years old, the Others at 37.1 years old, and finally the Malays at 35.1 years old.

[**] Others included mainly Eurasians, Caucasians, Javanese.

For the CDMP list of conditions, the Chinese had an average of 1.1 chronic conditions, followed by the Indians with 0.9, the Malays at 0.7, and the Others at 0.6. For the Fortin list of conditions, the Indians had the highest average of 1.2 chronic conditions, followed by the Chinese at 1.1, the Malays at 1.0, and the Others at 0.8.

Compared to the national population, there were slightly fewer female (50.9% vs 51.2%) and more male (49.1% vs 48.8%) patients in the study population. The mean age of the female patients was 2.9 years older than the male patients (45.3 vs 42.4). The mean number of chronic conditions was the same for both sexes, 1.0 for CDMP conditions and 1.3 for Fortin conditions.

Table 2-1. Demographics of the study population of patients (N=787,446)

	Number of patients (N)	Percentage (%)	National Proportion 2016 (%)	Age (years) Mean (SD)	Number of CDMP Conditions, Mean (SD)	Number of Fortin Conditions, Mean (SD)
Age Group						
0-24	201,839	25.6	26.9	12.9 (0.18)	0.1 (0.000)	0.1 (0.001)
25-44	165,212	21.0	30.5	34.0 (0.02)	0.2 (0.001)	0.4 (0.002)
45-64	252,206	32.0	29.3	55.4 (0.01)	1.3 (0.003)	1.7 (0.003)
65-99	168,189	21.4	13.3	73.5 (0.02)	2.4 (0.004)	3.0 (0.004)
Ethnic Group						
Chinese	537,234	68.2	74.3	47.1(0.03)	1.1 (0.002)	1.1 (0.002)
Malay	127,501	16.2	13.4	35.1 (0.06)	0.7 (0.004)	1.0 (0.005)
Indian	78,452	10.0	9.1	39.7 (0.08)	0.9 (0.005)	1.2 (0.006)
Others	44,529	5.6	3.2	37.1 (0.09)	0.6 (0.005)	0.8 (0.007)
Sex						
Female	400,965	50.9	51.2	45.3 (0.04)	1.0 (0.002)	1.3 (0.003)
Male	386,481	49.1	48.8	42.4 (0.04)	1.0 (0.002)	1.3 (0.003)

3.2 The CDMP and Fortin lists of chronic conditions

Sections 3.2 and 3.3 address objective 1, the epidemiology of chronic conditions depicted in the two lists for the sample population. Table 2-2 lists the patient counts and crude prevalence rates of all the single chronic conditions of both the CDMP and Fortin lists.

Four NHGP senior family physicians in the study team unanimously agreed that the ICD code for ‘back pain’ was not considered to be a chronic condition that was reliably coded in the context at our primary care setting for ‘chronic musculoskeletal conditions causing pain or limitation’ in the Fortin’s list. As such, we only used 19 out of the 20 conditions in the Fortin list.

Table 2-2. Crude prevalence rates of chronic conditions - CDMP and Fortin lists (N=787,446)

Rank	CDMP Conditions	Patient Count	%	Fortin Conditions	Patient Count	%
1	Hyperlipidaemia	257,114	32.7	Hyperlipidaemia	257,114	32.7
2	Hypertension	221,760	28.2	Hypertension	221,760	28.2
3	Diabetes	125,058	15.9	Diabetes	124,954	15.9
4	Ischaemic Heart Disease	36,401	4.6	Arthritis &/or Rheumatoid arthritis	100,838	12.8
5	Asthma	28,778	3.7	Obesity	48,893	6.2
6	Chronic Kidney Disease	21,638	2.7	Cardiovascular disease (Angina, Myocardial infarction, Atrial fibrillation, poor circulation of lower limbs)	43,559	5.5
7	Osteoarthritis	18,378	2.3	Asthma, COPD, or Chronic bronchitis	32,611	4.1
8	Benign Prostate Hypertrophy	13,031	1.7	Chronic hepatitis	25,918	3.3
9	Osteoporosis	7,283	0.9	Stroke and Transient Ischaemic Attack	23,628	3.0
10	Stroke	7,241	0.9	Stomach problem (reflux, heartburn, or gastric ulcer)	22,233	2.8
11	Anxiety	6,085	0.8	Kidney disease or failure	22,221	2.8
12	Chronic Obstructive Pulmonary Disease (COPD)	5,080	0.6	Thyroid disorder	20,781	2.6
13	Dementia	3,571	0.5	Heart failure (including valve problem or replacement)	20,538	2.6
14	Schizophrenia	2,889	0.4	Depression or anxiety	14,910	1.9
15	Epilepsy	2,734	0.3	Chronic urinary problem	13,031	1.7
16	Rheumatoid Arthritis	2,010	0.3	Any Cancer in the last 5 years	7,940	1.0
17	Parkinson's	1,900	0.2	Osteoporosis	7,283	0.9
18	Major Depression	1,700	0.2	Dementia or Alzheimer's disease	3,571	0.5
19	Bipolar Disorder	51	0.0[††]	Colon problem (irritable bowel)	1,571	0.2
20	Psoriasis	0	0			

The commonest three conditions for both lists were ‘hyperlipidaemia’, ‘hypertension’ and ‘diabetes’ in descending order (*Table 2-2*). There were three conditions in the CDMP list that were above 10.0% prevalence rate compared to four conditions in the Fortin list. There were eight conditions altogether with a prevalence rate of above 1.0% in the CDMP list compared to 16 conditions in the Fortin list. There was zero patient count for ‘psoriasis’ in the CDMP list.

Five of the conditions in the CDMP list were not found in the Fortin list. They were a dermatological condition – ‘psoriasis’; two neurological conditions – ‘epilepsy’ and ‘Parkinson’s disease’; and two psychiatric conditions – ‘bipolar disorder’ and ‘schizophrenia’.

[††] Actual value is 0.006%

There was a total of four psychiatric conditions in the CDMP list (anxiety, schizophrenia, major depression, and bipolar disorder), and all of them recorded a prevalence rate of less than 1.0% each.

Seven of the Fortin list conditions were not found in the CDMP list. They were three gastrointestinal conditions – 'chronic hepatitis', 'stomach problem', and 'colon problem'; two endocrine conditions – 'thyroid disorder' and 'obesity'; one cardiovascular condition – 'heart failure'; and 'any cancer in the last five years'. There was only one psychiatric condition ('depression or anxiety') in the Fortin list with a prevalence rate of more than 1.0%.

3.3 Prevalence of chronic conditions

Figures 2-1 and 2-2 report the percentage of patients with chronic conditions based on the standardised prevalence rate[a] for sex and ethnicity stratified by age. The proportion of patients with chronic conditions increased with the advancement of age.

For the CDMP list (*Figure 2-1*), the steepest gradient occurred at age 50-54 for those with two conditions; and for those with three conditions, the steepest gradient occurred at age 65-69 (*Appendix 2-4*). According to the CDMP list, 50% of the population in primary care would have one chronic condition in their 50s, two conditions in their 60s and three conditions in their 70s.

For the Fortin list (*Figure 2-2*), the steepest gradient occurred at age 45-49 for those with two conditions; and for those with three conditions, the steepest gradient occurred at age 50-54 (*Appendix 2-4*). According to the Fortin list, 50% of the population in primary care would have one chronic condition in their 40s, two conditions in their 50s, three conditions in their 60s, and four conditions in their 80s.

Figure 2-1. Number of chronic conditions by age-group (CDMP list)

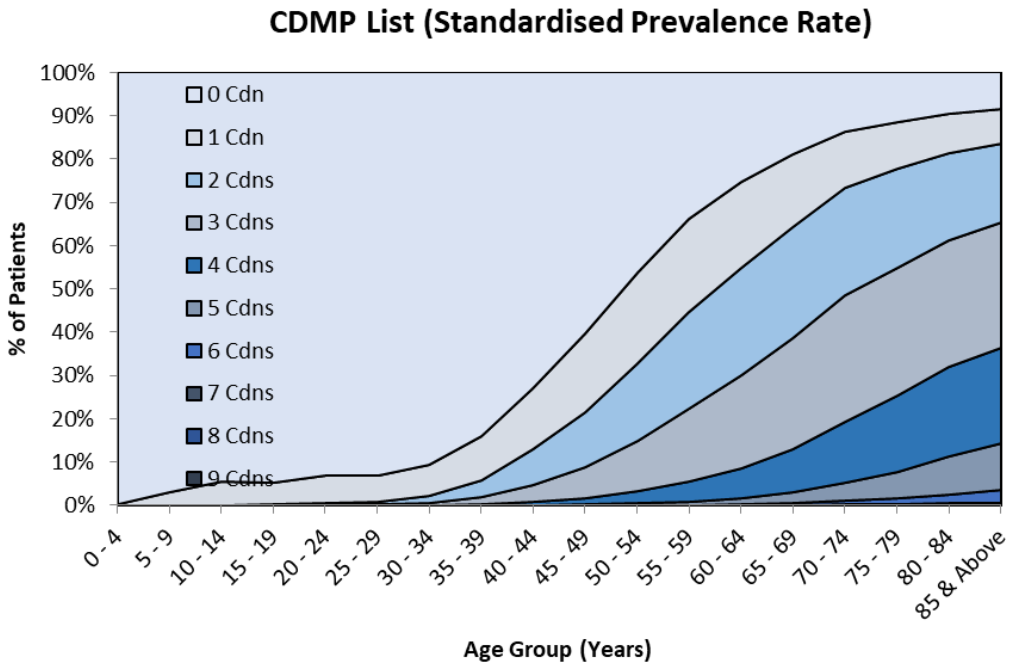
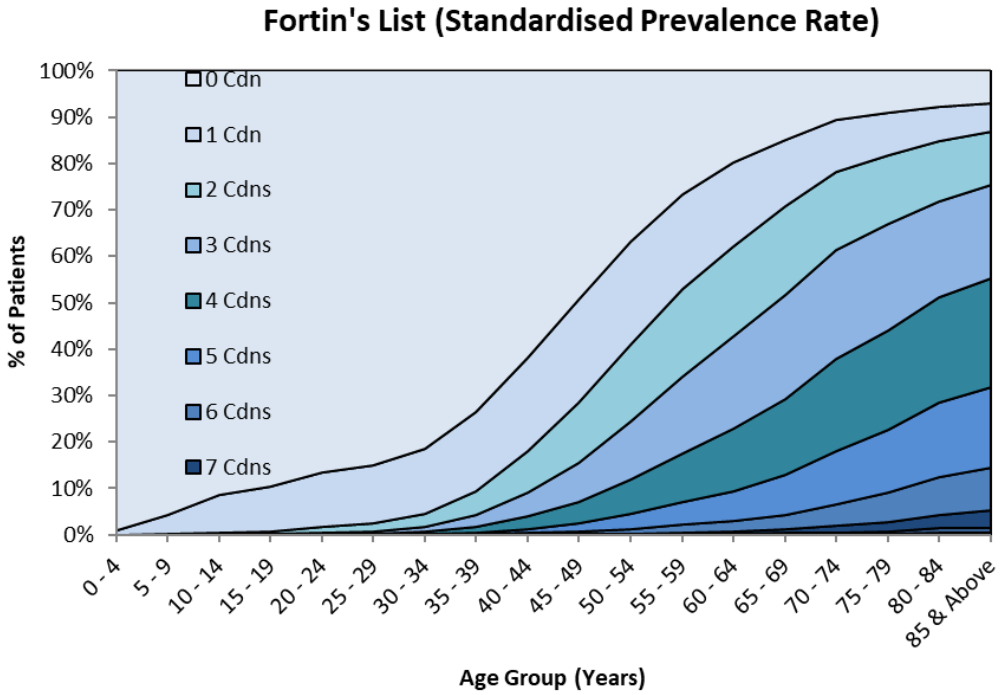


Figure 2-2. Number of chronic conditions by age-group (Fortin list)



3.4 Prevalence rates of multimorbidity

Section 3.4 addresses objective 2, the prevalence of multimorbidity using two different lists and two different cut-points. The standardised prevalence rates[t] of multimorbidity using the CDMP list were lower than that of the Fortin list (*Table 2-3*). The standardised prevalence rates[t] were also lower than that of the crude prevalence rate. The standardised prevalence rate[t] of multimorbidity was lower when MM3+ was used to define multimorbidity as compared to MM2+.

Table 2-3. Prevalence rates of multimorbidity

	CDMP MM2+ % (CI)	**Fortin MM2+ % (CI)**	**CDMP MM3+ % (CI)**	**Fortin MM3+ % (CI)**
Prevalence (Crude)	29.6	33.9	17.3	23.7
Age-sex-ethnicity standardised prevalence rate	21.9 (21.8, 22.0)	25.9 (25.8, 26.0)	12.0 (12.0, 12.1)	17.2 (17.2, 17.3)

[t] Age-sex-ethnicity standardised prevalence rate

3.5 Comparing the standardised prevalence rates of multimorbidity among age, sex and ethnic groups

Section 3.5 addresses objective 3, to determine whether there were differences in the standard prevalence rates among different age, sex, and ethnic groups.

3.5.1 Age

The prevalence rate of multimorbidity increased with age as shown in Table 2-4. The standardised prevalence rates[a] were generally lower than the crude prevalence rate for those in the '0-24' year age group. The standardised prevalence rates[a] were generally higher than the crude prevalence rate for those in the '25-44' year age group, lower for those in the '45-64' year age group, and about the same for those in the '65-99' year age group.

Patients under 25 years old had very low standardised prevalence rates[a] (range from 0.01% to 0.61%) of multimorbidity for both the CDMP and Fortin lists. Using the CDMP list and MM2+

[a] Age-stratified, sex-and-ethnicity standardised prevalence rate

definition, the standardised prevalence rate[a] of multimorbidity increased by more than six times from the ‘25-44’ year age group (5.7%) to the ‘45-64’ year age group (37.6%) and more than 12 times from the ‘25-44’ year age group to the ‘65-99’ year age group (72.3%).

Using the CDMP list and MM3+ definition, the standardised prevalence rate[a] of multimorbidity increased by more than 10 times from the ‘25-44’ year age group (1.8%) to the ‘45-64’ year age group (18.4%) and more than 26 times from the ‘25-44’ year age group to the ‘65-99’ year age group (48.5%).

Using the Fortin list and MM2+ definition, the standardised prevalence rate[a] of multimorbidity increased by more than five times from the ‘25-44’ year age group (8.9%) to the ‘45-64’ year age group (45.3%) and more than eight times from the ‘25-44’ year age group to the ‘65-99’ year age group (77.3%).

Using the Fortin list and MM3+ definition, the standardised prevalence rate[a] of multimorbidity increased by more than seven times from the ‘25-44’ year age group (4.0%) to the ‘45-64’ year age group (28.5%) and more than 15 times from the ‘25-44’ year age group to the ‘65-99’ year age group (60.9%).

There were clinically and statistically significant differences (after Bonferroni adjustment) among the standardised prevalence rates[a] of multimorbidity among all the four different age groups as there were no overlap of the confidence intervals and the absolute difference between them were at least 5.0% or more.

Table 2-4. Prevalence rates of multimorbidity stratified by age-groups

	0-24		25-44		45-64		65-99	
	Crude Prevalence %	Age-stratified, sex-and-ethnicity-standardised prevalence % (CI)	Crude Prevalence %	Age-stratified, sex-and-ethnicity-standardised prevalence % (CI)	Crude Prevalence %	Age-stratified, sex-and-ethnicity-standardised prevalence % (CI)	Crude Prevalence %	Age-stratified, sex-and-ethnicity-standardised prevalence % (CI)
CDMP MM2+	0.16	0.13 (0.12, 0.15)	5.2	5.7 (5.6,5.8)	40.4	37.6 (37.4, 37.9)	72.5	72.3 (71.9, 72.7)
CDMP MM3+	0.02	0.01 (0.01, 0.02)	1.7	1.8 (1.8, 1.9)	20.3	18.4 (18.3, 18.6)	48.8	48.5 (48.2, 48.9)
Fortin MM2+	0.73	0.61 (0.58, 0.65)	8.1	8.9 (8.7, 9.0)	48.2	45.3 (45.1, 45.6)	77.5	77.3 (76.9, 77.7)
Fortin MM3+	0.11	0.08 (0.07, 0.10)	3.7	4.0 (3.9, 4.1)	30.9	28.5 (28.3, 28.7)	61.1	60.9 (60.5, 61.2)

[a] Age-stratified, sex-and-ethnicity standardised prevalence rate

3.5.2 Sex

The standardised prevalence rates[g] of multimorbidity were higher for male patients when compared to female patients for both the CDMP and Fortin lists and both multimorbidity definitions (MM2+ and MM3+ cut-offs) as shown in Table 2-5. Although there were no overlaps between the confidence intervals indicating that the difference between the sexes were statistically significant (after Bonferroni adjustment), the difference in standardised prevalence rates between the two sexes were less than 5.0% and was therefore deemed not to be clinically significant.

Table 2-5. Prevalence rates of multimorbidity stratified by sex

	Female		Male	
	Crude Prevalence %	Sex-stratified, age-and-ethnicity-standardised prevalence % (CI)	Crude Prevalence %	Sex-stratified, age-and-ethnicity-standardised prevalence % (CI)
CDMP MM2+	29.4	20.4 (20.3, 20.5)	29.7	23.4 (23.3, 23.6)
CDMP MM3+	16.5	10.9 (10.8, 11.0)	18.1	13.2 (13.1, 13.3)
Fortin MM2+	34.6	25.0 (24.8, 25.1)	33.2	26.8 (26.7, 27.0)
Fortin MM3+	24.0	16.5 (16.4, 16.6)	23.4	18.0 (17.9, 18.1)

[g] Sex-stratified, age-and-ethnicity standardised prevalence rate

3.5.3 Ethnicity

We next compared the standardised prevalence rates[e] of multimorbidity among the different ethnic groups (*Table 2-6*). Using the CDMP list and MM2+ definition, the standardised prevalence rate[e] of multimorbidity in decreasing order for each ethnic group was Chinese (22.6%), Indian (21.1%), Malay (20.2%), followed by Others (14.3%). The order changed when the MM3+ definition was used. In decreasing order, the Indian ethnic group had the highest standardised prevalence rate[e] of multimorbidity at 12.9%, followed by Malay at 12.4%, then Chinese at 12.1%, and finally Others at 7.5%.

For CDMP MM2+, the differences in standardised prevalence rates[e] of multimorbidity were statistically different (after Bonferroni adjustment) among all ethnic groups but only the differences between the Others ethnic group and each of the three major ethnic groups were clinically significant. For CDMP MM3+, clinically significant difference (an absolute difference of 5% between standardised prevalence rates) was noted between the Others ethnic group and the Indian ethnic group only.

The ranking order of the ethnic groups based on the standardised prevalence rate[e] of the Fortin list was consistent for both MM2+ and MM3+ definitions. They were Chinese (MM2+ 26.8%, MM3+ 17.5%[‡‡]), followed by Indian (MM2+ 24.9%, MM3+ 17.5%[§§]), then Malay (MM2+ 23.5%, MM3+ 16.8%), and finally Others (MM2+ 17.3%, MM3+ 11.1%).

There were statistically significant differences (after Bonferroni adjustment) in the standardised prevalence rates[e] of the Fortin list among all the four ethnic groups except between the Chinese and Indian ethnic groups (Chinese – 17.5%, CI 17.4% - 17.6%; Indians – 17.5%, CI 17.3% - 17.8%) where the confidence intervals overlapped. Similar to the CDMP MM2+ list, only the differences between the Others ethnic group and each of the three major ethnic groups were clinically significant for both Fortin MM2+ and MM3+ cut-offs.

[‡‡] Actual standardised prevalence rate[e] was 17.548%
[§§] Actual standardised prevalence rate[e] was 17.545%.

Table 2-6. Prevalence rates of multimorbidity stratified by ethnicity

	Chinese		Malay		Indian		Others	
	Crude Prevalence %	Ethnicity-stratified, age-and-sex standardised prevalence % (CI)	Crude Prevalence %	Ethnicity-stratified, age-and-sex standardised prevalence % (CI)	Crude Prevalence %	Ethnicity-stratified, age-and-sex standardised prevalence % (CI)	Crude Prevalence %	Ethnicity-stratified, age-and-sex standardised prevalence % (CI)
CDMP MM2+	32.8	22.6 (22.5, 22.7)	21.7	20.2 (20.0, 20.5)	27.1	21.1 (20.8, 21.4)	16.7	14.3 (14.0, 14.7)
CDMP MM3+	18.7	12.1 (12.0, 12.2)	13.7	12.4 (12.2, 12.5)	17.4	12.9 (12.7, 13.1)	9.4	7.5 (7.3, 7.7)
Fortin MM2+	37.6	26.8 (26.7, 26.9)	24.9	23.5 (23.2, 23.8)	31.1	24.9 (24.6, 25.2)	19.7	17.3 (16.9, 17.7)
Fortin MM3+	26.0	17.5 (17.4, 17.6)	18.2	16.8 (16.6, 17.0)	23.0	17.5 (17.3, 17.8)	13.3	11.1 (10.8, 11.4)

[e] Ethnicity-stratified, age-and-sex standardised prevalence rate

3.6 The most common dyads and triads

Sections 3.6 and 3.7 address objective 4 regarding the dyads and triads of chronic conditions. Table 2-7 to 2-10 show a list of common dyads and triads for patients age 45 years and above for the overall population (n=420,395) for each of the multimorbidity lists and cut-points. The most common dyads and triads were defined by a crude prevalence of 1.0% or more. The list of common dyads and triads obtained was further stratified into different groups based on their ethnicity and sex. The Others ethnic group did not have any dyads or triads with a crude prevalence rate that exceeded any of the three major ethnic groups. As such, for the rest of this section, we described the patterns of multimorbidity among the three major ethnic groups only.

The dyad or triad with the highest crude prevalence rate among the different ethnic/sex groups would have a superscript '#' symbol tagged next to it. We considered an absolute difference in crude prevalence rates among the different subgroups of 10.0% or a relative difference of 300% for clinical significance. An asterisk was put next to a crude prevalence rate if it was lower than the highest crude prevalence rate for the specific dyad or triad based on the above two criteria.

3.6.1 CDMP Dyads

Table 2-7. The most common dyads using the CDMP list – Crude prevalence rates

Rank	CDMP Dyads	Overall (n = 420,395)	Chinese (n=323,941)		Malay (n=47,541)		Indian (n=33,870)	
			Female (n = 174,750)	Male (n=149,191)	Female (n=25,338)	Male (n=22,203)	Female (n=17,633)	Male (n=16.237)
1	Hyperlipidaemia/ Hypertension	44.1%	41.4%	47.4%	47.9%#	43.1%	44.3%	43.9%
2	Hypertension/ Diabetes	23.3%	20.0%*	23.7%	31.4%	26.5%	32.1%#	31.8%
3	Hyperlipidaemia/ Diabetes	5.1%	3.6%*	4.8%	6.0%	7.0%	10.7%	12.7%#
4	Diabetes/IHDα	4.6%	2.6%*	5.8%	3.7%*	7.5%	5.9%	11.6%#
5	Hypertension/IHD	3.4%	1.9%	5.3%#	1.5%*	4.5%	1.7%*	4.5%
6	Diabetes/CKDβ	2.3%	1.8%	2.5%	4.1%#	3.5%	2.0%	1.9%
7	Hypertension/CKD	1.4%	1.1%	2.0%#	1.1%	1.8%	0.5%*	0.7%
8	IHD/CKD	1.3%	0.8%*	1.7%	1.3%	2.4%#	1.0%	1.7%
9	Hypertension/ Osteoarthritis	1.1%	1.5%#	0.8%	1.2%	0.7%	1.1%	0.5%
10	Hypertension/Asthma	1.1%	0.9%	0.8%	2.2%#	1.4%	2.1%	1.0%
11	Diabetes/Asthma	1.0%	0.7%*	0.5%*	2.8%	1.2%*	4.3%#	2.1%

15,043 participants were excluded from the Others Ethnic Group. # Highest crude prevalence rate in that row; * Clinically significant lower crude prevalence rate than the prevalence rate that was tagged with # in the same row; α Ischaemic Heart Disease; β Chronic Kidney Disease

There were eleven CDMP dyads with a crude prevalence rate of 1.0% and above for the overall population (n=420,395) *(Table 2-7)*. The CDMP dyads consisted of different combinations of the seven most prevalent CDMP chronic conditions (hyperlipidaemia, hypertension, diabetes, IHD, asthma, CKD and osteoarthritis) listed in Table 2-2.

The top two dyads were hyperlipidaemia/hypertension (44.1%) and hypertension/diabetes (23.3%) with a crude prevalence rate of more than 10.0%. These two dyads were also the top two dyads for all the subgroups stratified by sex and ethnicity with a crude prevalence rate of more than 10.0%. In addition to these two dyads, the Indian females had one more dyad (hyperlipidaemia/diabetes), and the Indian males had two more dyads (hyperlipidaemia/diabetes and diabetes/IHD) with a crude prevalence rate of more than 10.0%.

The Chinese had three dyads with crude prevalence rates that surpassed the other ethnic groups, and the Malays and Indians had four dyads each.

The Chinese females had five dyads with crude prevalence rates that were clinically significantly lower than other ethnic/sex groups. The Indian males had no dyads with crude prevalence rates that were clinically significantly lower than the other ethnic/sex groups.

3.6.2 CDMP Triads

Table 2-8. The most common triads using the CDMP list – Crude prevalence rates

Rank	CDMP Triads	Overall (n = 420,395)	Chinese (n=323,941)		Malay (n=47,541)		Indian (n=33,870)	
			Female (n = 174,750)	Male (n=149,191)	Female (n=25,338)	Male (n=22,203)	Female (n=17,633)	Male (n=16.237)
1	Hyperlipidaemia/ Hypertension/ Diabetes	21.9%	19.0%*	22.1%	29.7%	24.8%	30.2%#	29.8%
2	Hypertension/ Diabetes/ IHD$^{\alpha}$	4.2%	2.5%*	5.2%	3.5%	6.7%	5.4%	9.8%#
3	Hyperlipidaemia/ Hypertension/IHD$^{\alpha}$	3.1%	1.8%	5.0%#	1.4%*	4.3%	1.5%*	4.3%
4	Hypertension/ Diabetes/CKD$^{\beta}$	2.2%	1.8%	2.4%	4.0%#	3.3%	1.9%	1.8%
5	Hyperlipidaemia/ Hypertension/CKD	1.2%	0.9%	1.6%#	0.9%	1.4%	0.4%*	0.6%

15,043 participants were excluded from the Others Ethnic Group. # Highest crude prevalence rate in that row; * Clinically significant lower crude prevalence rate than the prevalence rate that was tagged with # in the same row; $^{\alpha}$ Ischaemic Heart Disease; $^{\beta}$ Chronic Kidney Disease

There were five CDMP triads with a crude prevalence rate of 1.0% and above for the overall population (n=420,395) *(Table 2-8).* The CDMP triads consisted of different combinations of the four most prevalent and the sixth most prevalent CDMP chronic conditions (hyperlipidaemia, hypertension, diabetes, IHD, CKD) listed in Table 2-2. 'Asthma' (fifth most prevalent CDMP chronic condition) was not included in the top five CDMP triads.

Hyperlipidaemia/hypertension/diabetes was the top triad for all the ethnic groups for both sexes. Hypertension/diabetes/IHD was the second most common triad for all the ethnic groups for both sexes except the Malay females, where hypertension/diabetes/CKD (4.0%) was more common than hypertension/diabetes/IHD (3.5%). When comparing the crude prevalence rates, both the Chinese and Indians had two triads each that surpassed the other ethnic groups and the Malays had one. The males of all the three ethnic groups had no triads with crude prevalence rates that were clinically significantly lower than the other ethnic/sex groups.

3.6.3 Fortin Dyads

There were 19 dyads with a crude prevalence of rate of 1.0% and above for the overall population (n=420,395) *(Table 2-9)*. The Fortin dyads consisted of different combinations from the most prevalent Fortin chronic conditions as listed in Table 2-2. They included all the top eleven single chronic conditions (hyperlipidaemia, hypertension, diabetes, arthritis &/or rheumatoid arthritis, obesity, cardiovascular disease, chronic hepatitis, stroke/transient ischaemic attack, and kidney disease or failure) except 'asthma/COPD[χ] or chronic bronchitis' and 'stomach problems' (i.e., nine single conditions in total).

The top two dyads were hyperlipidaemia/hypertension (42.9%) and hypertension/diabetes (22.8%) with a crude prevalence rate of more than 10.0%. These two dyads were also the top two dyads for all the subgroups stratified by sex and ethnicity with a crude prevalence rate of more than 10.0%. In addition to these two dyads, Malay females had one more dyad (diabetes/obesity), Indian females had one more dyad (diabetes/arthritis), and Indian males had one more dyad (hyperlipidaemia/diabetes) with a crude prevalence rate of more than 10.0%. The Indians had nine dyads with crude prevalence rates that surpassed the other ethnic groups, and both the Chinese and Malays had five dyads each.

The Malay females had four dyads with crude prevalence rates that were clinically significantly lower than other ethnic/sex groups. The Malay males had no dyads with crude prevalence rates that were clinically significantly lower than the other ethnic/sex groups.

[χ] Chronic Obstructive Pulmonary Disease

Table 2-9. The most common dyads using the Fortin list – Crude prevalence rates

Rank	Fortin Dyads	Overall (n = 420,395)	Chinese (n=323,941)		Malay (n=47,541)		Indian (n=33,870)	
			Female (n = 174,750)	Male (n=149,191)	Female (n=25,338)	Male (n=22,203)	Female (n=17,633)	Male (n=16.237)
1	Hyperlipidaemia/ Hypertension	42.9	43.2%	45.9%	46.6%#	41.0%	43.3%	41.7%
2	Hypertension/ Diabetes	22.8	21.3%*	23.1%	30.6%	25.4%	31.3%#	30.3%
3	Hypertension/Arthritis	6.8	7.1%#	5.8%	6.5%	4.8%	6.8%	4.1%
4	Diabetes/Arthritis	6.3	5.5%	4.7%*	8.5%	6.1%	14.7%#	9.6%
5	Hyperlipidaemia/ Diabetes	4.6	3.8%	4.4%	5.2%	6.0%	9.3%	10.4%#
6	Diabetes/Obesity	4.1	3.0%*	3.1%*	11.9%#	6.6%	8.3%	6.0%
7	Diabetes/ Cardiovascular	3.5	3.3%	4.9%	2.3%*	5.3%	3.1%	7.9%#
8	Arthritis/ Obesity	3.1	2.2%*	1.5%*	8.2%	3.6%	9.6%#	3.4%
9	Hypertension/ Cardiovascular	2.8	3.0%	4.6%#	1.1%*	3.5%	0.9%*	3.1%
10	Hyperlipidaemia/ Arthritis	2.5	2.6%	1.7%	2.4%	1.5%	3.4%#	2.0%
11	Hypertension/Obesity	2.1	1.8%	1.9%	5.0%#	2.8%	2.8%	1.5%*
12	Arthritis/ Cardiovascular	1.9	1.8%	2.2%	1.0%*	2.1%	2.2%	3.7%#
13	Obesity/ Cardiovascular	1.3	1.0%	1.3%	2.3%	2.9%	2.6%	2.9%#
14	Hypertension/Stroke	1.3	1.5%	2.0%#	0.6%*	1.0%	0.4%*	0.8%
15	Cardiovascular/Stroke	1.3	1.3%	1.7%	1.0%	1.7%	0.9%	1.9%#
16	Diabetes/Stroke	1.2	1.3%	1.5%#	1.1%	1.3%	0.8%	1.4%
17	Cardiovascular/ Kidney	1.2	1.1%	1.4%	1.4%	2.3%#	1.0%	1.6%
18	Diabetes/Kidney	1.1	1.1%	1.3%	1.5%	1.6%#	0.8%	0.9%
19	Diabetes/ Chronic Hepatitis	1.1	1.2%	1.4%#	0.5%	0.7%	0.8%	1.1%

15,043 participants were excluded from the Others Ethnic Group. # Highest crude prevalence rate in that row; * Clinically significant lower crude prevalence rate than the prevalence rate that was tagged with # in the same row

3.6.4 Fortin Triads

There were 12 triads with a crude prevalence rate of 1.0% and above for the overall population (n=420,395) *(Table 2-10).* The Fortin triads included the top eleven single chronic conditions (hyperlipidaemia, hypertension, diabetes, arthritis &/or rheumatoid arthritis, obesity, cardiovascular disease, stroke and transient ischaemic attack, and kidney disease or failure) except 'asthma, COPD[χ], or chronic bronchitis', 'stomach problem', and 'chronic hepatitis' (i.e., eight single conditions in total).

[χ] Chronic Obstructive Pulmonary Disease

Table 2-10. The most common triads using the Fortin list – Crude prevalence rates

Rank	Fortin Triads	Overall (n = 420,395)	Chinese (n=323,941)		Malay (n=47,541)		Indian (n=33,870)	
			Female (n = 174,750)	Male (n=149,191)	Female (n=25,338)	Male (n=22,203)	Female (n=17,633)	Male (n=16.237)
1	Hyperlipidaemia/ Hypertension/Diabetes	21.9%	18.9%*	22.1%	29.7%	24.8%	30.2%#	29.8%
2	Hyperlipidaemia/ Hypertension/Arthritis	5.5%	6.7%#	4.7%	5.3%	4.0%	5.6%	3.3%
3	Hypertension/Diabetes/ Arthritis	5.2%	5.3%	3.9%	7.1%	5.1%	11.4%#	7.1%
4	Hypertension/Diabetes/ Obesity	3.8%	2.7%*	3.1%*	11.1%#	6.3%	6.9%	5.2%
5	Hypertension/Diabetes/ Cardiovascular	3.2%	1.9%*	4.4%	2.2%*	4.5%	2.7%	6.7%#
6	Hyperlipidaemia/ Hypertension/ Cardiovascular	2.5%	1.4%*	4.2%#	1.0%*	3.3%	0.7%*	2.9%
7	Hyperlipidaemia/ Hypertension/Obesity	2.0%	1.6%	1.8%	4.4%#	2.7%	2.3%	1.5%
8	Diabetes/Arthritis/ Obesity	1.7%	1.4%*	0.8%*	4.5%	2.1%	5.9%#	2.5%
9	Hyperlipidaemia/ Hypertension/Stroke	1.2%	1.0%	1.8%#	0.5%*	0.9%	0.3%*	0.7%
10	Hypertension/Arthritis/ Obesity	1.1%	1.2%	0.6%*	2.9%#	1.4%	2.5%	0.8%
11	Hypertension/Diabetes/ Stroke	1.1%	1.0%	1.4%#	1.0%	1.2%	0.7%	1.2%
12	Hypertension/Diabetes/ Kidney	1.0%	0.8%	1.2%	1.4%	1.5%#	0.8%	0.9%

15,043 participants were excluded from the Others Ethnic Group. # Highest crude prevalence rate in that row; * Clinically significant lower crude prevalence rate than the prevalence rate that was tagged with # in the same row

Hyperlipidaemia/hypertension/diabetes was the top triad for all the ethnic groups for both sexes with a crude prevalence rate of 10.0% and above. These top triad was also the top triad for all the subgroups stratified by sex and ethnicity with a crude prevalence rate of more than 10.0%. In addition to this triad, Malay females had one more triad (hypertension/diabetes/obesity), and Indian females had one more triad (hypertension/diabetes/arthritis) with a crude prevalence rate of more than 10.0%. In terms of the crude prevalence rate, each of the three ethnic groups had four triads that surpassed the other ethnic groups.

The Chinese females had five triads with crude prevalence rates that were clinically significantly lower than other ethnic/sex groups. Both the Malay and Indian males had no dyads with crude prevalence rates that were clinically significantly lower than other ethnic/sex groups.

3.7 Sub-group analysis of the common dyads and triads of multimorbidity

The Fortin list was found to have a higher standardised prevalence rate[t] compared with the CDMP list in Section 3.4 (*p44*). Therefore, we determined the common dyads and triads of the three major ethnic groups stratified by sex instead of the overall population using the Fortin list in this section. Table 2-11, 2-12 and 2-13 show the most common dyads and triads based on the total Chinese, Malay, and Indian patients age 45 years and above respectively. The most common dyads and triads were defined by a crude prevalence of 1.0% or more.

3.7.1 Chinese ethnic group (Table 2-11)

'Hypertension', 'stroke and transient ischaemic attack', and 'chronic hepatitis' tended to occur more in combination with other conditions to form a dyad or triad for Chinese males. 'Hypertension' and 'arthritis &/or rheumatoid arthritis' tended to occur more in combination with other conditions to form a dyad or triad for Chinese females. Although 'asthma, COPD, or chronic bronchitis', as a single condition, was ranked number seven in terms of prevalence rate (*Table 2-2*), it was not seen at all in the common dyads and triads of the Chinese ethnic group for both sexes.

3.7.2 Malay ethnic group (Table 2-12)

Both the Malay males and females tended to have more frequent occurrences of 'kidney disease or failure' in combination with other conditions to form a dyad or triad. None of the other female ethnic groups had 'kidney disease or failure' found in any of the triads at all with a crude prevalence rate of 1.0% and above. 'Obesity' was also a distinctly common condition in combination with other conditions to form a dyad or triad for the Malay females. Out of the 15 triads listed, nine of them consisted of 'obesity', of which six of the triads had the highest prevalence rate when compared to all the other subgroups (hypertension/diabetes/**obesity**, hyperlipidaemia/hypertension/**obesity**, hypertension/arthritis &/or rheumatoid arthritis/**obesity**, diabetes/**obesity**/chronic hepatitis, diabetes/**obesity**/kidney disease or failure, diabetes/**obesity**/asthma, COPD, or chronic bronchitis).

[t] Age-sex-ethnicity standardised prevalence rate

3.7.3 Indian ethnic group (Table 2-13)

'Diabetes' and 'cardiovascular disease' tended to occur more frequently in combination with other conditions to form a dyad or triad for both sexes of the Indians. Although 'kidney disease or failure', as a single condition, was ranked number eleven in terms of prevalence rate (*Table 2-2*), it was not seen at all in the common triads of the Indian ethnic group for both sexes. Only one dyad for Indian males had this condition. Only the Indian females had 'thyroid disorder' in combination with other conditions to form a dyad, none of the other subgroups had this condition found in combination with other conditions with a crude prevalence rate of 1.0% and above.

Table 2-11. The most common dyads and triads for Chinese patients above 45 years old stratified by sex (Fortin List, n = 323,941)

Rank	Female (n = 174,750)				Male (n=149,191)			
	Dyad	%	Triad	%	Dyad	%	Triad	%
1	Hyperlipidaemia/Hypertension	40.9	Hyperlipidaemia/Hypertension/Diabetes	18.9	Hyperlipidaemia/Hypertension	45.9	Hyperlipidaemia/Hypertension/Diabetes	22.1
2	Hypertension/Diabetes	19.7	Hyperlipidaemia/Hypertension/Arthritis	6.7#	Hypertension/Diabetes	23.1	Hyperlipidaemia/Hypertension/Arthritis	4.7
3	Hypertension/Arthritis	8.3#	Hypertension/Diabetes/Arthritis	5.3	Hypertension/Arthritis	5.8	Hypertension/Diabetes/Cardiovascular	4.4
4	Diabetes/Arthritis	6.2	Hypertension/Diabetes/Obesity	2.7	Diabetes/Cardiovascular	4.9	Hyperlipidaemia/Hypertension/Cardiovascular	4.2#
5	Hyperlipidaemia/Arthritis	3.4#	Hypertension/Diabetes/Cardiovascular	1.9	Diabetes/Arthritis	4.7	Hypertension/Diabetes/Arthritis	3.9
6	Hyperlipidaemia/Diabetes	3.3	Hyperlipidaemia/Hypertension/Obesity	1.6	Hypertension/Cardiovascular	4.6#	Hypertension/Diabetes/Obesity	3.1
7	Diabetes/Obesity	2.8	Diabetes/Arthritis/Obesity	1.4	Hyperlipidaemia/Diabetes	4.4	Hyperlipidaemia/Hypertension/Obesity	1.8
8	Arthritis/Obesity	2.8	Hyperlipidaemia/Hypertension/Cardiovascular	1.4	Diabetes/Obesity	3.1	Hyperlipidaemia/Hypertension/Stroke	1.8#
9	Diabetes/Cardiovascular	2.0	Hypertension/Arthritis/Obesity	1.2	Arthritis/Cardiovascular	2.2	Hypertension/Diabetes/Stroke	1.4#
10	Hypertension/Obesity	1.8			Hypertension/Stroke	2.0#	Hypertension/Diabetes/Kidney	1.2
11	Hypertension/Cardiovascular	1.6			Hypertension/Obesity	1.9	Hypertension/Diabetes/Chronic Hepatitis	1.1#
12	Arthritis/Cardiovascular	1.5			Hyperlipidaemia/Arthritis	1.7	Hyperlipidaemia/Hypertension/Chronic Hepatitis	1.1#
13	Arthritis/Chronic Hepatitis	1.1#			Cardiovascular/Stroke	1.7	Hypertension/Arthritis/Cardiovascular	1.0#
14	Hypertension/Stroke	1.1			Cardiovascular/Kidney	1.6		
15	Diabetes/Stroke	1.0			Diabetes/Stroke	1.5#		
16					Arthritis/Obesity	1.5		
17					Diabetes/Chronic Hepatitis	1.4#		
18					Hypertension/Chronic Hepatitis	1.3#		
19					Diabetes/Kidney	1.3		
20					Obesity/Cardiovascular	1.3		
21					Hypertension/Kidney	1.1#		
22					Hypertension/Urinary	1.0#		

# denotes the highest crude prevalence rate for that specific dyad or triad compared with other ethnic/sex subgroups across Table 2-11, Table 2-12 & Table 2-13.

Table 2-12. The most common dyads and triads for Malay patients above 45 years old stratified by sex (Fortin List, n = 47,541)

Rank	Female (n=25,338)				Male (n=22,203)			
	Dyad	**%**	**Triad**	**%**	**Dyad**	**%**	**Triad**	**%**
1	Hyperlipidaemia/Hypertension	46.6#	Hyperlipidaemia/Hypertension/Diabetes	29.7	Hyperlipidaemia/Hypertension	41.0	Hyperlipidaemia/Hypertension/Diabetes	24.8
2	Hypertension/Diabetes	30.6	Hypertension/Diabetes/Obesity	11.1#	Hypertension/Diabetes	25.4	Hypertension/Diabetes/Obesity	6.3
3	Diabetes/Obesity	11.9#	Hypertension/Diabetes/Arthritis	7.1	Diabetes/Obesity	6.6	Hypertension/Diabetes/Arthritis	5.1
4	Diabetes/Arthritis	8.5	Hyperlipidaemia/Hypertension/Arthritis	5.3	Diabetes/Arthritis	6.1	Hypertension/Diabetes/Cardiovascular	4.5
5	Arthritis/Obesity	8.2	Diabetes/Arthritis/Obesity	4.5	Hyperlipidaemia/Diabetes	6.0	Hyperlipidaemia/Hypertension/Arthritis	4.0
6	Hypertension/Arthritis	6.5	Hyperlipidaemia/Hypertension/Obesity	4.4#	Diabetes/Cardiovascular	5.3	Hyperlipidaemia/Hypertension/Cardiovascular	3.3
7	Hyperlipidaemia/Diabetes	5.2	Hypertension/Arthritis/Obesity	2.9#	Hypertension/Arthritis	4.8	Hyperlipidaemia/Hypertension/Obesity	2.7
8	Hypertension/Obesity	5.0#	Hypertension/Diabetes/Cardiovascular	2.2	Arthritis/Obesity	3.6	Diabetes/Arthritis/Obesity	2.1
9	Obesity/Asthma	2.4	Hyperlipidaemia/Diabetes/Obesity	1.6	Hypertension/Cardiovascular	3.5	Diabetes/Obesity/Cardiovascular	1.7#
10	Hyperlipidaemia/Arthritis	2.4	Hypertension/Diabetes/Kidney	1.4	Obesity/Cardiovascular	2.9	Hypertension/Diabetes/Kidney	1.5#
11	Obesity/Cardiovascular	2.3	Hyperlipidaemia/Diabetes/Arthritis	1.3	Hypertension/Obesity	2.7	Hypertension/Arthritis/Obesity	1.4
12	Diabetes/Cardiovascular	2.3	Diabetes/Obesity/Cardiovascular	1.3	Cardiovascular/Kidney	2.3#	Hypertension/Diabetes/Stroke	1.2
13	Obesity/Chronic Hepatitis	1.9#	Diabetes/Obesity/Kidney	1.2#	Arthritis/Cardiovascular	2.1	Diabetes/Arthritis/Cardiovascular	1.1
14	Obesity/Kidney	1.8#	Diabetes/Obesity/Asthma	1.0#	Cardiovascular/Stroke	1.7	Hyperlipidaemia/Diabetes/Arthritis	1.0
15	Diabetes/Kidney	1.5	Diabetes/Obesity/Chronic Hepatitis	1.0#	Diabetes/Kidney	1.6#		
16	Cardiovascular/Kidney	1.4			Hyperlipidaemia/Arthritis	1.5		
17	Hypertension/Cardiovascular	1.1			Diabetes/Stroke	1.3		
18	Diabetes/Stroke	1.1			Stroke/Kidney	1.1#		
19	Arthritis/Asthma	1.1			Obesity/Chronic Hepatitis	1.1		
20	Arthritis/Cardiovascular	1.0			Obesity/Kidney	1.0		
21	Cardiovascular/Stroke	1.0			Hypertension/Stroke	1.0		
22					Cardiovascular/Asthma	1.0		

# denotes the highest crude prevalence rate for that specific dyad or triad compared with other ethnic/sex subgroups across Table 2-11, Table 2-12 & Table 2-13.

Table 2-13. The most common dyads and triads for Indian patients above 45 years old stratified by sex (Fortin List, n = 33,870)

Rank	Female (n=17,633)				Male (n=16.237)			
	Dyad	%	Triad	%	Dyad	%	Triad	%
1	Hyperlipidaemia/Hypertension	43.3	Hyperlipidaemia/Hypertension/Diabetes	30.2#	Hyperlipidaemia/Hypertension	41.7	Hyperlipidaemia/Hypertension/Diabetes	29.8
2	Hypertension/Diabetes	31.3#	Hypertension/Diabetes/Arthritis	11.4#	Hypertension/Diabetes	30.3	Hypertension/Diabetes/Arthritis	7.1
3	Diabetes/Arthritis	14.7#	Hypertension/Diabetes/Obesity	6.9	Hyperlipidaemia/Diabetes	10.4#	Hypertension/Diabetes/Cardiovascular	6.7#
4	Arthritis/Obesity	9.6#	Diabetes/Arthritis/Obesity	5.9#	Diabetes/Arthritis	9.5	Hypertension/Diabetes/Obesity	5.2
5	Hyperlipidaemia/Diabetes	9.3	Hyperlipidaemia/Hypertension/Arthritis	5.6	Diabetes/Cardiovascular	7.9#	Hyperlipidaemia/Hypertension/Arthritis	3.3
6	Diabetes/Obesity	8.3	Hyperlipidaemia/Diabetes/Arthritis	3.1#	Diabetes/Obesity	6.0	Hyperlipidaemia/Hypertension/Cardiovascular	2.9
7	Hypertension/Arthritis	6.8	Hypertension/Diabetes/Cardiovascular	2.7	Hypertension/Arthritis	4.1	Diabetes/Arthritis/Obesity	2.5
8	Hyperlipidaemia/Arthritis	3.4	Hypertension/Arthritis/Obesity	2.5	Arthritis/Cardiovascular	3.7#	Hyperlipidaemia/Diabetes/Arthritis	2.5
9	Diabetes/Cardiovascular	3.1	Hyperlipidaemia/Hypertension/Obesity	2.3	Arthritis/Obesity	3.4	Diabetes/Arthritis/Cardiovascular	2.3#
10	Hypertension/Obesity	2.8	Hyperlipidaemia/Diabetes/Obesity	1.8#	Hypertension/Cardiovascular	3.1	Diabetes/Obesity/Cardiovascular	1.6
11	Obesity/Cardiovascular	2.6	Diabetes/Arthritis/Cardiovascular	1.6	Obesity/Cardiovascular	2.9#	Hyperlipidaemia/Hypertension/Obesity	1.5
12	Obesity/Asthma	2.5#	Arthritis/Obesity/Asthma	1.3#	Hyperlipidaemia/Arthritis	2.0	Hyperlipidaemia/Diabetes/Obesity	1.4
13	Arthritis/Cardiovascular	2.2	Diabetes/Obesity/Cardiovascular	1.2	Cardiovascular/Stroke	1.9#	Hypertension/Diabetes/Stroke	1.2
14	Arthritis/Asthma	2.0#	Arthritis/Obesity/Cardiovascular	1.1#	Cardiovascular/Kidney	1.6	Hyperlipidaemia/Diabetes/Cardiovascular	1.2#
15	Obesity/Thyroid	1.7#			Cardiovascular/Asthma	1.6#	Hypertension/Arthritis/Cardiovascular	1.0
16	Diabetes/Asthma	1.3#			Hypertension/Obesity	1.5		
17	Arthritis/Thyroid	1.2#			Diabetes/Stroke	1.4		
18	Diabetes/Thyroid	1.2#			Diabetes/Asthma	1.1		
19	Asthma/Thyroid	1.1#			Diabetes/Chronic Hepatitis	1.1		
20	Cardiovascular/Asthma	1.1						
21	Obesity/Chronic Hepatitis	1.1						

# denotes the highest crude prevalence rate for that specific dyad or triad compared with other ethnic/sex subgroups across Table 2-11, Table 2-12 & Table 2-13.

4 Discussion

4.1 Summary of results

This study described the epidemiology of multimorbidity of Singapore's primary care population. Patients under 25 years old had very low rates of chronic conditions for both the CDMP and Fortin lists. The prevalence of chronic conditions increased by several fold from the '25-44' year age group to the '45-64' year age group and with further increase to the '65-99' year age group for both the CDMP and Fortin lists. There were different findings when using the two different lists to describe the prevalence of chronic conditions and multimorbidity in the sample population. The two lists will be discussed in more detail in Section 4.3 (*p64*).

The standardised prevalence rate[t] of multimorbidity using CDMP MM2+ was 21.9%, 25.9% for Fortin MM2+, 12.0% for CDMP MM3+, and 17.2% for Fortin MM3+ (*Table 2-3*). The standardised prevalence rates[a] of all the four age groups were statistically and clinically different from each other (*Table 2-4*). There was no clinically significant difference in the standardised prevalence rates[g] of multimorbidity between the sexes (*Table 2-5*). There were also no clinically significant differences in the standardised prevalence rates[e] of multimorbidity among the three major ethnic groups in Singapore (*Table 2-6*).

The two most common dyads of chronic conditions based on crude prevalence rates for those 45 years old and above were hyperlipidaemia/hypertension and hypertension/diabetes for all the different ethnic groups and sexes (*Table 2-7 & Table 2-9*). The most common triad of chronic conditions was hyperlipidaemia/hypertension/diabetes (*Table 2-8 & Table 2-10*).

[t] Age-sex-ethnicity standardised prevalence rate
[g] Sex-stratified, age-and-ethnicity standardised prevalence rate
[e] Ethnicity-stratified, age-and-sex standardised prevalence rate

4.2 Comparison with other studies

4.2.1 Prevalence rate of multimorbidity

Comparing our results with those of other studies is difficult due to the different conditions, different number of conditions selected to form the multimorbidity list, data sources, and reference populations. When using two or more chronic conditions to define multimorbidity, most estimates from the primary care setting reported prevalence rates between 20-30% for the entire population and 50-90% for the elderly[1,5,23,25,42,43]. Ours were 21.9% (CDMP list) and 25.9% (Fortin list) for the entire population (*Table 2-3*), and 72.5% (CDMP list) and 77.5% (Fortin list) for the older adult population (age 65-99) (*Table 2-4*). As such, our estimates of the standardised prevalence rates[t] of multimorbidity were comparable to the international literature.

When using three or more chronic conditions to define multimorbidity, the age-standardised prevalence rate was 14.0-15.2% in the literature on practice-based populations[39,44]. Our estimates of 12.0% (CDMP list) and 17.2% (Fortin list) were comparable to their findings (*Table 2-3*).

4.2.2 Age and prevalence rate of multimorbidity

Similar to the prevalence rates of chronic conditions, patients under 25 years old had very low standardised prevalence rates[a] of multimorbidity for both the CDMP and Fortin lists. The standardised prevalence rates[a] of multimorbidity increased progressively from the '25-44' year age group to the '45-64' year age group and with further increase to the '65-99' year age group for both the CDMP and Fortin lists. Our findings confirmed the significant positive association between age and prevalence of multimorbidity, irrespective of the definitions used for multimorbidity, consistent with that found in a growing world literature[1,21,25,26,39,42,45-51].

[t] Age-sex-ethnicity standardised prevalence rate
[a] Age-stratified, sex-and-ethnicity standardised prevalence rate

4.2.3 Sex and prevalence rate of multimorbidity

The association between sex and the prevalence of multimorbidity has been less consistent across studies[2]. This study found no clinically statistically significant sex differences in the standardised prevalence rate[g] of multimorbidity. Other investigators who conducted multimorbidity studies in primary care also found no sex differences in the occurrences of multimorbidity[21,28,22,40,42,51]. Fortin et al.[44] observed that more females than males were found with multimorbidity were found in the general population, whereas the contrary was found in the practice-based population. However, in the population health index survey (community-dwelling individuals) conducted in Singapore, no sex differences were found in the prevalence rate of multimorbidity between males and females aged 21 years and above[6]. Further comparison studies locally using the same list of multimorbidity conditions would need to be conducted to confirm whether there are sex differences between the two settings.

Schafer et al.[51] reported that the difference in prevalence rates of multimorbidity between the sexes depended on the type of multimorbidity conditions considered. They explained that females seemed to be more vulnerable to anxiety, depression, somatoform disorders, and pain-related morbidity while males appeared to be more vulnerable to cardiovascular and metabolic diseases. In our study when we looked at the common dyads and triads of multimorbidity in Sections 3.6-3.7 *(p49-59*), the males also appeared to be more vulnerable to cardiovascular and metabolic diseases while the females were more vulnerable to arthritis.

4.2.4 Patterns of multimorbidity

The findings in our study showed that the most common dyads were hyperlipidaemia/hypertension and hypertension/diabetes. The most common triad was hyperlipidaemia/hypertension/diabetes. These findings were consistent with results from international[40,49,52] and local studies[6].

Hyperlipidaemia/hypertension/arthritis was found to be the second most common triad in the Chinese ethnic group (both males and females); for the Malay ethnic group,

[g] Sex-stratified, age-and-ethnicity standardised prevalence rate

hyperlipidaemia/hypertension/obesity took precedence; and hypertension/diabetes/arthritis took precedence for the Indian ethnic group.

Salive[9] in his review of multimorbidity in older adults stated that the most common combinations of chronic conditions could be predicted from the individual chronic condition prevalence rates. In our study, the different combinations of the most prevalent single chronic conditions (*Table 2-2*) were also the common dyads and triads seen. However, the condition 'asthma' and 'stomach problem' were not included in the most common dyads and triads indicating that the most prevalent single chronic conditions may not always be able to predict the most common combinations.

Furthermore, 'depression' and 'anxiety' were prominently not represented in all the patterns of this study compared to non-local studies. The conspicuous absence of mental disorders in the patterns of multimorbidity in this study could be because there is a lower prevalence of mental illness in Singapore. However, according to Chong et al.[53], the prevalence of major depression in a local population-based mental health survey was 5.8%, bipolar disorder was 1.2%, and generalised anxiety disorder was 0.9%. The prevalence rates of the above mental disorders were much lower in the present study – the crude prevalence rate of major depression was 0.2%, bipolar disorder was 0.006%, and generalised anxiety disorder was 0.8% (*Table 2-2*).

The other likely reason for the absence of mental disorders is the social stigma associated with these conditions resulting in the decreased help-seeking behaviour by the local population[54]. Chong et al.[55] found that only 50.1% of respondents with severe disability across any mental disorder had sought help from some service in the past year. Individuals with moderate or mild levels of mental disorder had lower rates of consultation. Their study found that the main sources of help were from religious or other non-medical healers rather than from family physicians or mental health specialists.

4.3 Comparison between CDMP and Fortin list with different cut-points - addressing objective 2

In this section, we discuss the advantages and disadvantages of the CDMP and Fortin lists of chronic conditions and also that of the different cut-points used for defining multimorbidity. We will address the controversial issues on multimorbidity research from Chapter One and attempt to make recommendations on lists and cut-points, based on this study.

4.3.1 The CDMP vs Fortin list

The CDMP list is based on the list of important chronic conditions that have a significant burden in the Singapore healthcare system where the Singapore Ministry of Health provides financial subsidy to patients who suffer from these conditions to help reduce their monetary burden. Therefore, these conditions are chosen based on the country's health burden and not strictly from the primary care perspective. A good example is the zero-patient count for psoriasis from the 787,446 primary care patients in this study (*Table 2-2*).

A team of well-established multimorbidity researchers developed the Fortin list after studying various multimorbidity lists used in several countries which targeted the primary healthcare system[36]. Conceptually, the Fortin list is more suitable for measuring multimorbidity in primary care.

Sixteen out of the 19 single conditions in the Fortin list had a prevalence rate of more than 1.0% while only eight out of the 20 conditions in the CDMP list had a prevalence rate of more than 1.0% (*Table 2-2*). The Fortin list consisted of categories of conditions and included 37 ICD-10 codes used in NHGP (*Appendix 2-2*). The CDMP list included 26 ICD-10 codes used in NHGP (*Appendix 2-1*). So, even though there were only 19 conditions used in the Fortin list, more ICD-10 diagnoses were captured than in the CDMP list. Using the Fortin list, the prevalence rate of multimorbidity was consistently higher than that of the CDMP list (*Table 2-3*). There were consistently more dyads and triads that had a prevalence rate of 1.0% and above when using the Fortin list than when using the CDMP list (*Table 2-7 to 2-10*). The Fortin list is more intuitive as it combines conditions like 'anxiety' and 'depression' into one category recognising perhaps that about 85% of patients with depression have significant anxiety and vice versa[56]. Therefore, in terms of practicality, the Fortin list picked up more chronic and

relevant conditions by merging frequently co-occurring conditions into one category in primary care than the CDMP list that kept all the conditions separate.

Although we noticed differences between the gradients in the increase in proportion of patients with chronic conditions using the two different lists (*Figures 2-1 & 2-2*), it was evident that the sudden surge in the proportion (by age) of chronic conditions occurs around the middle-age years of individuals. The increase in the number of chronic conditions for the Fortin list was more gradual, i.e., the steepest slope for two conditions at age 45-49 and for three conditions at age 50-54 (*Figure 2-2 & Appendix 2-4*), when compared to the CDMP list. The steepest slope for two conditions of the CDMP list was at age 50-54, and for three conditions at age 65-69 years old (*Figure 2-1 & Appendix 2-4*). In terms of capturing the full breadth of multimorbidity across the ages, the Fortin list appears to be more sensitive when compared to the CDMP list.

4.3.2 Cut-off for 'two or more' vs 'three or more' chronic conditions

As mentioned in Chapter One, one of the concerns of using the cut-off for two conditions is that a large majority of patients would be classified as having multimorbidity, making the classification less clinically meaningful[10].

When using the CDMP list with an MM2+ cut-off, the standardised prevalence rate[t] of multimorbidity was similar to using the Fortin list (CDMP MM2+ 21.9%, Fortin MM2+ 25.9%) (*Table 2-3*). As the surge in the proportion of chronic conditions occur around the middle-age years of an individual, we looked more carefully at the prevalence rates of multimorbidity for patients above 44 years old (*Table 2-4*).

When using the CDMP list with an MM2+ cut-off, more than one in three (37.6% of patients age 45-64) and close to three in four (72.3% of patients age 65-99) patients were classified as having multimorbidity for the '45-64' year and '65-99' year age groups respectively. When using the Fortin list with an MM2+ cut-off, almost one in two (45.3 % of patients age 45-64) patients and more than three in four (77.3% of patients age 65-99) patients were classified as

[t] Age-sex-ethnicity standardised prevalence rate

having multimorbidity. In general, a large proportion of older adults would be classified as having multimorbidity when we use the MM2+ cut-off.

When using CDMP list with an MM3+ cut-off, almost one in five (18.4% of patients age 45-64) and close to one in two (48.5% of patients age 65-99) patients were classified as having multimorbidity for the '45-64' year and '65-99' year age groups respectively. When using Fortin list with an MM3+ cut-off, more than one in four (28.5% of patients age 45-64) patients and about three in five (60.9% of patients age 65-99) patients were classified as having multimorbidity.

Compared to MM2+, MM3+ results in a lower prevalence of multimorbidity and likely better identify patients with higher needs and hence may be more meaningful for clinicians than MM2+ which is less discriminating[57].

In summary, the Fortin list is conceptually more suitable for measuring multimorbidity in primary care, more practical as it reflects disease categories rather than single conditions like the CDMP list, and is more sensitive in capturing the full breadth of multimorbidity across the ages, when compared to the CDMP list. Using MM3+ as the cut-off can identify a smaller number of patients with higher needs compared to MM2+. Putting these two considerations together, it would seem that the Fortin list with MM3+ cut-off is the most suitable definition of multimorbidity in the Singapore primary care setting. Further studies will need to be conducted to confirm this finding.

4.4 Distinct patterns of chronic conditions and multimorbidity noted in the different ethnic and sex groups – addressing objective 4

Using the Fortin list, the mean number of chronic conditions in descending order for each ethnic group was Indian (1.2), Chinese (1.1), Malay (1.0) and Others (0.8) (*Table 2-1 Fortin Conditions*). Despite being younger than the Chinese, the Indians (mean age of Chinese = 47.1 years old, Indians = 39.7 years old) had slightly more chronic conditions than the Chinese (1.2 vs 1.1). When looking at the overall dyads and triads with a crude prevalence rate of 1.0% and more (*Table 2-9 & 2-10*), the Indian ethnic group was also found to have the greatest number of dyads and triads with the highest crude prevalence rates when compared to the other ethnic groups.

Although the Malay males had the fewest number of dyads or triads that had the highest crude prevalence rate, they were also the only subgroup that did not differ significantly from all the other subgroups for every dyad and triad listed in Tables 2-9 and 2-10. Moreover, despite being younger than the Others group (mean age of Malays = 35.1 years old, Others = 37.1 years old), the Malays had more chronic conditions than the Others ethnic group (1.0 vs 0.8) (*Table 2-1 Fortin Conditions*). Therefore, the Malay males seemed to have the highest burden of multimorbidity compared to the other ethnic groups.

The Chinese males had more dyads and triads with higher crude prevalence rates when compared to the Chinese females, in general. For the other ethnic groups, it was usually the females who had more prevalent dyads and triads than the males. Together with having more dyads and triads with clinically significant lower crude prevalence rates compared to the other subgroups, this suggests that Chinese females had the lowest burden of multimorbidity among the subgroups.

The more frequent occurrences of 'kidney disease or failure' in combination with other conditions to form a dyad or triad for the Malay ethnic group is consistent with the findings in the National Health Survey 2010 where the Malay ethnic group was found to have a higher renal impairment prevalence (4.1%) compared with the Chinese (2.0%) and the Indians (2.0%)[32].

'Obesity' was also a distinctly common condition in combination with other conditions to form a dyad or triad for the Malay females. This finding is also consistent with that reported by the Health Promotion Board of Singapore. Among the ethnic groups in Singapore, 20.7% of Malays, 14.0% of Indians and 5.9% of Chinese were considered obese[59].

Looking at the different co-occurring conditions provides a fresh perspective and allows clinicians to see the fuller picture of the interactions of all these common chronic conditions. We summarised the overall picture of the patterns of multimorbidity seen in the three major ethnic groups of Singapore as follows.

The Chinese ethnic group had a higher prevalence rate of hypertension as a risk factor with the brain being the major end-organ disease target (i.e., stroke and transient ischaemic attack). The Malay ethnic group had a higher prevalence rate of obesity as a risk factor with the kidney

being the major end-organ disease target (i.e., kidney disease or failure). The Indian ethnic group had a higher prevalence rate of diabetes as a risk factor with the heart being the major end-organ disease target (i.e., cardiovascular disease). Hyperlipidaemia was the most prevalent single chronic condition and a significant risk factor for all ethnic groups. These findings would need to be further confirmed by future studies.

4.5 Strengths and Limitations

4.5.1 Strengths

There are several strengths in this study. First, we used a large data set which included all the patients who visited the National Healthcare Group Polyclinics, which was a good representation of the primary care population in the public health setting in Singapore. Second, we provided both crude and standardised rates that provided valuable information for both the burden of multimorbidity at the polyclinic level and possibly at the public health level. Third, we used diagnoses from the electronic health records instead of self-reports where the latter have been found to be inaccurate due to under-reporting or forgetfulness[60]. Last, we included the full age range of patients to describe multimorbidity across the whole age spectrum.

4.5.2 Limitations

This study also has several limitations. The study was cross-sectional and the prevalence rate provided a snapshot of the burden of disease in the population over one year. This may underestimate the actual prevalence of multimorbidity.

Several reasons may lead one to consider that the prevalence rates were an underestimate. The first is that patients who had chronic conditions but were seen at longer intervals than one year would not have been counted.

A second possible reason for an underestimate may be that, like most prevalence studies, we can only provide information on those conditions already diagnosed. There is a significant proportion of people in the community with undiagnosed chronic conditions. For example, 26.3% of patients with hypertension, 51.4% of patients with diabetes, and 44.1% of patients

with hyperlipidaemia were previously undiagnosed in the Singapore National Health Survey 2010[32]. However, the setting of this study is in primary care and the proportion of the undiagnosed common chronic conditions should be lower than that found in the National Health Survey 2010 as asymptomatic participants gave consent and were screened for a few common chronic conditions in the survey hence increasing the chance of chronic condition detection. In any case, this suggests that the estimates provided in this study may be conservative.

Another possible reason for an underestimate may be because in all large database studies, the findings are dependent on the fidelity with which actual patient diagnoses were recorded. Data from patients whose chronic conditons were treated outside the polyclinic were subjected to measurement error if the family physicians at National Healthcare Group Polyclinics did not update or include in the electronic medical records conditions treated by physicians outside of the polyclinics. Furthermore, there may be undetermined variation among physicians in the completeness and accuracy of their electronic medical record coding of chronic conditions[10].

Finally, an underestimate may have occurred as not all the 'chronic' conditions included may have been active or relevant for some patients during the study period. For example, a patient with mild asthma that presents intermittently may not visit the polyclinic at all during the study period.

Another limitation was the use of the 'de facto registration' method which excluded disease-free persons who were not seeking health care. We could not get the population at risk as the denominator because the study team did not have the utilisation correction factor. We also used one-year window period and this time frame might underestimate the denominator because well patients did not visit in that year; it may overestimate the denominator because people have died or moved away.

While the main limitation was a potential underestimate of the prevalence, another limitation may have been that this study did not provide any indication of the severity of individual chronic conditions. A count of chronic conditions may not be adequate to assess how much burden an individual patient experience. The lack of information on the severity of individual chronic conditions is common in prevalence studies and will be explored in the next chapter.

4.6 Clinical implications

4.6.1 Policy and decision-makers

Although the standardised prevalence rate of multimorbidity provides a good estimation of the burden of multimorbidity for primary care in Singapore, policymakers should be looking at the crude prevalence rate for better planning of services at the polyclinic level.

For decision-makers tasked with resource allocation, prevalence estimates in samples from primary care practices are more informative than estimates from the general population. This is because population prevalence has consistently been shown to be lower than primary care prevalence[23,44]. The population-based study in Singapore by Subramaniam et al.[3] (16.3%) supported this finding obviously. However, whether the other two population studies in Singapore by Picco et al.[4] (51.5%) and Ge et al.[6] (35.0%) showed a higher or lower prevalence rate of multimorbidity compared to this study is difficult to ascertain. This is due to the differences in the list of conditions used, the age of the reference population, and the methodology used among the studies. A comparison study using the same list of conditions, similar reference population, and methods for the two population sources would be necessary to confirm the relationship between prevalence estimates from primary care and the general population in Singapore.

The knowledge of the common patterns of multimorbidity will also allow delivery of care to be more targeted to ensure that the resources provided match the needs of patients with the same patterns of multimorbidity.

4.6.2 Primary care clinicians and educators

Up to nine single conditions were prominently featured when looking at the common dyads and triads of multimorbidity found in this study. Primary care practice guidelines could be developed for these common combinations of conditions to guide doctors in providing whole person care to patients with multimorbidity without dwelling on every single chronic condition individually and adding unnecessary treatment burden to patients.

These common dyads and triads included different combinations of conditions like hyperlipidaemia, hypertension, diabetes, arthritis, obesity, cardiovascular disease, kidney disease, stroke, and asthma. With the distinct patterns noted in each ethnic group, emphasis could be put on managing hypertension, hyperlipidaemia and arthritis in Chinese females; hypertension, hyperlipidaemia and stroke prevention in Chinese males. For the Malay ethnic group, emphasis could be put on weight management, hyperlipidaemia and kidney disease prevention. For the Indian ethnic group, attention could be placed on diabetes prevention and control, hyperlipidaemia, and cardiovascular disease prevention. Many of these conditions are cardiometabolic diseases and share common treatment goals. Only arthritis and asthma add to the discordance of treatment goals with possible pharmacological interactions. Special efforts involving the expertise of the specialists may be necessary to make the multimorbidity guidelines more complete.

4.6.3 Researchers

Including chronic diseases that are burdensome to the health care system but may not be prevalent to the list of conditions used in multimorbidity studies is debatable but essential. In this study, mental disorders were found not to be prevalent, and asthma did not appear in many patterns of multimorbidity especially in the Chinese ethnic group. It may be possible that the low prevalence of mental disorders is due to the social stigma attached to it[54]. The reason for low prevalence rates of dyads or triads consisting of asthma is less evident. However, the undeniable fact is that asthma management in Singapore may need improvement as the country's asthma mortality rate is three times that of other developed countries[61].

This emphasises the importance of the careful and precise documentation of chronic conditions by the family physician. Without this, both the doctor and the patient may forget to take into account other co-occurring and important conditions during a typical episode of care. The deliberate effort to register chronic conditions is a complex and laborious chore, but one that helps to make transparent the comprehensive reality of multimorbidity. How to help busy family physicians to record and update all the chronic conditions a patient has is of critical importance in the area of health services research[62].

There are also other ways to look at the non-random associations of chronic conditions using statistical tools including factor analysis or cluster analysis [63]. Investigators should work

collaboratively with statisticians to explore other patterns of multimorbidity not discovered by using the current combinations of the most common conditions as was done in this study[64]. Understanding the common patterns of the non-random clustering of some chronic conditions for specific ethnic groups not only provides insights for public health clinicians to prevent their development in the first place, but also provides practical evidence for basic science researchers to look at the reasons for co-occurrence at the molecular level.

4.7 Conclusion and future

This is the first epidemiology study of multimorbidity on a large database of primary care patients in Singapore. The standardised prevalence rate of multimorbidity based on Fortin's list with a cut-off of three conditions was 17.2% for primary care patients age between 0-99. This study showed that age increases the standardised prevalence rate of multimorbidity. However, the standardised prevalence rates of multimorbidity between the sexes and among the three major ethnic groups were not clinically significant even though they were all statistically significant.

This study has identified some distinct patterns of multimorbidity involving about nine conditions for the three major ethnic groups in Singapore. Knowing these patterns can allow clinicians, administrators, researchers and policymakers to work collaboratively to look at the aetiology, prevention, clinical management, resource allocation, and future research for handling this monumental problem of multimorbidity.

Since there is currently limited evidence of the effectiveness of interventions to improve care for patients with multimorbidity[65], identifying these patients by consistently documenting all chronic conditions in the list of multimorbidity for each family practice is the first requisite. The development of minimally disruptive clinical guidelines for the management of the common patterns of multimorbidity in the local context should follow next.

Although survivorship with minimal complications is the clinical aim of most clinicians managing patients with multimorbidity, the quality of life and psychological well-being of patients with multimorbidity are just as, if not more, important. We will explore the quality of life and psychological distress of patients with multimorbidity in Chapter Four. We have also

noted the limitation of this study by not including the severity of individual chronic conditions. This will be explored with a systematic review in Chapter Three.

5 References

1. Fortin M, Bravo G, Hudon C, et al. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med* 2005;3(3):223-8. doi: 10.1370/afm.272
2. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS ONE* 2014;9(7):e102149. doi: 10.1371/journal.pone.0102149
3. Subramaniam M, Abdin E, Picco L, et al. Multiple chronic medical conditions: prevalence and risk factors--results from the Singapore Mental Health Study. *Gen Hosp Psychiatry* 2014;36(4):375-81. doi: 10.1016/j.genhosppsych.2014.03.002
4. Picco L, Achilla E, Abdin E, et al. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res* 2016;16:173. doi: 10.1186/s12913-016-1421-7
5. Quah JH, Wang P, Ng RR, et al. Health-related quality of life of older Asian patients with multimorbidity in primary care in a developed nation. *Geriatr Gerontol Int* 2016 doi: 10.1111/ggi.12881
6. Ge L, Yap CW, Heng BH. Sex differences in associations between multimorbidity and physical function domains among community-dwelling adults in Singapore. *PLoS ONE* 2018;13(5):e0197443. doi: 10.1371/journal.pone.0197443
7. Stewart M, Fortin M, Britt HC, et al. Comparisons of multi-morbidity in family practice--issues and biases. *Fam Pract* 2013;30(4):473-80. doi: 10.1093/fampra/cmt012
8. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity is common to family practice: is it commonly researched? *Canadian family physician Medecin de famille canadien* 2005;51:244-5.
9. Salive ME. Multimorbidity in older adults. *Epidemiol Rev* 2013;35:75-83. doi: 10.1093/epirev/mxs009
10. Fortin M, Stewart M, Poitras ME, et al. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10(2):142-51. doi: 10.1370/afm.1337
11. Xu X, Mishra GD, Jones M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. *Ageing Res Rev* 2017;37:53-68. doi: 10.1016/j.arr.2017.05.003
12. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885
13. Lim W, AGL E. Primary Care. In: Lee CE, Satku K, eds. Singapore's Health Care System - What 50 Years Have Achieved. Singapore: World Scientific Publishing Co. Pte. Ltd. 2016:211.
14. Khoo HS, Lim YW, Vrijhoef HJ. Primary healthcare system and practice characteristics in Singapore. *Asia Pac Fam Med* 2014;13(1):8. doi: 10.1186/s12930-014-0008-x
15. MOH. Primary Healthcare Services. 2019. https://www.moh.gov.sg/our-healthcare-system/healthcare-services-and-facilities/primary-healthcare-services.
16. Gunapal PPG, Kannapiran P, Teow KL, et al. Setting up a regional health system database for seamless population health management in Singapore.pdf>. *Proceedings of Singapore Healthcare* 2015:1-8.
17. Rose G, Barker DJ. What is epidemiology? *Br Med J* 1978;2(6140):803-4.

18. Cherkin DC, Berg AO, Phillips WR. In search of a solution to the primary care denominator problem. *J Fam Pract* 1982;14(2):301-9. [published Online First: 1982/02/01]
19. Bass M. Approaches to the denominator problem in primary care research. *J Fam Pract* 1976;3(2):193-5.
20. Bartholomeeusen S, Kim CY, Mertens R, et al. The denominator in general practice, a new approach from the Intego database. *Fam Pract* 2005;22(4):442-7. doi: 10.1093/fampra/cmi054
21. Britt HC, Harrison CM, Miller GC, et al. Prevalence and patterns of multimorbidity in Australia. *Med J Aust* 2008;189(2):72-7.
22. Harrison C, Britt H, Miller G, et al. Prevalence of chronic conditions in Australia. *PLoS ONE* 2013;8(7):e67494. doi: https://dx.doi.org/10.1371/journal.pone.0067494
23. Harrison C, Henderson J, Miller G, et al. The prevalence of diagnosed chronic conditions and multimorbidity in Australia: A method for estimating population prevalence from general practice patient encounter data. *PLoS ONE* 2017;12(3):e0172935. doi: 10.1371/journal.pone.0172935
24. Knox SA, Harrison CM, Britt HC, et al. Estimating prevalence of common chronic morbidities in Australia. *Med J Aust* 2008;189(2):66-70.
25. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008;14 Suppl 1:28-32. doi: 10.1080/13814780802436093
26. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;61(582):e12-21. doi: https://dx.doi.org/10.3399/bjgp11X548929
27. van Oostrom SH, Picavet HS, van Gelder BM, et al. Multimorbidity and comorbidity in the Dutch population - data from general practices. *BMC Public Health* 2012;12:715. doi: 10.1186/1471-2458-12-715
28. Brett T, Arnold-Reed DE, Popescu A, et al. Multimorbidity in patients attending 2 Australian primary care practices. *Ann Fam Med* 2013;11(6):535-42. doi: 10.1370/afm.1570
29. Nimako BA, Baiden F, Sackey SO, et al. Multimorbidity of chronic diseases among adult patients presenting to an inner-city clinic in Ghana. *Global Health* 2013;9:61. doi: 10.1186/1744-8603-9-61
30. Jacob L, Breuer J, Kostev K. Prevalence of chronic diseases among older patients in German general practices. *Ger Med Sci* 2016;14:Doc03. doi: 10.3205/000230
31. Esteban-Vasallo MD, Dominguez-Berjon MF, Astray-Mochales J, et al. Epidemiological usefulness of population-based electronic clinical records in primary care: estimation of the prevalence of chronic diseases. *Fam Pract* 2009;26(6):445-54. doi: 10.1093/fampra/cmp062
32. MOH. National Health Survey 2010 Singapore2011 [Available from: https://www.moh.gov.sg/docs/librariesprovider5/resources-statistics/reports/nhs2010---low-res.pdf accessed 9 Dec 2018.
33. N'Goran AA, Blaser J, Deruaz-Luyet A, et al. From chronic conditions to relevance in multimorbidity: a four-step study in family medicine. *Fam Pract* 2016;33(4):439-44. doi: 10.1093/fampra/cmw030
34. O'Halloran J, Miller GC, Britt H. Defining chronic conditions for primary care with ICPC-2. *Fam Pract* 2004;21(4):381-6. doi: 10.1093/fampra/cmh407
35. Chronic Disease Management Programme Handbook for Healthcare Professionals 2018 [Available from:

https://www.primarycarepages.sg/Documents/Practice%20Management/CDMP%20Handbook%20for%20Healthcare%20Professionals%202018.pdf accessed 10 Dec 2018.
36. Fortin M, Almirall J, Nicholson K. Development of a research tool to document self-reported chronic conditions in primary care. *J Comorb* 2017;7(1):117-23. doi: 10.15256/joc.2017.7.122
37. Population Trends, 2016 - Table A1.3 Singapore Residents by Age Group, Ethnic Group and Sex, June 2016. In: Statistics, ed. Singapore, 2016:51.
38. Bains N. Standardization of rates. *Report from the Association of Public Health Epidemiologists in Ontario (APHEO) through the Core Indicators for Public Health in Ontario Project* 2009. http://core.apheo.ca/index.php?pid=193.
39. Ryan BL, Bray Jenkyn K, Shariff SZ, et al. Beyond the grey tsunami: a cross-sectional population-based study of multimorbidity in Ontario. *Can J Public Health* 2018 doi: 10.17269/s41997-018-0103-0
40. Ashman JJ, Beresovsky V. Multiple chronic conditions among US adults who visited physician offices: data from the National Ambulatory Medical Care Survey, 2009. *Prev Chronic Dis* 2013;10:E64. doi: 10.5888/pcd10.120308
41. Alison PD. Listwise Deletion: It's Not EVil 2014 [Available from: https://statisticalhorizons.com/listwise-deletion-its-not-evil accessed 13 Jan 2019.
42. Rizza A, Kaplan V, Senn O, et al. Age- and gender-related prevalence of multimorbidity in primary care: the Swiss FIRE project. *BMC Fam Pract* 2012;13:113. doi: 10.1186/1471-2296-13-113
43. Marengoni A, Angleman S, Fratiglioni L. Prevalence of disability according to multimorbidity and disease clustering: a population-based study. *J Comorb* 2011;1:11-18.
44. Fortin M, Hudon C, Haggerty J, et al. Prevalence estimates of multimorbidity: a comparative study of two sources. *BMC Health Serv Res* 2010;10:111. doi: 10.1186/1472-6963-10-111 [published Online First: 2010/05/13]
45. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population attending primary care in Portugal: a cross-sectional study. *BMJ Open* 2015;5(9):e009287. doi: https://dx.doi.org/10.1136/bmjopen-2015-009287
46. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2
47. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61
48. Glynn LG, Valderas JM, Healy P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28(5):516-23. doi: 10.1093/fampra/cmr013
49. Laux G, Kuehlein T, Rosemann T, et al. Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project. *BMC Health Serv Res* 2008;8:14. doi: 10.1186/1472-6963-8-14
50. Harrison C, Britt H, Miller G, et al. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014;4(7):e004694. doi: 10.1136/bmjopen-2013-004694
51. Schafer I, Hansen H, Schon G, et al. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. *BMC Health Serv Res* 2012;12:89.

52. Agborsangaya CB, Lau D, Lahtinen M, et al. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. *BMC Public Health* 2012;12:201. doi: 10.1186/1471-2458-12-201
53. Chong SA, Abdin E, Vaingankar JA, et al. A population-based survey of mental disorders in Singapore. *Ann Acad Med Singapore* 2012;41(2):49-66.
54. Subramaniam M, Abdin E, Picco L, et al. Stigma towards people with mental disorders and its components - a perspective from multi-ethnic Singapore. *Epidemiol Psychiatr Sci* 2017;26(4):371-82. doi: 10.1017/S2045796016000159
55. Chong SA, Abdin E, Vaingankar JA, et al. Where do people with mental disorders in Singapore go to for help? *Ann Acad Med Singapore* 2012;41(4):154-60.
56. Tiller JWG. Depression and anxiety. *Med J Aust* 2012;1(Supplement 4):28-32. doi: http://dx.doi.org/10.5694/mjao12.10628
57. Mokraoui NM, Haggerty J, Almirall J, et al. Prevalence of self-reported multimorbidity in the general population and in primary care practices: a cross-sectional study. *BMC Res Notes* 2016;9:314. doi: https://dx.doi.org/10.1186/s13104-016-2121-4
58. Lim RB, Zheng H, Yang Q, et al. Ethnic and gender specific life expectancies of the Singapore population, 1965 to 2009 - converging, or diverging? *BMC Public Health* 2013;13:1012. doi: 10.1186/1471-2458-13-1012
59. HPB-MOH. Clinical Practice Guidelines on Obesity 2016. https://www.hpb.gov.sg/docs/default-source/pdf/obesity-cpg_main_for-online-30-aug.pdf?sfvrsn=2288eb72_0 (accessed 28 Jan 2019).
60. Gross R, Bentur N, Elhayany A, et al. The validity of self-reports on chronic disease: characteristics of underreporters and implications for the planning of services. *Public Health Rev* 1996;24(2):167-82.
61. Koh MS, Yii AC, Ong YY. Asthma in Singapore: Past, Present and Future. *Ann Acad Med Singapore* 2017;46(3):81-83.
62. Terry AL, Stewart M, Fortin M, et al. Stepping Up to the Plate: An Agenda for Research and Policy Action on Electronic Medical Records in Canadian Primary Healthcare. *Healthc Policy* 2016;12(2):19-32.
63. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, et al. Multimorbidity patterns: a systematic review. *J Clin Epidemiol* 2014;67(3):254-66. doi: https://dx.doi.org/10.1016/j.jclinepi.2013.09.021
64. Nicholson K, Bauer M, Terry A, et al. The Multimorbidity Cluster Analysis Tool: Identifying Combinations and Permutations of Multiple Chronic Diseases Using a Record-Level Computational Analysis. *J Innov Health Inform* 2017;24(4):962. doi: 10.14236/jhi.v24i4.962
65. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev* 2016;3:CD006560. doi: 10.1002/14651858.CD006560.pub3

6 Appendices

Appendix 2-1. CDMP List of Conditions[35]

S/No	Category of Condition	ICD10 Code & Description
1	Diabetes	E10.9 (Type 1 diabetes mellitus without complication)
		E11.9 (Type 2 diabetes mellitus without complication)
		E14.2 (Diabetes mellitus with incipient diabetic nephropathy)
		E14.3 (Diabetes Mellitus with retinopathy)
		E14.31 (Unspecified diabetes mellitus with background retinopathy)
		E14.64 (Unspecified diabetes mellitus with hypoglycaemia)
		E14.73 (Unspecified diabetes mellitus with foot ulcer due to multiple causes)
2	Hypertension	I10 (Essential (primary) hypertension)
3	Lipids	E78.5 (Hyperlipidaemia, unspecified)
4	Stroke	I64 (Stroke, not specified as haemorrhage or infarction)
5	Asthma	J45.9 (Asthma, unspecified)
6	COPD	J44.9 (Chronic obstructive pulmonary disease, unspecified)
7	Chronic Kidney Disease	N18.9 (Chronic kidney disease, unspecified)
8	Osteoporosis	M81.99 (Other osteoporosis, site unspecified)
9	Rheumatoid Arthritis	M06.99 (Rheumatoid arthritis, unspecified, site unspecified)
10	Osteoarthritis	M15.9 Osteoarthritis (OA) - Generalised)
11	Major Depression	F32.20 (Severe depressive episode without psychotic symptoms, not specified as arising in the postnatal period)
12	Anxiety	F41.1 (ANXIETY DISORDER, UNSPECIFIED)
13	Dementia	F03 (Unspecified dementia)
14	Benign Prostate Hypertrophy	N40 (Hyperplasia of prostate)
15	Parkinson's	G20 (Parkinson's disease)
16	Epilepsy	G40.90 (Epilepsy, unspecified, without mention of intractable epilepsy)
17	Psoriasis	L40.8 (Other psoriasis)
18	Schizophrenia	F20.9 (Schizophrenia, unspecified)
19	Bipolar Disorder	F31.9 (Bipolar affective disorder, unspecified)
20	Ischaemic Heart Disease	I25.9 (Chronic ischaemic heart disease, unspecified)

Appendix 2-2. Fortin List of Conditions[36]

S/No	Category of Condition	ICD10 Code & Description
1	Any cancer in the last 5 years	C80 (Malignant neoplasm without specification of site)
2	Thyroid disorder	E03.9 (Hypothyroidism, unspecified)
		E05.9 (Thyrotoxicosis, unspecified)
3	Diabetes	E10.9 (Type 1 diabetes mellitus without complication)
		E11.9 (Type 2 diabetes mellitus without complication)
		E14.2 (Diabetes mellitus with incipient diabetic nephropathy)
		E14.64 (Unspecified diabetes mellitus with hypoglycaemia)
		E14.73 (Unspecified diabetes mellitus with foot ulcer due to multiple causes)
4	Obesity	E66.9 (Obesity, unspecified)
5	Hyperlipidaemia	E78.5 (Hyperlipidaemia, unspecified)
6	Dementia or Alzheimer's disease	F03 (Unspecified dementia)
7	Depression or anxiety	F32.20 (Severe depressive episode without psychotic symptoms, not specified as arising in the postnatal period)
		F32.90 (Depressive episode, unspecified, not specified as arising in the postnatal period)
		F41.1 (Anxiety disorder, unspecified)
8	Hypertension (high blood pressure)	I10 (Essential (primary) hypertension)
9	Cardiovascular disease (angina, MI, AF, poor circulation of lower limbs)	I25.9 (Chronic ischaemic heart disease, unspecified)
		I48 (Atrial fibrillation and flutter)
		I70.20 (Atherosclerosis of arteries of extremities, unspecified)
		I73.9 (Peripheral vascular disease, unspecified)
10	Heart failure (including valve problems or replacement)	I50.0 (Congestive heart failure)
		I51.9 (Heart disease, unspecified)
11	Stroke and TIA	G45.9 (Transient cerebral ischaemic attack, unspecified)
		I64 (Stroke, not specified as haemorrhage or infarction)
12	Asthma, COPD, or chronic bronchitis	J44.9 (Chronic Obstructive Pulmonary Disease, Unspecified)
		J45.9 (Asthma, unspecified)
13	Stomach problem (reflux, heartburn, or gastric ulcer)	K21.9 (Gastro-oesophageal reflux disease without oesophagitis)
		K27.9 (Peptic ulcer, unspecified as acute or chronic, without haemorrhage or perforation)
14	Colon problem (irritable bowel)	K58.9 (Irritable bowel syndrome without diarrhoea)
15	Chronic hepatitis	K76.9 (Liver disease, unspecified)
		Z22.51 (Carrier of viral hepatitis B)
16	Arthritis &/or rheumatoid arthritis	M06.99 (Rheumatoid arthritis, unspecified, site unspecified)
		M15.9 (Osteoarthritis (OA) - Generalised)
		M19.99 (Arthritis, Unspecified, Site Unspecified)
17	Osteoporosis	M81.99 (Other osteoporosis, site unspecified)
18	Kidney disease or failure	N03.9 (Unspecified nephritic syndrome, unspecified)
		N18.9 (Chronic kidney disease, unspecified)
19	Chronic urinary problem	N40 (Hyperplasia of prostate)
20	Chronic musculoskeletal condition causing pain or limitation	No matching ICD code

Appendix 2-3. Singapore residents by age group, ethnic group and sex, June 2016[37]

Number

Age Group (Years)	Total			Chinese			Malays			Indians			Others		
	Persons	Males	Females	Persons	Males	Females	Persons	Males	Females	Persons	Males	Females	Persons	Males	Females
Total	3,933,559	1,929,526	2,004,033	2,923,172	1,425,244	1,497,928	525,888	261,564	264,324	356,876	182,935	173,941	127,623	59,783	67,840
0 – 4	187,160	95,678	91,482	130,177	66,943	63,234	33,088	16,992	16,096	17,312	8,635	8,677	6,583	3,108	3,475
5 – 9	201,509	102,426	99,083	135,257	69,259	65,998	31,706	16,267	15,439	25,415	12,637	12,778	9,131	4,263	4,868
10 – 14	207,495	105,589	101,906	137,225	70,290	66,935	35,267	18,121	17,146	25,676	12,722	12,954	9,327	4,456	4,871
15 – 19	239,771	122,911	116,860	165,774	85,383	80,391	42,750	22,160	20,590	22,939	11,463	11,476	8,308	3,905	4,403
20 – 24	260,854	132,046	128,808	184,609	93,681	90,928	47,798	24,538	23,260	22,438	11,125	11,313	6,009	2,702	3,307
25 – 29	279,988	137,243	142,745	204,843	100,380	104,463	46,239	23,559	22,680	22,787	11,136	11,651	6,119	2,168	3,951
30 – 34	285,544	135,596	149,948	208,889	99,734	109,155	38,943	19,575	19,368	27,781	12,869	14,912	9,931	3,418	6,513
35 – 39	301,998	143,553	158,445	220,701	104,108	116,593	30,939	14,936	16,003	35,342	18,172	17,170	15,016	6,337	8,679
40 – 44	313,445	152,466	160,979	231,775	110,080	121,695	31,701	15,354	16,347	33,829	19,315	14,514	16,140	7,717	8,423
45 – 49	301,183	147,517	153,666	223,222	106,909	116,313	35,056	16,950	18,106	29,035	16,798	12,237	13,870	6,860	7,010
50 – 54	315,598	158,202	157,396	235,906	117,173	118,733	43,212	21,342	21,870	26,523	14,316	12,207	9,957	5,371	4,586
55 – 59	299,591	150,315	149,276	232,481	115,891	116,590	38,118	18,982	19,136	22,471	11,865	10,606	6,521	3,577	2,944
60 – 64	251,853	125,130	126,723	202,871	100,764	102,107	28,147	13,619	14,528	16,676	8,377	8,299	4,159	2,370	1,789
65 – 69	198,020	96,349	101,671	163,881	79,855	84,026	18,867	8,838	10,029	12,372	5,945	6,427	2,900	1,711	1,189
70 – 74	103,796	48,691	55,105	88,238	41,479	46,759	8,571	3,806	4,765	5,710	2,656	3,054	1,277	750	527
75 – 79	87,955	38,976	48,979	74,926	33,270	41,656	7,275	3,217	4,058	4,715	1,970	2,745	1,039	519	520
80 – 84	53,556	21,884	31,672	44,620	18,180	26,440	5,087	1,992	3,095	3,171	1,408	1,763	678	304	374
85 & Over	44,243	14,954	29,289	37,777	11,865	25,912	3,124	1,316	1,808	2,684	1,526	1,158	658	247	411

Appendix 2-4. Gradient calculation for Figure 2-1 and Figure 2-2

No. of CDMP Conditions Age band based on WHO categories Crosstabulation (ADJUSTED)

		Age band based on WHO categories																		
		0 - 4	5 - 9	10 - 14	15 - 19	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74	75 - 79	80 - 84	85 & Above	Total
Total	Count	187160	201509	207495	239771	260854	279988	285544	301998	313445	301183	315598	299591	251853	198020	103796	87955	53556	44243	3933559
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
At Least 2	Count	0	20	56	288	1102	2547	6576	17792	40518	64378	103142	133852	138015	127317	76064	68411	43632	37025	860736
	%	0.0%	0.0%	0.0%	0.1%	0.4%	0.9%	2.3%	5.9%	12.9%	21.4%	32.7%	44.7%	54.8%	64.3%	73.3%	77.8%	81.5%	83.7%	21.9%
	Gradient (% per year)	**0.00%**	**0.00%**	**0.02%**	**0.06%**	**0.10%**	**0.28%**	**0.72%**	**1.41%**	**1.69%**	**2.26%**	**2.40%**	**2.02%**	**1.90%**	**1.80%**	**0.90%**	**0.74%**	**0.44%**	**-12.36%**	
At Least 3	Count	0	0	0	30	128	475	1467	5353	14342	26186	46497	67003	75568	76363	50354	48281	32716	28868	473630
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.5%	1.8%	4.6%	8.7%	14.7%	22.4%	30.0%	38.6%	48.5%	54.9%	61.1%	65.2%	12.0%
	Gradient (% per year)	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.02%**	**0.07%**	**0.25%**	**0.56%**	**0.82%**	**1.21%**	**1.53%**	**1.53%**	**1.71%**	**1.99%**	**1.28%**	**1.24%**	**0.83%**	**-10.64%**	

No. of Fortin Conditions Age band based on WHO categories Crosstabulation (ADJUSTED)

		Age band based on WHO categories																		
		0 - 4	5 - 9	10 - 14	15 - 19	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74	75 - 79	80 - 84	85 & Above	Total
Total	Count	187160	201509	207495	239771	260854	279988	285544	301998	313445	301183	315598	299591	251853	198020	103796	87955	53556	44243	3933559
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
At Least 2	Count	11	165	579	1732	4251	6624	12878	28263	56748	85469	129234	158439	156581	140028	81083	71959	45431	38417	1017892
	%	0.0%	0.1%	0.3%	0.7%	1.6%	2.4%	4.5%	9.4%	18.1%	28.4%	40.9%	52.9%	62.2%	70.7%	78.1%	81.8%	84.8%	86.8%	25.9%
	Gradient (% per year)	**0.02%**	**0.04%**	**0.09%**	**0.18%**	**0.15%**	**0.43%**	**0.97%**	**1.75%**	**2.05%**	**2.51%**	**2.39%**	**1.86%**	**1.71%**	**1.48%**	**0.74%**	**0.60%**	**0.40%**	**-12.19%**	
At Least 3	Count	0	0	5	147	765	1633	4655	12536	28691	46843	76605	102119	107352	102114	63708	58991	38521	33355	678039
	%	0.0%	0.0%	0.0%	0.1%	0.3%	0.6%	1.6%	4.2%	9.2%	15.6%	24.3%	34.1%	42.6%	51.6%	61.4%	67.1%	71.9%	75.4%	17.2%
	Gradient (% per year)	**0.00%**	**0.00%**	**0.01%**	**0.05%**	**0.06%**	**0.21%**	**0.50%**	**1.00%**	**1.28%**	**1.74%**	**1.96%**	**1.71%**	**1.79%**	**1.96%**	**1.14%**	**0.97%**	**0.69%**	**-11.63%**	

Western University

CHAPTER THREE

A *S*ystematic review on the *I*nstruments used for measuring the level of *M*ultimorbidity (SIM)

Abbreviations

ACE-27	Adult Comorbidity Evaluation
ACG	Adjusted Clinical Groups
ACSH	Ambulatory Care Sensitive Hospitalisation
ADG	Aggregated Diagnostic Groups
ADL	Activities of daily living
AUC	Area Under the Curve
BI	Barthel Index
CC-AM	Chronic conditions – additive modelling
CCC (of ICD-9 Codes)	Clinical Classification Categories
CCC	Chronic Condition Count
CCI	Charlson Comorbidity Index
CCI-PSR	Charlson Comorbidity Index – Psychosocial Risk
CC-MM	Chronic conditions – minimum modelling
CC-MuM	Chronic conditions – multiplicative modelling
CDS	Chronic Disease Count
CGI-S	Clinical Global Impression – Severity scale
CIRS	Cumulative Illness Rating Scale
CLS	Comorbidity Linked Score
CMI	Cornell Medical Index
COSmm	Core Outcome Sets of multimorbidity
CPRD	Clinical Practice Research Datalink
DC	Disease Count
ED	Emergency Department
EDC	Expanded Diagnosis Clusters
EI	Elixhauser Index
EMR	Electronic Medical Record
EQ-5D-5L	EuroQoL-5 Dimensions
EQ-VAS	EuroQoL-Visual Analogue Scale
ERA	Elders Risk Assessment
GP	General Practice
HCC	Hierachical Condition Categories
HM	Hybrid Model (Minnesota Tiering and Elders Risk Assessment)
HPFS Cohort	Health Professionals Follow-up Study Cohort
HRQoL	Health-Related Quality of Life
HSMI	Health Search Morbidity Index
HUI3	Health Utility Index
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
ICPC-2	International Classification of Primary Care – Second Edition
M3 Index	Multi-Multimorbidity Measure Index
mCCI	modified Charlson Comorbidity Index
MDMS	Multidimensional Multimorbidity Score
MeSH	Medical subject heading
MM by ADL	Multimorbidity weighted by Activities of Daily Living scale
MM by HUI3	Multimorbidity weighted by Health Utility Index
MN Tier	Minnesota Tiering
MWI	Multimorbidity-Weighted Index
NHS	National Health Service

NHS II Cohort	Nurses' Health Study II Cohort Study
NOS	Newcastle-Ottawa Quality Assessment Scale
NS	Not stated
OARS	Older Americans Resources and Services
Organ-CDC	Organ systems with chronic disease count
Pra tool	Probability of repeated admission risk prediction tool
QALY	Quality-Adjusted Life Year
QOF	Quality and Outcomes Framework
QOF-E	Extended Quality and Outcomes Framework
QOF-S	Standard Quality and Outcomes Framework
QoL	Quality of Life
RoB	Risk of Bias
RUB	Resource Utilisation Band
RxRisk-V	A Veterans Association adapted pharmacy-based case-mix instrument
SF-12	12-item Short Form Survey
SF-36	36-item Short Form Survey
SF-6D	Short Form Six Dimensions
SRH	Self-Rated Health
TRIPOD	Transparent Reporting of Multivariable prediction models for individual prognosis or diagnosis
UK	United Kingdom
WHO-ATC	World Health Organisation – The Anatomical Therapeutic Chemical Classification System
Φc	Cramer's V

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1 Introduction

Given the clinical significance of multimorbidity in primary care, it is essential to consider how we quantify multimorbidity in community-dwelling individuals. We measured the prevalence and patterns of multimorbidity in Chapter Two. Chapter Three will now address the measurement of the level of multimorbidity.

Before moving on, it is pertinent to elucidate some terms used which are very similar but relate to different meanings and concepts. The first two terms to clarify are the 'severity of chronic condition' and the 'level of multimorbidity'. The next two terms to clarify are 'measuring multimorbidity' and 'measuring the level of multimorbidity'.

A consideration of the complexity of multimorbidity should address the 'severity of chronic condition', that is, the severity of individual conditions and its impact of multimorbidity on health outcomes[1]. However, less than a quarter of studies on multimorbidity reported the severity of individual conditions[2]. Reporting the severity of individual conditions does not automatically lead to an understanding of the combined effects of multiple conditions. The combined effect may be additive or multiplicative or may not even be synergistic at all[3]. The 'severity of chronic condition' refers to the severity of a single chronic condition which has been widely described in the medical literature and in daily clinical practice[4]. Most of the time, it can be measured by well-established clinical guidelines like the New York Heart Association for functional classification of heart failure; or suggested clinical parameter cut-off like blood pressure control; or sometimes from patients' self-reported severity of a condition[2]. Therefore, the term 'severity of chronic condition' is not to be confused with the term 'level of multimorbidity' which measures the combined effects of the multiple conditions that an individual has.

In scientific measurements, it is important to describe clearly the purpose of the measurement. According to de Vet et al.[5], the three main purposes of measurement are for diagnosis (discriminant measurement), evaluation of intervention (evaluation measurement), and prediction of outcome (predictive measurement). In Chapter Two, we used the term 'measuring multimorbidity' for the purpose of describing the prevalence and patterns of multimorbidity in the primary care population. For this systematic review, we searched for

studies that were 'measuring the level of multimorbidity'. The purpose was to describe the consequences, i.e., the prediction of future course[5], with varying 'levels of multimorbidity'. Referring to de Vet et al.'s[5] classification, discriminant measurement of multimorbidity was performed in Chapter Two. For Chapter Three, we looked at the predictive measurements of the different levels of multimorbidity that were described in the literature.

Smith et al.[6] published a list of 17 multimorbidity outcomes agreed to by international experts of multimorbidity intervention studies with quality of life, mental health outcomes, and mortality as the three essential core outcomes. These core outcome sets (COSmm) represent the minimum that should be measured and reported in all clinical studies of multimorbidity. In this study, we looked at whether the purposes of measuring the level of multimorbidity concurred with the 17 COSmm recommended by international experts of multimorbidity intervention studies.

Existing instruments for measuring the level of multimorbidity are heterogeneous in terms of the number, type, and weighting of conditions considered[7]. Several instruments have also been developed from highly selective study populations and may not be suitable for individuals from a different setting.

Multiple different opinions on what constitutes a useful instrument[***] for measurement of the level of multimorbidity exist in the literature. For example, counting diseases has been criticised for being less relevant compared to the disability connected with the level of the conditions when measuring multimorbidity[8]. This was supported by a systematic review that reported that interventions for multimorbidity were shown to be most effective when focusing on functional difficulties rather than on the individual diseases[9]. Other investigators argued that the number of conditions was associated with the number of consultations[10] and was inversely associated with continuity of care[11], highlighting that healthcare utilisation, costs, and patient satisfaction were just as important outcomes at both the system and patient levels. Some criticised that the reductive approaches based on the consequences, rather than the causes of multimorbidity, have led to an incorrect definition of the problem[12]. There is currently no

[***] We have used the term 'instruments' rather than 'indices' or 'scales' or 'measures' as a general term to encompass all the above in order not to create further confusion as some of the instruments are called a 'scale', an 'index', or a 'measure'.

consensus on these disputes because of the conceptual differences in the understanding and a lack of standardisation in instruments that measure the level of multimorbidity[13].

However, prognostic information (i.e., an outcome) has many meaningful uses[14]. Patients and clinicians can use it to plan for treatment priorities. Policy analysts can use it to evaluate the effectiveness of various treatment options. Administrators can also use it to anticipate patients' medical service utilisation and nursing needs. This is the reason why this chapter will only look at instruments measuring the level of multimorbidity with at least a specific purpose or outcome in mind.

Ideally, a single multimorbidity instrument should be able to predict a variety of relevant outcomes, such as death, hospital admission, and quality of life, in a variety of patient and population settings. However, Byles et al.[15] reported that no single instrument could predict a variety of outcomes. For example, an instrument developed to measure mental health is unlikely to be applicable to measure the physical function outcome. A range of different instruments for measuring different outcomes will be anticipated.

Huntley et al.[16] published a systematic review looking at the instruments for measuring morbidity burden used in the primary care and general population setting. They found 194 articles describing 17 different measures. Most instruments were diagnosis-based measures, but medication-based measures were also noted. The measures that were most widely used and for which there was the most significant evidence of validity were the Charlson index, disease counts, and the ACG (Adjusted Clinical Groups) System[16]. They concluded that the choice of an instrument would depend on the outcome (i.e., purpose) of interest and the type of data available (i.e., context).

The systematic review by Huntley et al.[16] has not been updated since 2009 and the amount of multimorbidity research has surged tremendously since 2010. Therefore, we proposed an updated review to list the suitable instruments for the measurement of level of multimorbidity in community-dwelling individuals.

This study aimed to perform a systematic review of relevant multimorbidity studies that measured the level of multimorbidity of patients from the primary care or general population to predict or explore the association with at least one specified outcome published from January

2010 onwards. Specific objectives were to: (1) provide a list of measurement instruments for measuring level of multimorbidity in the primary care or general population setting; (2) report the advantages and disadvantages of using these instruments in predicting the multimorbidity-related outcomes; (3) provide details of the data source(s) and resource(s) required by each of the instruments; and (4) compile a list of corresponding instruments for measuring the level of multimorbidity for the three essential core outcomes identified for COSmm[6] (quality of life, mental health, and mortality).

The systematic review will update investigators or clinicians targeting community-dwelling individuals with multimorbidity on the available instruments for the measurement of level of multimorbidity so that they can be better informed on the requirements, strengths and limitations of these instruments and select or develop one that matches their needs.

2 Methods

A protocol for the systematic review was developed using PRISMA-P guidelines[17,18] and was published on PROSPERO website[19]. CRD42018105297 dated 6th Sep 2018 is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=105297.

We did not seek ethics approval as the review used published data from secondary sources and did not involve any interactions with human subjects. We followed the PRISMA statement[20] and guidance on the conduct of narrative synthesis in systematic reviews[21] for the reporting of this systematic review. There was no funding for this project.

2.1 Search Strategy

We used OVID to search MEDLINE††† and EMBASE‡‡‡, and EBSCO for CINAHL§§§. We also manually searched the Journal of Comorbidity for potential articles. The search was from

††† A bibliographic database of life sciences and biomedical information. It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care from 1946 to present.
‡‡‡ A biomedical research database that covers the most international biomedical literature from 1947 to the present day. All articles are indexed in depth using Elsevier's Life Science thesaurus Embase Indexing and Emtree®.
§§§ An index of English-language and selected other-language journal articles about nursing, allied health, biomedicine and healthcare from 1961 to present.

January 2010 to 14th August 2018. A 'snowball' search, which is a hand search of the reference lists in the selected articles, was performed for comprehensiveness[22].

Several different search trials were performed before a structured search strategy that identified the best combination of Medical Subject Headings (MeSH) terms and keywords using proximity searching[****] was developed[23]. The final search strategy was developed between the principal investigator (LES) and a librarian trained in health sciences research (JC) after multiple iterations.

The MeSH terms were different for each electronic database and the proximity searching terms were also different among them as reflected in Appendix 3-1. For example, 'multiple chronic conditions' was a MeSH term in MEDLINE and EMBASE but not in CINAHL.

2.2 Inclusion and Exclusion criteria

The inclusion criteria were studies that included: (1) adult patients (ages 18 years and above) who visited primary care or were from the general population; (2) at least one specified outcome variable (e.g., mortality, quality of life) that was predicted by or associated with instruments used for measuring the level of multimorbidity; and (3) full-text articles published from January 2010 to August 2018.

The exclusion criteria were studies that: (1) selected patients from the hospital or nursing home only or patient data that were drawn solely from the hospital or the nursing home; or (2) selected patients with a prerequisite to have certain conditions prior to recruitment; or (3) used level of multimorbidity as a covariate and not the main independent variable; or (4) were not written in English.

[****] Proximity searching is a form of advanced search to specify two or more separately matching term occurrences are within a specified distance, where distance is the number of intermediate words or characters.

2.3 Study selection

LES conducted a preliminary screen of titles and abstracts to exclude records that were irrelevant. Records such as letters to editors, conference abstracts, protocols, editorials, reviews, qualitative research, and validation of questionnaires were removed. Abstracts of the remaining records were screened independently by two reviewers (LES & EH) to identify potentially relevant articles. Disagreements were resolved through discussion until a consensus was reached. The full-text articles were then retrieved for the agreed list and independently assessed for eligibility according to the inclusion and exclusion criteria as stated in Section 2.2 *(p90)* by the same reviewers.

The two reviewers used Covidence[24] (a Systematic Review management tool) independently that allowed blinding to minimise bias while the article selections were assigned neatly from each stage of the review process to the next. Disagreements at this stage were resolved through discussion with a third reviewer (TSH) until a consensus was reached. After agreement on the list of articles, the reference lists of included articles were hand-searched for additional papers that adhered to the inclusion and exclusion criteria.

2.4 Data Extraction

Specific data extraction forms were developed, and after being pilot-tested (KHL, MZ & LES), were used with each article for assessment of study quality and evidence synthesis. KHL and WFY performed the final data extraction. Weekly meetings were held whereby all the data extracted were checked by LES. Any discrepancies were discussed and rectified in meetings among LES, KHL and WFY. Outstanding disagreements on data extracted among the three were resolved by involving EH and TSH.

The extracted information from each article included (1) characteristics of participants (including population source, sample size, and the age range); (2) instruments used, definition of chronic diseases used in the instrument, the cut-off number of chronic conditions for definition of multimorbidity, and the total number of chronic conditions considered in the multimorbidity list; (3) type of outcomes measured; (4) results; (5) data sources and resources used to conduct the study; and (6) other information like financial conflict of interest. We

collated data as much as possible when multiple articles of the same study were found to avoid double counting of measurement instruments.

2.5 Assessment of risk of bias

Several rounds of calibration exercises were conducted with extensive discussions and iterations on the selection of a suitable risk of bias assessment tool. Pilot trials of potentially eligible articles were conducted by four of the team members – LES, MZ, KHL and EH. Eventually, the Newcastle-Ottawa Scale (NOS) was modified and used as the assessment tool to determine the risk of bias of each article[25,26]. Risk of bias assessment was appraised by three reviewers (LES, EH & TSH) independently for each included article. Each article was assessed as having good, fair or poor quality using the modified NOS which examined three broad categories: a) Selection; b) Comparability; and c) Outcome (*Appendices 3-2 & 3-3*).

We contacted the authors, as needed, for additional information or clarification for a maximum of three times spaced one week apart. The clarifications were mainly related to sampling and data analysis. We contacted 25 authors, and 19 of them replied. Any disagreements on the risk of bias were resolved among the three reviewers (LES, EH & TSH) through regular meetings. KHL and WFY were responsible for tracking and updating the final risk of bias assessment outcome.

2.6 Narrative synthesis of results

It was anticipated that the studies would be heterogeneous and therefore the decision was made *a priori* not to combine them for meta-analysis. Instead, we synthesised the evidence in tables and narrative text based on the data extracted.

Upon completion of the systematic review, we compiled a list of instruments for measuring the level of multimorbidity that were described in studies with low risk of bias and the outcomes that were used in the studies with those instruments (*Table 3-6*). We also compiled a list of the three essential core outcomes identified for COSmm[6] (quality of life, mental health, and mortality) and listed the corresponding instruments for measuring the level of multimorbidity from those studies with low risk of bias (*Table 3-7*). The intention was that the two lists

compiled from the findings of the systematic review would assist investigators in making informed choices in selecting appropriate instruments or outcomes for future research on level of multimorbidity.

3 Results

3.1 Search Results

A total of 67 studies involving 74 articles were identified for inclusion in the systematic review. The search of MEDLINE, EMBASE, CINAHL databases, and the Journal of Comorbidity provided a total of 9,122 records. After adjusting for duplicates, the remaining records were screened by looking at the titles and abstracts only. We then screened through the full text of all those articles that were selected from above. This first round of screening resulted in 55 articles. This number was relevant to the first step but not the final step, so it is not shown in Figure 3-1.

We hand-searched the lists of references of all the 55 included articles and added potentially eligible records to the 'additional records identified through other sources'. Many of these records were duplicates, but we went through the same process of screening the abstracts and titles, followed by full-text review and then hand-searching the list of references from the newly included articles. We repeated the whole process until no more potentially eligible articles were identified. A total of 134 articles were identified using this 'snowballing' process.

Ultimately, 7,481 records were screened, and 7,351 records were discarded during the title and abstract screening. The full text of all the 130 articles was found, and none was discarded during this screening process. We perused the full text of 130 articles in detail, and 56 of them were excluded due to the various reasons stated in Figure 3-1. The final number of included articles was 74 articles, representing 67 unique studies.

Table 3-1 summarised the risk of bias appraisals for the 35 cohort articles and Table 3-2 summarised the 39 cross-sectional articles. Table 3-3 summarised the 53 articles with a good risk of bias judgement including a summary of the results. Table 3-4 summarised the 21 articles with a fair or a poor risk of bias. The summary of results was not provided for Table 3-4 due to the possibility of bias in the study design or methodology. Table 3-5 described the unique instruments used for measuring the level of multimorbidity from the 74 included articles. Table 3-6 described the associated outcomes of each instrument that was reported in the 53 articles with a good risk of bias judgement. Table 3-7 compiled the list of the instruments that were

used for the three essential core outcomes of multimorbidity identified for COSmm[6] from the 53 articles with a good risk of bias judgement.

For the rest of the chapter, we describe the included 67 studies as much as possible rather than the 74 articles so as not to duplicate and confuse the reader.

3.2 Description of the included studies

There were 67 studies reported in 74 articles because 14 articles were from seven studies (two separate articles corresponding to each study) namely Barile et al.[27,28], Boeckxstaens et al.[29,30], Brilleman et al.[31,32], Crooks et al.[33,34], Formiga et al.[35,36], Payne et al.[37,38], and Wallace et al.[39,40].

Thirty studies selected participants from the general population and 37 studies selected participants from primary care. A majority of the studies were for participants 18 years old and above (n=28) and the second largest group was for older adults age 65 years old and above (n=20). More than half of the studies were from Europe (n=35), and 14 of these came from the United Kingdom. North America contributed 26 studies (the United States of America had 20 and Canada had 6). There were two studies from Australia and one study each from Israel, Japan, New Zealand, and South Africa.

Altogether, there were 117 instruments for measuring the level of multimorbidity used in the 67 studies, of which 33 were unique instruments. The instruments were categorised based on: 1) simple counts of individual conditions; 2) organ or system-based approaches; 3) conditions that have been weighted and combined into indices; and 4) other approaches including case - mix and pharmaceutical-based approaches as described by Sarfati[41,42].

A total of 112 outcomes were reported from all the studies. They were broadly categorised into eleven categories: Activities of Daily Living; Costs; Health care use; Health-related Quality of life; Mental health; Mortality; Physical activity; Physical function; Quality health care; Self-rated health; and Others. The top reported outcomes were health care use (n=34), mortality (n=14), and health-related quality of life (n=14).

The sample size of the 67 studies ranged from 113[43] to more than 9 million[44]. There were 28 cohort studies, 36 cross-sectional studies, and three mixed studies (i.e., cross-sectional and cohort). Twenty of these studies (23 articles) used prediction models.

Figure 3-1. PRISMA Flow Diagram

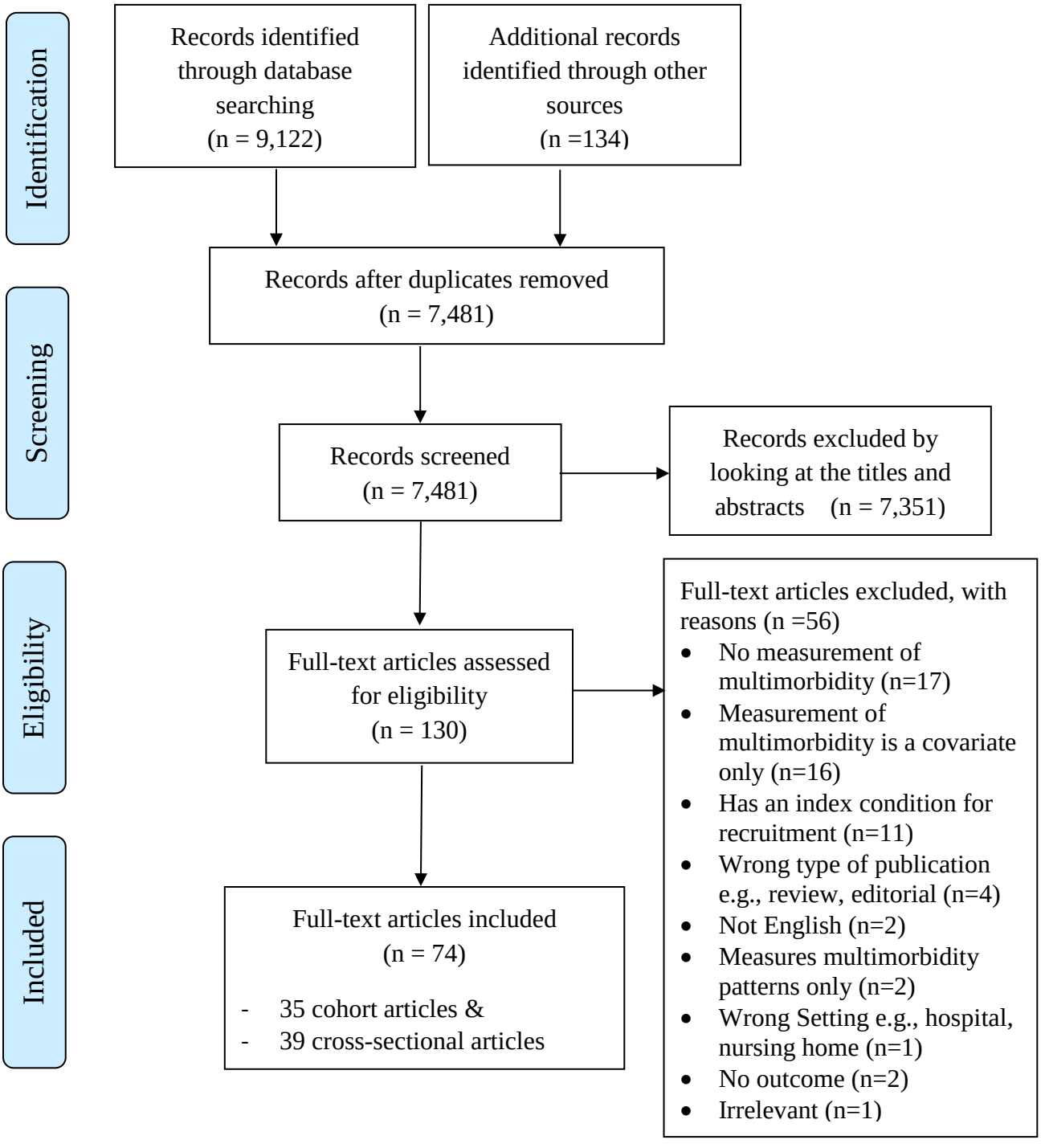

Table 3-1 summarised the details of the risk of bias (RoB) assessment using the modified Newcastle Ottawa Scale (NOS) for 35 cohort articles and Table 3-2 summarised the 39 cross-sectional articles. Of the 35 cohort articles, 29 articles were rated 'good', four articles were rated 'fair', and two articles were rated 'poor'. Of the 39 cross-sectional articles, 24 articles were rated 'good', five articles were rated 'fair', and ten articles were rated 'poor'. In total, there were 47 studies (53 articles) that were rated 'good', eight studies (nine articles) that were graded 'fair', and 12 studies (12 articles) that were graded 'poor'. (The articles are highlighted in light grey for combined studies and highlighted in dark grey for cohort studies in Tables 3-1 and 3-2)

All studies that were graded 'fair' were due to issues with the 'selection' criterion. Studies graded 'poor' were due to issues with a variety of criteria but mainly on the 'selection' and 'comparability' criteria. A higher proportion of cohort studies compared to cross-sectional studies were graded 'good' with the RoB assessment.

The justification for choosing a specific list of chronic conditions was not clearly stated in many of these studies. We found only 23 studies (34.3%) that provided at least a brief statement of what a chronic condition was. The total number of conditions in the multimorbidity list ranged from seven[45-47] to 147[10] conditions in this review but only slightly more than half of them, i.e., 38 studies (56.7%), provided the full list of the conditions. Finally, only 23 studies (34.3%) stated clearly the cut-points they used to define multimorbidity. A large majority of the studies used 'two or more' chronic conditions as the cut-off to define multimorbidity. We identified two studies that used 'three or more' chronic conditions[29,30,48] and another two studies that used 'four or more' conditions[28,30] as the cut-offs to define multimorbidity. In total, only 14 studies (20.9%) included all three components, i.e., the definition of chronic condition, list of conditions, and cut-points used to define multimorbidity. The data sources of the conditions and the reference populations were clearly stated in all the studies.

Hand-searching by the snowball method contributed 25% (n=19) of the final selected articles. All the objectives stated in every one of the 67 studies were fully reported. Only 15 articles declared financial sponsorship or funding from grants. Thirty-six articles declared no financial support or funding, and 23 of the articles did not make any statement on financial conflict of interest.

Table 3-1. Summary of risk of bias (RoB) appraisal of included cohort articles using the modified Newcastle-Ottawa Quality Assessment Scale (35 articles)

	Barile et al. (2013)[27]	Biehl et al. (2016)[49]	Boeckxstaens et al. (2015b)[30]	Brilleman et al. (2014)[31]	Brilleman and Salisbury (2013)[32]	Carey et al. (2013)[50]	Chapman et al. (2015)[51]	Crane et al. (2010)[52]	Crooks et al. (2016)[33]	Crooks et al. (2015)[34]	Formiga et al. (2013)[53]	Formiga et al. (2011a)[54]	Formiga et al. (2016)[35]	Fraccaro et al. (2016)[55]	Haas et al. (2013)[56]	Hwang et al. (2015)[57]	Jennings et al. (2015)[58]	Jia and Lubetkin (2016)[59]	Jia et al. (2018)[60]	Lemke et al. (2012)[61]	Md Yusof et al. (2010)[43]	Payne et al. (2014)[37]	Payne et al. (2013)[38]	Quail et al. (2011)[62]	Reyes et al. (2014)[63]	Salisbury et al. (2011)[11]	Saver et al. (2014)[64]	Stanley and Sarfati (2017)[65]	Streit et al. (2014)[66]	Takahashi et al. (2016)[67]	Takahashi et al. (2012)[47]	Tyack et al. (2016)[68]	Wallace et al. (2016a)[39]	Wallace et al. (2016b)[40]	Wei and Mukamal (2018)[69]
Selection Criteria																																		
Representativeness of the sample	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	-	*	*	*	*	*	*	*	*	*	-	*	*	*
Ascertainment of Multimorbidity	-	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	-	*	-	*	*	*	*	*	*	*	*	*	-	*	*	-
Demonstration that outcome of interest was not present at the start of the study	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Comparability Criteria																																		
Study controls for age and sex	*	-	*	*	*	*	*	-	*	*	-	*	-	*	*	*	*	*	-	*	-	*	*	*	-	*	*	*	*	*	*	*	*	-
Study controls for others	*	*	-	*	*	*	*	*	-	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*
Outcome Criteria																																		
Statistical test†	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessment of outcome	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Follow-up was long enough for outcomes to occur	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*
Overall RoB Judgement[a]	G	G	F	G	G	G	G	G	G	G	G	G	G	G	G	G	F	P	P	G	F	G	G	G	G	G	G	G	G	G	F	G	G	G

Note. G = Good; F = Fair; P = Poor.

†Statistical test must be clearly described and appropriate before assessing the other items under the Outcome category. [a] Good rating is given when there are 2 to 3 stars in Selection category (Representativeness of Sample must be fulfilled) AND 1 to 2 stars in Comparability category AND 2 to 3 stars in Outcome category; Fair rating is given when there are 1 to 2 stars in Selection category AND 1 to 2 stars in Comparability category AND 2 to 3 stars in Outcome category; Poor rating is given when there are 0 star in Selection category OR 0 star in Comparability category OR 0 to 2 stars in Outcome category.

"*" Study satisfies the criteria; "-" Study did not satisfy the criteria; "✓" Statistical test is clearly described and appropriate; "X" Statistical test is not described, incomplete or inappropriate.

NB: Articles highlighted in light grey are combined studies (see Table 3-2 with similar highlights) and articles highlighted in dark grey are cohort studies. Those not highlighted are single articles which are also single studies.

Table 3-2. Summary of risk of bias (RoB) appraisal of included cross-sectional articles using the modified Newcastle-Ottawa Quality Assessment Scale (39 articles)

	Agborsangaya et al. (2013)[70]	Barile et al. (2012)[28]	Barnett et al. (2012)[71]	Boeckxstaens et al. (2015a)[29]	Chen et al. (2011)[72]	DiNapoli et al. (2017)[73]	Formiga et al. (2011b)[36]	Galenkamp et al. (2011)[45]	Garin et al. (2014)[74]	Glynn et al. (2011)[10]	Gunn et al. (2012)[75]	Hanmer et al. (2010)[76]	Hu et al. (2017)[77]	Isaacs et al. (2014)[78]	Kojima et al. (2011)[46]	Kristensen et al. (2014)[79]	Lapi et al. (2015)[80]	Lawson et al. (2013)[81]	Li et al. (2016)[82]	Marengoni et al. (2011)[83]	McDaid et al. (2013)[84]	Muggah et al. (2012)[44]	Mujica-Mota et al. (2015)[3]	Naessens et al. (2011)[85]	Østergaard and Foldager (2011)[86]	Peters et al. (2018)[87]	Ranstad et al. (2014)[88]	Renne and Gobbens (2018)[89]	Ryu et al. (2015)[90]	Shadmi et al. (2011)[91]	Sibley et al. (2014)[92]	Sullivan et al. (2012)[93]	Ubalde-Lopez et al. (2016)[94]	van den Bussche et al. (2014)[48]	van Oostrom et al. (2014)[95]	Vos et al. (2013)[96]	Wei et al. (2018)[97]	Wikman et al. (2011)[98]	Wister et al. (2015)[99]
Selection																																							
Representativeness of the sample	*	*	*	-	*	*	*	*	*	*	*	*	-	*	-	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of Multimorbidity	*	-	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	-	*	*	*	-	*	*	-	*	-	-	*	*	*	*	*	*	*	*	*	*
Sample size	*	*	*	-	*	*	-	*	*	*	*	*	-	*	-	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*
Non-respondents	-	*	*	-	*	*	*	-	-	*	-	-	*	*	-	*	*	*	-	-	-	*	-	*	-	-	*	-	*	*	-	-	*	*	*	*	*	*	-
Comparability																																							
Study controls for age and sex	*	*	*	*	*	*	-	*	*	*	*	*	*	-	*	*	*	*	-	*	*	-	*	-	-	*	*	*	*	*	*	-	*	*	-	*	*	*	*
Study controls for others	*	*	*	*	*	*	*	-	*	*	*	*	*	-	*	*	*	*	-	*	*	-	*	-	-	*	*	*	*	*	-	-	*	*	-	*	*	*	-
Outcome																																							
Statistical test†	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessment of outcome	*	✓	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*
Overall RoB Judgement[a]	G	G	G	P	G	G	G	G	G	G	F	F	F	P	P	G	G	G	P	G	G	P	F	P	P	F	G	P	G	G	P	G	G	G	G	P	G	G	G

Note. G = Good; F = Fair; P = Poor.

†Statistical test must be clearly described and appropriate before assessing the other items under the Outcome category. [a] Good rating is given when there are 3 to 4 stars in Selection category (Representativeness of Sample must be fulfilled) AND 1 to 2 stars in Comparability category AND 1 star in Outcome category; Fair rating is given when there are 2 stars in Selection category AND 1 to 2 stars in Comparability category AND 1 star in Outcome category; Poor rating is given when there are 0 to 1 star in Selection category OR 0 star in Comparability category OR 0 star in Outcome category.

"*" Study satisfies the criteria; "-" Study did not satisfy the criteria; "✓" Statistical test is clearly described and appropriate; "X" Statistical test is not described, incomplete or inappropriate.

NB: Articles highlighted in light grey are combined studies (see Table 3-1 with similar highlights). Those not highlighted are single articles which are also single studies.

Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Agborsangaya et al. (2013)[70], Canada	Cross-sectional	General Population (N = 4,946)	≥ 18	a. DC	NS	a. 16 (2)	1. HRQoL	1. Number of conditions negatively associated with HRQoL*
Barile et al. (2013)[27], USA	Cohort - *Same study as Barile et al. (2012)[28]*	General Population (N = 27,334)	≥ 65	a. DC	NS	a. 11 (2)	1. ADL limitations 2. Number of physically unhealthy days 3. Number of mentally unhealthy days	1. DC positively associated with ADL limitations*** 2. DC positively associated with physically unhealthy days*** 3. DC positively associated with mentally unhealthy days***
Barile et al. (2012)[28], USA	Cross-sectional - *Same study as Barile et al. (2013)[27]*	General Population (*n* = 64,428)	≥ 65	a. DC	NS	1. 11 (4)	1. Physical HRQoL 2. Mental HRQoL	1. Number of conditions positively associated with number of physically unhealthy days 2. Number of conditions positively associated with number of mentally unhealthy days
Barnett et al. (2012)[71], UK	Cross-sectional	Primary Care (N = 1,751,841)	≥ 0	a. DC	Chronic diseases selected are those recommended as core for any multimorbidity measure by systematic review in QOF of the UK GP contract and long-term disorders identified as important by NHS Scotland	1. 40 (2)	1. Presence of mental health disorder	1. Presence of mental health disorder was positively associated with the number of physical disorders that an individual had*
Biehl et al. (2016)[49], USA	Cohort	Primary Care (N = 9,872)	≥ 65	a. ERA b. CCI	Chronic disease as identified in ICD-9	a. 9 (NS) b. NS (NS)	1. Presence of critical illness	1a. Both measures positively associated with critical illness*** 1b. CCI performed better in predicting critical illness

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Brilleman et al. (2014)[31], UK	Cohort - *Same study as Brilleman & Salisbury (2013)*[32]	Primary Care (N = 86,100)	≥ 18	a. QOF count b. CCI c. EDC count d. ACG e. RUB	Measure (a): Chronic disease as identified in the clinical domain of the UK QOF pay for performance scheme Measure (b): Chronic disease that are predictive of mortality	a. 17 (NS) b. 17 (NS) c. 114 (NS) d. 68 categories (NS) e. 6 categories (NS)	1. Primary healthcare cost	1a. All measures positively associated with outcome* 1b. EDC count has the best performance on the goodness of fit
Brilleman & Salisbury (2013)[32], UK	Cohort - *Same study as Brilleman et al. (2014)*[31]	Primary Care (N = 95,188)	≥ 18	a. QOF count b. CCI c. EDC count d. ACG e. RUB f. Prescribed drugs count	NS	a. 17 (NS) b. 17 (NS) c. 114 (NS) d. 68 categories (NS) e. 6 categories (NS) f. NS (NS)	1. Mortality (3-years period) 2. Number of primary care consultations (3-years period)	1. Best performing model was drugs count followed by ACG, EDC count, RUB, QOF count, and CCI 2. Best performing model was CCI followed by drugs count, QOF count, EDC count, and RUB
Carey et al. (2013)[50], UK	Cohort	Primary Care (*n* = 335, 904)	≥ 60	a. Standard QOF b. Extended QOF c. CCI (Khan)	Measure (a): Based on QOF disease definition from UK GP contract Measure (b): Based on QOF disease definition and additional 5 severe subgroups of standard QOF conditions Measure (c): Chronic diseases selected based on Read code list created by Khan	a. 9 (NS) b. 14 (NS) c. 17 (NS)	1. Mortality (1-year period)	1a. All measures positively associated with 1-year mortality risk* 1b. Fitting the weighted score as a 9-level variable, extended QOF score outperformed the rest of the measures in overall model performance
Chapman et al. (2015)[51], UK	Cohort	General Population (*n* = 3,237)	≥ 18	a. CCI b. CCI-PSR	NS	a. 9 categories (NS) b. 9 categories and 5 psycho-social factors (NS)	1. Mortality (5, 10, 15, 20, 25-years period)	1. CCI-PSR showed substantially better discrimination across all time horizons***

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement: Measure (s) used	Multimorbidity Measurement: Definition of chronic disease included in the scale	Multimorbidity Measurement: Number of conditions (MM cut-off)	Outcomes measured	Results
Chen et al. (2011)[72], USA	Cross-sectional	General Population (*n* = 430,912)	≥ 18	a. DC	NS	a. 8 (NS)	1. General Health 2. Mental Distress 3. Physical Distress 4. Activity limitations	1. Higher DC associated with poorer general health* 2. Higher DC associated with higher prevalence of mental distress* 3. Higher DC associated with higher prevalence of physical distress* 4. Higher DC associated with more frequent activity limitations*
Crane et al. (2010)[52], USA	Cohort	Primary Care (N = 12,650)	≥ 60	a. ERA	Chronic diseases identified from ICD-9 and selected based on consensus discussion regarding their known risk for recurrent hospitalization and greater complexity of care	a. NS (NS)	1. Number of hospital visits (1-year period) 2. Number of ED visits (1-year period) 3. Number of hospital admissions (1-year period) 4. Days hospitalised (1-year period)	1a. AUC = 0.705 1b. Increased with increasing ERA score** 2a. AUC = 0.64 2b. Increased with increasing ERA score** 3. Increased with increasing ERA score** 4. Increased with increasing ERA score**
Crooks et al. (2016)[33], UK	Cohort - *Same study as Crooks et al. (2015)[34]*	Primary Care (*n* = 328,636)	20 to 100	a. Co-morbidity linked score b. CCI c. Elixhauser Index	Measure (a): Chronic diseases identified from primary care in the CPRD and diagnostic ICD-10 from secondary care in English HES	a. NS (NS) b. NS (NS) c. NS (NS)	1. Mortality (1-year period)	1. Linked score improved discrimination and fit compared to CCI and Elixhauser Index

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Crooks et al. (2015)[34], UK	Cohort - *Same study as Crooks et al. (2016)[33]*	Primary Care (N = 657,264)	≥ 20	a. CCI (Read) b. CCI (ICD-10) c. CCI (Read and ICD-10)	NS	a. 19 (NS) b. 19 (NS) c. 19 (NS)	1. All-cause mortality (1-5 years)	1. No large difference in the discrimination of model for overall survival, whichever codes used to derive CCI
DiNapoli et al. (2017)[73], USA	Cross-sectional	Primary Care (*n* = 34,786)	≥ 50	a. Organ systems with chronic disease	NS	a. NS (NS)	1. Presence of depressive or anxiety disorder	1. Odds of having depressive and/or anxiety disorder increased with each additional organ system with chronic disease**
Formiga et al. (2013)[53], Spain	Cohort	Primary Care (N = 328)	85	a. CCI	NS	a. Assumed 17 (NS)	1. Mortality (3-years period)	1. Patients who did not survive had significantly higher CCI score***
Formiga et al. (2011a)[54], Spain	Cohort	General Population (including those in institutions) (N = 186)	90 to 99	a. CCI	NS	a. NS (NS)	1. Mortality (5-years period)	1. Patients who did not survive had significantly higher CCI score***
Formiga et al. (2011b)[36], Spain	Cross-sectional - *Same study as Formiga et al. (2016)[35]*	Primary Care (*n* = 328)	85	a. CCI	NS	a. NS (NS)	1. Successful aging	1. Successful aging was associated with lower values on the CCI*
Formiga et al. (2016)[35], Spain	Cohort - *Same study as Formiga et al. (2011b)[36]*	Primary Care (N = 328)	85	a. CCI	NS	a. NS (NS)	1. Mortality (5-years period)	1. Patients who survived after 5-year follow-up had significantly lower CCI score***

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Fraccaro et al. (2016)[55], UK	Cohort	Primary Care (N = 287,459)	≥ 18	a. CCI (Khan)	Chronic disease selected from a validated list of Read diagnostic codes for calculating CCI in UK primary care from Khan et al. (2010)	a. 22 (NS)	1. Mortality (1, 5, 10-years period) 2. Mortality (3, 6, 12-months period)	1. Mortality odds ratio positively associated with change in CCI at 1, 5, and 10 years follow-up* 2. Model consisting of sex, time-dependent age, CCI, and CCI change over consecutive time windows had the best fit to the data
Galenkamp et al. (2011)[45], The Netherlands	Cross-sectional	General Population (N = 2,046)	57 to 98	a. DC	Selection of chronic diseases was based on their prevalence in the 55+ age group in The Netherlands	a. 7 (NS)	1. SRH	1. SRH declines with each increase in number of co-occurring diseases***
Garin et al. (2014)[74], Spain	Cross-sectional	General Population (N = 3,625)	≥ 50	a. DC	NS	a. 11 (NS)	1. QOL 2. Disability	1. QoL decreased with increasing number of chronic conditions*** 2. Disability increased with increasing number of chronic conditions***
Glynn et al. (2011)[10], Ireland	Cross-sectional	Primary Care (*n* = 3,309)	> 50	a. DC	Health problems that require ongoing management over a period of years/decades	a. 147 (2)	1. Primary Care Consultations (1-year period) 2. Hospital outpatient visits (1-year period) 3. Hospital admissions (1-year period) 4. Healthcare cost	1. Mean primary care consultations increased with increasing number of conditions*** 2. Mean outpatient visits increased with increasing number of conditions*** 3. Higher number of conditions increased the odds of hospital admissions** 4. Total healthcare cost increased significantly with increasing number of chronic conditions***

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement: Measure (s) used	Multimorbidity Measurement: Definition of chronic disease included in the scale	Multimorbidity Measurement: Number of conditions (MM cut-off)	Outcomes measured	Results
Haas et al. (2013)[56], USA	Cohort	Primary Care (N = 83,187)	≥ 18	a. ACG b. Minnesota Health Care Home Tiering c. HCC d. ERA e. CCC f. CCI g. Hybrid Model	NS	a. 93 categories (NS) b. 5 levels (NS) c. 70 (NS) d. NS (NS) e. 6 categories (NS) f. 17 (NS) g. NS (NS)	1. Hospitalisation (1-year) 2. ED visits (1-year) 3. Readmission within 30 days (1-year) 4. Healthcare expenditure (1-year)	1. ACG model outperformed other models when predicting hospitalisation 2. ACG model outperformed other models when predicting ED visits 3. ACG model outperformed other models when predicting 30-days readmissions 4. ACG model outperformed other models when predicting healthcare expenditure
Hwang et al. (2015)[57], USA	Cohort	General Population (N = 42,038)	≥ 0	a. ACE-27 b. ACE-27 count	Measures (a) and (b) consist of 26 common patient conditions	a. 26 (NS) b. 26 (NS)	1. Healthcare expenditure	1a. Increasing number of comorbidity (Φc = 0.36) and comorbidity severity (Φc = 0.30) increased the likelihood of being persistent high healthcare users 1b. Exploratory predictive model of persistent high-user group reported an AUC value of 0.923
Kristensen et al. (2014)[79], Denmark	Cross-sectional	Primary Care (N = 139,527)	> 0	a. RUB	NS	a. 6 levels (NS)	1. Fee-for-services expenditures	1. RUB explained about 18% of the variance in expenditures
Lapi et al. (2015)[80], Italy	Cross-sectional	Primary Care (*n* = 26,903)	≥ 15	a. HSMI	Chronic disease is defined as being diagnosed with 1 of the selected conditions in the study at least once in an 18-month period	a. 73 (NS)	1. Total mean healthcare cost per year	1. HSMI explained 50.17% of the variation in costs

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Lawson et al. (2013)[81], UK	Cross-sectional	General Population (*n* = 7,054)	≥ 20	a. DC	Chronic conditions that are longstanding, as defined by "anything that has troubled you over a period of time"	a. 40 (2)	1. Preference_ Weighted HRQoL	1. Increasing number of conditions was associated with reduction in Preference Weighted HRQoL scores***
Lemke et al. (2012)[61], USA	Cohort	General Population (*n* = 4,707,001)	≥ 0	a. CCI b. ACG	NS	a. 17 (NS) b. NS (NS)	1. Inpatient Hospitalisations	1. ACG-based models were superior to the prior hospitalization model and Charlson inpatient hospitalization model (AUC 0.80 vs 0.75 vs 0.78)
Marengoni et al. (2011)[83], Sweden	Cross-sectional	General Population (*n* = 1,099)	≥ 75 (baseline) ≥ 77 (follow-up)	a. DC	Disease was classified as chronic if it met 1 or more of the following characteristics: (1) state of permanence, (2) caused by non-reversible pathological alternation, (3) requiring rehabilitation and (4) requiring a long period of care	a. 30 (2)	1. Disability	1. Increasing number of diseases was associated with increasing prevalence of disability***
McDaid et al. (2013)[84], Ireland	Cross-sectional	General Population (N = 6,159)	≥ 50	a. DC	NS	a. 8 (2)	1. Disability 2. QoL 3. SRH	1. Higher DC associated with higher risk of disability*** 2. Higher DC associated with poorer QoL*** 3. Higher DC associated with poorer SRH***
Payne et al. (2014)[37], UK	Cohort - *Same study as Payne et al. (2013)*[38]	Primary Care (N = 180,815)	≥ 20	a. DC	Conditions established by clinical expert consensus, sought to include morbidities recommended as core for any multimorbidity measure by a previous systematic review, diseases included in the UK primary care 'payment-for-performance' contract (QOF) and those considered important for health service planning by NHS Scotland. These conditions may significantly impact quality of life.	a. 40 (NS)	1. Unplanned hospital admissions (1-year period)	1. Number of clinical conditions positively associated with unplanned hospital admissions in a 12-month follow-up period***

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement: Measure (s) used	Multimorbidity Measurement: Definition of chronic disease included in the scale	Multimorbidity Measurement: Number of conditions (MM cut-off)	Outcomes measured	Results
Payne et al. (2013)[38], UK	Cohort - *Same study as Payne et al. (2014)[37]*	Primary Care (N = 180,815)	≥ 20	a. DC	NS	a. 40 (NS)	1. Unplanned hospital admission (1-year period) 2. Potentially preventable unplanned admission (1-year period)	1. Number of physical conditions positively associated with unplanned admission in a year*** 2. Number of physical conditions positively associated with preventable admission in a year***
Quail et al. (2011)[62], Canada	Cohort	General Population (N = 662,423)	≥ 20	a. DC b. CCI (Quan) c. Elixhauser (Quan) d. Number of different dispended drugs e. CDS	NS	a. NS (NS) b. 17 (NS) c. 31 (NS) d. NS (NS) e. NS (NS)	1. Mortality (1-year period) 2. One or more hospitalisations 3. Two or more hospitalisations	1. The addition of Elixhauser Index (Quan) to the base model yielded the largest improvement in c-statistic, followed by CCI (Quan) in predicting mortality 2. DC performed best in predicting one more or hospitalisations 3. DC performed best in predicting two or more hospitalisations
Ranstad et al. (2014)[88], Sweden	Cross-sectional	General Population (N = 151,731)	≥ 0	a. RUB	NS	a. NS (NS)	1. Registered active listing in primary care 2. Registered active listing in all healthcare	1a. Patients of high multimorbidity level are more likely to be actively listed in primary care* 1b. Multimorbidity level predicted active listing in primary care, significantly increasing for RUB 0-4*** 2a. Patients of high multimorbidity level are more likely to be actively listed in all healthcare* 2b. Multimorbidity level predicted active listing in all healthcare significantly*** increasing for RUB 0-4

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement: Measure (s) used	Multimorbidity Measurement: Definition of chronic disease included in the scale	Multimorbidity Measurement: Number of conditions (MM cut-off)	Outcomes measured	Results
Reyes et al. (2014)[63], Spain	Cohort	Primary Care (Men only) (N = 186,171)	≥ 65	a. CCI	NS	a. 17 (NS)	1. Hip fractures	1. Patients with CCI ≥ 3 had increased risk of hip fracture as compared to patients without co-morbidities***
Ryu et al. (2015)[90], USA	Cross-sectional	Primary Care (N = 21,736)	≥ 18	a. DC	NS	a. 80 (NS)	1. Deficits of perceived general health 2. Depressive symptoms	1. Disease burden was associated with higher risk of deficits in perceived general health* 2. Disease burden was associated with higher risk of deficits in depressive symptoms*
Salisbury et al. (2011)[11], UK	Cohort	Primary Care (N = 99,997)	≥ 18	a. QOF count EDC count	Measure (b): Chronic disease defined as one that normally lasts ≥ 6 months	a. 17 (2) b. 114 (NS)	1. Primary Care consultation rates (3-years period) 2. Continuity of care (3-years period)	1. Number of QOF conditions positively associated with consultation rates*** 2. QOF morbidity inversely associated with continuity of care*
Saver et al. (2014)[64], USA	Cohort	General Population (N = 106,930)	≥ 65	a. CCI (Romano) + Hypertension	NS	a. 19 (NS)	1. Acute ACSH 2. Chronic ACSH	1. Models containing flags for comorbidity showed greater predictive power for acute ACSH 2. Models containing flags for comorbidity showed greater predictive power for acute ACSH
Shadmi et al. (2011)[91], Israel	Cross-sectional	General Population (*n* = 279,241)	≥ 18	a. ADG b. CCI	NS	a. 32 (NS) b. 19 (NS)	1. Number of primary care physician visits 2. Number of specialist visits 3. Number of hospitalisation	1. ADGs explained 23% to 54% of the variance in health care resource utilization as compared to CCI, which explained only 11%-18%.

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Stanley & Sarfati (2017)[65], New Zealand	Cohort	Primary Care (*n* = 1,000,166)	≥ 18	a. M3 Index b. CCI c. Elixhauser (van Walraven)	Measure (a): Chronic diseases were identified from ICD-10 and based on the impact on quality and quantity of life, requiring complex healthcare management for coordination, and lasting for ≥ 3 months	a. 55 (NS) b. 17 (NS) c. 31 (NS)	1. Mortality (1-year period) 2. Overnight hospitalisation (1-year period)	1. M3 Index improved predictive performance for 1-year mortality risk over CCI and Elixhauser 2. M3 Index improved predictive performance for overnight hospitalisation over CCI and Elixhauser
Streit et al. (2014)[66], Switzerland	Cohort	Primary Care (N = 1,002)	50 to 80	a. CCI b. DC	Measure (b): Derived list of chronic diseases based on a large study by Higashi et al. (2007) and the CCI. Psychiatric conditions were also included based on consensus	a. 19 (NS) b. 17 (NS)	1. Quality of cardiovascular preventive care 2. Quality of preventive care	1. No association found between multimorbidity measures and outcome 2. No association found between multimorbidity measures and outcome
Sullivan et al. (2012)[93], USA	Cross-sectional	General Population (N = 47,178)	≥ 18	a. DC	CCC of ICD-9 codes - Chronic conditions is defined as lasting for more than 1 year	a. 118 (2)	1. Preference-based HRQoL	1a. The number of chronic conditions was negatively associated with EQ-5D-5L scores*** 1b. Inclusion of chronic co-morbidity to the baseline models explained more variance in EQ-5D-5L index scores than did age or other socio-demographic characteristics
Takahashi et al. (2016)[67], USA	Cohort	Primary Care (*n* = 42,368)	≥ 18	a. Minnesota Tiering (ACG) b. Enhanced model	NS	a. 42 (NS) b. 42 (NS)	1. Hospitalisation / ED visits	1a. Patients identified as high-risk in the enhanced model were much more likely to experience hospital utilization than those in the Minnesota medical tiering model*** 1b. Enhanced model (AUC = 0.711) is better at predicting hospitalization/ED visits as compared to Minnesota Medical Tiering (AUC = 0.667)

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Takahashi et al. (2012)[47], USA	Cohort	Primary Care (N = 12,650)	> 60	a. ERA	NS	a. 7 (NS)	1. Mortality (2-years period) 2. Nursing home placement (2-years period)	1. Being in the uppermost quartile of the ERA index significantly increased the risk for mortality in the subsequent 2 years*** 2. Being in the uppermost quartile of the ERA index significantly increased nursing home placement in the subsequent 2 years***
Ubalde-Lopez et al. (2016)[94], Spain	Cross-sectional	General Population (N = 372,370)	Female (Mean): 35.9 Male (Mean): 37.9	a. MDMS	NS	a. 14 (2)	1. Sickness absence episodes taken in last 2 years	1a. Higher risk of new episodes was observed among men as MDMS levels increased* 1b. Similar trend was observed among women but trend was statistically significant
van den Bussche et al. (2011)[48], Germany	Cross-sectional	Primary Care (N = 123,224)	≥ 65	a. DC	Chronicity of conditions was assessed using the "Expert Report for the Selection of 50 to 80 Diseases to be included in the morbidity based risk adjustment scheme" in the German Statutory Health Insurance. A person was defined as chronically ill if she/he had at least one of the 46 chronic conditions in at least three quarters within the one-year observation period 2004.	a. 46 (3)	1. Frequency of contacts with physicians (1-year) 2. Number of different ambulatory physicians contacted (1-year)	1. Number of chronic conditions is positively associated with the number of contacts with physicians*** 2. Number of chronic conditions is positively associated with the number of physicians contacted***

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
van Oostrom et al. (2014)[95], The Netherlands	Cross-sectional	Primary Care (N = 32,583)	≥ 55	a. DC	NS	a. 28 (2)	1. Number of contacts with general practice 2. Number of medications prescribed 3. Number of referrals	1. The number of chronic diseases was positively associated with the number of contacts for all types of contacts in the general practice*** 2. The number of chronic diseases was positively associated with the number of medications prescribed*** 3. The number of chronic diseases was positively associated with the number of referrals***
Wallace et al. (2016a)[39], Ireland	Cohort - *Same study as Wallace et al. (2016b)[40]*	Primary Care (N = 862)	≥ 70	a. Pra tool b. Modified Pra tool	NS	a. NS (NS) b. NS (NS)	1. Emergency hospital admission (1-year period)	1. Both measures demonstrated poor discrimination performance in predicting emergency hospital admission in a year
Wallace et al. (2016b)[40], Ireland	Cohort - *Same study as Wallace et al. (2016a)[39]*	Primary Care (N = 862)	≥ 70	a. DC b. Barnett conditions DC c. CCI d. Prescribed drugs count e. RxRisk-V	Measure (a): ICPC-2 definition of chronic disease was used Measure (b): Chronic conditions were selected based on health impact and prevalence	a. NS (2) b. 40 (2) c. 19 (NS) d. NS (NS) e. N3S (NS)	1. Emergency admission (2-years period) 2. Functional decline (2-years period)	1. All measures demonstrated poor discrimination for the emergency admission in 2 years 2. All measures demonstrated poor discrimination for functional decline

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Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Wei et al. (2018)[97], USA	Cross-sectional	General Population (N = 20,509)	≥ 51	a. MWI	NS	a. 81 (NS)	1. Subjective physical functioning 2. Grip strength 3. Gait speed 4. Cognitive performance 5. ADL limitations 6. IADL limitations	1. MWI negatively associated with physical functioning*** 2. MWI negatively associated with grip strength*** 3. No association found between MWI and gait speed 4. Higher MWI associated with poorer cognitive performance*** 5. Higher MWI associated with increased ADL limitations*** 6. Higher MWI associated with IADL limitations***
Wei & Mukamal◊ (2018)[69], USA	Cohort	General Population (N = 219,950)	≥ 36	a. MWI b. DC c. CCI	NS	a. 81 (NS) b. 81 (2) c. 19 (NS)	1. Mortality (10-years period) 2. Future physical functioning	1a. All three measures of multimorbidity were positively associated with mortality*** 1b. MWI performed best in predicting mortality as compared to DC and CCI in all three cohorts as well as combined cohorts 2. All three measures of multimorbidity were negatively associated with future physical functioning***

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◊ The youngest participant was from the NHS II cohort, aged 25 in 1989. Data collection for this study started in 2000 (NHS and HPFS cohorts) and 2001 (NHS II cohort) and hence, the age of the participants recruited in this study is 36 years old and above.

Table 3-3. Summary of included articles with good risk of bias judgement (47 studies including 53 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured	Results
				Measure (s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)		
Wikman et al. (2011)[98], UK	Cross-sectional	General Population (*n* = 11,532)	≥ 50	a. DC	NS	a. 8 (NS)	1. QoL 2. Affective well-being	1. Number of chronic conditions was negatively associated to QoL*** 2. Number of chronic conditions was negatively associated to affective well-being***
Wister et al. (2015)[99], Canada	Cross-sectional	General Population (*n* = 16,369)	≥ 65	a. Multimorbidity additive scale b. Multimorbidity weighted by HUI3 c. Multimorbidity weighted by ADL Scale d. Multimorbidity weighted by HUI3 betas	Conditions that are slow in progression, long in duration, and typically limit function, productivity and quality of life.	a. 19 (NS) b. 19 (NS) c. 19 (NS) d. 19 (NS)	1. Life satisfaction 2. Perceived health status	1. All measures are negatively associated with life satisfaction*** 2. All measures are negatively associated with perceived health status***

Note. ACE-27 = Adult Comorbidity Evaluation-27; ACG = Adjusted Clinical Groups; ACSH = Ambulatory Care Sensitive Hospitalisation; ADG = Aggregated Diagnosis Groups; ADL = Activities of Daily Living; AUC = Area Under the Curve; BI = Barthel Index; CCC = Chronic Condition Count; CCC (of ICD-9 codes) = Clinical Classification Categories; CCI = Charlson Comorbidity Index; CCI-PSR = Charlson Comorbidity Index-Psychosocial Risk; CDS = Chronic Disease Score; CPRD = Clinical Practice Research Datalink; DC = Disease Count (Unweighted); ED = Emergency Department; EDC = Expanded Diagnosis Clusters; EMR = Electronic Medical Record; EQ-VAS = EuroQoL-Visual Analogue Scale; EQ-5D-5L = EuroQoL-5 Dimensions; ERA = Elder Risk Assessment; GP = General Practice; HCC = Hierarchical Condition Categories; HRQoL = Health-related Quality of Life; HUI3 = Health Utility Index; IADL = Instrumental Activities of Daily Living; ICD-10 = International Classification of Diseases, Tenth Revision; ICD-9 = International Classification of Diseases, Ninth Revision; ICPC-2 = International Classification of Primary Care, second edition; MDMS = Multidimensional Multimorbidity Score; MM = Multimorbidity; MWI = Multimorbidity-Weighted Index; NHS = National Health Service; NS = Not Stated; Pra tool = Probability of repeated admission risk prediction tool; QOF = Quality and Outcomes Framework; QoL = Quality of Life; RUB = Resource Utilisation Band; RxRisk-V = A Veterans Association adapted pharmacy-based case-mix instrument; SRH = Self-Rated Health; UK = United Kingdom; Φc = Cramer's V

* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

Table 3-4. Summary of included studies with poor and fair risk of bias judgement (20 studies including 21 articles)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement: Measure(s) used	Multimorbidity Measurement: Definition of chronic disease included in the scale	Multimorbidity Measurement: Number of conditions (MM cut-off)	Outcomes measured
Boeckxstaens et al. (2015a)[29], Belgium	Cross-sectional - *Same study as* Boeckxstaens *et al. (2015b)*[30]	Primary Care (N = 567)	≥ 80	a. DC b. CCI c. CIRS	NS	a. 22 (3) b. 19 (5) c. 58 (3)	1. Disability 2. Frailty
Boeckxstaens et al. (2015b)[30], Belgium	Cohort - *Same study as* Boeckxstaens *et al. (2015a)*[29]	Primary Care (N = 567)	≥ 80	a. DC b. mCCI c. CIRS	NS	a. 22 ($3^{\nabla}/4^{\lozenge}$) b. 19 ($5^{\nabla}/4^{\lozenge}$) c. 58 ($3^{\nabla}/3^{\lozenge}$)	1. Mortality (3-years period) 2. Hospitalisation (3-years period) 3. Functional decline (19-months period)
Gunn et al. (2012)[75], Australia	Cross-sectional	Primary Care (*n* = 7,620)	18 to 76	a. DC	Chronic diseases selected were the commonly seen chronic physical conditions seen in Australian GP and the National health priority areas	a. 12 (2)	1. Depressive symptoms
Hanmer et al. (2010)[76], USA	Cross-sectional	General Population (*n* = 94,794)	22 to 106	a. Additive b. Minimum c. Multiplicative Models	Chronic disease defined as conditions that are chronic in nature and should affect the respondent's health at the point when they completed the survey	a. 15 (NS) b. 15 (NS) c. 15 (NS)	1. SF-6D health utility
Hu et al. (2017)[77], Canada	Cross-sectional	Primary Care (N = 265)	≥ 65	a. Age-adjusted CCI	NS	a. NS (NS)	1. Frequency of family physician visits
Isaacs et al. (2014)[78], South Africa	Cross-sectional	Primary Care (N = 4,184)	18 to 101	a. DC	Any condition requiring long-term (> 1 month) medication with repeat prescriptions	a. NS (2)	1. Prescription cost
Jennings et al. (2015)[58], USA	Cohort	Primary Care (N = 1,776)	≥ 75	a. Elixhauser Comorbidity Count	NS	a. NS (NS)	1. Number of fall-related injuries in 2 years

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$^{\nabla}$ Multimorbidity cut-off of the multimorbidity measure in relation to hospitalisation in 3-years period.
$^{\lozenge}$ Multimorbidity cut-off of the multimorbidity measure in relation to mortality risk in 3 years.

Table 3-4. Summary of included studies with poor and fair risk of bias judgement (20 studies including 21 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured
				Measure(s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)	
Jia and Lubetkin (2016)[59], USA	Cohort	General Population (N = 2,380)	≥ 65	a. DC	Chronic diseases are selected based on their inclusion in other national data sets, prevalence among elderly, being a leading cause of death and having a high mortality rate	a. 9 (NS)	1. QALY
Jia et al. (2018)[60], USA	Cohort	General Population (N = 96,481)	≥ 65	a. DC	NS	a. 15 (NS)	1. QALY
Kojima et al. (2011)[46], Japan	Cross-sectional	Primary Care (N = 262)	≥ 65	a. DC	NS	a. 7 (NS)	1. Fall tendency
Li et al. (2016)[82], UK	Cross-sectional	General Population (N = 27,806)	16 to 68	a. DC	Conditions can range across different long-term, illnesses, and health problems	a. 13 (2)	1. HRQoL
Md Yusof et al. (2010)[43], UK	Cohort	General Population (N = 113)	64 to 85	a. CCI b. CMI c. Count of prescribed drugs	NS	a. 19 (NS) b. NS (NS) c. NS (NS)	1. Mortality (7-years period)
Muggah et al. (2012)[44], Canada	Cross-sectional	General Population (N = 9,901,410)	≥ 20	a. DC	NS	a. 9 (NS)	1. Ambulatory care use
Mujica-Mota et al. (2015)[3], UK	Cross-sectional	Primary Care (*n* = 831,537)	≥ 18	a. DC	NS	a. 13 (2)	1. HRQoL
Naessens et al. (2011)[85], USA	Cross-sectional	General Population (N = 33,324)	18 to 64	a. DC	Chronic diseases as identified in ICD-9	a. NS (NS)	1. Healthcare cost
Østergaard and Foldager (2011)[86], Denmark	Cross-sectional	Primary Care (*n* = 4,271)	≥ 18	a. CGI-S b. DC	NS	a. 3 levels (NS) b. 9 (2)	1. Presence of major depressive episode

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Table 3-4. Summary of included studies with poor and fair risk of bias judgement (20 studies including 21 articles) (Continued)

Author (Year), Country	Study Design	Population source (Sample size)	Age	Multimorbidity Measurement			Outcomes measured
				Measure(s) used	Definition of chronic disease included in the scale	Number of conditions (MM cut-off)	
Peters et al. (2018)[87], UK	Cross-sectional	Primary Care (N = 848)	18 to 101	a. DC	NS	a. 11 (NS)	1. QoL
Renne and Gobbens (2018)[89], The Netherlands	Cross-sectional	Primary Care (N = 241)	≥ 70	a. DC	Chronic diseases selected were the most frequently present in the older Dutch population	a. 9 (2)	1. QoL
Sibley et al. (2014)[92], Canada	Cross-sectional	General Population (N = 16,357)	≥ 65	a. DC	Conditions lasting for 6 months or more and diagnosed by a health professional	a. 13 (2)	1. Self-reported falls in last 12 months
Tyack et al. (2016)[68], Australia	Cohort	Primary Care (N = 351)	≥ 18	a. DC	Chronic disease defined as requiring complex care management involving multiple providers and ideally coordinated care, and where they may be acute as well as chronic episodes	a. 25 (NS)	1. HRQoL
Vos et al. (2013)[96], The Netherlands	Cross-sectional	Primary Care (Women only) (N = 315)	70 to 74	a. DC	List of conditions developed under the auspices of Statistics Netherlands	a. 21 (NS)	1. SRH

Note. CCI = Charlson Comorbidity Index; CGI-S = Clinical Global Impression – Severity Scale; CIRS = Cumulative Illness Rating Scale; CMI = Cornell Medical Index; DC = Disease Count (Unweighted); EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; GP = General Practice; HRQoL = Health-related Quality of Life; ICD-9 = International Classification of Diseases, Ninth Revision; mCCI = modified Charlson Comorbidity Index; NS = Not Stated; QALY = Quality-adjusted Life Year; QoL = Quality of Life; SF-6D = Short-Form Six-Dimension.

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
A	**COUNT OF INDIVIDUAL CONDITIONS**									
A1	By Condition									
	1	DC	Disease Count	Condition	7 - 147	Unweighted	Condition count	0 to 147	EMR, GP records, Health service database, Hospital discharge abstract, Insurance claims or Questionnaires - telephone, face-to-face, mailed	42
A2	By Category									
	2	CCC	Chronic Condition Count	Condition	6 categories	Unweighted	Based on AHRQ's clinical classification software and number of conditions for each category	0 to 5	EMR	1
B	**ORGAN OR SYSTEM-BASED APPROACHES**									
	3	CIRS	Cumulative Illness Rating Scale	System	14 categories	0-4, based on clinical judgement	Summative	0 to 56	Structured questionnaire followed by encoding research assistants	1
	4	CMI	Cornell Medical Index	System - Regarded only for historical purposes and for research since 2001.	18 categories	195 yes-no questions collecting pertinent medical and psychiatric data	Sum of 'yes'	0-195	Self-reported questionnaire	1
	5	Organ - CDC	Organ systems with chronic disease count	Organ system	17 organ systems	Unweighted	Sum of organ systems	0 to 17	EMR	1

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required (Continued)

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
C	**WEIGHTED INDICES**									
	6	ACE-27	Adult Comorbidity Evaluation	Condition	27 conditions	1-3, based on severity of most severe condition	Highest score of single item	0 to 3	Insurance Claims' database	1
	7	CCI (Original and modified)	Charlson Comorbidity Index	Condition	Original 17 conditions. Modified - range from 9 conditions and 5 psychosocial factors to 19 conditions	1-6; based on impact on 1-year mortality (RR) - original	Sum of weighted conditions	0 to 37	Administrative database (e.g., Billing, Insurance Claims), EMR (primary care or integrated with secondary care), Medical chart review, Interviews (patients, caregivers, nurse or physicians) or postal questionnaire.	22
	8	CC-AM	Chronic conditions additive modelling	Condition	15 conditions	Weighted based on SF-6D	By adding the health utility scores of the conditions	Variable	Questionnaire on health conditions	1
	9	CC-MM	Chronic conditions minimum modelling	Condition	15 conditions	Weighted based on SF-6D	By using the minimum single condition utility score	Variable	Questionnaire on health conditions	1
	10	CC-MuM	Chronic conditions multiplicative modelling	Condition	15 conditions	Weighted based on SF-6D	By multiplying the health utility scores of all the conditions	Variable	Questionnaire on health conditions	1
	11	CLS	Comorbidity Linked Score	Condition	98 combined codes of sub-chapters in the Read code and the ICD10 code blocks	Based on impact for mortality (hazard ratio)	Sum of beta coefficients of each category	1 to 10	Linked patients' records of all primary care events, hospital admissions and causes of death.	1
	12	EI	Elixhauser Index (original and modified)	Condition	21 to 31 conditions	Based on impact on in-hospital mortality	Summing of beta coefficients	-19 to 89	Insurance Claims' or Medical services database	3

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required (Continued)

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
C	**WEIGHTED INDICES (continued)**									
	13	ERA	Elders Risk Assessment	Condition	6 to 9 conditions	Weighted, based on impact on future hospitalisation	Sum of weighted regression coefficients	Original: -1 to 43. Some modified from -7 to 43.	EMR and administrative database	4
	14	HCC	Hierachical Condition Categories	Condition	70 condition categories	Based on Medicare capitation payments for health expenditure	The most severe manifestation of a given disease process principally defines its impact on costs. Therefore, more severe manifestations of a condition dominating (and zeroing out the effect of) less serious ones. Other diseases are summed additively.	NS	EMR & HCC software licensing	1
	15	M3 Index	Multi-Morbidity Measure Index	Condition	55 conditions	Weighted based on 1-year mortality	Summing of beta coefficients	0.01 to 2.47	Linked patients' records	1
	16	MDMS	Multidimensional multimorbidity score	Condition	7 chronic conditions, 2 health behaviours for 1st dimension & 5 symptoms for 2nd dimension	Weighted but not based on any specific outcome	Sum of the value for the weighted absolute contributions of each of the dimensions.	Men - 9 to 100 Women - 7 to 100	Standardised medical evaluation (Interviewer-administered)	1

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required (Continued)

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
C	**WEIGHTED INDICES (continued)**									
	17	MM by ADL	Multimorbidity weighted by ADL Scale	Condition	19 conditions	Weighted based on OARS functional status scale measuring ADL	Sum of weighted conditions	0 to 1.8	Face-to-face or telephone interviews	1
	18	MM by HUI3	Multimorbidity weighted by Health Utility Index	Condition	19 conditions	Weighted based on correlation with health utility index	Sum of weighted conditions	0 to 2.46	Face-to-face or telephone interviews	1
	19	MM by HUI3 betas	Multimorbidity weighted by Health Utility Index betas	Condition	19 conditions	Weighted based on correlation with health utility index and adjusted for age and sex	Summing of beta coefficients	0 to 1.18	Face-to-face or telephone interviews	1
	20	MWI	Multimorbidity-Weighted Index	Condition	81 conditions	Weighted based on impact on SF-36 physical functioning scale	Sum of weights	Variable	Interviewer-administered or mail questionnaire	2
	21	QOF-E	Extended QOF (weighted)	Condition	14 conditions	0-6, based on impact on 1-year mortality (RR)	Sum of weighted conditions	Not described	EMR	1
	22	QOF-S	Standard QOF (weighted)	Condition	9 conditions	1-3, based on impact on 1-year mortality (RR)	Sum of weighted conditions	0 to 17	EMR	1

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required (Continued)

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
D	**OTHER APPROACHES**									
D1	**Case-Mix**									
	23	ACG	Adjusted Clinical Groups	Condition	93 mutually exclusive ACGs. Some are modified to 68 ACGs	Incorporated into ACGs based on impact on resource use (proprietary)	Variable	N/A	EMR & ACG software licensing	3
	24	ADG	Aggregated Diagnostic Groups	Condition	32 groups	Based on duration, severity, diagnostic certainty, aetiology, and need for specialty care	Variable	NS	EMR & ACG software licensing	1
	25	HM	Hybrid Model (MN Tier + ERA)	Condition	NS	Only MN tier 4 + MN tier 3 with ERA > 10	Variable	NS	EMR, HCC software licensing & administrative data	1
	26	HSMI	Health Search Morbidity Index	Condition	73 chronic and acute conditions	Based upon yearly health care costs directly derived from primary care setting	Sum of regression coefficients (range from -0.06 to 1.04)	Variable	EMR	1
	27	MN Tier	Minnesota Tiering	Condition	NS	Grouping patients into 'complexity tiers' based on the number of major condition categories	Condition count	Tier 0 to 4	EMR or administrative data & MN Tiering software licensing	2
	28	RUB	Resource Utilisation Band	Condition	6 mutually exclusive bands	Based upon ACG algorithm on impact on resource use (proprietary)	Variable	N/A	EMR & ACG software licensing	3

Table 3-5. Description of instruments used for measurement of multimorbidity and the data sources and resources required (Continued)

	Category	Instrument	Instrument (Full Name)	Description					Data source(s) & resources required	Number of studies using the instrument
				System or Condition based	Items	Weightage	Scoring Method	Score Range		
D	**OTHER APPROACHES (Continued)**									
D2	Pharmaceutical-based									
	29	CDS	Chronic Disease Score	Condition	17 conditions	Weighted 1-5	Sum of weights based on pharmacological database	0 to 35	Prescription drug database	1
	30	Drug Count	Drug Count	NA	Variable. Some may be based on pharmacologic-therapeutic classification system	Weighted	Medication count	Variable	Self-reported questionnaire	4
	31	Modified Pra	Modified Pra tool using RxRisk-V	NA	Pra tool + RxRisk-V	Weighted due to RxRisk-V	4 categories	0 to 1	GP medical record + linked pharmacy claims database	1
	32	RxRisk-V	RxRisk-V	NA	WHO-ATC classification system	Weighted according to the diagnostic group of drugs to predict future health care costs	Sum of weights	NA	GP medical record + linked pharmacy claims database	1
D3	Clinical Judgement									
	33	CGI-S	Clinical Global Impression - Severity Scale	NA	NA	1-6; based on clinical judgement of GP	Rating of severity was only carried out for physical illness in general and not for each individual disease	1 to 6	GP Questionnaire	1

3.3 Description of all the instruments used

Table 3-6 summarised all the 27 instruments that were identified from the studies with low risk of bias.

3.3.1 Count of Individual Conditions

Disease count was based on the unweighted count of all the conditions an individual had usually from a pre-specified number of chronic conditions. It was used in 42 out of the 67 studies (62.7%). Disease counts were positively associated with activity limitations, continuity of care, disability, healthcare cost, healthcare utilisation, medications, mental disorders, and mortality; and negatively associated with general health, physical function, quality of life, and self-rated health. The only outcome that was not associated with disease count was preventive care[66] (*Table 3-6*).

The data sources and resources used ranged from medical records (manual to electronic) or administrative records like billing reports to insurance reports, self-administered questionnaires by using mail, or telephone to interviewer-administered questionnaires. As such, information collected could be from participants' recall or medical records (*Table 3-5*).

Under the category of count of individual conditions, Chronic Condition Count[56] (CCC) was a unique instrument. The difference between disease count and CCC was that although the number of conditions was counted for CCC, they were further divided into six categories based on a clinical classification software developed by the United States government agency. The score ranged from zero to five. Only one study used this instrument, and the investigators retrieved all the information from the electronic medical records.

3.3.2 Organ or system-based approaches

There were three instruments in this category. They were Cumulative Illness Rating Scale (CIRS)[29,30], Cornell Medical Index (CMI)[43], and Organ Systems with chronic disease count (Organ-CDC)[73] represented by one study each.

The CIRS is a system-based instrument divided into 14 categories[100]. Weightage is applied to each category with a scoring of zero to four based on clinical judgement. The score ranges from 0-56 and requires the summation of individual scores from each category.

Cornell Medical Index was created in 1949 and has been declared by the Cornell Medical Centre to be no longer of clinical use since 2001. It was a self-reported questionnaire. (https://library.weill.cornell.edu/archives/about-us/cornell-medical-index)

The Organ-CDC has 17 organ systems summed to form a score range of zero to seventeen. Data were collected from electronic medical records. The instrument was found to be associated with the presence of depressive or anxiety disorder[73].

The two studies that used the instruments CIRS and Cornell Medical Index were not rated 'good' after the risk of bias assessment, and therefore the outcomes being examined in these two studies were not reported in our summary Table 3-6. The outcomes examined for these two instruments were disability[29,30], frailty[29,30], functional decline[29,30], and mortality[30,43].

3.3.3 Weighted Indices

There were seventeen unique weighted instruments found in the included studies. The original Charlson Comorbidity Index (CCI) with its different modifications was the most frequently used instrument and was found in 22 studies. Trailing behind were four studies using the Elder Risk Assessment (ERA), three studies using Elixhauser Index (EI), and two studies using Multimorbidity-Weighted Index (MWI). The other 13 studies had a unique weighted index each. Some of these indices were used in prediction models.

The CCI was based on disease count, but the 17 conditions were weighted originally based on its impact on one-year mortality[101]. The final score was derived by the summation of all the weighted conditions. The score ranges from 0-37. There were many variations and modifications of the score including the addition of psychosocial factors. The data sources and resources used ranged from medical records (manual to electronic), or administrative records like billing reports or insurance reports, to self-administered questionnaires by using mail, telephone, or interviewer-administered. As such, information collected could be from

participants' recall or from medical records. The instrument was found to be associated with multiple outcomes other than one-year mortality (*Table 3-6*).

The ERA was based on disease count, but the conditions were weighted based on the impact on future hospitalisation[52]. The instrument had six to nine conditions, and the final score was derived from the sum of the weighted regression coefficients. The data sources were obtained from electronic medical records or administrative data. The instrument was found to be associated with critical illness[49], healthcare expenditure[56], mortality[47], and readmission[56].

The EI was developed from large administrative inpatient datasets[102]. It was based on disease count with conditions ranging from 21 to 31 due to its many variations. The conditions were weighted based on hospital mortality. The final score was also from the sum of the weighted regression coefficients. Like the above two indices, association with outcomes other than hospital mortality were found.

The MWI was a newer instrument that had 81 conditions weighted based on the impact on physical functioning[97]. The final score was from the sum of the weights. The investigators used an interviewer-administered or mailed questionnaire. The instrument was also associated with cognitive performance[97], grip strength[97] , and mortality[69]. There was no association found between MWI and gait speed[97].

Most of the other instruments were novel like MWI where the investigators built multivariable prognostic models from a set of potential predictor conditions (including non-clinical factors) and weighted the conditions based on an outcome of clinical interest. The most common outcomes chosen were mortality and physical function. Others included health expenditure[56], health utility index[99], and severity of the most severe condition[57]. However, Multidimensional multimorbidity score (MDMS)[94] was unique in that it was weighted but not based on any specific outcome.

Ubalde-Lopez et al.[94] used statistical methods to develop MDMS based on seven chronic conditions and two health behaviours. The conditions were weighted but were not based on any specific outcome. The instrument required a standardised medical evaluation. The investigators reported that MDMS was found to be positively associated with sickness absence for males, but no association was found for females.

3.3.4 Other Approaches

Other approaches included case-mix, pharmaceutical-based, and using clinical judgement for measuring the level of multimorbidity.

For case-mix, Adjusted Clinical Groups (ACG) and Resource Utilisation Band (RUB) were the most commonly used. Most of the case-mix instruments required proprietary software licenses from the United States of America. Large data sets from electronic medical records or administrative data were also needed (*Table 3-5*).

The second group in this category was related to pharmaceutical data. The most frequent type was the unweighted drug count. The other three (Chronic disease score, Modified Pra tool using RxRisk-V, and RxRisk-V) were all weighted indices. Except for the drug count that was based on a self-report questionnaire, the rest required a prescription drug database to obtain the data.

Clinical global impression - severity score (CGI-S) was an exceptional instrument that was not based on any of the above but solely based on clinical judgement of the attending physician. The study looked at the outcome of the presence of major depressive episode[86].

3.3.5 Prediction Models

Twenty studies (with 23 articles) used different multimorbidity instruments together with non-clinical predictors like social deprivation, age, sex, marital status into a multivariable regression analysis to predict outcomes including emergency department visits, health-related quality of life, hospitalisations, mortality, number of primary care consultations, primary healthcare cost, readmission (*Appendix 3-4*).

The c-statistic (concordance index), area under the receiver operating curve (AUC), and the square of the correlation between the observed outcome and the predicted risk (R^2) are the general statistics tests to summarise the discrimination between individuals with and without the outcome event in the regression model[103]. Of the 20 studies (23 articles), ten articles used c-statistic, five articles used AUC, and four articles used R^2. Additionally, two articles used

Akaike information criterion (AIC) and another two used Bayesian information criterion (BIC) for model selection.

The predictive ability of the instruments varied widely. Performances varied according to the specific instrument used and the outcome measured. The c-statistic†††† ranged from 0.55 to 0.931. In general, models that compared different outcomes consistently showed better c-statistic when the model was used to predict mortality[33,34,62,65]. Similar variability was noted with AUC‡‡‡‡ that ranged from 0.640 to 0.923, and R^2 §§§§ that ranged from 0.11 to 0.793.

3.4 Instruments used for measuring the three core outcomes in intervention studies

Table 3-7 identified the instruments that were used to explore the association with the three essential core outcomes selected for the core outcomes set of multimorbidity research (COSmm)[6]. Three categories of instruments were used for measuring mortality. The three categories were counts of individual conditions (DC), weighted indices (CCI, CLS, EI, ERA, M3 Index, MWI, QoF-E & QoF-S), and other approaches including case-mix (ACG & RUB) and pharmaceutical-based approaches (CDS & Drug Count). For mental health as an outcome, only two categories of multimorbidity measures were identified. They were counts of individual conditions (DC), and organ or systems-based approaches (Organ-CDC). Finally, for the quality of life, only counts of individual conditions (DC) was identified. Disease count was the only instrument identified for all three outcomes.

†††† Concordance index (c-statistic): 0.50-0.69 (poor), 0.70-0.79 (good), >0.80 (excellent)
‡‡‡‡ There are no recommended cut-offs for Area Under the receiver operating Curve (AUC)
§§§§ There are no recommended cut-offs for observed outcome and the predicted risk (R^2)

Table 3-6. Summary of multimorbidity instruments and their associations with outcomes measured

Multimorbidity Measures	Association between Outcomes and Multimorbidity		
	Positive Association	Negative Association	No Association
Count of Individual Conditions			
By Condition			
Disease Count (Many different groupings ranging from 7 [45-47] to 147 [10] conditions and some are further categorised [56])	Activities of Daily Living (ADL) limitations [27] Activity limitations [72] Continuity of care (3-years) [11] Deficits of perceived general health [90] Depressive symptoms [90] Disability [74,83,84] Emergency hospital admission (2-years) [40] Frequency of contacts with physicians (1-year) [48] Functional decline (2-years) [40] Healthcare costs [57,57] Hospital admissions (1-year) [37 38 62] Hospital outpatient visits (1-year) [67] Hospitalisation/Emergency Department Visits [67] Mental distress [72] Mortality (1-year) [62], (3-years) [32], (10-years) [69] Number of contacts with general practice (1-year) [95] Number of medications prescribed (1-year) [95] Number of mentally unhealthy days [27,28] Number of physically unhealthy days [27,28] Number of different ambulatory physicians contacted (1-year) [48] Number of primary care consultations (1-year) [32], (3-years) [32] Number of referrals (1-year) [95] Physical distress [72] Presence of mental health disorder [10] Primary care consultations (1-year period) [11], (3-years) [11] Primary healthcare cost [31] Potentially preventable unplanned admission (1-year period) [38]	Affective well-being [98] Future physical functioning [69] General health [72] Life satisfaction [99] Perceived health status [99] Self-rated Health [45,84]	Quality of cardiovascular preventive care [66] Quality of preventive care [66]
By Category			
Chronic Condition Count	Healthcare costs [56] Hospital admissions (1-year) [56] Number of emergency department visits (1-year) [56] Readmission within 30 days (1-year) [56]		

Table 3-6. Summary of multimorbidity instruments and their associations with outcomes measure (Continued)

Multimorbidity Measures	Association between Outcomes and Multimorbidity		
	Positive Association	Negative Association	No Association
Organ or system-based approaches			
Organ systems with chronic disease	Presence of depressive or anxiety disorder [73]	-	-
Weighted Indices			
Adult Comorbidity Evaluation-27 (ACE-27)	Healthcare expenditure [57]	-	-
Charlson Comorbidity Index (CCI)	Ambulatory care sensitive hospitalisations (acute & chronic) [64] Emergency department visits (1-year) [56] Emergency hospital admission (2-years) [40] Functional decline (2-years) [40] Healthcare expenditure [56] Hip fractures [63] Hospitalisation (1-year) [56,61,62,65,91] Mortality (1-year) [50,55,62,65], (5-years) [51,55], (10-years) [51,55], (15, 20, 25-years) [51] Number of primary care consultations (3-years) [32] Number of primary care physician visits (1-year) [91] Number of specialist visits (1-year) [91] Potentially preventable unplanned admission (1-year) [37] Presence of critical illness [49] Primary healthcare cost [31] Mortality (1-year) [33,34], (3-years) [32,53], (5-years) [34,54,35], (10-years) [69] Readmission within 30 days (1-year) [56]	Future physical functioning [69] Successful aging [36]	Quality of cardiovascular preventive care [66] Quality of preventive care [66]
Comorbidity Linked Score	Mortality (1-year) [33]	-	-
Elders Risk Assessment (ERA)	Healthcare expenditure [56] Mortality (2-years) [47] Number of days hospitalised (1-year) [52] Number of emergency department visits (1-year) [52,56] Number of hospital admissions (1-year) [52,56] Number of hospital visits (1-year) [52] Nursing home placement (2-years) [47] Presence of critical illness [49] Readmission within 30 days (1-year) [56]	-	-

Table 3-6. Summary of multimorbidity instruments and their associations with outcomes measure (Continued)

Multimorbidity Measures	Association between Outcomes and Multimorbidity		
	Positive Association	Negative Association	No Association
Weighted Indices (Continued)			
Elixhauser Index (Original and Modified)	Hospitalisation (1-year) [62,65] Mortality (1-year) [33,62,65]	-	-
Hierachical Condition Categories (HCC)	Hospitalisation (1-year) [56] ED visits (1-year) [56] Readmission within 30 days (1-year) [56] Healthcare expenditure (1-year) [56]	-	-
Multi-Morbidity Measure (M3) Index	Hospitalisation (1-year) [65] Mortality (1-year) [65]		
Multidimensional Multimorbidity Score (MDMS)	Sickness absence episodes taken in 2 years (male) [94]	-	Sickness absence episodes taken in 2 years (female) [94]
Multimorbidity weighted by Activities of Daily Living (ADL) Scale	-	Life satisfaction [99] Perceived health status [99]	-
Multimorbidity weighted by Health Utility Index (HUI3)	-	Life satisfaction [99] Perceived health status [99]	-
Multimorbidity weighted by Health Utility Index (HUI3) betas	-	Life satisfaction [99] Perceived health status [99]	-
Multimorbidity-Weighted Index (MWI)	ADL limitations [97] IADL limitations [97] Mortality (10-years) [69]	Cognitive performance [97] Future physical functioning [69] Grip strength [97] Subjective physical functioning [97]	Gait speed [97]
Quality and Outcomes Framework (QOF) (Standard)	Mortality (1-year) [50]	-	-
Quality and Outcomes Framework (QOF) (Extended)	Mortality (1-year) [50]		
Other Approaches			
Case-Mix			
Adjusted Clinical Groups (ACG)	Hospitalisation (1-year) [61] Mortality (3-years) [32] Number of primary care consultations (3-years) [32] Primary healthcare cost [31] Readmission within 30 days (1-year) [56]	-	-

Table 3-6. Summary of multimorbidity instruments and their associations with outcomes measure (Continued)

Multimorbidity Measures	Association between Outcomes and Multimorbidity		
	Positive Association	Negative Association	No Association
Other Approaches (Continued)			
Case-Mix (Continued)			
Aggregated Diagnostic Groups (ADG)	Hospitalisation (1-year) [91] Number of primary care physician visits (1-year) [91] Number of specialist visits (1-year) [91]	-	-
Hybrid Model (Minnesota Tiering + ERA)	Emergency department visits (1-year) [56] Healthcare expenditure [56] Hospitalisation (1-year) [56] Readmission within 30 days (1-year) [56]	-	-
Health Search Morbidity Index (HSMI)	Healthcare cost (primary care) [80]	-	-
Minnesota Tiering (MN Tier)	Emergency department visits (1-year) [56,67] Healthcare expenditure [56] Hospitalisation (1-year) [56,67] Readmission within 30 days (1-year) [56]	-	-
Resource Utilisation Band (RUB)	Fee-for-service expenditures [79] Primary healthcare cost [31] Mortality (3-years) [32] Number of primary care consultations (3-years) [32] Registered active listing in primary care [88] Registered active listing in all healthcare [88]	-	-
Pharmaceutical-based			
Chronic Disease Score (CDS)	Hospitalisation (1-year) [62] Mortality (1-year) [62]		
Prescribed drug count	Emergency hospital admission (2-years) [40] Functional decline (2-years) [40] Hospitalisation (1-year) [62] Mortality (1-year) [62], (3-years) [32] Number of primary care consultations (3-years) [32]	-	-
Pra Tool Modified	Emergency hospital admission (1-year) [39]	-	-
RxRisk-V	Emergency hospital admission (2-years) [40] Functional decline (2-years) [40]	-	-

Table 3-7. Summary of the three essential core outcomes* of multimorbidity and their corresponding instruments

Outcomes	Corresponding multimorbidity measures
Mortality	**Counts of Individual Conditions** Disease count [32,62,69] **Weighted Indices** Charlson Comorbidity Index [32 50 51,33-35 53-55,62,65,69] Co-morbidity linked score [33] Elderly Risk Assessment [47] Elixhauser Index (original and modified) [33,62,65] Multi-Morbidity Measure (M3) Index [65] Multimorbidity Weighted Index (MWI) [69] Quality and Outcomes Framework (Standard and Extended) [50] **Other approaches** Case-Mix Adjusted Clinical Groups [32] Resource Utilisation Band [32] Pharmaceutical-based Chronic Disease Score [62] Drug Count [32,62]
Mental Health	**Counts of Individual Conditions** Disease count [72,90] **Organ or system-based approaches** Organ systems with chronic disease [73]
Quality of Life	**Counts of Individual Conditions** Disease count [27,28,70,74,81,84,98]

* The outcomes were based on the Core Outcome Set for Multimorbidity Research (COSmm) by Smith et al.[6]

4 Discussion

4.1 Summary of findings

Thirty-three unique instruments for measuring the level of multimorbidity were identified from all the included studies using the classification by Sarfati[41]. The most commonly used instrument in the count of individual conditions category was 'Disease Count'. In the organ or system-based approaches category, three instruments were found but they were not commonly used. The weighted indices category had the most variety of different instruments (up to 17), and within this category, Charlson Comorbidity index (with its different variations) was the most commonly used. Finally, for the 'other approaches' category, case-mix and pharmaceutical-based instruments were also commonly used. The full list and description of the instruments are provided in Table 3-5.

Disease count is the only instrument that was associated with all three essential core outcomes identified for COSmm, i.e., quality of life, mental health, and mortality (*Table 3-7*). In summary, all the study findings showed the association between the explanatory variables and outcomes were in the same direction and did not conflict with each other (*Table 3-6*). The outcomes not found to have any association with the instruments for measuring the level of multimorbidity were preventive care[66], sickness absence episodes (female)[94], and gait speed[97].

4.2 Comparison with previous research

We identified five other review articles describing the instruments for measuring the level of multimorbidity in the literature: Huntley et al.[16], Sharabiani et al.[104], Yurkovich et al.[105], Diederichs et al.[106], and de Groot et al.[13] Huntley et al.[16] was mentioned in the introduction as the review that this study was updating. It was also the only study that targeted participants from the primary care or general population. Sharabiani et al.[104] (2012) and Yurkovich et al.[105] (2015) were reviews of multimorbidity instruments using administrative data, Diederichs et al.[106] (2011) was a review that looked specifically at weighted indices for measuring the level of multimorbidity, and de Groot et al.[13] (2003) was the oldest study that looked at all instruments using all kinds of data.

Huntley et al.[16], consistent with this systematic review, listed the most frequently used instruments for measuring the level of multimorbidity while the other four reviews[13,104-106] recommended the most suitable instruments. We found the most common instruments used for measuring the level of multimorbidity in primary care similar to the systematic review done by Huntley et al. However, several of the instruments including Duke Severity of Illness Checklist (DUSOI) and Functional Comorbidity Index (FCI) identified in their paper were not found in this systematic review.

The original DUSOI has been adapted and renamed the Duke and World Organisation of Family Doctors Severity of Illness Checklist (DUSOI/WONCA) in 2011[107]. However, a quick search for use of the instrument in PubMed[*****] showed the last publication using the instrument was in 2004[108]. An article on FCI in chronic rhinosinusitis was published in 2016[109], and another study showed that FCI had higher inter-rater reliability in patients with acute lung injury in 2012[110]. The reasons for not identifying these instruments in this review may be because of the lack of interest on the instrument by the research community for DUSOI in the recent years, or that the search strategy in the review excluded studies that have an index condition or were not from the primary care or general population like the FCI.

Under the 'count of individual conditions' category, disease count was found to be one of the most frequently used instruments in this review and Huntley et al.'s[16]. For this review, there were multiple and variable outcomes associated with this measure. These outcomes included disability, healthcare costs, hospitalisation, mental health, mortality, quality of life, and self-rated health.

Under the 'organ or system-based approaches' category, the Cumulative Illness Rating Scale was the only instrument recommended by one review[13]. The outcomes were, activities of daily living (ADL), instrumental ADL, and medication usage. However, the predictive validities were only small to fair for positive correlation.

For the category on 'weighted indices', three instruments were highlighted by the six reviews (including this review): Charlson Comorbidity Index (CCI), Elixhauser Index (EI), and Elders Risk Assessment (ERA). CCI was recommended by two of the reviews. Multiple outcomes

[*****] The free search engine provided by the United States National Library of Medicine at the National Institutes of Health.

were found to be associated with CCI, but mortality and hospitalisation were the main ones. The EI was recommended by two of the reviews. Sharabiani et al.[104] recommended that EI was the best predictor for long-term mortality. Yurkovich et al.[105] recommended using the Quan and van Walraven versions of the EI, or the Romani version of CCI for measuring mortality. The ERA was not found by any of the other reviews but was one of the common instruments found in this systematic review. The outcomes predicted were hospitalisation and mortality. Diederichs et al.[106] looked exclusively at the development of weighted multimorbidity indices in the general population but did not make any particular recommendation as the authors pointed out the heterogeneity of existing indices and the need for a new, established instrument to assess multimorbidity.

Under the 'other approaches' category, RxRisk-V was recommended by Yurkovich et al.[105] for evaluating health care utilisation, in which medication data were available. Adjusted Clinical Group (ACG) was a frequently used instrument for various outcomes including healthcare resources, health care costs, health care utilisation, hospitalisation, and mortality found in this study and by Huntley et al.[16]

4.3 Advantages and disadvantages of selected instruments

4.3.1 Disease count

Summing the number of conditions from among a list of candidate chronic conditions provides an ordinal score[111]. This method has the advantage of simplicity and ease of data ascertainment with minimal resources required. Despite its simplicity, the disease count was not only associated with the three essential core outcomes (quality of life, mental health, and mortality) but also six others outcomes (activities of daily living, costs, health care use, physical activity, physical function, and self-rated health) suggested by the Core Outcome Set for Multimorbidity Research (COSmm) by Smith et al.[6]

However, using disease count to measure the level of multimorbidity does not appear appropriate conceptually. For example, the same category - 'secondary malignancies' includes diagnoses that have a nearly nine-fold difference in mortality, and grouping all 'secondary malignancies' into one category oversimplifies the differences within this category seen in the

Elixhauser Index[102]. Moreover, analytic strategies often incorrectly force a linear relationship with the ordinal scale, ignoring the fact that an additional unit of increase in 'disease count' will most likely have a diminishing impact. Finally, a summed measure also ignores potentially important relationships between diseases that might differ from their simple sum[111].

The other disadvantage noted in this systematic review is that many investigators using disease counts as an instrument did not state clearly on what basis certain chronic conditions were included or excluded, the total number of conditions in the multimorbidity list, and the cut-points used to define multimorbidity. This lack of information makes the comparison with other studies difficult, and also impossible to replicate or confirm previous findings.

4.3.2 Weighted Indices

Calculation of weights was usually based on three methods. The first method was by directly getting self-reported information from patients, for example, directly asking patients whether a particular condition interfered with their daily activities on a Likert scale. The second method was by deriving weights from the literature according to the individual impact of diseases on different outcomes. This was the commonest method and utilised in prognostic models to build complex multivariable regression models whereby the weights were calculated from hazard ratios, odds ratios, or regression coefficients[112]. A third method was to apply weights by defining specific criteria, based on clinical parameters such as fasting glucose for a physiologic index of comorbidity[113] or cholesterol level for Chronic Disease Score (CDS)[114]. In the next chapter of this thesis, the Chronic Disease Control Score (CDCS) used the third method as an independent variable for measuring the level of multimorbidity.

The common weighted indices identified in this systematic review were Charlson Comorbidity Index, Elders Risk Assessment, Elixhauser Index and Multimorbidity-weighted Index. All of them belonged to the second method of weighting diseases. The other 13 weighted indices identified in this systematic review were novel and were also developed using this second method. These instruments have been found by other included studies in this systematic review to be associated with four outcomes from the Core Outcome Set for Multimorbidity Research (COSmm) suggested by Smith et al.[6] These outcomes included activities of daily living, costs, health care use, physical function.

The advantage of these weighted indices is that the weights allow the adaptation of an index to a specific outcome. An investigator could recalibrate the correct weight by creating a prognostic model to produce a contextualised instrument for a different setting. Prognostic models can provide clinically relevant risk stratification and help to allocate resources[115].

One disadvantage of such indices is the number of resources required to develop a new instrument. Even adopting well-established indices would still require validation studies meaningful to the local context. This is made more difficult as there is also a lack of **t**ransparent **r**eporting of multivariable prediction models for **i**ndividual **p**rognosis **o**r **d**iagnosis (TRIPOD)[103]. Moreover, calculated weights are greatly influenced by the population, outcomes used, and the instrument's original conception and purpose. Therefore, addressing different outcomes may necessitate using different instruments.

4.3.3 Case-Mix

The ease of obtaining and using the data needed to characterise multimorbidity make the ACG system a preferred method for analyses in different domains and suitable for comparison across areas within and between countries[116]. The advantage of the instrument is its good track record in the United States and several other countries. However, the instrument is proprietary, and the exact algorithm of the instrument is not open to the public and may not be suitable in certain nuance settings. Another disadvantage is the financial costs involved in obtaining the license.

4.3.4 Pharmaceutical-based instruments

Medication-based indices include versions of the Chronic Disease Score[114], which later became known as the RxRisk[117], and its adaptation for use in the veteran population, the RxRisk-V[118]. The advantage of using these instruments is when prescription datasets are easily obtainable.

Drug count is one of the common instruments reported in this systematic review. Like disease count, the main advantage is its ease of use with minimal resources required. In this systematic review, it was found to be associated with health care use and physical function. However, it was also not clearly described in many studies regarding which type of drugs were counted and which were not.

4.4 Data sources

Data sources for using these various instruments rely on medical record information, patient self-report, clinical judgment, or large administrative databases. Regardless of the data source, errors can be introduced. For patient self-report, patients with cognitive impairment may under-report symptoms and may be seen less frequently by their physicians, resulting in an under-recognition or under-treatment of conditions[111]. Administrative data may not truly reflect the exact list of chronic conditions of patients as that is not the primary purpose of collecting the data. It has been shown that health administrative data based on billing system underestimated the prevalence of many chronic conditions[119].

Some of these instruments mentioned have been developed exclusively for use with administrative data such as Elixhauser Index[102], whereas others have been developed in other contexts but adapted for use with administrative data such as the Charlson Comorbidity Index[101]. Many weighted indices require medical records or administrative data which may not be readily available. It is time-consuming to engage research team members in the examination of individual clinical notes.

The available data in a particular setting may strongly influence the ultimate instrument chosen for multimorbidity research. As there is currently no consensus on the gold standard for sources of data, it is difficult to assess which data source performs the best. The next chapter of this thesis will explore the agreement between self-reported data and the electronic medical records.

4.5 Clinical Implications

Seventeen multimorbidity outcomes were identified by a Delphi panel of international experts of multimorbidity intervention studies[6]. However, only ten out of the seventeen outcomes were reported in the 67 studies identified in this systematic review. None of the other seven outcome measures (adherence, communications, prioritisation, self-management behaviour, self-efficacy, shared decision-making, and treatment burden) was explored in any of the 67 studies included in this systematic review. Most of these outcomes were patient-centred outcomes. The outcome that was investigated the most was health care utilisation. In the search strategy

for this systematic review, there was no restriction on the type of studies to be included or not. However, we only found observation studies (cohort and cross-sectional) and did not find any interventional studies. This could be the reason why the other seven outcome measures were not reported, but it is also reflective of the lack of interventional studies on multimorbidity in primary care and the general population generally. There is still much to do to improve on the body of knowledge of multimorbidity when most investigators in the last ten years measured multimorbidity without including some of the important outcome measures of multimorbidity.

Ideally, a single instrument for measuring the level of multimorbidity should be able to predict a variety of relevant outcomes, but Byles et al.[15] reported that a single index could not predict a variety of outcomes, in different patient groups and settings. The investigators suggested that prediction of multiple outcomes within one study may not necessitate more than one instrument if the same instrument could still be utilised by using different weights for the same items in calculating the scoring systems. Such multiple-scoring instruments may be the way forward for validation of prognostic models for different outcomes and different populations with established multimorbidity instruments. The choice of conditions included in such an instrument should include those with a high prevalence in the population being served and with a severe impact on affected people. The definition of high prevalence and severe impact would have to be defined by each health care setting or geography. However, for pragmatic reasons, the final selection of the conditions to be included in such a multiple-scoring instrument may have to take into account the availability of relevant and reliable data.

Interestingly, in a systematic review of studies on hospitalisation risk prediction models, more than half of the studies did not include multimorbidity in the modelling[120]. However, the authors noted that the studies with the best-performing models were those that considered multimorbidity. It was observed that well-performing prediction models were distinguished by taking into account multi-dimensional scales instead of multimorbidity scores alone[121]. Therefore, in building the predictor variables for the model, relevant clinical and non-clinical profiles should be considered on top of a level of multimorbidity measurement instrument.

Multimorbidity is a complex phenomenon, and the current definition maybe overly simplistic and not able to ideally capture the complexity of multimorbidity. The complex interactions of several co-occurring chronic conditions often include the additional consideration of social, psychological, and emotional factors. Social networks and support, coping strategies,

individual preferences, and living conditions would have to be considered in the assessment of multimorbidity[122].

In conclusion, a certain degree of reductionism will have to be accepted because a multimorbidity measurement instrument will not be able to encompass all the nuances of the different interactions of chronic conditions on an individual living in his/her unique milieu. Moreover, most of the studies in this systematic review were from Europe and North America with very few Asian studies. Applying the findings to the local setting of Singapore should not be taken wholesale. The current instruments should not be the only tool for investigators and clinicians to assess all the dimensions of multimorbidity. Ultimately, the most suitable instrument will depend on the specified outcome of interest, the study population, and the type of data and resources available.

4.6 Strengths and limitations of the study

One of the main strengths of this systematic review was that we involved a health science librarian at the start of the review and had several rounds of iterations and cross-checks before finalising the search strategy.

We also published our protocol before embarking on the review and adhere to what we proposed to report without changes during the systematic review process[123]. We followed the PRISMA statement[20] for systematic review of observational studies and guidance on the conduct of narrative synthesis in systematic reviews[21] for the reporting of this systematic review.

The systematic review had several limitations. Grey literature was not included in this review, which may have introduced study selection bias[124]. However, we excluded grey literature based on evidence suggesting that the quality of research in the grey literature is lower and more difficult to appraise compared with research in journal articles[124]. We excluded abstracts, as abstracts with positive findings tend to be accepted for presentation at conferences more frequently than those with negative or null findings[124]. Another limitation was that we only included articles that were published in the English language.

Although our search strategy was comprehensive, it was far from complete. The use of electronic databases has been found to retrieve only half of all relevant studies[125]. We did not contact authors directly for a suggestion of studies. We also did not identify a list of instruments from the preliminary search and then perform an additional search using the same databases as suggested by Yurkovich et al.[105] However, given the consistency of our results, it is unlikely that missed studies would significantly alter the main findings of our review.

As there was a lack of consensus for qualitative assessment tool for observational studies[126], we chose Newcastle Ottawa Scale (NOS) and then modified it with careful consideration after testing two other risk of assessment tools. The modified NOS may not be a perfectly reliable tool for risk of assessment, but the Cochrane Collaboration has recommended it for assessing nonrandomised studies[127].

4.7 Conclusion

In this systematic review, we found 33 instruments for measuring the level of multimorbidity of community-dwelling individuals that predict or explore the association with at least one specified outcome. Disease count and weighted indices like the Charlson Comorbidity Index, the Elders Risk Assessment, and Elixhauser Index were commonly used for measuring the level of multimorbidity. Other approaches to measuring the level of multimorbidity included case-mix or pharmaceutical-based instruments.

We compiled a list of these instruments and discussed the advantages and disadvantages of the commonly-used instruments. A certain degree of reductionism will have to be accepted for each instrument as no one single instrument for measuring the level of multimorbidity will be able to encompass all different dimensions of multimorbidity. There has been a rise in the development of novel weighted indices by using prognostic models or validation of an existing well-established instrument. The reporting of such studies would need to follow the TRIPOD guidelines to allow potential users to replicate and confirm the findings[103].

There are continuing interests in measuring the level of multimorbidity with disease count and drug count. A clear description of the instruments is required in the publication of

multimorbidity studies to counter the frequent lack of information currently seen so as to contribute to robust multimorbidity research in future.

There is currently an absence of a gold standard for where to obtain chronic disease information. Most data sources are from medical record information, patient self-report, clinical judgment, or large administrative databases. Ultimately, the most suitable instrument will depend on the specified outcome of interest, the study population, and the type of data and resources available.

Finally, we compiled a list of instruments that were used to explore the association with the three essential core outcomes selected for the core outcomes set of multimorbidity research (COSmm)[6]. Disease count was the only instrument identified for all three outcomes.

5 References

1. Salive ME. Multimorbidity in older adults. *Epidemiol Rev* 2013;35:75-83. doi: 10.1093/epirev/mxs009
2. Willadsen TG, Bebe A, Koster-Rasmussen R, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scand J Prim Health Care* 2016;34(2):112-21. doi: 10.3109/02813432.2016.1153242
3. Mujica-Mota RE, Roberts M, Abel G, et al. Common patterns of morbidity and multi-morbidity and their impact on health-related quality of life: evidence from a national survey. *Qual Life Res* 2015;24(4):909-18. doi: 10.1007/s11136-014-0820-7
4. Sundar S. Categorising severity of disease is inevitable and essential in routine medical practice. *Bmj* 2018;361:k2556. doi: 10.1136/bmj.k2556
5. de Vet HCW, Terwee CB, Mokkink LB, et al. Chapter 3 - Development of a measurement instrument. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
6. Smith SM, Wallace E, Salisbury C, et al. A Core Outcome Set for Multimorbidity Research (COSmm). *Ann Fam Med* 2018;16(2):132-38. doi: 10.1370/afm.2178
7. Diederichs CP, Wellmann J, Bartels DB, et al. How to weight chronic diseases in multimorbidity indices? Development of a new method on the basis of individual data from five population-based studies. *J Clin Epidemiol* 2012;65(6):679-85. doi: 10.1016/j.jclinepi.2011.11.006
8. Ryan A, Wallace E, O'Hara P, et al. Multimorbidity and functional decline in community-dwelling adults: a systematic review. *Health & Quality of Life Outcomes* 2015;13:168. doi: https://dx.doi.org/10.1186/s12955-015-0355-9
9. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *The Cochrane database of systematic reviews* 2016;3:CD006560. doi: 10.1002/14651858.CD006560.pub3
10. Glynn LG, Valderas JM, Healy P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28(5):516-23. doi: 10.1093/fampra/cmr013
11. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;61(582):e12-21. doi: https://dx.doi.org/10.3399/bjgp11X548929
12. Lefevre T, d'Ivernois JF, De Andrade V, et al. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. *Rev Epidemiol Sante Publique* 2014;62(5):305-14. doi: 10.1016/j.respe.2014.09.002
13. de Groot V, Beckerman H, Lankhorst G, et al. How to measure comorbiditya critical review of available methods. *J Clin Epidemiol* 2003;56(3):221-29. doi: 10.1016/s0895-4356(02)00585-1
14. Alemi F, Levy CR, Kheirbek RE. The Multimorbidity Index: A Tool for Assessing the Prognosis of Patients from Their History of Illness. *EGEMS (Wash DC)* 2016;4(1):1235. doi: 10.13063/2327-9214.1235
15. Byles JE, D'Este C, Parkinson L, et al. Single index of multimorbidity did not predict multiple outcomes. *J Clin Epidemiol* 2005;58(10):997-1005. doi: 10.1016/j.jclinepi.2005.02.025
16. Huntley AL, Johnson R, Purdy S, et al. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med* 2012;10(2):134-41. doi: 10.1370/afm.1363

17. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi: 10.1186/2046-4053-4-1
18. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Bmj* 2015;350:g7647. doi: 10.1136/bmj.g7647
19. Page MJ, Shamseer L, Tricco AC. Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Syst Rev* 2018;7(1):32. doi: 10.1186/s13643-018-0699-4
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006
21. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narative synthesis in systematic reviews. A product from the ESRC methods Programme.: ESRC; 2006 [Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.178.3100&rep=rep1&type=pdf accessed 30 May 2018.
22. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, et al. Multimorbidity patterns: a systematic review. *J Clin Epidemiol* 2014;67(3):254-66. doi: https://dx.doi.org/10.1016/j.jclinepi.2013.09.021
23. Briscoe S. Guide to proximity seaching. 2018. https://medicine.exeter.ac.uk/media/universityofexeter/medicalschool/research/pentag/documents/Guide_to_proximity_searching.pdf (accessed 10 Jul 2018).
24. Kellermeyer L, Harnke B, Knight S. Covidence and Rayyan. *Journal of the Medical Library Association* 2018;106(4) doi: 10.5195/jmla.2018.513
25. Wells GA, Shhea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed 6 Apr 2018.
26. Alshabanat A, Zafari Z, Albanyan O, et al. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PLoS ONE* 2015;10(9):e0136065. doi: 10.1371/journal.pone.0136065
27. Barile JP, Thompson WW, Zack MM, et al. Multiple chronic medical conditions and health-related quality of life in older adults, 2004-2006. *Prev Chronic Dis* 2013;10:E162. doi: 10.5888/pcd10.120282
28. Barile JP, Thompson WW, Zack MM, et al. Activities of daily living, chronic medical conditions, and health-related quality of life in older adults. *J Ambul Care Manage* 2012;35(4):292-303. doi: 10.1097/JAC.0b013e31826746f5
29. Boeckxstaens P, Vaes B, Legrand D, et al. The relationship of multimorbidity with disability and frailty in the oldest patients: a cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. *Eur J Gen Pract* 2015;21(1):39-44. doi: 10.3109/13814788.2014.914167
30. Boeckxstaens P, Vaes B, Van Pottelbergh G, et al. Multimorbidity measures were poor predictors of adverse events in patients aged >/=80 years: a prospective cohort study. *J Clin Epidemiol* 2015;68(2):220-7. doi: 10.1016/j.jclinepi.2014.08.010
31. Brilleman SL, Gravelle H, Hollinghurst S, et al. Keep it simple? Predicting primary health care costs with clinical morbidity measures. *J Health Econ* 2014;35:109-22. doi: https://dx.doi.org/10.1016/j.jhealeco.2014.02.005
32. Brilleman SL, Salisbury C. Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study. *Fam Pract* 2013;30(2):172-8. doi: https://dx.doi.org/10.1093/fampra/cms060

33. Crooks CJ, Card TR, West J. The Use of a Bayesian Hierarchy to Develop and Validate a Co-Morbidity Score to Predict Mortality for Linked Primary and Secondary Care Data from the NHS in England. *PLoS ONE* 2016;11(10):e0165507. doi: https://dx.doi.org/10.1371/journal.pone.0165507
34. Crooks CJ, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. *BMJ Open* 2015;5(6):e007974. doi: https://dx.doi.org/10.1136/bmjopen-2015-007974
35. Formiga F, Ferrer A, Padros G, et al. Evidence of functional declining and global comorbidity measured at baseline proved to be the strongest predictors for long-term death in elderly community residents aged 85 years: A 5-year follow-up evaluation, the OCTABAIX study. *Clin Interv Aging* 2016;11:437-44. doi: http://dx.doi.org/10.2147/CIA.S101447
36. Formiga F, Ferrer A, Megido MJ, et al. Low co-morbidity, low levels of malnutrition, and low risk of falls in a community-dwelling sample of 85-year-olds are associated with successful aging: the Octabaix study. *Rejuvenation Res* 2011;14(3):309-14. doi: https://dx.doi.org/10.1089/rej.2010.1131
37. Payne RA, Abel GA, Avery AJ, et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *British Journal of Clinical Pharmacology* 2014;77(6):1073-82. doi: http://dx.doi.org/10.1111/bcp.12292
38. Payne RA, Abel GA, Guthrie B, et al. The effect of physical multimorbidity, mental health conditions and socioeconomic deprivation on unplanned admissions to hospital: a retrospective cohort study. *Cmaj* 2013;185(5):E221-8. doi: https://dx.doi.org/10.1503/cmaj.121349
39. Wallace E, McDowell R, Bennett K, et al. External validation of the Probability of repeated admission (Pra) risk prediction tool in older community-dwelling people attending general practice: a prospective cohort study. *BMJ Open* 2016;6(11):e012336. doi: https://dx.doi.org/10.1136/bmjopen-2016-012336
40. Wallace E, McDowell R, Bennett K, et al. Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study. *BMJ Open* 2016;6(9):e013089. doi: https://dx.doi.org/10.1136/bmjopen-2016-013089
41. Sarfati D. Review of methods used to measure comorbidity in cancer populations: no gold standard exists. *J Clin Epidemiol* 2012;65(9):924-33. doi: 10.1016/j.jclinepi.2012.02.017
42. Sarfati D. How Do We Measure Comorbidity? In: Koczwara B, ed. Cancer and Chronic Conditions - Addressing the problem of multimorbidity in cancer patients and survivors: Springer 2016:35-70.
43. Md Yusof MY, Horan MA, Jones M, et al. Developing a self-reported comorbidity index to predict mortality of community-dwelling older adults. *Arch Gerontol Geriatr* 2010;50(3):e63-7. doi: 10.1016/j.archger.2009.05.012
44. Muggah E, Graves E, Bennett C, et al. The impact of multiple chronic diseases on ambulatory care use; a population based study in Ontario, Canada. *BMC Health Serv Res* 2012;12:452.
45. Galenkamp H, Braam AW, Huisman M, et al. Somatic Multimorbidity and Self-rated Health in the Older Population. *Journals of Gerontology Series B: Psychological Sciences & Social Sciences* 2011;66B(3):380-86.

46. Kojima T, Akishita M, Nakamura T, et al. Association of polypharmacy with fall risk among geriatric outpatients. *Geriatr Gerontol Int* 2011;11(4):438-44. doi: 10.1111/j.1447-0594.2011.00703.x
47. Takahashi PY, Tung EE, Crane SJ, et al. Use of the elderly risk assessment (ERA) index to predict 2-year mortality and nursing home placement among community dwelling older adults. *Arch Gerontol Geriatr* 2012;54(1):34-8. doi: 10.1016/j.archger.2011.02.012
48. van den Bussche H, Schon G, Kolonko T, et al. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC geriatr* 2011;11:54. doi: 10.1186/1471-2318-11-54
49. Biehl M, Takahashi PY, Cha SS, et al. Prediction of critical illness in elderly outpatients using elder risk assessment: a population-based study. *Clin Interv Aging* 2016;11:829-34. doi: https://dx.doi.org/10.2147/CIA.S99419
50. Carey IM, Shah SM, Harris T, et al. A new simple primary care morbidity score predicted mortality and better explains between practice variations than the Charlson index. *J Clin Epidemiol* 2013;66(4):436-44. doi: https://dx.doi.org/10.1016/j.jclinepi.2012.10.012
51. Chapman BP, Weiss A, Fiscella K, et al. Mortality Risk Prediction: Can Comorbidity Indices Be Improved With Psychosocial Data? *Med Care* 2015;53(11):909-15. doi: 10.1097/MLR.0000000000000428
52. Crane SJ, Tung EE, Hanson GJ, et al. Use of an electronic administrative database to identify older community dwelling adults at high-risk for hospitalization or emergency department visits: the elders risk assessment index. *BMC Health Serv Res* 2010;10:338.
53. Formiga F, Ferrer A, Chivite D, et al. Utility of geriatric assessment to predict mortality in the oldest old: the Octabaix study 3-year follow-up. *Rejuvenation Res* 2013;16(4):279-84. doi: 10.1089/rej.2013.1422
54. Formiga F, Ferrer A, Chivite D, et al. Predictors of long-term survival in nonagenarians: the NonaSantfeliu study. *Age Ageing* 2011;40(1):111-6. doi: 10.1093/ageing/afq127
55. Fraccaro P, Kontopantelis E, Sperrin M, et al. Predicting mortality from change-over-time in the Charlson Comorbidity Index: A retrospective cohort study in a data-intensive UK health system. *Medicine (United States)* 2016;95 (43) (no pagination)(e4973) doi: http://dx.doi.org/10.1097/MD.0000000000004973
56. Haas LR, Takahashi PY, Shah ND, et al. Risk-stratification methods for identifying patients for care coordination. *Am J Manag Care* 2013;19(9):725-32.
57. Hwang W, LaClair M, Camacho F, et al. Persistent high utilization in a privately insured population. *Am J Manag Care* 2015;21(4):309-16.
58. Jennings LA, Reuben DB, Kim SB, et al. Targeting a high-risk group for fall prevention: strategies for health plans. *The American journal of managed care* 2015;21(9):e519-e26.
59. Jia H, Lubetkin EI. Impact of nine chronic conditions for US adults aged 65 years and older: an application of a hybrid estimator of quality-adjusted life years throughout remainder of lifetime. *Qual Life Res* 2016;25(8):1921-9. doi: 10.1007/s11136-016-1226-5
60. Jia H, Lubetkin EI, Barile JP, et al. Quality-adjusted life years (QALY) for 15 chronic conditions and combinations of conditions among US adults aged 65 and older. *Med Care* 2018;56(8):740-46. doi: http://dx.doi.org/10.1097/MLR.0000000000000943

61. Lemke KW, Weiner JP, Clark JM. Development and validation of a model for predicting inpatient hospitalization. *Med Care* 2012;50(2):131-9. doi: 10.1097/MLR.0b013e3182353ceb
62. Quail JM, Lix LM, Osman BA, et al. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. *BMC Health Serv Res* 2011;11:146. doi: 10.1186/1472-6963-11-146
63. Reyes C, Estrada P, Nogues X, et al. The impact of common co-morbidities (as measured using the Charlson index) on hip fracture risk in elderly men: a population-based cohort study.[Erratum appears in Osteoporos Int. 2014 Sep;25(9):2333 Note: Macias, J G [corrected to Gonzalez-Macias, J]]. *Osteoporos Int* 2014;25(6):1751-8. doi: https://dx.doi.org/10.1007/s00198-014-2682-9
64. Saver BG, Wang CY, Dobie SA, et al. The central role of comorbidity in predicting ambulatory care sensitive hospitalizations. *Eur J Public Health* 2014;24(1):66-72. doi: 10.1093/eurpub/ckt019
65. Stanley J, Sarfati D. The new measuring multimorbidity index predicted mortality better than Charlson and Elixhauser indices among the general population. *J Clin Epidemiol* 2017;92:99-110. doi: https://dx.doi.org/10.1016/j.jclinepi.2017.08.005
66. Streit S, da Costa BR, Bauer DC, et al. Multimorbidity and quality of preventive care in Swiss university primary care cohorts. *PLoS ONE* 2014;9(4):e96142. doi: https://dx.doi.org/10.1371/journal.pone.0096142
67. Takahashi PY, Heien HC, Sangaralingham LR, et al. Enhanced risk prediction model for emergency department use and hospitalizations in patients in a primary care medical home. *Am J Manag Care* 2016;22(7):475-83.
68. Tyack Z, Frakes KA, Barnett A, et al. Predictors of health-related quality of life in people with a complex chronic disease including multimorbidity: a longitudinal cohort study. *Qual Life Res* 2016;25(10):2579-92. doi: https://dx.doi.org/10.1007/s11136-016-1282-x
69. Wei MY, Mukamal KJ. Multimorbidity, Mortality, and Long-Term Physical Functioning in 3 Prospective Cohorts of Community-Dwelling Adults. *Am J Epidemiol* 2018;187(1):103-12. doi: 10.1093/aje/kwx198
70. Agborsangaya CB, Lau D, Lahtinen M, et al. Health-related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res* 2013;22(4):791-9. doi: 10.1007/s11136-012-0214-7
71. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2
72. Chen HY, Baumgardner DJ, Rice JP. Health-related quality of life among adults with multiple chronic conditions in the United States, Behavioral Risk Factor Surveillance System, 2007. *Prev Chronic Dis* 2011;8(1):A09.
73. DiNapoli EA, Bramoweth AD, Whiteman KL, et al. Mood Disorders in Middle-Aged and Older Veterans With Multimorbidity. *Journal of aging and health* 2017;29(4):657-68. doi: http://dx.doi.org/10.1177/0898264316641082
74. Garin N, Olaya B, Moneta MV, et al. Impact of multimorbidity on disability and quality of life in the Spanish older population. *PLoS ONE* 2014;9(11):e111498. doi: 10.1371/journal.pone.0111498
75. Gunn JM, Ayton DR, Densley K, et al. The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. *Soc Psychiatry Psychiatr Epidemiol* 2012;47(2):175-84. doi: https://dx.doi.org/10.1007/s00127-010-0330-z

76. Hanmer J, Vanness D, Gangnon R, et al. Three methods tested to model SF-6D health utilities for health states involving comorbidity/co-occurring conditions. *J Clin Epidemiol* 2010;63(3):331-41. doi: 10.1016/j.jclinepi.2009.06.013
77. Hu T, Dattani ND, Cox KA, et al. Effect of comorbidities and medications on frequency of primary care visits among older patients. *Can Fam Physician* 2017;63(1):45-50.
78. Isaacs AA, Manga N, Le Grange C, et al. A snapshot of noncommunicable disease profiles and their prescription costs at ten primary healthcare facilities in the western half of the Cape Town Metropole. *South African Family Practice* 2014;56(1):43-49.
79. Kristensen T, Olsen KR, Schroll H, et al. Association between fee-for-service expenditures and morbidity burden in primary care. *Eur J Health Econ* 2014;15(6):599-610. doi: https://dx.doi.org/10.1007/s10198-013-0499-7
80. Lapi F, Bianchini E, Cricelli I, et al. Development and Validation of a Score for Adjusting Health Care Costs in General Practice. *Value Health* 2015;18(6):884-95. doi: https://dx.doi.org/10.1016/j.jval.2015.05.004
81. Lawson KD, Mercer SW, Wyke S, et al. Double trouble: the impact of multimorbidity and deprivation on preference-weighted health related quality of life a cross sectional analysis of the Scottish Health Survey. *Int J Equity Health* 2013;12:67. doi: 10.1186/1475-9276-12-67
82. Li J, Green M, Kearns B, et al. Patterns of multimorbidity and their association with health outcomes within Yorkshire, England: baseline results from the Yorkshire Health Study. *BMC Public Health* 2016;16:649. doi: https://dx.doi.org/10.1186/s12889-016-3335-z
83. Marengoni A, Angleman S, Fratiglioni L. Prevalence of disability according to multimorbidity and disease clustering: a population-based study. *J Comorb* 2011;1:11-18.
84. McDaid O, Hanly MJ, Richardson K, et al. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. *BMJ Open* 2013;3(6) doi: 10.1136/bmjopen-2013-002571
85. Naessens JM, Stroebel RJ, Finnie DM, et al. Effect of multiple chronic conditions among working-age adults. *Am J Manag Care* 2011;17(2):118-22.
86. Ostergaard SD, Foldager L. The association between physical illness and major depressive episode in general practice. *Acta Psychiatr Scand* 2011;123(4):290-96. doi: http://dx.doi.org/10.1111/j.1600-0447.2010.01668.x
87. Peters M, Kelly L, Potter CM, et al. Quality of life and burden of morbidity in primary care users with multimorbidity. *Patient relat* 2018;9:103-13. doi: https://dx.doi.org/10.2147/PROM.S148358
88. Ranstad K, Midlöv P, Halling A. Importance of healthcare utilization and multimorbidity level in choosing a primary care provider in Sweden. *Scand J Prim Health Care* 2014;32(2):99-105. doi: 10.3109/02813432.2014.929819
89. Renne I, Gobbens RJJ. Effects of frailty and chronic diseases on quality of life in dutch community-dwelling older adults: A cross-sectional study. *Clin Interv Aging* 2018;13:325-34. doi: http://dx.doi.org/10.2147/CIA.S156116
90. Ryu E, Takahashi PY, Olson JE, et al. Quantifying the importance of disease burden on perceived general health and depressive symptoms in patients within the Mayo Clinic Biobank. *Health and Quality of Life Outcomes* 2015;13 (1) (no pagination)(95) doi: http://dx.doi.org/10.1186/s12955-015-0285-6

91. Shadmi E, Balicer RD, Kinder K, et al. Assessing socioeconomic health care utilization inequity in Israel: impact of alternative approaches to morbidity adjustment. *BMC Public Health* 2011;11:609. doi: http://dx.doi.org/10.1186/1471-2458-11-609
92. Sibley KM, Voth J, Munce SE, et al. Chronic disease and falls in community-dwelling Canadians over 65 years old: a population-based study exploring associations with number and pattern of chronic conditions. *BMC geriatr* 2014;14:22. doi: https://dx.doi.org/10.1186/1471-2318-14-22
93. Sullivan PW, Ghushchyan VH, Bayliss EA. The impact of co-morbidity burden on preference-based health-related quality of life in the United States. *Pharmacoeconomics* 2012;30(5):431-42. doi: 10.2165/11586840-000000000-00000
94. Ubalde-Lopez M, Delclos GL, Benavides FG, et al. Measuring multimorbidity in a working population: the effect on incident sickness absence. *Int Arch Occup Environ Health* 2016;89(4):667-78. doi: 10.1007/s00420-015-1104-4
95. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61
96. Vos HM, Bor HH, Rangelrooij-Minkels MJ, et al. Multimorbidity in older women: the negative impact of specific combinations of chronic conditions on self-rated health. *Eur J Gen Pract* 2013;19(2):117-22. doi: https://dx.doi.org/10.3109/13814788.2012.755511
97. Wei MY, Kabeto MU, Langa KM, et al. Multimorbidity and Physical and Cognitive Function: Performance of a New Multimorbidity-Weighted Index. *J Gerontol A Biol Sci Med Sci* 2018;73(2):225-32. doi: 10.1093/gerona/glx114
98. Wikman A, Wardle J, Steptoe A. Quality of life and affective well-being in middle-aged and older people with chronic medical illnesses: a cross-sectional population based study. *PLoS ONE* 2011;6(4):e18952. doi: 10.1371/journal.pone.0018952
99. Wister AV, Levasseur M, Griffith LE, et al. Estimating multiple morbidity disease burden among older persons: a convergent construct validity study to discriminate among six chronic illness measures, CCHS 2008/09. *BMC geriatr* 2015;15:12. doi: https://dx.doi.org/10.1186/s12877-015-0001-8
100. Hudon C, Fortin M, Soubhi H. Abbreviated guidelines for scoring the Cumulative Illness Rating Scale (CIRS) in family practice. *J Clin Epidemiol* 2007;60(2):212. doi: 10.1016/j.jclinepi.2005.12.021
101. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
102. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Med Care* 1998;36(1):8-27.
103. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162(1):W1-73. doi: 10.7326/M14-0698
104. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. *Med Care* 2012;50(12):1109-18. doi: 10.1097/MLR.0b013e31825f64d0
105. Yurkovich M, Avina-Zubieta JA, Thomas J, et al. A systematic review identifies valid comorbidity indices derived from administrative health data. *J Clin Epidemiol* 2015;68(1):3-14. doi: 10.1016/j.jclinepi.2014.09.010
106. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci* 2011;66(3):301-11. doi: 10.1093/gerona/glq208

107. Consortium PHCC. Description of the DUSOI - WONCA severity of illness instrument. 2011. http://www.ph3c.org/4daction/w3_CatVisu/en/description-of-the-dusoi----wonca--severity-of-illness-instrument.html?wDocID=157 (accessed 10 Mar 2019).
108. Moll van Charante E, Hartman E, Yzermans J, et al. The first general practitioner hospital in The Netherlands: towards a new form of integrated care? *Scand J Prim Health Care* 2004;22(1):38-43. [published Online First: 2004/05/04]
109. Levine CG, Davis GE, Weaver EM. Functional Comorbidity Index in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6(1):52-7. doi: 10.1002/alr.21620 [published Online First: 2016/01/13]
110. Fan E, Gifford JM, Chandolu S, et al. The functional comorbidity index had high inter-rater reliability in patients with acute lung injury. *BMC anesthesiol* 2012;12:21-21. doi: 10.1186/1471-2253-12-21
111. Lash TL, Mor V, Wieland D, et al. Methodology, design, and analytic techniques to address measurement of comorbid disease. *J Gerontol A Biol Sci Med Sci* 2007;62(3):281-5.
112. Moons KG, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: what, why, and how? *Bmj* 2009;338:b375. doi: 10.1136/bmj.b375
113. Newman AB, Boudreau RM, Naydeck BL, et al. A physiologic index of comorbidity: relationship to mortality and disability. *J Gerontol A Biol Sci Med Sci* 2008;63(6):603-9.
114. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992;45(2):197-203.
115. Alonso-Moran E, Nuno-Solinis R, Onder G, et al. Multimorbidity in risk stratification tools to predict negative outcomes in adult population. *Eur J Intern Med* 2015;26(3):182-9. doi: 10.1016/j.ejim.2015.02.010
116. Starfield B, Kinder K. Multimorbidity and its measurement. *Health Policy* 2011;103(1):3-8. doi: 10.1016/j.healthpol.2011.09.004
117. Fishman PA, Goodman MJ, Hornbrook MC, et al. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care* 2003;41(1):84-99. doi: 10.1097/01.MLR.0000039830.19812.29
118. Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care* 2003;41(6):761-74. doi: 10.1097/01.MLR.0000064641.84967.B7
119. Fortin M, Haggerty J, Sanche S, et al. Self-reported versus health administrative data: implications for assessing chronic illness burden in populations. A cross-sectional study. *CMAJ Open* 2017;5(3):E729-E33. doi: 10.9778/cmajo.20170029
120. Wallace E, Stuart E, Vaughan N, et al. Risk prediction models to predict emergency hospital admission in community-dwelling adults: a systematic review. *Med Care* 2014;52(8):751-65. doi: 10.1097/MLR.0000000000000171
121. Abbatecola AM, Spazzafumo L, Corsonello A, et al. Development and validation of the HOPE prognostic index on 24-month posthospital mortality and rehospitalization: Italian National Research Center on Aging (INRCA). *Rejuvenation Res* 2011;14(6):605-13. doi: 10.1089/rej.2011.1171
122. Koch G, Wakefield BJ, Wakefield DS. Barriers and facilitators to managing multiple chronic conditions: a systematic literature review. *West J Nurs Res* 2015;37(4):498-516. doi: 10.1177/0193945914549058
123. Kirkham JJ, Altman DG, Williamson PR. Bias due to changes in specified outcomes during the systematic review process. *PLoS ONE* 2010;5(3):e9810. doi: 10.1371/journal.pone.0009810

124. McAuley L, Pham B, Tugwell P, et al. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* 2000;356(9237):1228-31. doi: 10.1016/S0140-6736(00)02786-0
125. McManus RJ, Wilson S, Delaney BC, et al. Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *Bmj* 1998;317(7172):1562-3.
126. Lang S, Kleijnen J. Quality assessment tools for observational studies: lack of consensus. *Int J Evid Based Healthc* 2010;8(4):247. doi: 10.1111/j.1744-1609.2010.00195.x
127. Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med* 2015;8(1):2-10. doi: 10.1111/jebm.12141

6 Appendices

Appendix 3-1. Search Strategy

Table 1. Medline Search 1946 to August 13, 2018

#	Searches	Results
1	exp comorbidity/ or multiple chronic conditions/	95224
2	(multimorbid* or multi-morbid* or comorbid* or co-morbid*).ab,ti,kw.	147739
3	((multiple or coexist* or co-exist* or concurrent* or simultaneous*) adj2 (disease* or illness* or diagnos* or condition* or morbid* or disorder*)).ab,ti,kw.	45667
4	1 or 2 or 3	247802
5	primary health care/ or "continuity of patient care"/ or exp general practice/ or ambulatory care/ or physicians, family/ or physicians, primary care/ or community health services/ or general practitioners/	229791
6	((ambulatory or community or general or family or primary) adj2 (care or health* or practi* or physician* or medicine or center* or centre* or facilit* or clinic*)).ab,ti,kw.	350963
7	5 or 6	461463
8	epidemiologic measurements/ or risk assessment/ or "Outcome Assessment (Health Care)"/ or patient reported outcome measures/ or health status indicators/ or "severity of illness index"/ or sickness impact profile/ or diagnosis-related groups/ or case mix/	516146
9	((health status or risk or outcome* or sickness impact) adj2 (appraisal* or assessment* or evaluation* or measur* or index* or indic* or profile*)).ab,ti,kw.	344511
10	((severity or burden) adj2 (illness* or diseas* or disorder* or condition* or diagnos*)).ab,ti,kw.	72588
11	(charlson comorbidity index or charlson index or charlson score or elixhauser* or cumulative illness rating scale* or CIRS or adjusted clinical group* or ACG* or disease count or Duke severity* or DUSOI or casemix or case-mix).ab,ti,kw.	18192
12	8 or 9 or 10 or 11	808827
13	4 and 7 and 12	4172
14	limit 13 to (english language and yr="2010 -Current")	2173

Table 2. Embase Classic+Embase 1947 to August 13, 2018

#	Searches	Results
1	comorbidity/ or multiple chronic conditions/	196646
2	(multimorbid* or multi-morbid* or comorbid* or co-morbid*).ab,ti,kw.	244599
3	((multiple or coexist* or co-exist* or concurrent* or simultaneous*) adj2 (disease* or illness* or diagnos* or condition* or morbid* or disorder*)).ab,ti,kw.	66050
4	1 or 2 or 3	378500
5	primary health care/ or patient care/ or primary medical care/ or general practice/ or general practitioner/ or ambulatory care/ or family medicine/ or community care/ or community health services/	578870
6	((ambulatory or community or general or family or primary) adj2 (care or health* or practi* or physician* or medicine or center* or centre* or facilit* or clinic*)).ab,ti,kw.	453501
7	5 or 6	811904
8	risk assessment/ or outcome assessment/ or patient reported outcome/ or health status indicator/ or disease activity score/ or global disease burden/ or organ dysfunction score/ or "severity of illness index"/ or sickness impact profile/ or general health status assessment/ or disease severity/ or diagnosis related group/ or charlson comorbidity index/ or comorbidity assessment/ or elixhauser comorbidity index/ or case mix/	1257685
9	((health status or risk or outcome* or sickness impact) adj2 (appraisal* or assessment* or evaluation* or measur* or index* or indic* or profile*)).ab,ti,kw.	438484
10	((severity or burden) adj2 (illness* or diseas* or disorder* or condition* or diagnos*)).ab,ti,kw.	106531
11	(charlson comorbidity index or charlson index or charlson score or elixhauser* or cumulative illness rating scale* or CIRS or adjusted clinical group* or ACG* or disease count or Duke severity* or DUSOI or casemix or case-mix).ab,ti,kw.	32221
12	8 or 9 or 10 or 11	1613925
13	4 and 7 and 12	9317

14	limit 13 to (english language and yr="2010 -Current")	6113

Table 3. CINAHL – since inception to August 14, 2018

#	Searches	Results
1	(MH “comorbidity”)	30423
2	multimorbid* or multi-morbid* or comorbid* or co-morbid*	49461
3	(multiple or coexist* or co-exist* or concurrent* or simultaneous*) N2 (disease* or illness* or diagnos* or condition* or morbid* or disorder*)	9374
4	1 or 2 or 3	57381
5	(MH “primary health care”) or (MH “family practice”) or (MH “ambulatory care") or (MH “ambulatory care facilities") or (MM “community health services”) or (MM “community health centers”) or (MH “physicians, family”) or (MH “continuity of patient care")	83299
6	(ambulatory or community or general or family or primary) N2 (care or health* or practi* or physician* or medicine or center* or centre* or facilit* or clinic*)	205406
7	5 or 6	211994
8	(MH “risk assessment”) or (MH "Outcome Assessment") or (MH “patient-reported outcomes) or (MH “health status indicators”) or (MH "severity of illness indices") or (MH “sickness impact profile”) or (MH “diagnosis-related groups”) or (MH “case mix”)	69377
9	(health status or risk or outcome* or sickness impact) N2 (appraisal* or assessment* or evaluation* or measur* or index* or indic* or profile*)	165689
10	(severity or burden) N2 (illness* or diseas* or disorder* or condition* or diagnos*)	51231
11	(charlson comorbidity index or charlson index or charlson score or elixhauser* or cumulative illness rating scale* or CIRS or adjusted clinical group* or ACG* or disease count or Duke severity* or DUSOI or casemix or case-mix)	4820
12	8 or 9 or 10 or 11	211895
13	4 and 7 and 12	1454
14	limit 13 to (english language and yr="2010 -Current")	800

Appendix 3-2. Coding Description for the Modified Newcastle-Ottawa Scale for Cohort Studies

Category	Description
Selection	
1) Representativeness of the sample	This item assesses the representativeness of sample in the community, not from some general population. a) Truly representative***** (e.g., everyone from the database) b) Somewhat representative***** (with at least 2 criteria but selection method was convincing due to random sampling) c) Selected group (e.g., only certain socio-economic groups or areas) d) No description of sampling strategy
2) Ascertainment of multimorbidity	This item assesses the method by which multimorbidity was confirmed. a) Secure record***** (e.g., GP questionnaire) b) Structured interview***** (e.g., interviewer-administered questionnaire) c) Written self-report (e.g., mailed survey, if items are unable to be confirmed by objective measure) d) No description / Other
3) Demonstration that outcome of interest was not present at start of study	A statement of no history of disease earns a star. In the case of mortality studies, outcome of interest is still the presence of a disease, rather than death. a) Yes***** b) No
Comparability	
1) Study controls for age and sex	Covariates must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the covariates listed, then the groups will be considered to be comparable on each variable used. a) Yes***** b) No
2) Study controls for other factors	a) Yes***** b) No
Outcome	
1) Statistical test	Statistical test(s) must be clearly described and appropriate before assessing the other items under the Outcome category. a) Clearly described and appropriate b) Not described, incomplete or inappropriate
2) Assessment of outcome	This item assesses the method by which the outcome of interest was confirmed. For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required. a) Independent or blind assessment***** (e.g., interviewer-administered questionnaire) b) Record linkage***** (e.g., identified through ICD codes on database records) c) Self-report (i.e., no reference to original medical records)

		d) No description / Other
3)	Was follow-up long enough for outcomes to occur?	An acceptable length of time was at least 1 year of follow-up. a) Yes***** b) No
4)	Adequacy of follow-up of cohorts	This item assesses the follow-up of the sample to ensure that losses are not related to the outcome. a) Complete follow-up - all subject accounted for***** b) Subjects lost to follow-up unlikely to introduce bias***** (Number lost ≤20% or description of those lost suggested no different from those followed.) c) Follow-up rate less than 80% and no description of those lost d) No statement

Thresholds for converting the modified Newcastle-Ottawa scales to Good, Fair, and Poor Quality:

- Good Quality - 2-3 stars in Selection category (Representativeness of Sample item must be fulfilled) AND 1-2 stars in Comparability category AND 2-3 stars in Outcome category.
- Fair Quality - 1-2 stars in Selection category AND 1-2 stars in Comparability category AND 2-3 stars in Outcome category.
- Poor Quality - 0 star in Selection category OR 0 stars in Comparability category OR 0-2 stars in Outcome category.

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Modifications from original NOS include:

- 'Statistical test' was added to the Outcome category
- 'Representativeness of sample' item under Selection category and 'Statistical test' item under Outcome category must both be fulfilled for study to be considered Good Quality.
- 'Selection of the non-exposed cohort' item was removed from Selection category as most studies did not describe a non-exposed cohort, and this review sought to compare the different levels of multimorbidity within the group.
- 'Representativeness of the exposed cohort' item under Selection category was renamed 'Representativeness of the sample' since the 'non-exposed cohort' was removed above.
- 'Ascertainment of exposure' under the Selection category was renamed as 'Ascertainment of multimorbidity' to specify that multimorbidity is the exposure in this review.
- 'Study controls for age and sex' and 'Study controls for other factors' were revised to be items under Comparability category
- The thresholds for converting the scales to quality were amended accordingly due to the above modifications.

Consensus:

- The study team decided that a period of one-year was a reasonable period of follow-up under 'Was follow-up long enough for outcomes to occur?' item under Outcome category.

Appendix 3-3. Coding Description for the Modified Newcastle-Ottawa Scale for Cross-sectional Studies

Category	Description
Selection	
1) Representativeness of the sample	This item assesses the representativeness of sample in the specified population, not from some general population. e) Truly representative***** (e.g., everyone from the database, random sampling) f) Somewhat representative***** (with at least 2 criteria but selection method was convincing due to random sampling) g) Selected group (e.g., only certain socio-economic groups or areas) h) No description of sampling strategy
2) Ascertainment of multimorbidity	This item assesses the method by which multimorbidity was confirmed. e) Secure record***** (e.g., Clinical records, GP questionnaire) f) Structured interview***** (e.g., interviewer-administered questionnaire) g) Written self-report (e.g., mailed survey, if items are unable to be confirmed by objective measure) h) No description / Other
3) Sample Size	If there is no description, a reported sample size of 800 and above is satisfactory. c) Justified and satisfactory***** d) Not justified
4) Non-respondents	Acceptable response rates for surveys through various methods† • In-person: 57% • Mail: 50% • Average: 33% • Email: 30% • Internet: 29% • Telephone: 18% • In-app: 13% a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory.***** b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c) No description of the response rate or the characteristics of the responders and the non-responders
Comparability	
3) Study controls for age and sex	Confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. c) Yes***** d) No
4) Study controls for other factors	c) Yes***** d) No

Outcome	
5) Statistical test	Statistical test(s) must be clearly described and appropriate before assessing the other items under the Outcome category. c) Clearly described and appropriate d) Not described, incomplete or inappropriate
6) Assessment of outcome	This item assesses the method by which the outcome of interest was confirmed. For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required. e) Independent or blind assessment***** f) Record linkage***** (e.g., identified through ICD codes on database records) g) Self-report (i.e., no reference to original medical records) h) No description / Other

Thresholds for converting the modified Newcastle-Ottawa scales to Good, Fair, and Poor Quality:

- Good Quality – 3-4 stars in Selection category (Representativeness of Sample item must be fulfilled) AND 1-2 stars in Comparability category AND 1 star in Outcome category.
- Fair Quality - 2 stars in Selection category AND 1-2 stars in Comparability category AND 1 star in Outcome category.
- Poor Quality - 0 star in Selection category OR 0 stars in Comparability category OR 0 stars in Outcome category.

†Lindermann N. What's the average survey response rate? [2018 benchmark]. SurveyAnyplace. Available from: https://surveyanyplace.com/average-survey-response-rate/.

Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): a systematic review and meta-analysis. PLoS ONE. 2015;10(9):e0136065. Doi:10.1371/journal.pone.0136065.

Modifications from original NOS include:

- 'Ascertainment of exposure' item under Selection category was renamed as 'Ascertainment of multimorbidity' to specify that multimorbidity is the exposure in this review.
- The ratings for the 'Ascertainment of exposure' item under Selection category were revised to 'secure record, structured interview, written self-report, no description/other' to align with the Modified NOS for cohort studies in this review.
- 'Study controls for age and sex' and 'Study controls for other factors' items were revised to be items under Comparability category.
- 'Was follow-up long enough for outcomes to occur' item under Outcome category was renamed as 'Statistical test'. This item must be fulfilled for the study to be considered as Good Quality.
- The thresholds for converting the scales to quality were amended accordingly due to the above modifications.

Consensus:

- The study team decided on a list of acceptable response rates for various survey methods for the 'Non-respondents' item under Selection category.
- The study team decided that a sample size of 800 was reasonable under 'Sample size' item under Selection category.

Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Cohort Studies						
Brilleman et al. (2014)[31], UK	a. ACG b. CCI c. CCI dummy d. EDC count e. EDC dummy f. QOF count g. QOF dummy h. RUB	1. Primary healthcare cost	Model 1:	Age and sex	BIC = 1320939	1. Under OLS estimation, the EDC measures performed best followed by the QOF and ACG measures. The CCI measures had the worst performance but still improved markedly on models containing only age, sex, deprivation and practice effects.
			Model 2:	Age, sex, and deprivation	BIC = 1320555	
			Model 3:	Age, sex, and practice	BIC = 1322027	
			Model 4:	Age, sex, deprivation, and practice	BIC = 1321883	
			Model 5:	Model 4 and QOF dummy	BIC = 1302791	
			Model 6:	Model 4 and QOF count	BIC = 1305547	
			Model 7:	Model 4 and CCI dummy	BIC = 1310235	
			Model 8:	Model 4 and CCI	BIC = 1311982	
			Model 9:	Model 4 and EDC dummy	BIC = 1295660	
			Model 10:	Model 4 and EDC count	BIC = 1302546	
			Model 11:	Model 4 and ACG	BIC = 1308944	
			Model 12:	Model 4 and RUB	BIC = 1312522	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Brilleman & Salisbury (2013)[32], UK	a. ACG b. CCI c. EDC count d. Prescribed drugs count e. QOF count f. RUB	1. Mortality (3-years period)	Model 1:	Age, sex, and deprivation	BIC = 20250	1. Measures of multimorbidity made little difference to the fit of a model predicting 3-year mortality. Nonetheless, the CCI was the best performing measured followed by the number of prescribed drugs.
			Model 2:	Model 1 and QOF count	BIC = 19854	
			Model 3:	Model 1 and CCI	BIC = 19443	
			Model 4:	Model 1 and EDC count	BIC = 19979	
			Model 5:	Model 1 and RUB	BIC = 19946	
			Model 6:	Model 1 and prescribed drugs count	BIC = 19693	
		2. Number of primary care consultations (3-years period)	Model 1:	Age, sex, age-by-sex interaction, deprivation, and GP practice	BIC = 650373	2. All of the multimorbidity measures had moderate predictive validity in relation to consultation in primary care, in which the number of prescribed drugs had the greatest predictive validity followed by the ACG based measures (ACG, EDC count, and RUB).
			Model 2:	Model 1 and QOF count	BIC = 638720	
			Model 3:	Model 1 and CCI	BIC = 644908	
			Model 4:	Model 1 and EDC count	BIC = 629766	
			Model 5:	Model 1 and ACG	BIC = 628438	
			Model 6:	Model 1 and RUB	BIC = 631863	
			Model 7:	Model 1 and prescribed drugs count	BIC = 620799	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Carey et al. (2013)[50], UK	a. Standard QOF b. Extended QOF c. CCI (Khan)	1. Mortality (1-year period)	Model 1:	Age and sex	C-statistics = 0.776	1. A simple count of the morbidities in each of the multimorbidity measurements produced significant improvement from a basic model adjusting for age and sex. 2. Fitting the weighted score as a nine-level variable further improved discrimination, with the standard QOF score outperforming the Charlson index. The extended QOF score produced only a modest improvement in overall model performance.
			Model 2:	Age, sex, and Standard QOF count	C-statistics = 0.806	
			Model 3:	Age, sex, and Standard QOF weighted score	C-statistics = 0.823	
			Model 4:	Age, sex, and Standard QOF weighted score (9 levels)	C-statistics = 0.826	
			Model 5:	Age, sex, and CCI count	C-statistics = 0.809	
			Model 6:	Age, sex, and CCI weighted score	C-statistics = 0.816	
			Model 7:	Age, sex, and CCI weighted score (9 levels)	C-statistics = 0.818	
			Model 8:	Age, sex, and Extended QOF count	C-statistics = 0.813	
			Model 9:	Age, sex, and Extended QOF weighted score	C-statistics = 0.826	
			Model 10:	Age, sex, and Extended QOF weighted score (9 levels)	C-statistics = 0.829	
Chapman et al. (2015)[51], UK	a. CCI b. CCI-PSR	1. Mortality (5, 10, 15, 20, 25-years period)	CCI Model:	Age, sex, chronic asthma/emphysema, arthritis/rheumatism, cancer, diabetes, gastrointestinal disease, heart disease, kidney disease, and stroke	AUC = 0.75 (5-yrs) AUC = 0.74 (10-yrs) AUC = 0.74 (15-yrs) AUC = 0.76 (20-yrs) AUC = 0.77 (25-yrs)	1. Across 5-, 10-, 15-, 20-, and 25-year time horizons, the CCI-PSR showed substantially better discrimination than the CCI.
			CCI-PSR Model:	CCI model, income, education, type A personality, communalism, and lie scale	AUC = 0.83 (5-yrs) AUC = 0.83 (10-yrs) AUC = 0.83 (15-yrs) AUC = 0.84 (20-yrs) AUC = 0.84 (25-yrs)	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Crane et al. (2010)[52], USA	a. ERA	1. Number of hospital visits (1-year period)	ERA Model:	Age, marital status, number of days hospitalised in 2003 or 2004, history of diabetes, history of CAD/MI/CHF, history of stroke, history of COPD, history of cancer, and history of dementia	AUC = 0.705	1. Results suggest that the ERA index is an effective risk identification model to identify population of older, community-dwelling adults who are at increased risk of hospitalisation and ED encounters.
		2. Number of ED visits (1-year period)			AUC = 0.640	
		3. Number of hospital admissions (1-year period)			AUC not reported	
		4. Number of days hospitalised (1-year period)			AUC not reported	
Crooks et al. (2016)[33], UK	a. Co-morbidity linked score b. CCI c. Elixhauser Index	1. Mortality (1-year period)	Elixhauser:	Elixhauser Index, age, sex, and recent hospitalisation	C-statistics = 0.868	1. The linked score had significantly improved discrimination and fit compared to the CCI and the Elixhauser Index
			CCI:	CCI, age, sex, and recent hospitalisation	C-statistics = 0.872	
			Linked score (Categorical):	Linked score (Categorical), age, sex, and recent hospitalisation	C-statistics = 0.879	
			Linked score (Continuous):	Linked score (Continuous), age, sex, and recent hospitalisation	C-statistics = 0.878	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Crooks et al. (2015)[34], UK	a. CCI (Read) b. CCI (ICD-10) c. CCI (Read and ICD-10)	1. All-cause mortality	Model 1:	Sex	C-statistics = 0.513	1. There was no large difference in the discrimination of the model for overall survival, whichever codes were used to derive the CCI. Including a marker for a recent hospital admission resulted in a slightly improved discrimination for each Charlson derivation.
			Model 2:	Age and sex	C-statistics = 0.844	
			Model 3:	Age, sex, and CCI (Read)	C-statistics = 0.861	
			Model 4:	Age, sex, recent hospitalisation, and CCI (Read)	C-statistics = 0.868	
			Model 5:	Age, sex, and CCI (ICD-10)	C-statistics = 0.870	
			Model 6:	Age, sex, recent hospitalisation, and CCI (ICD-10)	C-statistics = 0.872	
			Model 7:	Age, sex, CCI (Read and ICD-10)	C-statistics = 0.869	
			Model 8:	Age, sex, recent hospitalisation, and CCI (Read and ICD-10)	C-statistics = 0.873	
Fraccaro et al. (2016)[55], UK	a. CCI (Khan)	1. Mortality (6-month period)	Model 1:	Age, sex, and baseline CCI	AIC = 362230	1. Model 5 had the best fit to the data but had equivalent discrimination to the other time-dependent models.
			Model 2:	Sex, time-dependent age, and CCI	AIC = 358054	
			Model 3:	Sex, baseline CCI, time-dependent age, and CCI	AIC = 357290	
			Model 4:	Sex, baseline CCI, time-dependent age, and cumulative CCI change	AIC = 357290	
			Model 5:	Sex, time-dependent age, CCI, and CCI change over consecutive time windows	AIC = 357000	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study	Statistics	Conclusion
Haas et al. (2013)[56], USA	a. ACG b. Minnesota Health Care Home Tiering c. HCC d. ERA e. CCC f. CCI g. Hybrid Model	1. Hospitalisation 2. ED visits 3. Readmission within 30 days 4. Healthcare expenditure	ACG Minnesota Health Care Home Tiering HCC ERA CCC CCI	C-statistics = 0.73 (Hospitalised) C-statistics = 0.67 (ED visits) C-statistics = 0.81 (Readmission) C-statistics = 0.76 (Expenditure) C-statistics = 0.71 (Hospitalised) C-statistics = 0.66 (ED visits) C-statistics = 0.79 (Readmission) C-statistics = 0.74 (Expenditure C-statistics = 0.67 (Hospitalised) C-statistics = 0.58 (ED visits) C-statistics = 0.74 (Readmission) C-statistics = 0.70 (Expenditure) C-statistics = 0.71 (Hospitalised) C-statistics = 0.61 (ED visits) C-statistics = 0.78 (Readmission) C-statistics = 0.72 (Expenditure) C-statistics = 0.69 (Hospitalised) C-statistics = 0.61 (ED visits) C-statistics = 0.77 (Readmission) C-statistics = 0.72 (Expenditure) C-statistics = 0.68 (Hospitalised) C-statistics = 0.59 (ED visits) C-statistics = 0.75 (Readmission) C-statistics = 0.70 (Expenditure)	1. The ACG model outperformed the other 5 models in predicting hospitalisation. 2. In models predicting ED visits, the ACG model had the best predictive ability. 3. The ACG model outperformed other models when predicting 30-day readmissions 4. When predicting healthcare expenditures for the top 10% high-cost users, the performance of the ACG model was superior to that of other models
Hwang et al. (2015)[57], USA	1. ACE-27 2. ACE-27 count	1. Healthcare expenditure	Exploratory predictive model consists of age, sex, rurality of residence, logarithms of total, inpatient, medication, outpatient, and professional expenditures, number and overall severity of patient conditions defined by ACE-27 score, and each of the 26 individual comorbidities in ACE-27	AUC = 0.923	1. The model, using year 1 data to determine if an individual would be classified into the persistent high-user group for the following 3 years, indicates a very high level of accuracy in predicting membership in a high-user group.

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study	Statistics	Conclusion
Lemke et al. (2012)[61], USA	a. CCI b. ACG	1. Inpatient hospitalisations	Model 1: **Prior Inpatient Hospitalisation** Age, sex, count of hospitalisations within the previous 12 months	AUC = 0.75	1. ACG-based predictive model for inpatient hospitalisation was superior to the prior hospitalisation model and the Charlson inpatient model
			Model 2: **Charlson Inpatient Hospitalisation** Age, sex, prior hospitalisations, emergency department episodes not resulting in inpatient hospitalisations, outpatient visits, markers for dialysis services, nursing services and major procedures and 17 Charlson comorbidities	AUC = 0.78	2. The difference between the ACG and Charlson inpatient models was statistically significant ($p<0.0001$)
			Model 3: **ACG Inpatient Hospitalisation** Age, sex, diagnosis-based morbidity categories and disease cluster markets, medication-based morbidity groups, count of previous hospitalisations	AUC = 0.80	
			Model 4: **ACG ICU/CCU Hospitalisation** Age, sex, diagnosis-based morbidity categories and disease cluster markets, medication-based morbidity groups, count of ICU/CCU hospitalisation	AUC = 0.85	
			Model 5: **ACG Extended Hospitalisation** Age, sex, diagnosis-based morbidity categories and disease cluster markets, medication-based morbidity groups, count of extended hospitalisation	AUC = 0.87	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Quail et al. (2011)[62], Canada	a. DC b. CCI (Quan) c. Elixhauser Index (Quan) d. Number of dispensed drugs e. Chronic Disease Score	1. Death 2. One or more hospitalisations 3. Two or more hospitalisations	Model 1 (Base Model):	Age, age^2, sex, income quintile, and geography	C-statistic = 0.880 (Death) C-statistic = 0.652 (≥1 hospitalisations) C-statistic = 0.706 (≥2 hospitalisations)	In predicting all outcomes, the addition of a comorbidity measure to the base model yielded a statistically significant improvement in the c-statistic. 1. Elixhauser Index (Quan) performed best in improving the c-statistic, followed by CCI. 2. Disease count (number of different diagnoses) was the best performing comorbidity measure for one or more hospitalisations 3. Disease count (number of different diagnoses) was the best performing comorbidity measure Disease count (number of different diagnoses) was the best performing comorbidity measure for two or more hospitalisations
			Model 2:	Model 1 + Number of different diagnoses	C-statistic = 0.901 (Death) C-statistic = 0.722 (≥1 hospitalisations) C-statistic = 0.782 (≥2 hospitalisations)	
			Model 3:	Model 1 + Charlson Comorbidity Index (Quan)	C-statistic = 0.905 (Death) C-statistic = 0.671 (≥1 hospitalisations) C-statistic = 0.731 (≥2 hospitalisations)	
			Model 4:	Model 1 + Elixhauser (Quan)	C-statistic = 0.913 (Death) C-statistic = 0.682 (≥1 hospitalisations) C-statistic = 0.748 (≥2 hospitalisations)	
			Model 5:	Model 1 + Number of dispensed drugs	C-statistic = 0.894 (Death) C-statistic = 0.688 (≥1 hospitalisations) C-statistic = 0.744 (≥2 hospitalisations)	
			Model 6:	Model 1 + Chronic Disease Score	C-statistic = 0.889 (Death) C-statistic = 0.672 (≥1 hospitalisations) C-statistic = 0.729 (≥2 hospitalisations)	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Saver et al. (2014)[64], USA	a. CCI (Romano) + Hypertension	1. Acute ACSH 2. Chronic ACSH	Model 1: Model 2: Model 3: Model 4:	Age, sex, and race Model 1, rural-urban residence, state of residence, availability of healthcare services, continuity of care, household income, education, original source of Medicare eligibility, number of outpatient visits in prior year, and previous year ACSHs Model 2, comorbidity flags (CHF, COPD, diabetes, hypertension and, for acute ACSHs, dementia), and precious year ACSHs Model 1 and comorbidity flags (CHF, COPD, diabetes, hypertension and, for acute ACSHs, dementia)	C-statistics = 0.68 C-statistics = 0.72 C-statistics = 0.87 C-statistics = 0.87	1. Model with limited set of comorbidity flags (model 3 and model 4) had far grater predictive power for acute and chronic ACSHs.
Stanley and Sarfati (2017)[65], New Zealand	a. M3 Index b. CCI c. Elixhauser (van Walraven)	1. Mortality (1-year period) 2. Overnight hospitalisation (1-year period)	Model 1: Model 2: Model 3: Model 4:	Age and sex Age, sex, and CCI Age, sex, and Elixhauser Age, sex, and M3 Index	C-statistics = 0.887 (Mortality) C-statistics = 0.656 (Hospitalised) C-statistics = 0.921 (Mortality) C-statistics = 0.683 (Hospitalised) C-statistics = 0.922 (Mortality) C-statistics = 0.676 (Hospitalised) C-statistics = 0.931 (Mortality) C-statistics = 0.703 (Hospitalised)	1. M3 Index outperformed both CCI and Elixhauser in predicting mortality 2. M3 Index performed better than CCI and Elixhauser when considering overnight hospitalisation.

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Takahashi et al. (2016)[67], USA	a. DC using Minnesota Medical Tiering (ACG)	1. Hospitalisation / ED visits	Minnesota Medical Tiering		AUC = 0.667	1. The enhanced model is better at predicting hospitalisation/ED visits than models that utilise only Minnesota medical tiering as it takes into consideration previous hospitalisation, specific high-risk illnesses, mental health conditions, and high-risk medication use (eg, warfarin, narcotics) that are not universally accounted for in other models.
			Enhanced Model	Age, sex, BMI, marital status, insurance, prior ED visits, prior hospitalisations, more than 3 specialists seen in 2010, mental health disorders, substance-related disorders, narcotic prescription order, epilepsy, hyperlipidemia, warfarin prescription order	AUC = 0.711	
Wallace et al. (2016a)[39], Ireland	a. Pra tool b. Modified Pra tool	1. Emergency hospital admission (1-year period)	Pra tool	Age, sex, presence of diabetes, presence of coronary heart disease, hospital admission in previous year, > 6 physician visits in previous year, self-rated health, and availability of an informal caregiver	C-statistics = 0.65	1. Both models demonstrated poor model discrimination for the outcome for emergency admission during the 1-year follow-up period.
			Modified Pra	Pra tool and RxRisk-V	C-statistics = 0.67	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Wallace et al. (2016b)[40], Ireland	a. DC b. Barnett conditions DC c. CCI d. Prescribed drugs count e. RxRisk-V	1. Emergency admission (2-years period) 2. Functional decline (2-years period)	Model 1: Model 2: Model 3: Model 4: Model 5:	Age, sex, deprivation, and DC Age, sex, deprivation, and Barnett DC Age, sex, deprivation, and CCI Age, sex, deprivation, and RxRisk-V Age, sex, deprivation, and prescribed drugs count	C-statistics = 0.61 (Admission) C-statistics = 0.55 (Functional) C-statistics = 0.63 (Admission) C-statistics = 0.55 (Functional) C-statistics = 0.58 (Admission) C-statistics = 0.60 (Functional) C-statistics = 0.63 (Admission) C-statistics = 0.61 (Functional) C-statistics = 0.62 (Admission) C-statistics = 0.57 (Functional)	1. All measures demonstrated poor discrimination in predicting emergency admission. 2. All measures demonstrated poor discrimination in predicting emergency admission.
Wei and Mukamal (2018)[69], USA	a. MWI b. DC c. CCI	1. Mortality (10-years period)	MWI DC CCI		C-statistics = 0.67 (NHS Cohort) C-statistics = 0.70 (HPFS Cohort) C-statistics = 0.64 (NHS II Cohort) C-statistics = 0.68 (Combined) C-statistics = 0.65 (NHS Cohort) C-statistics = 0.68 (HPFS Cohort) C-statistics = 0.62 (NHS II Cohort) C-statistics = 0.66 (Combined) C-statistics = 0.64 (NHS Cohort) C-statistics = 0.64 (HPFS Cohort) C-statistics = NA (NHS II Cohort) C-statistics = 0.64 (Combined)	1. MWI performed best in predicting mortality as compared to DC and CCI, with the greatest C-statistics in all cohorts as well as the combined cohorts.

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Cross-Sectional Studies						
Kristensen et al. (2014)[79], Denmark	a. RUB	1. Fee-for-services expenditures	Model 1:	Age, age squared, and sex	R^2 = 0.133	1. Morbidity measures were significant patient-related fee-for-services expenditures drivers.
			Model 2:	Model 1 and RUB markers	R^2 = 0.316	
			Model 3:	Model 2 and ICPC-2 chapter markers	R^2 = 0.437	
			Model 4:	Model 2 and chapter components markers	R^2 = 0.372	
			Model 5:	Model 2, ICPC-2 chapter markers, and chapter components markers	R^2 = 0.444	
			Model 6:	Model 5 and volume markers	R^2 = 0.793	
Lapi et al. (2015)[80], Italy	a. Health Search Morbidity Index (HSMI)	1. Total mean healthcare cost per year	Model 1:	Interaction between age and sex, province of patient's residence, and GP	R^2 = 50.17	1. The HSMI explained 50.17% of the variation in costs.
			Model 2:	Interaction between age and sex, and region of patient's residence	R^2 = 50.16	
			Model 3:	Province of patient's residence and GP	R^2 = 49.71	
			Model 4:	Model 1 and cubic fractional polynomial transformation of age	R^2 = 50.51	

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study	Statistics	Conclusion
Ranstad et al. (2014)[88], Sweden	RUB	1. Registered active listing in primary care 2. Registered active listing in all healthcare	Model 1: Multimorbidity, primary care Model 2: Multimorbidity, all healthcare Model 3: Interaction between number of consultations and multimorbidity, primary care Model 4: Interaction between number of consultations and multimorbidity, all healthcare	AIC = 141110.9 AIC = 145361.5 AIC = 140007.6 AIC = 144595.7	1. Multimorbidity level predicted active listing, significantly increasing for RUB0-4 in primary care 2. Multimorbidity level predicted active listing, significantly increasing for RUB0-4 in all healthcare
Shadmi et al. (2011)[91], Israel	ADGs CCI	1. Number of primary care physician visits 2. Number of specialist visits 3. Performance of diagnostic tests 4. Number of hospitalisations	Model 1: Age and sex Model 2: Age, sex, CCI Model 3: Age, sex, ADGs	R^2 = 0.13 (Primary care visits) R^2 = 0.12 (Specialist visits) R^2 = 0.13 (Diagnostic tests) R^2 = 0.05 (Hospitalisations) R^2 = 0.18 (Primary care visits) R^2 = 0.13 (Specialist visits) R^2 = 0.15 (Diagnostic tests) R^2 = 0.11 (Hospitalisations) R^2 = 0.54 (Primary care visits) R^2 = 0.45 (Specialist visits) R^2 = 0.37 (Diagnostic tests) R^2 = 0.24 (Hospitalisations)	1. ADGs explained the largest percent of variance or in health care resource use, ranging from 23% to 54% in primary care physician visits, specialist visits, performance of diagnostic tests, and hospitalisations

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Appendix 3-4. Summary of included articles where multimorbidity measures were added into prediction models (20 studies including 23 articles)(Continued)

Author (Year), Country	Multimorbidity Measurement(s)	Outcomes measured	Models used in the study		Statistics	Conclusion
Sullivan et al. (2012)[93], USA	DC	1. Preference-based HRQoL	Model 1:	Age, number of chronic conditions	Pseudo R^2 = 0.2316	1. The inclusion of chronic co-morbidity to the baseline models explained more of the variance in EQ-5D-5L index scores than did age or other sociodemographic characteristics
			Model 2:	Age, income, sex, race, education, ethnicity, physical activity, smoking status	Pseudo R^2 = 0.1462	
			Model 3:	Number of chronic conditions	Pseudo R^2 =0.1994	
			Model 4:	Age, income, sex, race, education, ethnicity, physical activity, smoking status, number of chronic conditions	Pseudo R^2 =0.2360	

Note. ACE-27 = Adult Comorbidity Evaluation-27; ACG = Adjusted Clinical Groups; ACSH = Ambulatory Care Sensitive Hospitalisation; AUC = Area Under the Curve; BIC = Bayesian Information Criterion; CAD = Coronary Artery Disease; CCC = Chronic Conditions Count; CCI = Charlson Comorbidity Index; CCI-PSR = Charlson Comorbidity Index-Psychosocial Risk; CCU = Critical Care Unit; CHF = Congestive Heart Failure; COPD = Chronic Obstructive Pulmonary Disease; DC = Disease Count (Unweighted); ED = Emergency Department; EDC = Expanded Diagnosis Clusters; ERA = Elder Risk Assessment; GP = General Practice; HCC = Hierarchical Condition Categories; HSMI = Health Search Morbidity Index; ICD-10 = International Classification of Diseases, Tenth Revision; ICPC-2 = International Classification of Primary Care, Second Edition; ICU = Intensive Care Unit; MI = Myocardial Infarction; OLS = Ordinary Least Squares; QOF = Quality and Outcomes Framework; RUB = Resource Utilisation Band.

Western University

CHAPTER FOUR

A cross-sectional study on the level of Multimorbidity and its association with Depression, *A*nxiety and *Q*uality of Life (MDAQ)

Abbreviations

ADC-EMR	Additional Disease Count - Electronic Medical Record
ADC-SR	Additional Disease Count - Self-reported
BI	Bias index
BMI	Body Mass Index
BP	Blood pressure
CDCS	Chronic Disease Control Score
CMC	Chronic Medication Count
DBP	Diastolic Blood Pressure
EMR	Electronic Medical Records
EQ-5D	EuroQol Office Quality of life scale
GAD-7	Generalised Anxiety Disorder Scale
HbA1c	Glycated Haemoglobin
HDB	Housing Development Board
HUDC	Housing and Urban Development Company
IQR	Inter-quartile range
LD	Listwise Deletion
LDL-C	Low-density lipoprotein
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple Imputation
MNAR	Missing not at random
NHGP	National Healthcare Group Polyclinics
OR	Odds ratio
PABAK	Prevalence-adjusted bias-adjusted kappa
PHQ-9	Patient Health Questionnaire Depression Scale
PI	Prevalence index
SBP	Systolic Blood Pressure
SD	Standard deviation
SE	Standard error
SPSS	IBM Statistical Analysis Software
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UI	EuroQol Office Quality of life scale - Utility Index
VAS	EuroQol Office Quality of life scale - Visual Analogue Scale
VIF	Variance inflation factor
W	Width
κ	Cohen's kappa statistic

1 Introduction

A clear association between illness burden and psychological distress has been reported in the literature[1]. It is believed that psychological distress arises through progressive loss of independence, self-esteem, and self-identity as the number of chronic conditions increase[2]. Chapter two reported that the most common co-occurring chronic conditions found in primary care patients in Singapore are hyperlipidaemia, hypertension, and diabetes with a prevalence rate of 21.9% in the primary care setting (*Chapter Two Table 2-10 p54*). If every chronic condition is poorly-controlled in a patient with multimorbidity, it is logical to assume that the illness burden would have been higher or worse than a patient whose multiple chronic conditions were well-controlled for every condition. Moreover, it has been shown that reducing numerous risks simultaneously is beneficial because risk factors for cardiovascular disease tend to cluster and interact which exerts a greater combined risk[3].

Clinical practice guidelines on the control of clinical parameters of single diseases are widely available in the medical literature. Based on the guidelines of specialty societies, optimal thresholds for some of these clinical parameters were combined from separate clinical practice guidelines as composite measures for reducing cardiovascular disease and were widely accepted as standards of care since the end of the 20th century[4]. These standards of care quickly became performance measures for clinicians[5]. The Ministry of Health (MOH) in Singapore also followed suit with the MOH's Diabetes Mellitus Clinical Practice Guidelines published in 2006[6].

One success story of using a composite score for both clinical outcomes of patients with multimorbidity and provider's performance measures of clinicians was reported in Taiwan[7]. However, adhering to the current clinical practice guidelines in caring for an older person with multimorbidity may result in undesirable effects[8]. There is concern that performance measures may direct healthcare providers' focus on improving outcomes of single diseases, rather than to manage the interactions of multiple chronic conditions[9]. This is made worse when clinicians are blind to the extent to which treatment burden can unintentionally drag people down[10].

Findings from a qualitative study reported that patient's perspectives of living with multimorbidity speak more to lower quality of life and functional challenges than to disease-

specific issues[11]. The inverse relationship between the level of multimorbidity and quality of life has been reported by multiple other studies using different methodologies[12-21]. Patients with multimorbidity were also more likely to be screened positive for depression[22]. Clinical depression was two to three times more likely in people with multimorbidity compared to people without multimorbidity[23-25]. However, clinically depressed patients with multimorbidity were inconsistently picked up in primary care[26].

Although multimorbidity is commonly observed in Singapore, very few investigators have looked into the phenomenon locally, and even fewer studies were conducted to look at patient-reported outcomes like depression, anxiety, and quality of life. One exception is Quah et al.[27] who surveyed older adults in the primary care setting locally and found that multimorbidity was associated with lower quality of life. Many of the multimorbidity studies that contributed to the burgeoning literature on the topic were conducted in North America or Europe. However, findings reported elsewhere may not apply to the local context.

The entity of 'diseases' used by doctors do not always explain the individuals' illness, and patient needs and symptom experience are not necessarily an indication of an underlying disease[28]. Many multimorbidity studies were conducted by directly obtaining self-reported medical conditions from the patients. Several studies have reported variable concordance rates that were reported by patients and what were recorded in their medical notes[29-31]. A growing body of literature has raised concerns about the reliability of respondent recall, poor respondent understanding, and labelling of medical conditions when self-reporting of medical conditions was used in such studies[29,32].

Therefore, in this study, we proposed to look at the association of a composite score for measuring the level of multimorbidity derived from clinical data among patients with the triad of hyperlipidaemia, hypertension, and diabetes in primary care and determine its association with patient-reported outcome measures like depression, anxiety and quality of life. Our primary research hypothesis was that with a higher level of multimorbidity, patients would experience a higher degree of depression and anxiety symptoms, and a lower quality of life. The second objective of the study was to describe the prevalence of depression and anxiety, and the average score of quality of life in individuals with the commonest triad of multimorbidity in primary care. Our third objective was to determine the factors associated

with depression, anxiety or poor quality of life for patients with the commonest triad of multimorbidity. Our final objective of this study was methodological as we determine the concordance rate between self-reported medical conditions by patients and medical conditions recorded in their clinical records.

2 Methods

This was a cross-sectional interviewer-administered questionnaire study conducted in the primary care population at one of the National Healthcare Group Polyclinics (NHGP) between August 2014 and June 2016. The study team received approval from the ethics review board (National Healthcare Group Domain Specific Review Board Reference number 2013/01053) on 5 June 2014, and the first patient was recruited on 12 August 2014. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[33] in reporting this study. This study received funding from an intramural grant.

2.1 Setting

Hougang Polyclinic is one of the nine polyclinics in the National Healthcare Group Polyclinics (NHGP) in the north-eastern part of Singapore. Hougang Polyclinic provides a comprehensive range of health services for the family, functioning as a one-stop health centre providing treatment for acute medical conditions, management of chronic diseases, women and child health services, and dental care. It operates with close to 180 staff including 24 doctors and 18 nurses servicing up to 1,200 patients daily from 8 am to 4.30 pm. It is opened for half a day every Saturday and closed on Sunday.

2.2 Sampling

The full inclusion criteria were listed as follows:

a. Patients who were 21 years old and below 80 years old
b. Patients with current co-existence of at least three chronic conditions, i.e., hyperlipidaemia, hypertension, and diabetes mellitus Type 1 or 2

c. Patients who were seen in Hougang Polyclinic at least twice in the last six months[†††††] for chronic disease management (information obtained from diagnosis codes) prior to commencement of the study
d. Patients who were able to understand spoken English, Mandarin, Malay or Tamil and provided written informed consent
e. Patients who consented to allow the study team to access their medical notes at Hougang Polyclinic

A random sample of the eligible population in Hougang polyclinic was selected using the IBM Statistical Analysis software version 21 (SPSS). Potential participants from this selected list were approached before/during/after their scheduled appointments at Hougang Polyclinic and invited to go to a nearby interview room where the research assistant would explain the research study. All eligible participants were given the opportunity to ask questions and given ample time to think about participation. Informed consent was obtained when the patient was agreeable to participate in the study. This consent also permitted the research team to obtain further data like recent biomedical results, medication list and other medical conditions from the electronic medical records (EMR). We excluded pregnant women and patients who were cognitively not capable of providing consent. The team members excluded pregnant women because the outcome measures on depression, anxiety and quality of life may be strongly influenced by pregnancy rather than multimorbidity.

2.3 Conduct of the interview

All our research assistants and coordinators met regularly and practised interviewing on each other under the supervision of the principal investigator to ensure that the assistance provided and answers to anticipated questions raised by participants were standardised as much as possible before embarking on the actual research to reduce interviewer bias.

We used all four official languages of Singapore to conduct the interviews according to the choice of the participants. The principal research assistant was proficient in English and Mandarin only. For Malay and Tamil-speaking participants, we made special arrangements to

[†††††] We selected patients who visited two visits in the last six months as a proxy to represent patients who have chosen Hougang Polyclinic as the designated polyclinic for management of their chronic medical conditions.

bundle the appointments together so that other research assistants proficient in those languages would meet potential participants at Hougang Polyclinic on a pre-arranged date and time. We also arranged a convenient time for participants to return to the polyclinic for the interview if their agendas were not able to accommodate the interview during their polyclinic scheduled appointments.

The study questionnaire was programmed on the QuickTapSurvey (www.quicktapsurvey.com) app on a tablet computer. The questionnaire included all the demographic questions, outcome variables described in 2.4, and the independent variables described in section 2.5. Data were entered by the research assistant directly into the tablet computer. Each interview took approximately 30 minutes. All patient information was de-identified upon completion of the relevant data collection from the EMR before analysis was commenced.

2.4 Outcome variables

The three outcome variables were Patient Health Questionnaire Depression Scale (PHQ-9)[34,35], Generalised Anxiety Disorder Scale (GAD-7)[36], EuroQol Office Quality of life scale (EQ-5D-3L) Utility index (UI)[37] and EuroQol Office Quality of life scale (EQ-5D-3L) Visual Analogue Scale (VAS)[37] score. Both EQ-5D-3L UI and VAS were continuous variables.

(1) The PHQ-9[34] is a nine-item depression measure where respondents were asked whether they were bothered by a series of problems in the past two weeks and if so, how often, using a four-point scale from 'not at all' to 'nearly every day'. Individual scores from each item were summed, and a higher total score indicated greater depression as shown in Appendix 4-1. The PHQ-9 is a valid and reliable measure of depression screening in Singapore[38]. Using the cut-off score of 10, the PHQ-9 has a sensitivity of 88% and a specificity of 88% for major depression[35]. We chose values equal to or greater than five as being indicative of symptoms of depression[39,40]. PHQ-9 was a dichotomous variable ('<5' as equivalent to 'minimal depressive symptoms' and '>=5' as 'mild to severe depressive symptoms')

(2) The GAD-7[36] is a seven-item anxiety measure where respondents were asked whether they were bothered by a series of problems in the past two weeks and if so, how often, using a four-point scale from 'not at all' to 'nearly every day'. Individual scores of each item were

summed, and a higher score indicated greater anxiety as shown in Appendix 4-2. Though designed primarily as a screening and severity measure for generalised anxiety disorder, the GAD-7 also has moderately good operating characteristics for three other common anxiety disorders – panic disorder, social anxiety disorder, and post-traumatic stress disorder. Using the threshold score of 10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for generalised anxiety disorder[36]. We chose values equal to or greater than five as being indicative of symptoms of anxiety to account for emotional morbidity[39,40]. GAD-7 was a dichotomous variable ('<5' as equivalent to 'minimal anxiety symptoms' and '>=5' as 'mild to severe anxiety symptoms')

(3a) The EQ-5D-3L[37] is a standardised measure of health status comprising a descriptive system - Utility Index (UI) and a Visual Analogue Scale (VAS).

The Utility Index (UI) assessed five domains (i.e., mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and participants were asked to rate their health on that day of the interview on a three-point scale (no problem/moderate problem/extreme problem). Responses to these five domains were converted into one of 243 different health state descriptions which ranged between no problems on all five dimensions (11111) and severe/extreme problems on all five dimensions (33333). (*Appendix 4-3*)

The utility of EQ-5D health states was originally elicited using the time trade-off method from a representative sample of the United Kingdom general population to value a number of potential EQ–5D states (the time trade-off seeks to establish by how much one would be willing to reduce one's life expectancy in order to obtain full health)[41]. The EQ-5D-3L UI used in this study was based on a representative sample of a Singapore general population that has been validated and ranged from -0.769 to 1.000[42]. Negative values represent health states worse than being dead, '0' representing being dead, and '1.000' representing a state of full health.

(3b) The EQ-5D-3L VAS recorded the participant's self-rated health on a vertical, visual analogue scale where the endpoints were labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0). (*Appendix 4-4*)

2.5 Independent variables

All the demographic information was obtained during the interview. These included the year of birth (age was calculated from the interview date), sex, ethnicity, first language, marital status, education level, housing type, ownership status of current housing, and monthly household income. We obtained the body mass index (BMI) within 12 months before the interview as a continuous variable from the EMR. We measured the level of multimorbidity in four ways – Chronic Disease Control Score (CDCS), Additional Disease Count - Self-Reported (ADC-SR), Additional Disease Count - Electronic Medical Record (ADC-EMR) and Chronic Medication Count (CMC). 'Disease count' and 'Chronic Medication Count' are described in the systematic review of the literature found in Chapter Three of this thesis. We refer to these four measures as the 'instruments for measuring the level of multimorbidity' from hereon. All the instruments for measuring the level of multimorbidity were not pre-existing clinical measurements and were created for this study by referring to the instruments listed in the systematic review in Chapter three. Appendix 4-5 summarises a list of all the independent and outcomes variables.

We grouped the independent variables into the following categories after exploring the data set using SPSS. The age range was grouped into four categories[‡‡‡‡‡] – '< 55', '55-64', '65-74', and '≥ 75' according to the Singapore population census classification[43]. We grouped 'sex' into two categories – 'Male' and 'Female', and 'ethnicity' into two categories – 'Chinese' and 'Non-Chinese'. 'First language' was grouped into four categories – 'English', 'Mandarin', 'Chinese dialects', and 'Others'. 'Marital status' was grouped into two categories – 'Married', and 'Single/Separated/Divorced/Widowed'. 'Education level' was grouped into four categories – 'No formal education', 'Primary', 'Secondary' and 'Post-Secondary'. 'Housing type' was grouped into four categories – 'HDB[§§§§§] 1/2/3 room', 'HDB 4 room', 'HDB 5 room & HUDC[******]', and 'Private Housing'. 'Ownership status of current housing' was grouped into two categories – 'Owner' and 'Non-owner'. Finally, we grouped 'Monthly household

[‡‡‡‡‡] Policymakers in Singapore prefer to have age as a categorical variable instead of a continuous variable

[§§§§§] Housing Development Board (public housing in Singapore) – the type of HDB flat has been used as a proxy for measuring socioeconomic status in Singapore. An HDB 1-room flat is typically about 23 square metres and a HDB 5-room flat is typically about 110 square metres in area.

[******] Housing and Urban Development Company (for Singaporeans who can afford something better than the typical public housing but still find private housing unaffordable)

income' into five categories – '< SGD[††††††] 2,000', 'SGD 2,000-3,999', 'SGD 4,000-5,999', 'SGD ≥ 6,000', and 'Income not disclosed'.

The level of multimorbidity was measured in four ways. The first was CDCS, a composite score on whether all three conditions – hyperlipidaemia[44,45], hypertension[46,45], and diabetes[47,45] were optimally controlled strictly according to each of their respective clinical practice guidelines. The clinical parameters obtained were based on the last single clinical parameter measured that was closest to the date of the interview. This was based on the latest single clinical parameter of glycated haemoglobin (HbA1c) within six months prior to the interview, low-density lipoprotein (LDL-c) within twelve months before or four weeks after the interview, systolic blood pressure (SBP), and diastolic (DBP) recorded in the electronic medical record (EMR) within six months before the interview. CDCS was grouped into four categories – '1','2','3', and '4' (*Appendix 4-6*). '1' means that all of the three conditions (hyperlipidaemia, hypertension and diabetes) were optimally controlled; '2' means that one of the three conditions was sub-optimally controlled and the other two were optimally controlled; '3' means that two of the three conditions were sub-optimally controlled and the other one was optimally controlled; and '4' means that all three conditions were sub-optimally controlled.

The second measure for the level of multimorbidity, the Additional Disease Count - Self-Reported (ADC-SR), was based on the total number of other chronic condition (i.e., excluding hyperlipidaemia, hypertension, and diabetes) that was reported by the participant to the interviewer.

The third measure for the level of multimorbidity, the Additional Disease count – Electronic Medical Records (ADC-EMR), was based on the total number of other chronic condition (i.e., excluding hyperlipidaemia, hypertension, and diabetes) that was ever coded in the EMR of that participant. The list of 15 chronic conditions was based on the Chronic Disease Management Program[‡‡‡‡‡‡] list of chronic conditions stipulated by the Ministry of Health, Singapore in 2014[45] (*Appendix 4-7*). This was one of the two lists of chronic conditions for measuring the prevalence of multimorbidity in Chapter Two of this thesis. We used O'Halloran and colleagues' definition of chronicity of a disease as lasting at least six months, having a

[††††††] SGD – Singapore Dollar (1.00 Singapore dollare = 0.99 Canadian dollar)

[‡‡‡‡‡‡] The number of chronic conditions has increased over the years. There were 18 conditions in 2014 and 20 conditions in 2018. Chapter Two used 20 conditions.

documented pattern of recurrence or deterioration, and having an impact on an individual's quality of life[48].

After exploring the data set using SPSS, we found that the frequency distributions for ADC-SR and ADC-EMR were heavily right-skewed with clustering at 0 (*Appendix 4-8*). As such, they were grouped into three categories – '0',1', and '2 or more' additional chronic conditions.

The fourth measure for the level of multimorbidity, the Chronic Medication Count (CMC), was based on the total number of chronic medications currently prescribed in the EMR. We excluded medications prescribed for acute conditions and also excluded supplements except for patients with known nutritional deficiency recorded in the clinical notes, e.g., iron supplements for patients with anaemia. CMC was a count variable (*Appendix 4-8*).

2.6 Sample size calculation

A regression model was used to answer the primary research hypothesis on whether a higher level of multimorbidity was associated with a higher degree of depression and anxiety symptoms, and a lower quality of life. We also used the same regression model for determining the association between the sociodemographic variables and the outcome variables. We used the 'rules of thumb' for determining sample size for regression equations using six or more predictors[49]. VanVoorhis and Morgan[49] suggested that approximately 30 or more participants per variable would be adequate to achieve 80% power, especially when the dependent variable may be skewed or the effect size expected is small. We decided to use 50 participants per variable to account for the above as the outcome variable (EQ-5D) is expected to be negatively skewed with clustering at '1' for utility index and '80-90' for visual analogue scale[50]. Therefore, a sample size of 700 was required for a regression with 14 independent variables.

For the prevalence of depression and anxiety, the sample size calculation was based on Jani et al.'s[22] report that the prevalence of having depressive and anxiety symptoms in a population with multimorbidity was 24.3% by using the Hospital Anxiety and Depression Score. By using a 5% significance level and 10% total width of confidence interval with an estimated proportion of 25% (round up from 24.3% from Jani et al.'s study), a sample size of 288 was required to estimate the prevalence in this study[51].

For the quality of life outcome, where we determined the mean score of the utility index and visual analogue scale of EQ-5D, the sample size calculation was based on Abdin et al.'s[52] report that the mean EQ-5D index score for the Singapore population was 0.95 with a standard error (SE) of 0.002 and a total sample size of 5,594. From the study, we calculated the standard deviation (SD) using the formula SD=SE*√n (i.e., SD=0.002*√5594=0.150)[51]. Using a total width (W) of the mean EQ-5D UI score as 0.020, the standardized width would be 0.133 (i.e., W/SD = 0.020/0.150=0.133). By using a confidence level of 95%, and a 0.150 standardised width (round up from 0.133), a sample size of 683 was required[51].

Finally, for determining the concordance between self-reported and medical records conditions, the sample size calculation was based on Wu et al.'s[30] report that the concordance rate kappa statistic (κ) between self-reported medical conditions and those recorded in clinical notes ranged between 0.4 to 0.6 (fair to moderate concordance). By using table 3 from Temel and Erdogan's paper[53] on sample size determination in agreement studies, we required a sample size of 847 when we chose a confidence level of 95%, a power of 80% with a disagreement probability of 0.1 based on an expected κ of 0.4.

The largest sample size from all the above calculations was used to account for enough power to answer all the research questions in the study. Taking into account 5% missing data whereby listwise deletion could be safely practiced[54], a sample size of 892 was considered desirable. While it might be decided to conduct multiple imputation, assuming listwise deletion provides a conservative estimate of sample size calculation. We rounded the number up to 900 and assuming a 50% response rate from the respondents, we used a computerised randomisation program and tagged 1800 potential participants in the electronic medical records.

2.7 Statistical Analysis

Descriptive analysis was used to describe the characteristics of the data set. We described the mean and median for continuous variables with their respective standard deviation and interquartile range. For categorical variables, we described proportions. Frequencies, percentages, cross-tabulations, and graphical display were used to present results.

Bivariate analyses were conducted to examine the associations between the outcomes and different instruments for measuring the level of multimorbidity without controlling for each other. Non-parametric tests were used for EQ-5D UI and EQ-5D VAS as they failed the normality tests[56] (*Appendix 4-9*). CMC was considered to have a normal distribution and parametric test was used[55] (*Appendix 4-8*).

We used the chi-square tests to examine the association between the level of multimorbidity (CDCS) with depression (PHQ-9) and anxiety (GAD-7) (*Table 4-7*). The Kruskal Wallis tests were used to examine the association between the level of multimorbidity (CDCS) with the quality of life (EQ-5D UI and EQ-5D VAS) (*Table 4-8*). Chi-square tests were conducted to examine the level of multimorbidity (ADC-SR and ADC-EMR) with depression (PHQ-9) and anxiety (GAD-7) (*Table 4-9*). The Kruskal Wallis tests were used to examine the association between the level of multimorbidity (ADC-SR and ADC-EMR) with the quality of life (EQ-5D UI and EQ-5D VAS) (*Table 4-10*). Student t-tests were used to examine the association between the level of multimorbidity (CMC) with depression (PHQ-9) and anxiety (GAD-7) (*Table 4-11*). Spearman correlation was used to examine the relationship between the level of multimorbidity (CMC) with the quality of life (EQ-5D UI and EQ-5D VAS) (*Table 4-11*). We did not adjust for multiple paired comparisons using Bonferroni adjustment as the main findings were explained by the multivariable regression analyses as described below.

Binary logistic regression was used to test the association between the two outcomes of depression (PHQ-9) and anxiety (GAD-7) and the four instruments for measuring the level of multimorbidity (*Table 4-12*). Linear regression with the log link function was used to test the association between the two quality of life outcomes (EQ-5D UI and EQ-5D VAS) and four instruments for measuring the level of multimorbidity after log transformation[§§§§§§] of EQ-5D UI and EQ-5D VAS (*Table 4-13*). We adjusted all regression analyses for age, sex, and the other eight independent variables including ethnicity, first language, marital status, education level, housing type, ownership status of current housing, monthly household income, and body mass index. We measured multicollinearity for the independent variables by using the variance inflation factor (VIF) which assessed how much the variance of an estimated regression coefficient increased if the predictors were correlated with some of the other independent

[§§§§§§] We log transformed the variables EQ-5D UI and EQ-5D VAS as both variables and their residuals failed the normality tests (*Appendix 4-9*).

variables[57] (*Appendix 4-10*). We used the lower conventional VIF cut-off of greater than five as suggestive for detecting multicollinearity[57].

Concordance for the additional chronic conditions between self-reported and those recorded in electronic medical records was evaluated using Cohen's kappa statistics (κ) (*Table 4-14*). This was a methodological section embedded within the cross-sectional study. Cohen's kappa is a measure that adjusts for the agreement that is expected by chance[58]. However, on its own, a kappa value is not very informative and it is strongly recommended that the positive and negative agreements be presented together[58]. Therefore, we also reported the bias index (BI), prevalence index (PI), and the prevalence-adjusted bias-adjusted kappa (PABAK) as the magnitude of κ is highly influenced by the prevalence of the condition as well as the bias between the two data sources[59].

Statistical significance was defined as $p < 0.05$ and confidence intervals were set at 95% for both bivariate and multivariable analysis. The interpretation for kappa (κ) was based on Landis and Koch's classification[60].

We carried out a sensitivity analysis on the multivariable regression analyses to assess the robustness of the results to probable departures from the missing data assumption made in the main analysis. IBM SPSS version 24 was used for all statistical analysis.

2.8 Handling of missing data

We employed several approaches to look at the extent of missing data, the missing data mechanism and patterns of missing data[61]. First, we used SPSS to find the variables with missing data and also the total number of cases with missing data. We next conducted the Little's test[62] to check for the missing data mechanism to determine whether they were missing completely at random (MCAR). If the missing data were not MCAR, we explored the missingness to make a judgement call on whether they were missing at random (MAR) or missing not at random (MNAR). Finally, we looked at the patterns of missingness to see whether they were monotone (i.e., if a participant drops out at one point, his/her data are missing on subsequent measures) or arbitrary (i.e., random fashion) in nature[63]. Depending on

the above findings, our team would consider using the conventional approach like listwise or pairwise deletion, or the principled method to deal with missing data like multiple imputation[64].

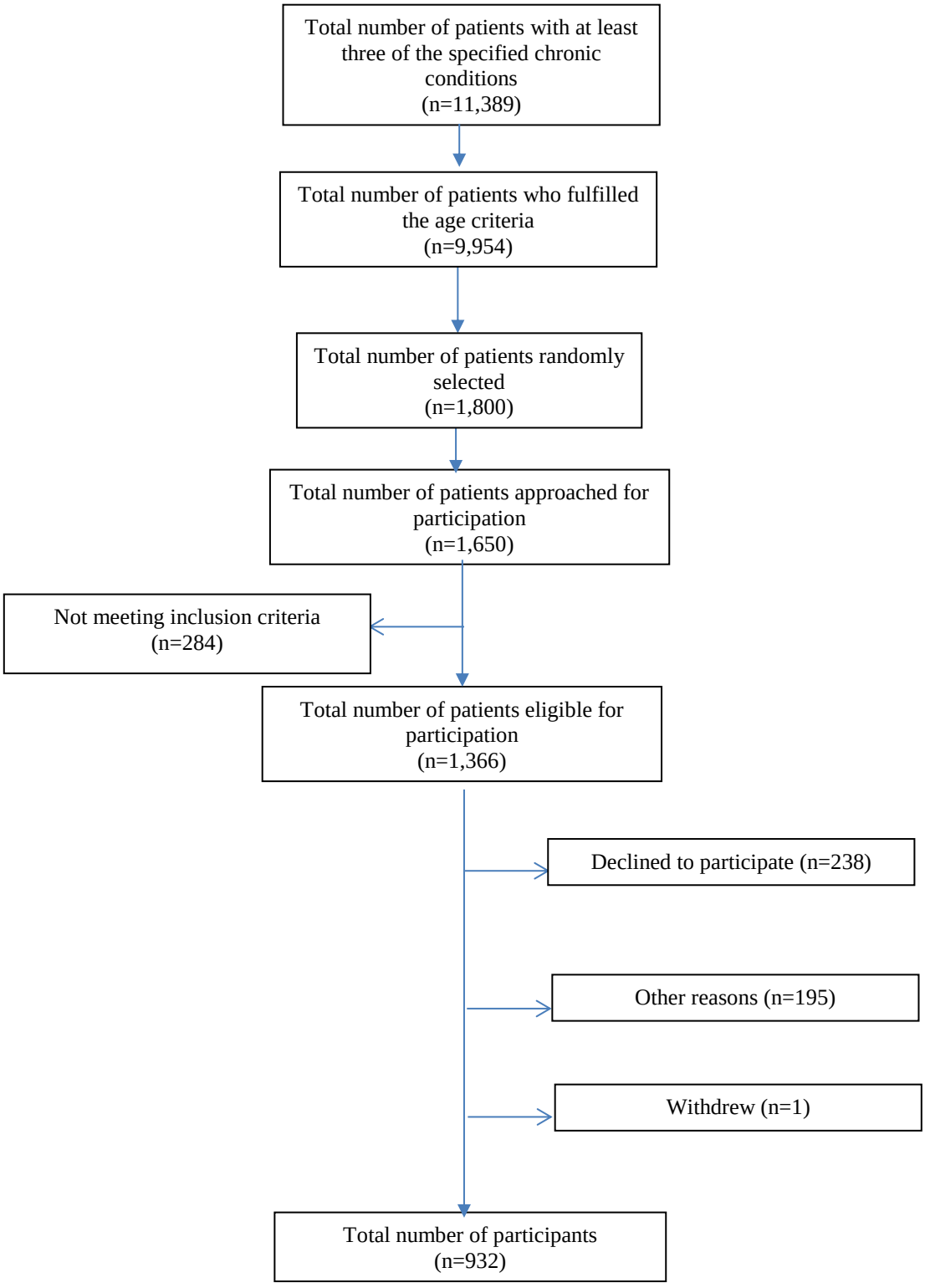
If multiple imputation was used, the number of imputations used would be higher than the percentage of the missing data in the analysis[65] (i.e., if 7.9% of data was missing, the number of imputations used should be eight).

2.9 Subgroup Analysis

We used chi-square tests for comparing proportions to examine the difference between the demographic characteristics of participants who did not disclose their household income with those who declared.

3 Results

Figure 4-1. Flow chart of participant recruitment



3.1 Patient participation

We approached 1,650 potential participants and invited them to participate in this study. There were 284 of these potential participants who were deemed not meeting inclusion criteria leaving 1,366 eligible patients. The main reason was due to the language barrier. Of these 1,366 eligible potential participants, there were 238 patients who refused to participate, 195 patients who were not able to participate due to various reasons (mainly due to inability to get a scheduled appointment for interview), and one patient who withdrew the next day after completing the interview. The final number of participants recruited was 932 out of 1,366 giving a response rate of 68.2%.

Four hundred and thirty-four potential participants did not join the study due to various reasons. We collected the de-identified information of the sex and ethnicity characteristics of all potential participants who declined to take part in the study to detect whether there were differences in characteristics between them and those who participated in the study.

Table 4-1. Demographic Characteristics of patients who Declined participation and patients who were Recruited for the Study

	Declined (n=434)	**Recruited (n=932)**	**p-value^**
Sex			
Male	209 (48.2%)	513 (55.0%)	**0.02***
Female	225 (51.8%)	419 (45.0%)	
Ethnicity			
Chinese	347 (80.0%)	769 (82.5%)	0.56
Malay	33 (7.6%)	70 (7.5%)	
Indian	46 (10.6%)	77 (8.3%)	
Others	8 (1.8%)	16 (1.7%)	

We performed a chi-square test to explore whether there were differences between sex and ethnicity of those who participated and those who did not (*Table 4-1*). The difference between the sex composition was statistically significant ($p = 0.02$). There were significantly more men than women in the study as more women than men declined to participate.

3.2 Missing Values

There were six variables with missing data (*Figure 4-2*), namely monthly household income, BMI, ADC-SR, CDCS due to various missing data of glycated haemoglobin (HbA1c), low-density lipoprotein (LDL-C), and/or blood pressure (BP), housing type, and house ownership (*Table 4-2*). In total, there were 306 participants or 32.8% of the data with missing data from the 932 participants (*Figure 4-3*).

We conducted the Little's test to check for the null hypothesis that all the missing values were missing completely at random (MCAR) using SPSS[62]. The null hypothesis was rejected[*******], and therefore the missing data were not MCAR. As more than 25% of participants did not declare their household income, we assumed that missing data of household income might not be missing at random (MAR). We aggregated all those with missing data for the declaration of household income into one new category - 'Income not disclosed', and treated that as a valid response category in the analysis.

Figure 4-2. Missing data by variables

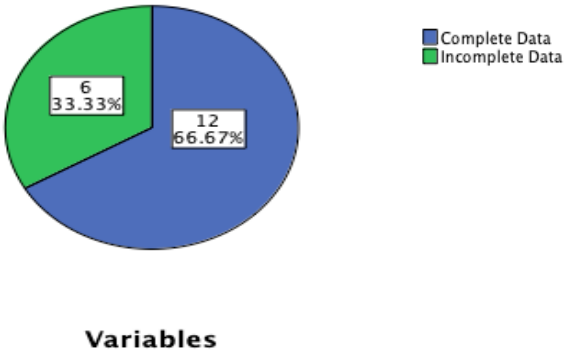
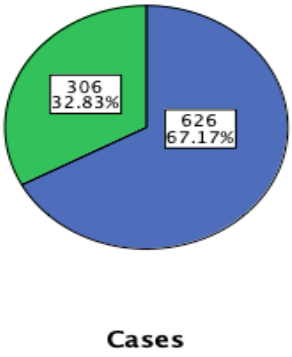


Figure 4-3. Missing data by cases



[*******] The Little's MCAR test showed a Chi-Square value of 117.630 (14), $p < 0.001$

Table 4-2. Predictor Variables with Missing Data

Predictor Variables	Missing Values		Valid N
	N	%	
Monthly Household Income	238	25.5	694
BMI	38	4.1	894
ADC-SR	29	3.1	903
CDCS	19	2.0	913
Housing Type	2	0.2	930
House Ownership	1	0.1	931

After excluding this variable, we repeated the Little's test, and the null hypothesis[†††††††] was again rejected despite having 9.12% (n=85) of all cases having a missing value (Figures 4-4 & 4-5). We explored the missingness of the data and concluded that these missing data were likely to be missing at random (MAR). For example, the missing values for BMI were likely due to sporadic weighing machine downtime that failed to port over the values to the EMR. Consequently, the team concluded that listwise deletion (LD) would introduce bias and multiple imputation (MI) using SPSS would be used for determining the relationship between the level of multimorbidity and depression, anxiety and quality of life. MI was also used to determine the factors associated with the three outcomes. We used MI as it is a powerful statistical tool for handling missing data and have an advantage of including auxiliary information about the missing data into the final analysis[66]. With 9.12% missing data, we performed multiple imputation using ten imputations for all our analyses[65]. For preserving the maximum amount of data collected from all the participants, we described the data in Tables 4-4 and 4-5 using pairwise deletion. We also used pairwise deletion for determining the concordance rate between additional chronic conditions self-reported (ADC-SR) and electronic medical records (ADC-EMR) (*Table 4-14*).

[†††††††] The Little's MCAR test showed a Chi-Square value of 122.372 (14), $p < 0.001$

Figure 4-4. Missing data by variables (excluding Monthly household income)

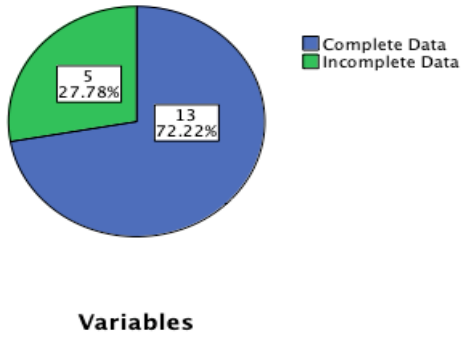


Figure 4-5. Missing data by cases (excluding Monthly household income)

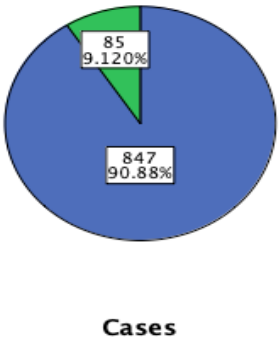


Table 4-3. Predictor Variables (exclusion of Monthly Household Income) with Missing Data

Predictor Variables	Missing Values		Valid N
	N	%	
BMI	38	4.1	894
ADC-SR	29	3.1	903
CDCS	19	2.0	913
Housing Type	2	0.2	930
House Ownership	1	0.1	931

3.3 Descriptive Data

Table 4-4 summarises the sociodemographic characteristics of 932 recruited participants. The median age of the participants was 65.0 years (IQR 58.0 – 71.0). There were more male participants than female participants (55%:45%), and the majority of the participants were of Chinese ethnicity (82.5%). More than 37% of participants used Mandarin, ¼ of them used English with close to another ¼ of them using Chinese dialects as their first language. Close to 80% of the participants were married. Approximately half of them had primary education and below; the other half had secondary education and above. A large majority of them stayed in subsidised housing, and more than 80% of them owned their own homes. The largest group of participants had a household income of less than SGD 2,000. Slightly more than ¼ of the participants did not disclose their monthly household income.

Table 4-5 summarises the clinical parameters and characteristics of the study population. The median body mass index (BMI) was 26.0 kg/m^2 (IQR 23.7 – 28.8). Based on the Asian cut-off of BMI at 23 kg/m^2, 80.3% of the participants were overweight. The median HbA1c was 7.1% (IQR 6.5 – 7.8) with 57.1% of the participants having sub-optimal diabetes control according to the cut-off of 7.0%. The median LDL-C level was 2.20 mmol/L (IQR 1.78 – 2.48) indicating that a large majority of the participants (80.2%) were optimally controlled with a cut-off of 2.6 mmol/L. Blood pressure using a cut-off of 140/80 mmHg showed that 66.1% of the participants were optimally controlled. Using the Chronic Disease Control Score (CDCS) to classify participants into the various levels of multimorbidity based on the four individual biomedical parameters, 235 or 25.7% of the participants had all three conditions optimally controlled (CDCS '1'). The majority (433 or 47.4%) had at least one out of the three chronic conditions that was controlled sub-optimally (CDCS '2').

The mean number of ADC-SR by the participants was 0.7 (SD‡‡‡‡‡‡‡ 0.8), and the mean number identified for ADC-EMR was 1.2 (SD 1.0). The mean number of chronic medication count (CMC) retrieved from the electronic medical records was 4.5 (SD 2.1).

Table 4-6 summarises the proportion of participants that belonged to each category for the outcome variables. The prevalence of participants reporting depressive symptoms was 12.0%. The prevalence of participants reporting anxiety symptoms was 11.8%. The mean EQ-5D UI score for the participants was 0.890 (SD§§§§§§§ 0.190). The median VAS score was 75.0 (IQR 65.0 - 80.0).

‡‡‡‡‡‡‡ SD – standard deviation. The mean instead of the median was presented for easier comparison between ADC-SR and ADC-EMR because median was 1.0 for both the variables due to the skewed frequency distribution.
§§§§§§§ SD – standard deviation. The mean and standard deviation was given for EQ-5D UI as the median was 1.000 due to the ceiling effect of the scale.

Table 4-4. Sociodemographic Characteristics of Recruited Participants

Parameters and Characteristics	Descriptive Statistics	%
Age		
n	932	
Mean ± SD	64.5 ± 8.5	
Median (IQR)	65.0 (58.0 – 71.0)	
<55 years old	115	12.3
55-64 years old	330	35.4
65-74 years old	360	38.6
≥75 years old	127	13.6
Sex		
n	932	100.0
Male	513	55.0
Female	419	45.0
Ethnicity		
n	932	100.0
Chinese	769	82.5
Non-Chinese	163	17.5
Malay	70	7.5
Indian	77	8.3
Others	16	1.7
First Language		
n	932	100.0
English	233	25.0
Mandarin	348	37.3
Chinese Dialects	227	24.4
Others	124	13.3
Marital Status		
n	932	100.0
Married	739	79.3
Single/Separated/Divorced/Widowed	193	20.7
Education Level		
n	932	100.0
No Formal Education	172	18.5
Primary	294	31.5
Secondary	315	33.8
Post-Secondary	151	16.2
Housing Type		
n	930	100.0
HDB 1/2/3 Room	194	20.9
HDB 4 Room	390	41.9
HDB 5 Room/Executive/HUDC	233	25.1
Private Housing	113	12.1
Ownership Status of Current Housing		
n	931	100.0
Owner	766	82.3
Non-Owner	165	17.7
Monthly Household Income		
n	932	100.0
<SGD2,000	340	36.5
SGD2,000 – SGD3,999	160	17.2
SGD4,000 – SGD5,999	99	10.6
≥SGD6,000	95	10.2
Income Not Disclosed	238	25.5

Table 4-5. Clinical Parameters and Characteristics of Recruited Participants

Parameters and Characteristics	Descriptive Statistics	%
Body Mass Index (BMI) (kg/m^2)		
n	894	
Mean ± SD	26.5 ± 4.2	
Median (IQR)	26.0 (23.7, 28.8)	
Normal (<23.0 kg/m^2)	176	19.7
Overweight (≥23.0 kg/m^2)	718	80.3
Glycated Haemoglobin (HbA1c) (%)		
n	930	100.0
Mean ± SD	7.3 ± 1.3	
Median (IQR)	7.1 (6.5, 7.8)	
Optimal Control (<7.0%)	399	42.9
Sup-Optimal Control (≥7.0%)	531	57.1
Low Density Lipoprotein Cholesterol (LDLc) (mmol/L)		
n	915	100.0
Mean ± SD	2.20 ± 0.64	
Median (IQR)	2.20 (1.78, 2.48)	
Optimal Control (<2.6mmol/L)	734	80.2
Sup-Optimal Control (≥2.6mmol/L)	181	19.8
Systolic Blood Pressure (SBP) (mmHg)		
n	931	100.0
Mean ± SD	130 ± 14	
Median (IQR)	130 (120, 138)	
Optimal Control (<140mmHg)	726	78.0
Sup-Optimal Control (≥140mmHg)	205	22.0
Diastolic Blood Pressure (DBP) (mmHg)		
n	931	100.0
Mean ± SD	72 ± 9	
Median (IQR)	70 (66, 78)	
Optimal Control (<80mmHg)	722	77.6
Sup-Optimal Control (≥80mmHg)	209	22.4
Blood Pressure (BP) (mmHg)		
n	931	100.0
Optimal Control	615	66.1
Sup-Optimal Control	316	33.9
Chronic Disease Control Score (CDCS)		
n	913	100.0
Median (IQR)	2 (1, 3)	
1 (All 3 conditions optimally controlled)	235	25.7
2 (1 condition sub-optimally controlled)	433	47.4
3 (2 conditions sub-optimally controlled)	197	21.6
4 (3 conditions sub-optimally controlled)	48	5.3
Additional Disease Count – Self Reported (ADC-SR)		
n	932	100.0
Mean ± SD	0.7 ± 0.8	
Median (IQR)	1.0 (0.0, 1.0)	
0	467	50.1
1	356	38.2
2+	109	11.7
Additional Disease Count – Electronic Medical Records (ADC-EMR)		
n	932	100.0
Mean ± SD	1.2 ± 1.0	
Median (IQR)	1.0 (1.0, 2.0)	
0	230	24.7
1	385	41.3
2+	317	34.0
Chronic Medication Count (CMC)		
n	932	100.0
Mean ± SD	4.5 ± 2.1	
Median (IQR)	4.0 (3.0, 6.0)	

Table 4-6. Outcome Variables Obtained from PHQ-9, GAD-7, EQ-5D Questionnaires of Recruited Participants

Outcome Variables	Frequency (n=932)	%
PHQ-9		
Mean ± SD	1.6 ± 2.7	
Median (IQR)	1.0 (0.0, 2.0)	
Minimal (0-4)	820	88.0
Mild to Severe (5-27)	112	12.0
GAD-7		
Mean ± SD	1.5 ± 3.0	
Median (IQR)	0.0 (0.0, 2.0)	
Minimal (0-4)	822	88.2
Mild to Severe (5-21)	110	11.8
EQ-5D Utility Index (UI)		
Mean ± SD	0.890 ± 0.190	
Median (IQR)	1.000 (0.850, 1.000)	
EQ-5D Visual Analogue Scale (VAS)		
Mean ± SD	73.6 ± 15.5	
Median (IQR)	75.0 (65.0, 80.0)	

3.4 Bivariate Analyses

There were no associations found between Chronic disease count score (CDCS) and depressive symptoms (PHQ-9), and CDCS and anxiety symptoms (GAD-7) (*Table 4-7*). There were also no associations found between CDCS and quality of life for both utility index (EQ-5D UI) and visual analogue scale (EQ-5D VAS) (*Table 4-8*).

A higher number of self-reported additional disease count (ADC-SR) was associated with higher depressive symptoms (PHQ-9) (*Table 4-9*), and with a lower quality of life score for EQ-5D UI (*Table 4-10*). ADC-SR was not associated with anxiety symptoms (GAD-7) (*Table 4-9*) nor EQ-5D VAS (*Table 4-10*). A higher number of additional disease count from the electronic medical records (ADC-EMR) was associated with a lower quality of life (EQ-5D UI) (*Table 4-10*). There were no associations found between ADC-EMR and depressive symptoms (PHQ-9), anxiety symptoms (GAD-7) and EQ-5D VAS (*Table 4-9 & 4-10*).

Chronic medication count (CMC) was not associated with depressive nor anxiety symptoms (*Table 4-11*). Although a weak negative correlation was noted between CMC and quality of life (both EQ-5D UI and EQ-5D VAS), statistical significance was not reached (*Table 4-11*).

Table 4-7. Effect of Chronic Disease Count Score on Depression and Anxiety (n=932)

Outcome	Chronic Disease Count Score (CDCS)				p-value*
	1	2	3	4	
PHQ-9	n	n	n	n	
Minimal	209	384	181	46	
Mild to Severe	30	57	21	4	0.58
% of mild to severe depression	12.6%	12.9%	10.4%	8.0%	
GAD-7					
Minimal	212	390	175	45	0.74
Mild to Severe	27	51	28	4	
% of mild to severe anxiety	11.3%	11.6%	13.8%	8.2%	

[s]p-value was obtained from chi-square test comparing between CDCS and PHQ-9 or GAD-7. *p<0.05 is considered statistically significant

Table 4-8. Effect of Chronic Disease Count Score on Quality of Life (n=932)

Outcome	Chronic Disease Count Score (CDCS)				p-value*
	1	2	3	4	
EQ5D-UI					
n	239	441	202	50	0.09
Mean Rank	452.23	479.91	442.41	514.49	
EQ5D-VAS					
n	239	441	202	50	0.61
Mean Rank	448.17	474.79	465.90	483.74	

[x]p-value was obtained from Kruskall-Wallis test comparing between CDCS and ED5D-UI or EQ5D-VAS. *p<0.05 is considered statistically significant.

Table 4-9. Effect of Additional Disease Count on Depression and Anxiety (n=932)

Outcome	Level of Multimorbidity Measures							
	ADC-SR				ADC-EMR			
	0	1	≥2	p-value	0	1	≥2	p-value
	n	n	n		n	n	n	
PHQ-9								
Minimal	425	312	84	**<0.01***	209	340	271	0.16
Mild to Severe	42	44	25		21	45	46	
% of mild to severe depression	9.0%	12.4%	22.9%		9.1%	11.7%	14.5%	
GAD-7								
Minimal	415	318	89	0.07	194	348	280	0.08
Mild to Severe	52	38	20		36	37	37	
% of mild to severe anxiety	11.1%	10.7%	18.4%		15.7%	9.6%	11.7%	

[ˇ]p-value was obtained from chi-square test between ADC-SR or ADC-EMR and PHQ-9 or GAD-7, [ˆ]p-value was obtained from t-test comparing between CMC and PHQ-9 or GAD-7; **p<0.05 is considered statistically significant.

Table 4-10. Effect of Additional Disease Count on Depression, Anxiety and Quality of Life (n=932)

Outcome	Level of Multimorbidity Measures							
	ADC-SR				ADC-EMR			
EQ5D-UI	0	1	≥2	p-value[#]	0	1	≥2	p-value[#]
n	467	356	109	**<0.01***	230	385	317	**<0.01***
Mean Rank	518.91	434.50	346.58		499.43	485.05	420.08	
EQ5D-VAS								
n	467	356	109	0.37	230	385	317	0.384
Mean Rank	474.54	465.53	435.18		472.20	476.81	449.85	

p-value was obtained from Kruskall-Wallis test comparing between ADC-SR or ADC-EMR and EQ5D-UI or EQ5D-VAS, *p<0.05 is considered statistically significant.

Table 4-11. Effect of Chronic Medication Count on Quality of Life (n=932)

Outcome	Chronic Medication Count			
	n	Mean	Correlation coefficient (Rho)	p-value*
PHQ-9				
Minimal	820	4.51	NA	0.40
Mild to Severe	112	4.69		
GAD-7				
Minimal	822	4.51	NA	0.37
Mild to Severe	110	4.68		
EQ5D-UI	NA	NA	-0.054	0.10
EQ5D-VAS	NA	NA	-0.060	0.07

*p-value was obtained from t-test comparing between CMC and PHQ-9 or GAD-7, and p-value was obtained from Spearman's Correlation test comparing between CMC and EQ5D-UI or EQ5D-VAS. *p<0.05 is considered statistically significant.

3.5 Multivariable Regression Analysis

We measured multicollinearity for the independent variables by using the variance inflation factor (VIF) which assessed how much the variance of an estimated regression coefficient increased if the predictors were correlated with some of the other independent variables[57]. The VIFs obtained were around 1.000, and therefore, we retained all the independent variables in the regression analysis (*Appendix 4-10*).

3.5.1 Depression and Anxiety

Logistic regression was performed to assess the impact of several factors on the likelihood that participants would report that they had a problem with depressive symptoms (*Table 4-12*). Only two of the independent variables made a unique statistically significant contribution to

the model: marital status; and ADC-SR. This indicated that participants who were single/separated/divorced/widowed had 1.69 times greater odds of reporting a higher score for depressive symptoms using the PHQ-9 scale compared to those who were married (p=0.048). Participants who self-reported two or more additional chronic conditions had 3.09 times greater odds of reporting a higher score for depressive symptoms than those who did not report any additional chronic conditions ($p < 0.01$).

Another logistic regression was conducted to assess the impact of the 14 predictor variables on the likelihood that participants would report that they had a problem with anxiety symptoms (*Table 4-12*). Two of the independent variables made a unique statistically significant contribution to the model – ADC-SR and ADC-EMR. Participants who self-reported two or more additional chronic conditions had 2.07 times greater odds of reporting a higher score for anxiety symptoms than those who did not report any additional chronic conditions (p=0.02). However, participants who had one additional chronic condition recorded in their electronic medical records had lower odds of reporting a lower score for anxiety symptoms using the GAD-7 scale than those who had no additional chronic conditions recorded in their notes (OR=0.53, p=0.02).

Table 4-12. The Effect of Sociodemographic and Clinical Predictor Variables on Depression and Anxiety of Recruited Participants (n=932)

Predictor Variables	PHQ9			GAD7		
	Odds Ratio^	**95% CI^**	**p-value^**	**Odds Ratio^**	**95% CI^**	**p-value^**
Age						
<55 years old	REF			REF		
55-64 years old	1.62	0.73, 3.60	0.24	0.93	0.49, 1.79	0.84
65-74 years old	1.14	0.50, 2.61	0.75	0.71	0.35, 1.43	0.34
≥75 years old	1.61	0.61, 4.21	0.33	0.91	0.37, 2.23	0.84
Sex						
Male	REF			REF		
Female	0.90	0.57, 1.40	0.63	1.18	0.75, 1.85	0.47
Ethnicity						
Chinese	REF			REF		
Non-Chinese	0.92	0.33, 2.57	0.87	0.63	0.23, 1.72	0.37
First Language						
English	REF			REF		
Mandarin	0.84	0.45, 1.58	0.59	0.74	0.40, 1.36	0.33
Chinese Dialects	0.87	0.43, 1.77	0.70	0.56	0.27, 1.16	0.12
Others	1.41	0.48, 4.18	0.53	1.89	0.66, 5.44	0.24
Marital Status						
Married	REF			REF		
Single/Separated/Divorced/Widowed	1.69	1.01, 2.85	**0.048***	1.66	0.98, 2.82	0.06
Education Level						
No Formal Education	REF			REF		
Primary	1.12	0.62, 2.04	0.71	1.09	0.58, 2.03	0.80
Secondary	0.72	0.36, 1.42	0.34	0.53	0.26, 1.09	0.08
Post-Secondary	0.49	0.19, 1.23	0.13	0.73	0.31, 1.74	0.48
Housing Type						
HDB 1/2/3 Room	REF			REF		
HDB 4 Room	0.68	0.40, 1.14	0.14	0.79	0.45, 1.40	0.42
HDB 5 Room/HUDC	0.70	0.37, 1.33	0.28	1.39	0.74, 2.58	0.30
Private Housing	0.84	0.37, 1.94	0.69	0.86	0.35, 2.09	0.73
Ownership Status of Current Housing						
Owner	REF			REF		
Non-Owner	1.11	0.64, 1.93	0.71	0.86	0.47, 1.56	0.61
Monthly Household Income						
<SGD2,000	REF			REF		
SGD2,000 – SGD3,999	1.07	0.59, 1.95	0.83	1.58	0.88, 2.82	0.12
SGD4,000 – SGD5,999	1.17	0.52, 2.60	0.71	0.97	0.44, 2.13	0.93
≥SGD6,000	1.45	0.66, 3.17	0.35	1.23	0.56, 2.72	0.61
Income not disclosed	0.63	0.35, 1.12	0.11	0.82	0.45, 1.48	0.51

^Odds ratio, 95% CI and p-values were obtained from logistic regression; REF – reference group; *p<0.05 is considered statistically significant.

Table 4-12. The Effect of Sociodemographic and Clinical Predictor Variables on Depression and Anxiety of Recruited Participants (n=932) (continued)

Predictor Variables	PHQ9			GAD7		
	Odds Ratio^	**95% CI^**	**p-value^**	**Odds Ratio^**	**95% CI^**	**p-value^**
Body Mass Index (BMI)	0.97	0.92, 1.02	0.26	1.01	0.96, 1.06	0.78
Chronic Disease Control Score (CDCS)						
1 (All 3 conditions optimally controlled)	REF			REF		
2 (1 condition sub-optimally controlled)	1.15	0.69, 1.91	0.59	1.06	0.62, 1.80	0.83
3 (2 conditions sub-optimally controlled)	0.83	0.43, 1.58	0.57	1.06	0.57, 1.97	0.86
4 (3 conditions sub-optimally controlled)	0.51	0.15, 1.68	0.27	0.63	0.20, 1.99	0.43
Additional Disease Count – Self Reported (ADC-SR)						
0	REF			REF		
1	1.36	0.84, 2.20	0.21	1.05	0.65, 1.69	0.85
2+	3.09	1.71, 5.58	**<0.01***	2.07	1.12, 3.84	**0.02***
Additional Disease Count – Electronic Medical Records (ADC-EMR)						
0	REF			REF		
1	1.11	0.62, 1.99	0.72	0.53	0.31, 0.90	**0.02***
2+	1.16	0.62, 2.14	0.65	0.61	0.34, 1.07	0.09
Chronic Medication Count (CMC)	1.04	0.94, 1.16	0.43	1.06	0.95, 1.18	0.33

^Odds ratio, 95% CI and p-values were obtained from logistic regression; REF – reference group; *p<0.05 is considered statistically significant.

3.5.2 Quality of Life (EQ-5D UI and EQ-5D VAS)

We conducted a linear regression with log link function to explore the impact of using the same predictor variables with the quality of life (EQ-5D UI) as the dependent variable (*Table 4-13*).

There were four independent predictors with a statistically significant lower quality of life score. Participants who were 75 years old and above were more likely to report a lower UI score compared to those younger than 55 years old (p=0.03). Those who received primary educational level were more likely to report a lower UI score compared to those who had no formal education (p=0.01). A higher body mass index was associated with a lower UI score (p=0.01). Finally, participants who reported one or more additional chronic conditions were more likely to report a lower UI score when compared with those who did not self-report any additional chronic conditions (one condition, $p < 0.01$; and two or more conditions, $p < 0.01$).

There were two independent predictors that were associated with a statistically significant higher quality of life score. Participants who stayed in private housing were more likely to report a higher UI score as compared to those who stayed in the smallest public housing (p=0.03). Participants who had all three chronic conditions (hyperlipidaemia, hypertension, and diabetes) sub-optimally controlled also reported a higher UI score when compared to those participants who had all three chronic conditions optimally controlled (p=0.03).

We conducted a second linear regression with log link function to explore the impact of using the same predictor variables with the quality of life (EQ-5D VAS) as the dependent variable (*Table 4-13*). There were three independent predictors with a statistically significant lower quality of life.

Participants who had higher education were more likely to report a lower VAS score compared to those who had no formal education ($p < 0.01$ for all three categories). The trend seemed to suggest that the higher the education, the lower the VAS score. Participants who did not disclose their income also reported lower VAS score when compared to those who earned less than SGD 2,000 ($p < 0.01$). A higher chronic medication count was associated with a lower VAS score (p=0.02).

Table 4-13. The Effect of Sociodemographic and Clinical Predictor Variables on Quality of Life of Recruited Participants (n=932)

Predictor Variables	EQ5D-UI					EQ5D-VAS				
	Unadjusted Mean (SD)	Adjusted Mean (SE)	Beta Coefficient^	95% CI^	p-value^	Unadjusted Mean (SD)	Adjusted Mean (SE)	Beta Coefficient^	95% CI^	p-value^
Age										
<55 years old	0.910 (0.177)	0.883 (0.021)	REF			72.3 (17.1)	74.2 (1.7)	REF		
55-64 years old	0.899 (0.169)	0.881 (0.016)	-0.002	-0.045, 0.042	0.94	72.6 (14.8)	74.2 (1.3)	-0.001	-0.045, 0.044	0.98
65-74 years old	0.895 (0.194)	0.877 (0.015)	-0.007	-0.053, 0.039	0.77	74.1 (15.6)	75.2 (1.3)	0.014	-0.033, 0.061	0.57
≥75 years old	0.837 (0.241)	0.825 (0.020)	-0.068	-0.128, -0.008	**0.03***	75.9 (15.0)	76.6 (1.8)	0.032	-0.027, 0.090	0.29
Sex										
Male	0.904 (0.192)	0.877 (0.015)	REF			72.3 (14.7)	74.4 (1.2)	REF		
Female	0.873 (0.190)	0.856 (0.014)	-0.025	-0.053, 0.004	0.09	75.1 (16.3)	75.7 (1.2)	0.018	-0.010, 0.046	0.22
Ethnicity										
Chinese	0.893 (0.194)	0.861 (0.015)	REF			73.2 (15.2)	73.1 (1.2)	REF		
Non-Chinese	0.877 (0.180)	0.871 (0.022)	0.012	-0.050, 0.073	0.71	75.4 (16.7)	77.1 (2.0)	0.054	-0.008, 0.116	0.09
First Language										
English	0.922 (0.140)	0.877 (0.018)	REF			71.3 (15.0)	74.7 (1.5)	REF		
Mandarin	0.892 (0.206)	0.875 (0.019)	-0.003	-0.040, 0.035	0.89	73.8 (14.6)	76.4 (1.7)	0.022	-0.017, 0.061	0.27
Chinese Dialects	0.872 (0.212)	0.867 (0.021)	-0.011	-0.056, 0.033	0.61	74.5 (15.8)	74.8 91.8)	0.000	-0.045, 0.045	0.99
Others	0.862 (0.191)	0.846 (0.023)	-0.036	-0.103, 0.031	0.29	75.7 (17.4)	74.4 (2.0)	-0.005	-0.071, 0.061	0.89
Marital Status										
Married	0.899 (0.187)	0.853 (0.017)	REF			73.4 (15.2)	75.3 (1.2)	REF		
Single/Separated/Divorced/Widowed	0.857 (0.206)	0.880 (0.014)	-0.031	-0.067, 0.005	0.10	74.5 (16.2)	74.8 (1.4)	-0.008	-0.043, 0.027	0.67
Education Level										
No Formal Education	0.883 (0.172)	0.886 (0.020)	REF			79.8 (17.2)	81.9 (1.7)	REF		
Primary	0.855 (0.243)	0.839 (0.016)	-0.055	-0.096, -0.014	**0.01***	73.0 (16.1)	74.7 (1.4)	-0.092	-0.130, -0.053	**<0.01***
Secondary	0.912 (0.155)	0.871 (0.016)	-0.017	-0.061, 0.027	0.44	72.3 (13.6)	73.4 (1.3)	-0.11	-0.153, -0.068	**<0.01***
Post-Secondary	0.922 (0.156)	0.869 (0.019)	-0.019	-0.073, 0.035	0.49	70.3 (13.7)	70.7 (1.6)	-0.147	-0.202, -0.093	**<0.01***
Housing Type										
HDB 1/2/3 Room	0.864 (0.230)	0.844 (0.017)	REF			73.7 (15.8)	73.7 (1.5)	REF		
HDB 4 Room	0.886 (0.183)	0.860 (0.015)	0.019	-0.018, 0.055	0.31	74.1 (14.8)	75.1 (1.3)	0.019	-0.017, 0.054	0.30
HDB 5 Room/HUDC	0.899 (0.193)	0.866 (0.016)	0.026	-0.016, 0.068	0.23	73.4 (16.7)	75.9 (1.4)	0.029	-0.012, 0.070	0.17
Private Housing	0.935 (0.132)	0.895 (0.021)	0.059	0.007, 0.111	**0.03***	72.4 (14.6)	75.6 (1.9)	0.026	-0.027, 0.079	0.34

^Beta coefficient, 95% CI and p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 are considered statistically significant

Table 4-13. The Effect of Sociodemographic and Clinical Predictor Variables on Quality of Life of Recruited Participants (n=932) (continued)

Predictor Variables	EQ5D-UI					EQ5D-VAS				
	Unadjusted Mean (SD)	**Adjusted Mean (SE)**	**Beta Coefficient^**	**95% CI^**	**p-value^**	**Unadjusted Mean (SD)**	**Adjusted Mean (SE)**	**Beta Coefficient^**	**95% CI^**	**p-value^**
Ownership Status of Current Housing										
Owner	0.899 (0.176)	0.866 (0.014)	REF			73.3 (15.0)	74.6 (1.1)	REF		
Non-Owner	0.849 (0.250)	0.866 (0.018)	0.000	-0.039, 0.039	0.99	74.7 (17.4)	75.6 (1.5)	0.013	-0.024, 0.051	0.49
Monthly Household Income										
<SGD2,000	0.887 (0.198)	0.877 (0.015)	REF			75.8 (15.3)	76.6 (1.3)	REF		
SGD2,000 – SGD3,999	0.903 (0.140)	0.872 (0.019)	-0.005	-0.045, 0.034	0.80	72.1 (15.0)	73.8 (1.6)	-0.036	-0.076, 0.004	0.08
SGD4,000 – SGD5,999	0.930 (0.140)	0.876 (0.021)	0.000	-0.048, 0.047	0.99	74.1 (13.7)	76.9 (1.9)	0.005	-0.044, 0.053	0.86
≥SGD6,000	0.918 (0.158)	0.859 (0.022)	-0.020	-0.070, 0.030	0.43	72.7 (15.0)	76.3 (2.0)	-0.003	-0.054, 0.048	0.91
Income not disclosed	0.859 (0.235)	0.847 (0.016)	-0.035	-0.071, 0.001	0.06	71.6 (16.5)	71.8 (1.4)	-0.065	-0.100, -0.030	**<0.01***
Body Mass Index (BMI)	NA	NA	-0.006	-0.010, -0.002	**0.01***	NA	NA	-0.002	-0.006, 0.001	0.24
Chronic Disease Control Score (CDCS)										
1 (All 3 conditions optimally controlled)	0.874 (0.230)	0.846 (0.016)	REF			72.5 (15.6)	73.2 (1.3)	REF		
2 (1 condition sub-optimally controlled)	0.901 (0.181)	0.864 (0.014)	0.022	-0.012, 0.055	0.20	73.9 (15.5)	75.4 (1.2)	0.031	-0.003, 0.064	0.07
3 (2 conditions sub-optimally controlled)	0.878 (0.178)	0.851 (0.017)	0.006	-0.035, 0.047	0.77	73.9 (15.3)	75.8 (1.4)	0.035	-0.005, 0.075	0.08
4 (3 conditions sub-optimally controlled)	0.940 (0.099)	0.905 (0.027)	0.068	0.006, 0.130	**0.03***	74.9 (16.4)	75.9 (2.3)	0.037	-0.027, 0.101	0.26
Additional Disease Count – Self Reported (ADC-SR)										
0	0.929 (0.145)	0.920 (0.015)	REF			73.6 (15.5)	75.8 (1.2)	REF		
1	0.865 (0.214)	0.871 (0.015)	-0.056	-0.085, -0.026	**<0.01***	73.2 (15.4)	75.3 (1.3)	-0.006	-0.036, 0.024	0.72
2+	0.802 (0.251)	0.811 (0.020)	-0.127	-0.174, -0.080	**<0.01***	71.8 (15.1)	74.1 (1.7)	-0.023	-0.068, 0.023	0.33
Additional Disease Count – Electronic Medical Records (ADC-EMR)										
0	0.925 (0.120)	0.878 (0.017)	REF			73.8 (15.5)	75.5 (1.5)	REF		
1	0.902 (0.182)	0.874 (0.015)	-0.004	-0.038, 0.029	0.79	74.2 (15.4)	75.6 (1.3)	0.001	-0.032, 0.035	0.93
2+	0.851 (0.235)	0.847 (0.015)	-0.036	-0.074, 0.002	0.07	72.7 (15.5)	74.0 (1.3)	-0.020	-0.058, 0.017	0.29
Chronic Medication Count (CMC)	NA	NA	-0.005	-0.012, 0.001	0.13	NA	NA	-0.008	-0.015, -0.001	**0.02***

^Beta coefficient, 95% CI and p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 is considered statistically significant

3.6 Concordance of self-reported additional chronic conditions and those recorded in Electronic Medical Records (EMR)

We explored the agreement between self-reported additional chronic conditions and those recorded in the electronic medical records by using kappa statistics in SPSS (*Table 4-14*). We excluded 29 cases with missing data in this analysis.

We considered κ values of < 0.20 as slight, 0.21 - 0.40 as fair, 0.41 - 0.60 as moderate, 0.61 – 0.80 as substantial, and 0.81 – 1.00 as almost perfect according to the Landis and Koch's classification[60]. Out of fifteen conditions, ten of them showed a statistically significant difference in the concordance rate between self-reported conditions and those reported in the EMR. Stroke was the only condition that had substantial agreement with a concordance rate (κ) of 0.61. Parkinson's disease, Schizophrenia, and Asthma had a moderate agreement with a concordance rate (κ) of 0.44, 0.43, and 0.42 respectively. Dementia and Major Depression had a fair agreement with a concordance rate (κ) of 0.31 and 0.27 respectively. Osteoporosis, Anxiety, Osteoarthritis, and Chronic Kidney Disease (CKD) had a slight agreement with a concordance rate (κ) of 0.13, 0.10, 0.06, and 0.01 respectively. Benign prostate hypertrophy, Rheumatoid Arthritis, and Bipolar Disorder had no agreement and were not statistically significant. The concordance rate was not calculated for COPD and Psoriasis as no patients self-reported the former condition and the EMR did not record any participant for the latter condition.

The positive agreement ranged from 0.04 to 0.65 for the ten conditions that were found to have a p-value for prevalence-adjusted bias-adjusted kappa (PABAK) < 0.05. The negative agreement ranged from 0.58 to 1.00. In general, κ was aligned with the positive and negative agreement. However, PABAK was very different ranging from -0.18 to 0.99. κ was consistently lower than PABAK with the difference ranging from 0.19 (chronic kidney disease) to 0.86 (anxiety).

Table 4-14. Concordance of Additional Disease Count between Self-Reported and Electronic Medical Records of Recruited Participants (n=903)

		ADC-EMR						Positive Agreement	Negative Agreement	Kappa	Bias Index	Prevalence Index	PABAK	p-value for PABAK
		No	%	Yes	%	Total	%							
Stroke								0.65	0.96	0.61	0.06	0.78	0.84	**<0.01***
ADC-SR	No	769	85.2	62	6.9	831	92.0							
	Yes	8	0.9	64	7.1	72	8.0							
	Total	777	86.0	126	14.0	903	100.0							
Parkinson's Disease								0.44	1.00	0.44	0.00	0.99	0.99	**<0.01***
ADC-SR	No	896	99.2	3	0.3	899	99.6							
	Yes	2	0.2	2	0.2	4	0.4							
	Total	898	99.4	5	0.5	903	100.0							
Schizophrenia								0.43	1.00	0.43	0.01	0.98	0.98	**<0.01***
ADC-SR	No	892	98.8	7	0.8	899	99.6							
	Yes	1	0.1	3	0.3	4	0.4							
	Total	893	98.9	10	1.1	903	100.0							
Asthma								0.44	0.98	0.42	0.01	0.92	0.91	**<0.01***
ADC-SR	No	847	93.8	14	1.6	861	95.3							
	Yes	26	2.9	16	1.8	42	4.7							
	Total	873	96.7	30	3.3	903	100.0							
Dementia								0.31	0.99	0.31	0.01	0.99	0.98	**<0.01***
ADC-SR	No	892	98.8	9	1.0	901	99.8							
	Yes	0	0.0	2	0.2	2	0.2							
	Total	892	98.8	11	1.2	903	100.0							
Major Depression								0.29	0.98	0.27	0.02	0.95	0.93	**<0.01***
ADC-SR	No	867	96.0	23	2.5	890	98.6							
	Yes	7	0.8	6	0.7	13	1.4							
	Total	874	96.8	29	3.2	903	100.0							
Osteoporosis								0.14	0.98	0.13	0.02	0.95	0.92	**<0.01***
ADC-SR	No	864	95.7	28	3.1	892	98.8							
	Yes	8	0.9	3	0.3	11	1.2							
	Total	872	96.6	31	3.4	903	100.0							
Anxiety								0.11	0.99	0.10	0.01	0.98	0.96	**<0.01***
ADC-SR	No	885	98.0	11	1.2	896	99.2							
	Yes	6	0.7	1	0.1	7	0.8							
	Total	891	98.7	12	1.3	903	100.0							

kappa< 0 no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement. *p<0.05 is considered statistically significant.

Table 4-14. Concordance of Additional Disease Count between Self-Reported and Electronic Medical Records of Recruited Participants (n=903)(Continued)

		ADC-EMR						Positive Agreement	Negative Agreement	Kappa	Bias Index	Prevalence Index	PABAK	p-value for PABAK
		No	%	Yes	%	Total	%							
Osteoarthritis								0.10	0.93	0.06	0.10	0.86	0.75	**0.01***
ADC-SR	No	783	86.7	102	11.3	885	98.0							
	Yes	12	1.3	6	0.7	18	2.0							
	Total	795	88.0	108	12.0	903	100.0							
CKD								0.04	0.58	0.01	0.59	0.39	-0.18	**0.03***
ADC-SR	No	361	40.0	530	58.7	891	89.7							
	Yes	1	0.1	11	1.2	12	1.3							
	Total	362	40.1	541	59.9	903	100.0							
Benign Prostate Hypertrophy								0.06	0.98	0.04	0.00	0.96	0.93	0.22
ADC-SR	No	870	96.3	17	1.9	887	98.2							
	Yes	15	1.7	1	0.1	16	1.8							
	Total	885	98.0	18	2.0	903	100.0							
Rheumatoid Arthritis								0.04	0.97	0.03	0.05	0.94	0.89	0.07
ADC-SR	No	853	94.5	3	0.3	856	94.8							
	Yes	46	5.1	1	0.1	47	5.2							
	Total	899	99.6	4	0.4	903	100.0							
Bipolar Disorder								0.00	1.00	-0.002	0.00	1.00	0.99	NA
ADC-SR	No	899	99.6	2	0.2	901	99.8							
	Yes	2	0.2	0	0.0	2	0.2							
	Total	901	99.8	2	0.2	903	100.0							
COPD								0.00	0.99	NA	0.02	0.98	0.97	NA
ADC-SR	No	889	98.4	14	1.6	903	100.0							
	Yes	0	0.0	0	0.0	0	0.0							
	Total	889	98.4	14	1.6	903	100.0							
Psoriasis								0.00	1.00	NA	0.00	1.00	0.99	NA
ADC-SR	No	899	99.6	0	0.0	899	99.6							
	Yes	4	0.4	0	0.0	4	0.4							
	Total	903	100.0	0	0.0	903	100.0							

kappa< 0 no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement. *p<0.05 is considered statistically significant.

3.7 Subgroup Analysis

We examined the difference in demographic characteristics between those who did not disclose their household income with those who did using a chi-square test (*Table 4-15*). Six of the eight demographic variables showed statistically significant differences.

Table 4-15. Sociodemographic and Clinical Characteristics of Recruited Participants Who Declared or Refused to Declare Monthly Household Income

Predictor Variables	Declared Household Income (n=694)		Refused to Declare Household Income (n=238)		p-value^
	n	%	n	%	
Age					
<55 years old	98	14.1	17	7.1	
55-64 years old	265	38.2	65	27.3	
65-74 years old	256	36.9	104	43.7	**<0.01***
≥75 years old	75	10.8	52	21.8	
Sex					
Male	411	59.2	102	42.9	
Female	283	40.8	136	57.1	**<0.01***
Ethnicity					
Chinese	548	79.0	221	92.9	
Non-Chinese	146	21.0	17	7.1	**<0.01***
First Language					
English	193	27.8	40	16.8	
Mandarin	249	35.9	99	41.6	
Chinese Dialects	140	20.2	87	36.6	**<0.01***
Others	112	16.1	12	5.0	
Marital Status					
Married	558	80.4	181	76.1	
Single/Separated/Divorced/Widowed	136	19.6	57	23.9	0.15
Education Level					
No Formal Education	107	15.4	65	27.3	
Primary	205	29.5	89	37.4	
Secondary	253	36.5	62	26.1	**<0.01***
Post-Secondary	129	18.6	22	9.2	
Housing Type					
HDB 1/2/3 Room	146	21.0	48	20.2	
HDB 4 Room	292	42.1	98	41.2	
HDB 5 Room/HUDC	178	25.6	55	23.1	0.40
Private Housing	77	11.1	36	15.1	
Ownership Status of Current Housing					
Owner	602	86.7	164	68.9	
Non-Owner	91	13.1	74	31.1	**<0.01***

^ p-values were obtained from chi-square tests; *p<0.05 is considered statistically significant.

Those who did not disclose their household income were more likely to be older, be women rather than men, be of Chinese ethnicity, use Mandarin and Chinese dialects as their first language, have no formal or only primary education, and more likely not to own their current housing.

3.8 Sensitivity Analysis

We carried out a sensitivity analysis by comparing the different methods of dealing with missing data on the multivariable regression analysis for the four outcome variables. We considered the use of listwise deletion because a large enough sample was available, the listwise deletion method was not prone to Type 1 error, the method was simple, and it provided 'factual' standard errors that reflected the actual amount of information obtained from the study[54,67]. Furthermore, the regression analysis would have chosen listwise deletion by default as SPSS software would delete cases with any missing data on the variables of interest for complete case analysis or listwise deletion[67].

Therefore, regression analyses were conducted using listwise deletion. The two tables in Appendix 4-11 show the full multivariable regression for complete case analysis of 847 participants. Multiple imputation and listwise deletion provided exactly similar analysis results for three outcome variables PHQ-9, GAD-7, and EQ-5D VAS. However, for EQ-5D UI, there were four discrepancies. Conflicting results are compared in Tables 4-16 & 4-17 to that found with multiple imputation (*Tables 4-12 & 4-13*).

Using the multiple imputation method, age group (p=0.03) and chronic disease control score (CDCS) (p=0.03) were found to be associated with EQ-5D UI score but the listwise deletion method did not pick up these two predictor variables (*Table 4-16*).

The listwise deletion method also picked up two other predictor variables that were negatively associated with EQ-5D UI. These two variables were sex (p=0.09) and marital status (p=0.10) which were not picked up by the multiple imputation method (*Table 4-17*). We noted that the mean EQ-5D UI score for male and female participants who were excluded from the listwise deletion method (n=85) was 0.721 and 0.842 respectively. For the same group of participants

who were excluded from the listwise deletion, the mean EQ-5D UI score for those who were married and those who were not married were 0.764 and 0.831 respectively (*Table 4-17*).

Table 4-16. Two variables where Multiple Imputation method showed significant p-value but not Listwise Deletion method

Variables	n = 932			n = 847		
	EQ-5D UI Unadjusted mean (Multiple Imputation)	Beta-Coefficient	p-value^	EQ-5D UI Unadjusted mean (Listwise Deletion)	Beta-Coefficient	p-value^
Age						
< 55 years old	0.910	REF	REF	0.900	REF	REF
≥ 75 years old	0.837	-0.068	0.03*	0.869	-0.039	0.15
Chronic Disease Control Score						
1 (All conditions optimally controlled)	0.874	REF	REF	0.894	REF	REF
4 (All conditions not optimally controlled)	0.940	0.068	0.03*	0.939	0.047	0.08

^ p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 is considered statistically significant.

Table 4-17. Two variables where Listwise Deletion method showed significant p-value but not Multiple Imputation method

Variables	n = 932			n = 847			n = 85
	EQ-5D UI Unadjusted mean (Multiple Imputation)	Beta-Coefficient	p-value^	EQ-5D UI Unadjusted mean (Listwise Deletion)	Beta-Coefficient	p-value^	EQ-5D UI Unadjusted mean (Excluded participants from Listwise Deletion)
Sex							
Male	0.904	REF	REF	0.922	REF	REF	0.721
Female	0.873	-0.025	0.09	0.877	-0.036	<0.01*	0.842
Marital Status							
Married	0.899	REF	REF	0.913	REF	REF	0.764
Not married	0.857	-0.031	0.10	0.859	-0.042	0.01*	0.831

^ p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 is considered statistically significant.

4 Discussion

There were four objectives to this study. The primary objective was to determine whether a higher level of multimorbidity was associated with a higher degree of depression and anxiety symptoms, and a lower quality of life. We found that all four different instruments for measuring the level of multimorbidity were variably associated with the three outcomes. Comparisons of our findings and the possible reasons for the associations are discussed in more detail in Sections 4.1 to 4.5.

The second objective of the study was to describe the prevalence of depression and anxiety, and the average score of quality of life in individuals with the commonest triad of multimorbidity in primary care in Singapore. We found that the prevalence of depression was 12.0%, the prevalence of anxiety was 11.8%, the mean score of EQ-5D utility index score was 0.890, and the mean score of EQ-5D visual analogue scale score was 73.6.

Our third objective was to determine the factors associated with depression, anxiety or poor quality of life for patients with the commonest triad of multimorbidity in Singapore. We found that marital status was associated with depression. Age, education level, housing type, and body mass index were associated with quality of life. Comparisons of our findings and the possible reasons for the associations are discussed in more detail in Sections 4.1 to 4.3.

The final objective of this study was to determine the concordance rate between self-reported medical conditions by patients and medical conditions recorded in their electronic medical records. We found that ten out of the fifteen conditions had a slight to substantial agreement. We will discuss this further in Section 4.6.

4.1 Depression

The prevalence of mild to severe depression was 12.0% in this study. This was consistent with rates of 6-22% which were reported in clinical trials of depression screening[68]. Compared to the 11.4% prevalence of depression in individuals 55 years and above with coexisting medical comorbidity using the Geriatric Depressive Scale in the local community[69], the prevalence rate was slightly higher in the primary care setting.

The only sociodemographic factor that was found to be associated with depression was marital status. In our study, we found that the odds ratio of participants who were not married compared to those who were married was 1.69 (p = 0.048). It has been reported that different marital statuses were found to be associated with depression but the strength of association was modified by age and sex[70]. As a large majority of participants were married, our study did not have ample power to further differentiate whether there were differences between those who were single, separated, divorced, or widowed.

4.2 Anxiety

The prevalence of subthreshold generalised anxiety disorder reported in a systematic review ranged from 1.3% to 8.3% for primary care patients[71] and 2.1% in the local general population[72]. Therefore, the prevalence of 11.8% for mild to severe anxiety in this study indicated that anxiety level was generally higher for the most common pattern of multimorbidity compared to other studies that included people with and without multimorbidity. No sociodemographic factors were found to be associated with anxiety.

4.3 Quality of life (Utility Index)

The EQ-5D UI value norms for 20 countries based on country-specific time trade-off values ranged from 0.855 to 0.958[73]. The mean score of EQ-5D UI was 0.890 in this study population. This was lower than the mean score of 0.95 that was reported for the general population in Singapore[52]. The EQ-5D UI score was 0.87 for patients with diabetes, and 0.91 for patients with hypertension indicating that the mean EQ-5D UI score in this study was not dissimilar in those with chronic conditions.

Those aged 75 years and older reported lower quality of life compared with those younger than 55 years old. The negative correlation between age and quality of life, even after adjustment for the effect of chronic conditions, was supported by several studies[74,75]. Hunger et al.[76] showed that the age-related decline in the quality of life was only observed from the age of 70 years old onwards which was very similar to this study.

Those with primary school education reported a poorer quality of life compared to those who had no formal education. Looking at the adjusted mean EQ-5D UI score, those with secondary education or above also seemed to have a poorer quality of life score compared to those with no formal education without statistical significance (*Table 4-13*). This finding is more pronounced in the EQ-5D VAS score and will be discussed more in the next section.

Using housing as a measure of socioeconomic status, we found those in private housing reported better quality of life compared to those who stayed in HDB 1/2/3 room flats. Many other studies supported this finding of better housing being associated with better quality of life[80-83].

An increased body mass index has been found to be strongly associated with health-related quality of life[77-79]. Our study result was consistent with this finding.

4.4 Quality of life (Visual Analogue Scale)

The EQ-5D VAS value norms for 20 countries based on country-specific time trade-off values ranged from 70.4 to 83.3[73]. The mean score of EQ-5D VAS was 73.6 in this study population. The VAS score for the patients with diabetes was 69.9 in a 2012 local study[84].

Generally, international studies have shown that the amount of schooling was positively associated with quality of life in the physical, psychological, social and environmental domains across countries, culture, sex and age[85]. This differs from what we found in this study. Our results showed that participants who had any level of education were found to have a lower quality of life compared to those who had no formal education. The trend seemed to suggest that the higher the education level, the lower the quality of life.

Powdthavee[86] in a study in 2008 found that after controlling for income and employment status, life satisfaction was on average lower for those with higher levels of education. She cited a plausible explanation for this was that a comparison effect could be present where a higher education level raised the expectation of quality of life. It is highly possible that her findings and explanation for the British citizens may be similar for our population in Singapore too.

More than 25% of participants did not disclose their household income. This is not uncommon in surveys and ways to improve the response rates to this sensitive question have been reported[87]. We found that participants who did not disclose their income reported lower VAS score when compared to those who earned less than SGD 2,000 ($p < 0.01$). We explored the characteristics for participants who did not disclose their income in Table 4-15. Those who did not disclose their household income were more likely to be older, be women rather than men, be of Chinese ethnicity, use Mandarin and Chinese dialects as their first language, have no formal or only primary education, and were more likely not to own their current housing. Answers to sensitive question are subject to normal sources of reporting errors but they also have an added problem whereby respondents basically do not want to tell the truth[88]. As such, interpreting the findings from household income may not be accurate and alternative ways of getting such information should be considered in future studies.

Six independent predictor variables were associated with EQ-5D UI while three independent predictor variables were associated with EQ-5D VAS. Out of these, education was the only factor where the EQ-5D UI and EQ-5D VAS data was aligned. The observed differences in results between EQ-5D UI and EQ-5D VAS have been reported by other studies[89]. Compared to the EQ-5D UI where participants were asked to rate their quality of life based on five dimensions, the EQ-5D VAS asked for the participants' overall rating of their health. Any aspects of health-related quality of life that mattered to the participants (i.e., not just the five dimensions) would influence the way they rate their overall health. Our study confirms that the visual analogue scale (EQ-5D VAS) measures a broader underlying construct of health summarising overall health that is closer to the patient's perspective compared to the utility index (EQ-5D UI)[89].

4.5 Instruments for measuring the level of multimorbidity

We included all four instruments in the same regression model and found that there was no multicollinearity (*Appendix 4-10*). This indicated the multi-dimensional nature of multimorbidity as all four instruments for measuring the level of multimorbidity were associated with all the outcome measures (depression, anxiety and quality of life) in some way or another with differing results.

4.5.1. Chronic Disease Control Score (CDCS)

No associations were found between the CDCS and depression or anxiety symptoms. However, CDCS showed an association with quality of life using EQ-5D UI (not EQ-5D VAS). Interestingly, patients classified as CDCS '4' (all three chronic conditions sub-optimally controlled) was associated with a better quality of life when compared with those who were optimally controlled, i.e., CDCS '1'. This was contrary to our hypothesis.

There could be several explanations to this observation. Firstly, the trajectory of living with chronic disease is not linear[90]. The period directly after newly acquiring a chronic disease may lead to a decreased quality of life that might diminish or disappear when a patient has adjusted to the newly acquired illness[91]. Adaptation and resilience may be at play here where the quality of life is maintained or in this case, better, in the face of objectively poor health conditions[92]. Our study did not look at the duration of the chronic conditions which could have helped to shed more information on this phenomenon.

Secondly, poor agreement between patients and doctors on their diverging views on patients' suffering and quality of life is not new[93-95]. It is plausible that a poorer quality of life resulted from the treatment burden imposed on patients when they work hard to keep all the three clinical parameters optimally controlled. Conversely, those patients who chose not to be restrained by the treatment burden resulting in sub-optimal control of their clinical conditions experienced a better quality of life before illness burden became overbearing. This explanation further highlights the chasm that may exist between patients and doctors' perspectives on multimorbidity.

4.5.2 Additional disease count – self-reported (ADC-SR) and electronic medical records (ADC-EMR)

The association of higher disease count and poorer mental health has been well-documented[96-98]. The inverse relationship between the number of self-reported chronic conditions and quality of life has also been shown in multiple studies[12, 15-17, 19, 99]. Our results in this study were consistent with these findings. The ADC-SR was found to be positively associated with depressive symptoms, anxiety symptoms, and negatively associated with quality of life using

the EQ-5D (UI) (not EQ-5D VAS). When more chronic conditions were self-reported, the more likely the patient had a lower quality of life.

ADC-EMR did not show a similar result. On the contrary, the anxiety score of patients who had one additional chronic condition compared to those with none was reduced. The direction of the anxiety score seemed to be similar when more additional chronic conditions were considered even though there was no statistical significance (*Table 4-12*). One explanation for this might be that when physicians documented conditions that mattered to the patients, their anxiety level dropped. It was plausible that anxiety level went up if patients were concerned with certain chronic conditions but these conditions were not acknowledged and documented by their doctors (as in ADC-SR). Our postulation of the above relationship between ADC-EMR and anxiety symptoms would need to be further explored in future studies.

4.5.3 Chronic medication count (CMC)

A higher CMC was found to be associated with a poorer quality of life using the EQ-5D VAS (not EQ-5D UI). This was consistent with findings on the effects of polypharmacy and quality of life in several studies[100,101].

4.6 Concordance

There are several clinical implications for the findings from the concordance study. First of all, Singapore had consistently ranked as one of the top five countries in the world with the highest number of end-stage renal disease[102]. Alarmingly, more than half of the patients (58.7%) with chronic kidney disease (CKD) recorded in their EMR did not self-report about the condition (*Table 4-14*). There could be several reasons for this discrepancy. From the clinicians' perspectives, this could imply that either the doctors were downplaying the significance of early stage CKD and not informing patients, or they were not explaining the condition well to patients. From the patients' perspectives, it could be that they had been informed but did not consider the condition important enough to be reported during the interview, or they did not understand what was explained to them.

Secondly, it has been reported that patients often confused the term 'rheumatoid arthritis' with rheumatism[103]. The results of this study also seemed to suggest that as 'rheumatoid arthritis' had the lowest positive agreement of only 0.04. This was one of the three conditions where patients self-reported more than that recorded in the EMR. Health literacy and communication between care providers and patients may be the main issue here.

Thirdly, according to the kappa statistic, the majority of conditions in this study had only slight to fair agreement between what was self-reported by patients and what was recorded in the EMR. Adjusting for the low prevalence of the conditions studied, resulted in substantially higher agreement coefficients as measured by PABAK, except for CKD. However, the very high PABAK values with low positive agreement e.g., anxiety and osteoarthritis, raise doubt about its reliability as an agreement statistic. Therefore, PABAK values should still be interpreted with caution and the evaluation and conclusion for the strength of agreement should be judged from many aspects[104].

Fourthly, all ten conditions that were statistically significant had a high negative agreement of more than 0.90 except CKD which was only at 0.58. From the results of this study, sole reliance on the use of medical records may not be warranted. This is especially so in a fee-for-service environment where patients may obtain multiple sources of care for different health conditions. Self-reporting of medical conditions allows patients to provide their perception of those problems that interfere more in their everyday lives and are in line with the concept of the evidence-based patient information[105]. Therefore, self-reports may better reflect conditions more likely to affect patients' mental health status and quality of life. The discrepancy between the two sources of medical diagnoses is a concern for epidemiological research[106].

On average, patients in this study reported fewer additional chronic conditions during the interview than what was documented in the EMR (twelve conditions had lower self-reported 'yes' compared to EMR). This was contrary to what was reported in a similar study in 2008[107].

The possible reasons for the lower self-reports are summarised below. Firstly, it could be due to a lack of awareness on the part of the patients about the presence of a condition[108]. Secondly, patients might consider some health conditions were not important enough to use health services and failed to report them. Thirdly, because the study was conducted as a face-to-face

interview, the social desirability effect could be at play especially for mental disorders[109]. Fourthly, sporadic diseases from the patients' perspective may not be reported; studies have reported that conditions like osteoarticular diseases tend to be reported less frequently by patients due to its sporadic course[110].

4.7 Multiple imputation and Listwise deletion

We explored the reasons for the discrepancy between the results in the multivariable regression analysis that we found when we used the two methods of dealing with missing data as demonstrated in the sensitivity analysis.

For the two predictors 'age' and 'CDCS', type II error was introduced due to the loss of sample size when listwise deletion was used (*Table 4-16*). The loss of data led to larger standard errors, wider confidence intervals, and a loss of power in hypotheses testing[67].

We next explored the reasons for the listwise deletion method identifying two predictor variables as significant – sex and marital status which the multiple imputation did not find. The mean EQ-5D UI scores were lower for the male participants (0.721) and for participants who were married (0.764) than the mean EQ-5D UI scores for the males (0.922) and those married (0.913) for the complete case analysis using the listwise deletion method (*Table 4-17*). As such, when these participants were included in the multiple imputation method, the mean EQ-5D score was pulled down and did not achieve a significant difference for either the female participants or those who were not married resulting in a Type I error when using listwise deletion.

When data were not missing completely at random, listwise deletion may have introduced bias. This was clearly demonstrated in our case above for selecting the EQ-5D UI as an outcome even though the two methods provided similar results for the other three outcomes - PHQ-9, GAD-7 and EQ-5D VAS. Multiple imputation is therefore advocated because it uses information in the incomplete cases, performs better as more variables are included in the analysis model, and it is valid when values were missing at random (MAR) where listwise deletion is biased[111].

4.8 Strengths and Limitations of the study

4.8.1 Strengths

The strengths of the study include the following. First of all, we randomly selected all patients known in Hougang Polyclinic that had come for follow-up of the most common triad of multimorbidity instead of convenience sampling. This helps to reduce selection bias by including patients who made unplanned visits. It is a known fact that patients who attend physician visits that are unplanned consistently have a poorer state of health[112]. Second, we used all the official languages in Singapore to interview our participants so as not to exclude potential patients from the minority group. Third, we took into account the implications of missing value and conducted a sensitivity analysis. We further provided a detailed analysis of the possible reasons for the discrepancies noted between the two different analyses. Fourth, we provided the positive and negative agreements and preference-adjusted and bias-adjusted kappa (PABAK) to better understand the agreement between self-reported medical conditions and those recorded in the EMR. Finally, we provided the report of the study based on the STROBE guidelines[33].

4.8.2 Limitations

Our study also has several limitations other than some that have been mentioned before. First, this was a cross-sectional study using the point estimate of depression, anxiety, quality of life, and only the last single clinical parameter during and around the period of the interview. Causation cannot be determined because of the design of the study. Second, the quality of morbidity coding in primary care consultations may be variable among diagnoses, e.g., coding of diabetes tended to be of higher quality than coding of asthma[113]. Third, the study did not take into account other missing data mechanisms under which multiple imputation is biased and listwise deletion is not. These mechanisms do not correspond to missing completely at random, missing at random or missing not at random categories, but cut across this classification[111]. Fourth, despite the random selection of eligible participants, we found that there were more male to female participants and therefore the study findings may not be generalisable. Lastly, we did not include lifestyle behaviours that may have impact on the three outcomes including smoking, physical activity, diet and sleep.

4.9 Conclusion and future

Out of the four instruments for measuring the level of multimorbidity, only Additional Disease Count - Self-Reported (ADC-SR) was positively associated with depression and anxiety symptoms, and negatively associated with quality of life (Utility Index). Patients with all three chronic conditions that were sub-optimally controlled reported a higher score for quality of life compared to those who were optimally controlled (Chronic Disease Control Score). A higher chronic medication count was also associated with a poorer quality of life. Finally, a higher number of additional chronic conditions using electronic medical records was associated with a lower score for anxiety symptoms reported by participants. These findings together with the finding that, for the majority of chronic conditions, there was only slight to fair concordance between ADC-SR and AC-EMR further highlights the discrepancy of the source of chronic conditions reported by patients and those reported by the doctors i.e., medical records.

The prevalence of depressive symptoms was 12.0% and the prevalence of anxiety symptoms was 11.8% for patients with the most common triad of multimorbidity in primary care; both prevalence rates were higher than the general population in Singapore. The average score of quality of life using the EQ-5D utility index for patients with multimorbidity in primary care was 0.890 which was lower that of the general population but comparable to those with chronic diseases. The average score of quality of life using the EQ-5D visual analogue scale was 73.6 which was higher than 69.9 reported by patients with diabetes in Singapore.

Factors found in our study that were associated with depression, anxiety and quality of life were largely consistent with those found in the current literature. These included older age of 75 years and above, participants living in small public housing, and those with higher body mass index being associated with poorer quality of life; and unmarried participants being associated with higher levels of depressive symptoms. Contrary to most other studies, a higher education level was associated with a poorer quality of life.

We found that only the condition, stroke showed substantial agreement between patients' self-reported medical conditions and the electronic medical records (EMR). The majority of chronic conditions had only slight to fair concordance, and this study further highlights the incongruency of the source of chronic conditions reported by patients and those reported by

the doctors, i.e., medical records. In general, patients self-reported fewer conditions than what was recorded in the EMR. More than half of the patients with chronic kidney disease (58.7%) recorded in their EMR did not self-report about the condition.

Understanding the patients' expectations and experiences of multimorbidity would improve the alignment of goals of clinicians and patients in the documentation of medical conditions that truly matter to the patients, and may alleviate health care systems' and clinicians' obsession with surrogate clinical parameters. It is essential to include the perspective of patients themselves who are the real experts in the day-to-day reality of living with multimorbidity thereby potentially embracing patient-centredness and reducing treatment burden. Better communication with patients could also improve patient knowledge of their actual conditions. Future studies should look at the psychological process underlying patient adjustment to multimorbidity because of its potential to predict clinical, quality of life, and mental health outcomes.

5 References

1. Haggerty J, Fortin M, Beaulieu MD, et al. At the interface of community and healthcare systems: a longitudinal cohort study on evolving health and the impact of primary healthcare from the patient's perspective. *BMC Health Serv Res* 2010;10:258. doi: https://dx.doi.org/10.1186/1472-6963-10-258
2. Ceramidas DM, Glasgow NJ. Multi-morbidity: A system design challenge in delivering patient-centred care. *Aust Health Rev* 2013;37(3):309-11. doi: http://dx.doi.org/10.1071/AH13003
3. Blank RC, Brunton S. Managing multiple cardiovascular risk factors. *J* 2008;57(3):S1-S8.
4. Pogach L, Engelgau M, Aron D. Measuring progress toward achieving hemoglobin A1c goals in diabetes care: pass/fail or partial credit. *Jama* 2007;297(5):520-3. doi: 10.1001/jama.297.5.520
5. Pogach L, Aron DC. Sudden acceleration of diabetes quality measures. *Jama* 2011;305(7):709-10. doi: 10.1001/jama.2011.153
6. MOH. MOH Clinical Practice Guidelines 3/2006 - Diabetes Mellitus (Withdrawn). 2006. https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_diabetes-mellitus-jun-2006.pdf (accessed 2 Feb 2019).
7. Huang Y-C, Lee M-C, Chou Y-J, et al. Disease-specific Pay-for-Performance Programs: Do the P4P Effects Differ Between Diabetic Patients With and Without Multiple Chronic Conditions? *Med Care* 2016;54(11):977-83.
8. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. *Journal of the American Medical Association* 2005;294(6):716-24. doi: http://dx.doi.org/10.1001/jama.294.6.716
9. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *Bmj* 2009;339:b2803. doi: 10.1136/bmj.b2803
10. Abu Dabrh AM, Gallacher K, Boehmer KR, et al. Minimally disruptive medicine: the evidence and conceptual progress supporting a new era of healthcare. *J R Coll Physicians Edinb* 2015;45(2):114-7. doi: 10.4997/JRCPE.2015.205
11. Liddy C, Blazkho V, Mill K. Challenges of self-management when living with multiple chronic conditions: systematic review of the qualitative literature. *Canadian family physician Medecin de famille canadien* 2014;60(12):1123-33.
12. Agborsangaya CB, Lau D, Lahtinen M, et al. Health-related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res* 2013;22(4):791-9. doi: 10.1007/s11136-012-0214-7
13. Barile JP, Thompson WW, Zack MM, et al. Multiple chronic medical conditions and health-related quality of life in older adults, 2004-2006. *Prev Chronic Dis* 2013;10:E162. doi: 10.5888/pcd10.120282
14. Barile JP, Thompson WW, Zack MM, et al. Activities of daily living, chronic medical conditions, and health-related quality of life in older adults. *J Ambul Care Manage* 2012;35(4):292-303. doi: 10.1097/JAC.0b013e31826746f5
15. Garin N, Olaya B, Moneta MV, et al. Impact of multimorbidity on disability and quality of life in the Spanish older population. *PLoS ONE* 2014;9(11):e111498. doi: 10.1371/journal.pone.0111498
16. Lawson KD, Mercer SW, Wyke S, et al. Double trouble: the impact of multimorbidity and deprivation on preference-weighted health related quality of life a cross sectional

analysis of the Scottish Health Survey. *Int J Equity Health* 2013;12:67. doi: 10.1186/1475-9276-12-67
17. McDaid O, Hanly MJ, Richardson K, et al. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. *BMJ Open* 2013;3(6) doi: 10.1136/bmjopen-2013-002571
18. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61
19. Wikman A, Wardle J, Steptoe A. Quality of life and affective well-being in middle-aged and older people with chronic medical illnesses: a cross-sectional population based study. *PLoS ONE* 2011;6(4):e18952. doi: 10.1371/journal.pone.0018952
20. Fortin M, Lapointe L, Hudon C, et al. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004;2:51. doi: 10.1186/1477-7525-2-51
21. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: A systematic review of the literature. *Ageing Research Reviews* 2011;10(4):430-39. doi: http://dx.doi.org/10.1016/j.arr.2011.03.003
22. Jani BD, Purves D, Barry S, et al. Challenges and Implications of Routine Depression Screening for Depression in Chronic Disease and Multimorbidity: A Cross Sectional Study. *PLoS ONE* 2013;8 (9) (no pagination)(e74610) doi: http://dx.doi.org/10.1371/journal.pone.0074610
23. Read JR, Sharpe L, Modini M, et al. Multimorbidity and depression: A systematic review and meta-analysis. *J Affect Disord* 2017;221:36-46. doi: 10.1016/j.jad.2017.06.009
24. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *Gen Hosp Psychiatry* 2007;29(5):409-16. doi: 10.1016/j.genhosppsych.2007.06.002
25. Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007;370(9590):851-8. doi: 10.1016/S0140-6736(07)61415-9
26. Menear M, Dore I, Cloutier AM, et al. The influence of comorbid chronic physical conditions on depression recognition in primary care: a systematic review. *Journal of psychosomatic research* 2015;78(4):304-13. doi: 10.1016/j.jpsychores.2014.11.016
27. Quah JH, Wang P, Ng RR, et al. Health-related quality of life of older Asian patients with multimorbidity in primary care in a developed nation. *Geriatr Gerontol Int* 2016 doi: 10.1111/ggi.12881
28. Undeland M, Malterud K. Diagnostic work in general practice: more than naming a disease. *Scandinavian journal of primary health care* 2002;20(3):145-50.
29. Knox SA, Harrison CM, Britt HC, et al. Estimating prevalence of common chronic morbidities in Australia. *Med J Aust* 2008;189(2):66-70.
30. Wu CS, Lai MS, Gau SS, et al. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. *PLoS ONE* 2014;9(12):e112257. doi: 10.1371/journal.pone.0112257
31. Jiang L, Zhang B, Smith ML, et al. Concordance between Self-Reports and Medicare Claims among Participants in a National Study of Chronic Disease Self-Management Program. *Front Public Health* 2015;3:222. doi: 10.3389/fpubh.2015.00222
32. Britt H, Harris M, Driver B, et al. Reasons for encounter and diagnosed health problems: convergence between doctors and patients. *Fam Pract* 1992;9(2):191-4.

33. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007;4(10):e297. doi: 10.1371/journal.pmed.0040297
34. Gilbody S, Richards D, Brealey S, et al. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med* 2007;22(11):1596-602. doi: 10.1007/s11606-007-0333-y
35. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606-13.
36. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092
37. van Reenen M, Oppe M. EQ-5D-3L User Guide - Basic information on how to use the EQ-5D-3L instrument. 2015. https://www.euroqol.org/wp-content/uploads/2016/09/EQ-5D-3L_UserGuide_2015.pdf (accessed 6 Apr 2019).
38. Sung SC, Low CC, Fung DS, et al. Screening for major and minor depression in a multiethnic sample of Asian primary care patients: a comparison of the nine-item Patient Health Questionnaire (PHQ-9) and the 16-item Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16). *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists* 2013;5(4):249-58. doi: 10.1111/appy.12101
39. Bayliss EA, Ellis JL, Shoup JA, et al. Association of patient-centered outcomes with patient-reported and ICD-9-based morbidity measures. *Ann Fam Med* 2012;10(2):126-33. doi: http://dx.doi.org/10.1370/afm.1364
40. Kroenke K, Spitzer RL, Williams JBW, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A systematic review. *Gen Hosp Psychiatry* 2010;32(4):345-59. doi: http://dx.doi.org/10.1016/j.genhosppsych.2010.03.006
41. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35(11):1095-108.
42. Luo N, Wang P, Thumboo J, et al. Valuation of EQ-5D-3L health states in Singapore: modeling of time trade-off values for 80 empirically observed health states. *Pharmacoeconomics* 2014;32(5):495-507. doi: 10.1007/s40273-014-0142-1
43. Population Trends, 2016 - Table A1.3 Singapore Residents by Age Group, Ethnic Group and Sex, June 2016. In: Statistics, ed. Singapore, 2016:51.
44. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American association of clinical endocrinologists and American college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017;23(Suppl 2):1-87. doi: 10.4158/ep171764.appgl [published Online First: 2017/04/25]
45. Chronic Disease Management Programme Handbook for Healthcare Professionals 2018 [Available from: https://www.primarycarepages.sg/Documents/Practice%20Management/CDMP%20Handbook%20for%20Healthcare%20Professionals%202018.pdf accessed 10 Dec 2018.
46. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34(28):2159-219. doi: 10.1093/eurheartj/eht151
47. ADA. Standards of medical care in diabetes - 2013. *Diabetes Care* 2013;36(SUPPL.1):S11-S66. doi: http://dx.doi.org/10.2337/dc13-S011
48. O'Halloran J, Miller GC, Britt H. Defining chronic conditions for primary care with ICPC-2. *Fam Pract* 2004;21(4):381-6. doi: 10.1093/fampra/cmh407

49. VanVoorhis CRW, Morgan BL. Understanding Power and Rules of Thumb for Determining Sample Sizes. *Tutorials in Quantitative Methods for Psychology* 2007;3(2):43-50.
50. McCaffrey N, Kaambwa B, Currow DC, et al. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes* 2016;14(1):133. doi: 10.1186/s12955-016-0537-0
51. Browner WS, Newman TB, Hulley SB. Estimating Sample Size and Power: Applications and Examples. In: Gaertner R, ed. Designing Clinical Research. 4th ed. USA: Lippincott Williams and Wilkins 2013:81.
52. Abdin E, Subramaniam M, Vaingankar JA, et al. Population norms for the EQ-5D index scores using Singapore preference weights. *Qual Life Res* 2015;24(6):1545-53. doi: 10.1007/s11136-014-0859-5
53. Temel G, Erdogan S. Determining the sample size in agreement studies. *Marmara Medical Journal* 2017:101-12. doi: 10.5472/marumj.344822
54. Alison PD. Listwise Deletion: It's Not EVil 2014 [Available from: https://statisticalhorizons.com/listwise-deletion-its-not-evil accessed 13 Jan 2019.
55. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. *Int J Endocrinol Metab* 2012;10(2):486-9. doi: 10.5812/ijem.3505
56. Pallant J. SPSS Survival Manual: A Step By Step Guide to Data Analysis Using SPSS Program 6th ed. London: McGraw-Hill Education 2016.
57. Vatcheva KP, Lee M, McCormick JB, et al. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. *Epidemiology (Sunnyvale)* 2016;6(2) doi: 10.4172/2161-1165.1000227
58. de Vet HCW, Terwee CB, Mokkink LB, et al. Chapter 5 - Reliability. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
59. Kottner J, Audige L, Brorson S, et al. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *J Clin Epidemiol* 2011;64(1):96-106. doi: 10.1016/j.jclinepi.2010.03.002
60. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-74.
61. Penny KI, Atkinson I. Approaches for dealing with missing data in health care studies. *J Clin Nurs* 2012;21(19-20):2722-9. doi: 10.1111/j.1365-2702.2011.03854.x [published Online First: 2011/09/08]
62. Little R. A Test of Missing Completely at Random for Multivariate Data with Missing Values. *Journal of the American Statistical Association* 1988;83(404):1198-202. doi: 10.1080/01621459.1988.10478722
63. Dong Y, Peng CY. Principled missing data methods for researchers. *Springerplus* 2013;2(1):222. doi: 10.1186/2193-1801-2-222 [published Online First: 2013/07/16]
64. El-Masri MM, Fox-Wasylyshyn SM. Missing data: an introductory conceptual overview for the novice researcher. *Can J Nurs Res* 2005;37(4):156-71. [published Online First: 2006/03/18]
65. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30(4):377-99. doi: 10.1002/sim.4067
66. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012;367(14):1355-60. doi: 10.1056/NEJMsr1203730
67. Alison PD. Chapter 4 - Missing Data. In: Millsap RE, Maydeu-Olivares A, eds. The SAGE Handbook of Quantitative Methods in Psychology. Singapore: SAGE Publications Asia-Pacific Pte Ltd 2009:72-90.

68. Thombs BD, de Jonge P, Coyne JC, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *Jama* 2008;300(18):2161-71. doi: 10.1001/jama.2008.667
69. Ho C, Feng L, Fam J, et al. Coexisting medical comorbidity and depression: multiplicative effects on health outcomes in older adults. *Int Psychogeriatr* 2014;26(7):1221-9. doi: 10.1017/S1041610214000611
70. Bulloch AGM, Williams JVA, Lavorato DH, et al. The depression and marital status relationship is modified by both age and gender. *J Affect Disord* 2017;223:65-68. doi: 10.1016/j.jad.2017.06.007 [published Online First: 2017/07/22]
71. Haller H, Cramer H, Lauche R, et al. The prevalence and burden of subthreshold generalized anxiety disorder: a systematic review. *BMC Psychiatry* 2014;14:128. doi: 10.1186/1471-244X-14-128
72. Lee SP, Sagayadevan V, Vaingankar JA, et al. Subthreshold and threshold DSM-IV generalized anxiety disorder in Singapore: Results from a nationally representative sample. *J Anxiety Disord* 2015;32:73-80. doi: 10.1016/j.janxdis.2015.03.008
73. Janssen MF, Szende A, Cabases J, et al. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Health Econ* 2018 doi: 10.1007/s10198-018-0955-5
74. Saarni SI, Harkanen T, Sintonen H, et al. The impact of 29 chronic conditions on health-related quality of life: a general population survey in Finland using 15D and EQ-5D. *Qual Life Res* 2006;15(8):1403-14. doi: 10.1007/s11136-006-0020-1
75. Heyworth IT, Hazell ML, Linehan MF, et al. How do common chronic conditions affect health-related quality of life? *Br J Gen Pract* 2009;59(568):e353-8. doi: 10.3399/bjgp09X453990
76. Hunger M, Thorand B, Schunk M, et al. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. *Health Qual Life Outcomes* 2011;9:53. doi: 10.1186/1477-7525-9-53
77. Sach TH, Barton GR, Doherty M, et al. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. *Int J Obes (Lond)* 2007;31(1):189-96. doi: 10.1038/sj.ijo.0803365
78. Yan LL, Daviglus ML, Liu K, et al. BMI and health-related quality of life in adults 65 years and older. *Obes Res* 2004;12(1):69-76. doi: 10.1038/oby.2004.10
79. Soltoft F, Hammer M, Kragh N. The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. *Qual Life Res* 2009;18(10):1293-9. doi: 10.1007/s11136-009-9541-8
80. Park B, Ock M, Lee HA, et al. Multimorbidity and health-related quality of life in Koreans aged 50 or older using KNHANES 2013-2014. *Health Qual Life Outcomes* 2018;16(1):186. doi: 10.1186/s12955-018-1016-6
81. Katikireddi SV, Skivington K, Leyland AH, et al. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. *BMC Med* 2017;15(1):152. doi: 10.1186/s12916-017-0913-6
82. Schiotz ML, Stockmarr A, Host D, et al. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health* 2017;17(1):422. doi: 10.1186/s12889-017-4314-8
83. Ki M, Lee YH, Kim YS, et al. Socioeconomic inequalities in health in the context of multimorbidity: A Korean panel study. *PLoS ONE* 2017;12(3):e0173770. doi: 10.1371/journal.pone.0173770

84. Luo N, Cang SQ, Quah HM, et al. The discriminative power of the EuroQol visual analog scale is sensitive to survey language in Singapore. *Health Qual Life Outcomes* 2012;10:32. doi: 10.1186/1477-7525-10-32
85. Skevington SM. Qualities of life, educational level and human development: an international investigation of health. *Soc Psychiatry Psychiatr Epidemiol* 2010;45(10):999-1009. doi: 10.1007/s00127-009-0138-x
86. Powdthavee N. Putting a price tag on friends, relatives, and neighbours: Using surveys of life satisfaction to value social relationships. *The Journal of Socio-Economics* 2008;37(4):1459-80. doi: 10.1016/j.socec.2007.04.004
87. Schwartz L, Paulin G. Improving response rates to income question. 2000. http://www.asasrms.org/Proceedings/papers/2000_165.pdf (accessed 26 Feb 2019).
88. Tourangeau R, Yan T. Sensitive questions in surveys. *Psychol Bull* 2007;133(5):859-83. doi: 10.1037/0033-2909.133.5.859
89. Feng Y, Parkin D, Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. *Qual Life Res* 2014;23(3):977-89. doi: 10.1007/s11136-013-0537-z
90. Plsek PE, Greenhalgh T. Complexity science: The challenge of complexity in health care. *Bmj* 2001;323(7313):625-8.
91. Aarts S, den Akker MV, Bosma H, et al. The effect of multimorbidity on health related functioning: Temporary or persistent? Results from a longitudinal cohort study. *J Psychosom Res* 2012;73(3):211-17. doi: http://dx.doi.org/10.1016/j.jpsychores.2012.05.014
92. Netuveli G, Blane D. Quality of life in older ages. *Br Med Bull* 2008;85:113-26. doi: 10.1093/bmb/ldn003
93. Junius-Walker U, Stolberg D, Steinke P, et al. Health and treatment priorities of older patients and their general practitioners: a cross-sectional study. *Qual Prim Care* 2011;19(2):67-76.
94. Lesho E, Foster L, Wang Z, et al. The accuracy of physicians' perceptions of patients' suffering: findings from two teaching hospitals. *Acad Med* 2009;84(5):636-42. doi: 10.1097/ACM.0b013e31819facf1
95. Pearlman RA, Uhlmann RF. Quality of life in chronic diseases: perceptions of elderly patients. *Journal of gerontology* 1988;43(2):M25-30. [published Online First: 1988/03/01]
96. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2
97. Chen HY, Baumgardner DJ, Rice JP. Health-related quality of life among adults with multiple chronic conditions in the United States, Behavioral Risk Factor Surveillance System, 2007. *Prev Chronic Dis* 2011;8(1):A09.
98. Ryu E, Takahashi PY, Olson JE, et al. Quantifying the importance of disease burden on perceived general health and depressive symptoms in patients within the Mayo Clinic Biobank. *Health and Quality of Life Outcomes* 2015;13 (1) (no pagination)(95) doi: http://dx.doi.org/10.1186/s12955-015-0285-6
99. Sullivan PW, Ghushchyan VH, Bayliss EA. The impact of co-morbidity burden on preference-based health-related quality of life in the United States. *Pharmacoeconomics* 2012;30(5):431-42. doi: 10.2165/11586840-000000000-00000
100. Montiel-Luque A, Nunez-Montenegro AJ, Martin-Aurioles E, et al. Medication-related factors associated with health-related quality of life in patients older than 65 years with polypharmacy. *PLoS ONE* 2017;12(2):e0171320. doi: 10.1371/journal.pone.0171320

101. Henderson JA, Buchwald D, Manson SM. Relationship of Medication Use to Health-Related Quality of Life Among a Group of Older American Indians. *Journal of Applied Gerontology* 2016;25(1_suppl):89S-104S. doi: 10.1177/0733464805283035
102. Wong LY, Liew AST, Weng WT, et al. Projecting the Burden of Chronic Kidney Disease in a Developed Country and Its Implications on Public Health. *Int J Nephrol* 2018;2018:5196285. doi: 10.1155/2018/5196285
103. Harrison C, Britt H, Miller G, et al. Prevalence of chronic conditions in Australia. *PLoS ONE* 2013;8(7):e67494. doi: https://dx.doi.org/10.1371/journal.pone.0067494
104. Chen G, Faris P, Hemmelgarn B, et al. Measuring agreement of administrative data with chart data using prevalence unadjusted and adjusted kappa. *BMC Med Res Methodol* 2009;9:5. doi: 10.1186/1471-2288-9-5
105. Bunge M, Muhlhauser I, Steckelberg A. What constitutes evidence-based patient information? Overview of discussed criteria. *Patient Educ Couns* 2010;78(3):316-28. doi: 10.1016/j.pec.2009.10.029
106. Preen DB, Holman CD, Lawrence DM, et al. Hospital chart review provided more accurate comorbidity information than data from a general practitioner survey or an administrative database. *J Clin Epidemiol* 2004;57(12):1295-304. doi: 10.1016/j.jclinepi.2004.03.016
107. Corser W, Sikorskii A, Olomu A, et al. Concordance between comorbidity data from patient self-report interviews and medical record documentation. *BMC Health Serv Res* 2008;8:85. doi: 10.1186/1472-6963-8-85
108. Skinner KM, Miller DR, Lincoln E, et al. Concordance between respondent self-reports and medical records for chronic conditions: experience from the Veterans Health Study. *J Ambul Care Manage* 2005;28(2):102-10.
109. Tisnado DM, Adams JL, Liu H, et al. What is the concordance between the medical record and patient self-report as data sources for ambulatory care? *Med Care* 2006;44(2):132-40.
110. Esteban-Vasallo MD, Dominguez-Berjon MF, Astray-Mochales J, et al. Epidemiological usefulness of population-based electronic clinical records in primary care: estimation of the prevalence of chronic diseases. *Fam Pract* 2009;26(6):445-54. doi: 10.1093/fampra/cmp062
111. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med* 2010;29(28):2920-31. doi: 10.1002/sim.3944
112. Surate Solaligue DE, Hederman L, Martin CM. What weekday? How acute? An analysis of reported planned and unplanned GP visits by older multi-morbid patients in the Patient Journey Record System database. *J Eval Clin Pract* 2014;20(4):522-6. doi: 10.1111/jep.12171
113. Jordan K, Porcheret M, Croft P. Quality of morbidity coding in general practice computerized medical records: a systematic review. *Fam Pract* 2004;21(4):396-412. doi: 10.1093/fampra/cmh409

6 Appendices

Appendix 4-1. PHQ-9 Questionnaire

SECTION B: PHQ9				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	***Not at all***	***Several days***	***More than half the days***	***Nearly every day***
1. Little interest or pleasure in doing things	☐ 0	☐ 1	☐ 2	☐ 3
2. Feeling down, depressed, or hopeless	☐ 0	☐ 1	☐ 2	☐ 3
3. Trouble falling or staying asleep, or sleeping too much	☐ 0	☐ 1	☐ 2	☐ 3
4. Feeling tired or having little energy	☐ 0	☐ 1	☐ 2	☐ 3
5. Poor appetite or overeating	☐ 0	☐ 1	☐ 2	☐ 3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	☐ 0	☐ 1	☐ 2	☐ 3
7. Trouble concentrating on things, such as reading the newspaper or watching television	☐ 0	☐ 1	☐ 2	☐ 3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	☐ 0	☐ 1	☐ 2	☐ 3
9. Thoughts that you would be better off dead, or of hurting yourself	☐ 0	☐ 1	☐ 2	☐ 3

add columns	+	+	+	
Total	=			

Appendix 4-2. GAD-7 Questionnaire

SECTION A: GAD7				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	***Not at all***	***Several days***	***More than half the days***	***Nearly every day***
1. Feeling nervous, anxious, or on edge	☐ 0	☐ 1	☐ 2	☐ 3
2. Not being able to stop or control worrying	☐ 0	☐ 1	☐ 2	☐ 3
3. Worrying too much about different things	☐ 0	☐ 1	☐ 2	☐ 3
4. Trouble relaxing	☐ 0	☐ 1	☐ 2	☐ 3
5. Being so restless that it's hard to sit still	☐ 0	☐ 1	☐ 2	☐ 3
6. Becoming easily annoyed or irritable	☐ 0	☐ 1	☐ 2	☐ 3
7. Feeling afraid as if something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3

add columns	+	+	+	
Total	=			

Appendix 4-3. EQ-5D Utility Index

Questionnaire 5: Quality of Life Questionnaire (EQ5D)

SECTION A: OWN HEALTH QUESTIONS
By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.
1) Mobility ☐ (1A) I have no problems in walking about ☐ (1B) I have some problems in walking about ☐ (1C) I am confined to bed
2) Self-Care ☐ (2A) I have no problems with self-care ☐ (2B) I have some problems washing or dressing myself ☐ (2C) I am unable to wash or dress myself
3) Usual Activities *(e.g. work, study, housework, family, or leisure activities)* ☐ (3A) I have no problems with performing my usual activities ☐ (3B) I have some problems with performing my usual activities ☐ (3C) I am unable to perform my usual activities
4) Pain/ Discomfort ☐ (4A) I have no pain or discomfort ☐ (4B) I have moderate pain or discomfort ☐ (4C) I have extreme pain or discomfort
5) Anxiety/ Depression ☐ (5A) I am not anxious or depressed ☐ (5B) I am moderately anxious or depressed ☐ (5C) I am extremely anxious or depressed

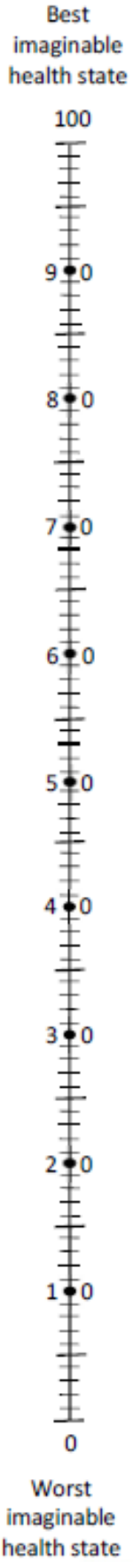
Appendix 4-4. EQ-5D Visual Analogue Scale

SECTION B: OWN HEALTH SCALE

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today in your opinion. Please do this by drawing a line from the **BLACK BOX** below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 4-5. A summary list of all the outcome and independent variables

	Variable name	Abbreviation	Type
1	Age	Age	Categorical (4)
2	Sex	Sex	Dichotomous
3	Ethnicity	Ethnicity	Dichotomous
4	First language	Language	Categorical (4)
5	Marital status	Marital status	Categorical (4)
6	Education level	Education	Categorical (4)
7	Housing type	Housing	Categorical (4)
8	Ownership status	Ownership	Dichotomous
9	Monthly household income	Income	Categorical (5)
10	Body Mass Index	BMI	Continuous
11	Chronic Disease Control Score	CDCS	Categorical (4)
12	Additional disease count – self-reported	ADC-SR	Categorical (3)
13	Additional disease count – electronic medical records	ADC-EMR	Categorical (3)
14	Chronic medical count	CMC	Count
15	Depression score	PHQ-9	Dichotomous
16	Anxiety score	GAD-7	Dichotomous
17	Quality of life – utility index	EQ-5D UI	Continuous
18	Quality of life – visual analogue scale	EQ-5D VAS	Continuous

Appendix 4-6. Chronic Disease Condition Score (CDCS)

Table 1 – Clinical control of chronic conditions based on Chronic Disease Management Program Handbook[45]

Chronic Condition	**Optimally controlled**	**Sub-optimally controlled**
Diabetes[47]	HbA1c < 7.0%	HbA1c ≥ 7.0 %
Hyperlipidaemia[44]	LDL-c < 2.6mmol/L	LDL-c ≥ 2.6 mmol/L
Hypertension[46]	SBP < 140mmHg and DBP < 80mmHg	SBP ≥ 140mmHg or DBP ≥ 80mmHg

Table 2 – Chronic Disease Condition Score (CDCS) definition

Score	**Explanation and remarks**
1	All three conditions were optimally controlled
2	One of the three conditions was sub-optimally controlled and the other two were optimally controlled
3	Two of the three conditions were sub-optimally controlled and the other one was optimally controlled
4	All three conditions were sub-optimally controlled

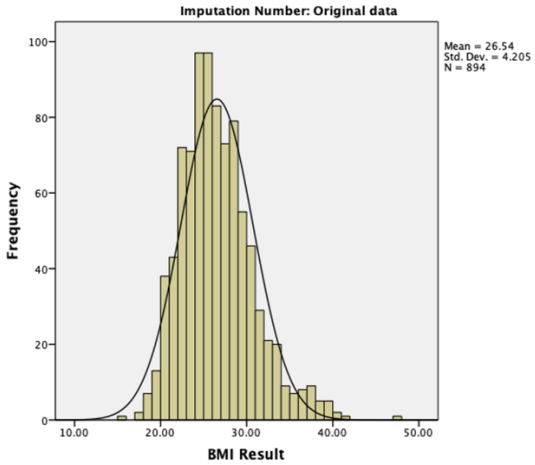
Appendix 4-7. List of additional disease counts for ADC-SR & ADC-EMR

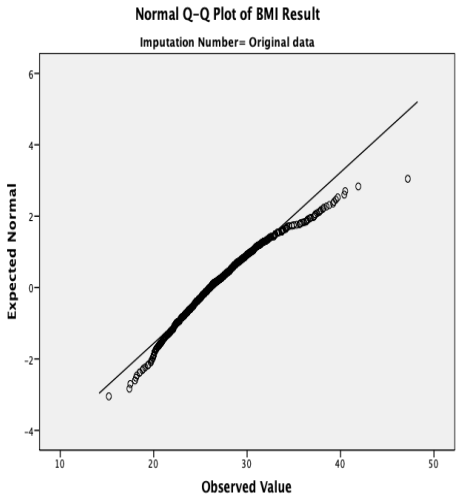
List of Other Chronic Conditions for determining Additional Disease Count – self-reported and Additional Disease Count – Electronic Medical Record

1. Stroke
2. Asthma
3. Chronic Obstructive Pulmonary Disease (COPD)
4. Major Depression
5. Schizophrenia
6. Dementia
7. Bipolar Disorder
8. Anxiety
9. Parkinson's Disease
10. Chronic Kidney Disease
11. Benign Prostate Hypertrophy
12. Osteoarthritis
13. Rheumatoid Arthritis
14. Osteoporosis
15. Psoriasis
16. Others, please specify: _____

Appendix 4-8. Normality tests for independent variables - BMI, CMC, ADC-SR & EMR

BMI (Body Mass Index)

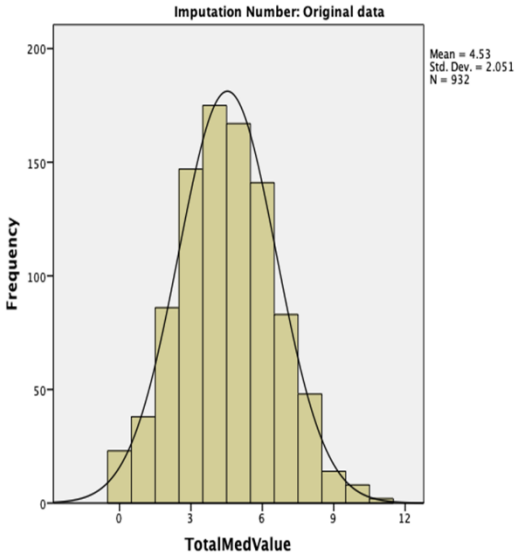


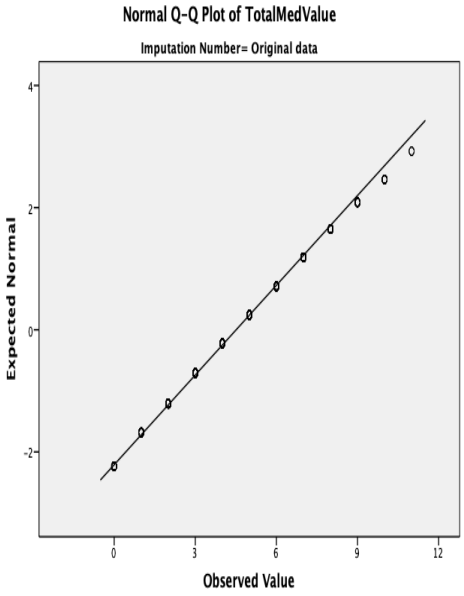


Variable	Kolmogorov-Smirnov test			Shapiro-Wilk test		
	Statistic	df	Sig.	Statistic	df	Sig.
BMI	.063	866	.000	.970	866	.000

From visual inspection, the variable BMI was considered not to be normally distributed as the frequency distribution showed right skewness, and the Q-Q plot did not form a straight diagonal line[55]. Moreover, both the Lilliefors corrected Kolmogorov-Smirnov and Shapiro-Wilks's tests were statistically significant ($p < 0.05$). Therefore, the variable BMI was not normally distributed.

CMC (Chronic Medication Count)



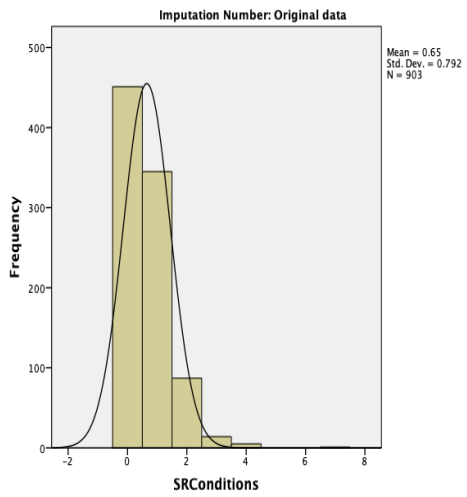


Variable	Kolmogorov-Smirnov test			Shapiro-Wilk test		
	Statistic	df	Sig.	Statistic	df	Sig.
CMC	.105	866	.000	.977	866	.000

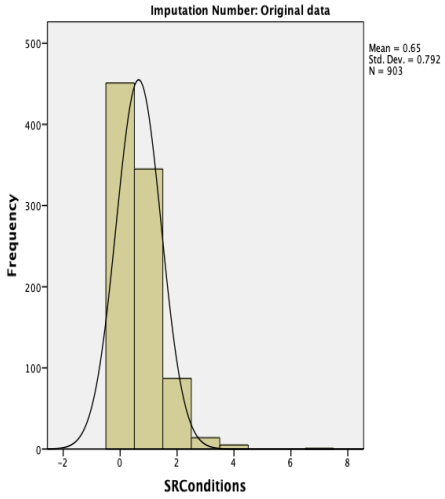
The variable CMC was considered to be normally distributed as the frequency distribution and the Q-Q plot satisfied the visual methods for assessing normality despite having significant test results for both the Lilliefors corrected Kolmogorov-Smirnov and Shapiro-Wilks's tests[55].

Appendix 4-8. Normality tests for independent variables - BMI, CMC, ADC-SR & EMR (Continued)

ADC-SR
(Additional Disease Count – Self-Reported)



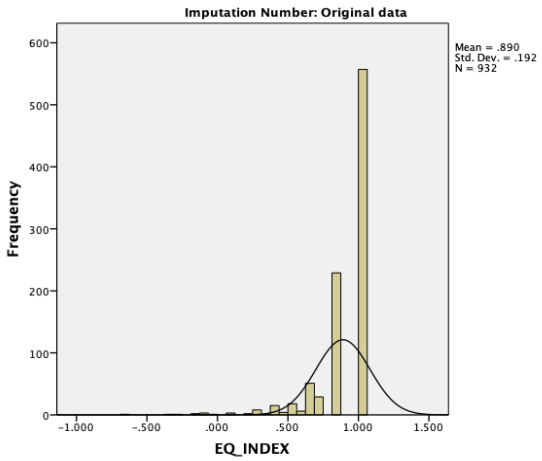
ADC-EMR
(Additional Disease Count – Electronic Medical Record)

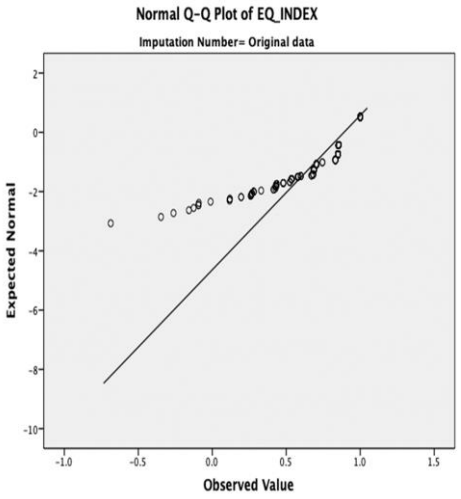


The distribution frequency of ADC-SR and ADC-EMR were both positive skewed with clustering at '0'. Therefore, the two variables were changed to categorical variables with three categories of '0', '1', '2 and more'.

Appendix 4-9. Normality tests for dependent variables – EQ-5D UI & EQ-5D VAS

EQ-5D Utility Index

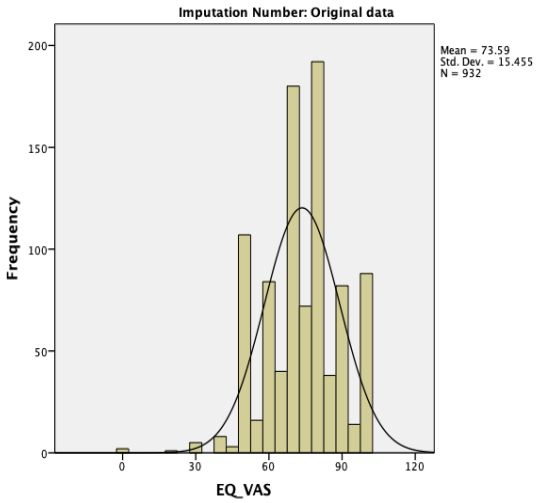


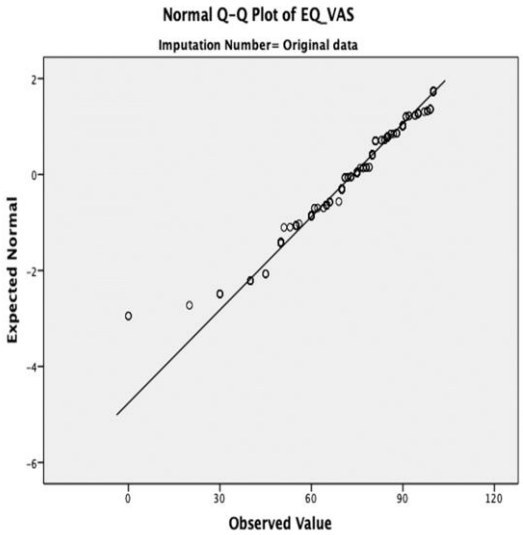


Variable	Kolmogorov-Smirnov test			Shapiro-Wilk test		
	Statistic	df	Sig.	Statistic	df	Sig.
EQ-5D UI	.314	932	.000	.615	932	.000

From visual inspection, the variable EQ-5D UI was considered not to be normally distributed as the frequency distribution showed left skewness with clustering at '1.000', and the Q-Q plot did not form a straight diagonal line[55]. Moreover, both the Lilliefors corrected Kolmogorov-Smirnov and Shapiro-Wilks's tests were statistically significant ($p < 0.05$). Therefore, the variable EQ-5D UI was not normally distributed.

EQ-5D Visual Analogue Scale



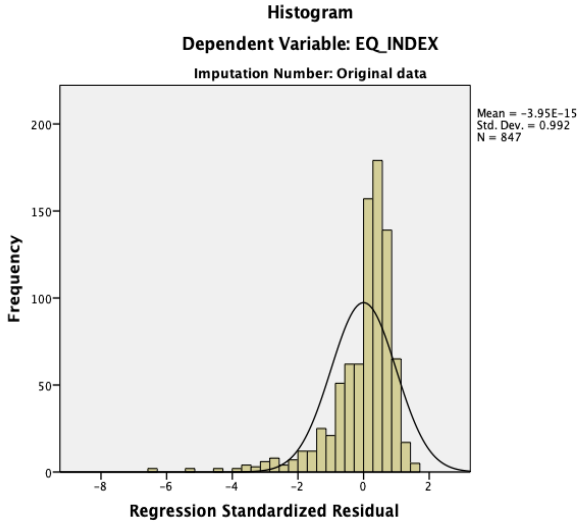


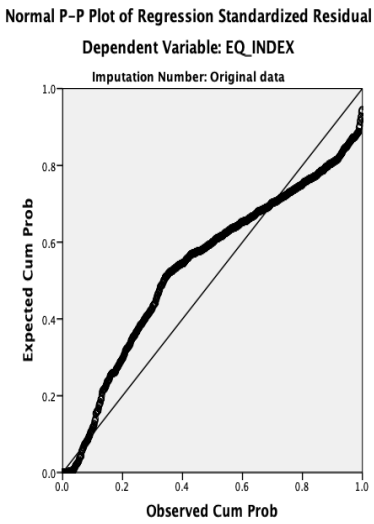
Variable	Kolmogorov-Smirnov test			Shapiro-Wilk test		
	Statistic	df	Sig.	Statistic	df	Sig.
EQ-5D VAS	.122	932	.000	.957	932	.000

From visual inspection, the variable EQ-5D VAS was considered not to be normally distributed as the frequency distribution showed left skewness, and the Q-Q plot did not form a straight diagonal line[55]. Moreover, both the Lilliefors corrected Kolmogorov-Smirnov and Shapiro-Wilks's tests were statistically significant ($p < 0.05$). Therefore, the variable EQ-5D VAS was not normally distributed.

Appendix 4-9. Normality tests for dependent variables – EQ-5D UI & EQ-5D VAS (Continued)

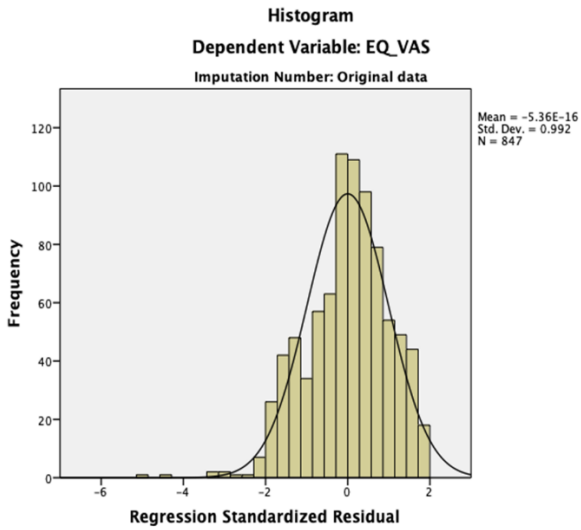
EQ-5D UI Residual

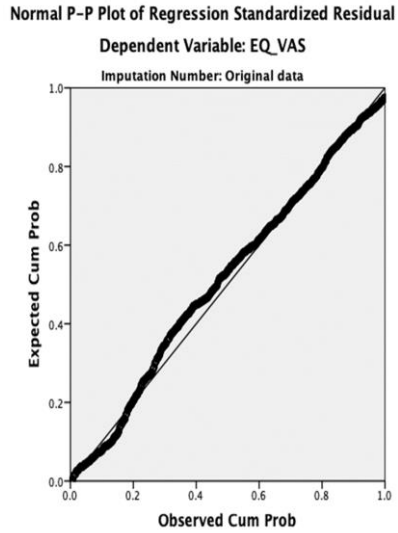




From visual inspection, the EQ-5D UI residuals showed left skewness in the frequency distribution, and the P-P plot did not form a straight diagonal line[55]. Therefore, the residuals of EQ-5D UI was not normally distributed.

EQ-5D VAS Residual





From visual inspection, the EQ-5D VAS residuals showed left skewness in the frequency distribution, and the P-P plot did not form a straight diagonal line[55]. Therefore, the residuals of EQ-5D VAS was not normally distributed.

Appendix 4-10. Multicollinearity Tests

Variance Inflation Factor

Variables	**VIF**
First Language	Constant
Marital Status	1.141
Education Level	1.205
Housing Type	1.212
Ownership Status of Current Housing	1.192
Monthly Household Income	1.078

Variables	**VIF**
CDCS	Constant
ADC-SR	1.062
SDC-EMR	1.071
CMC	1.136

Appendix 4-11. Multivariable Regression Analysis using listwise deletion (n=847)

Table 1A: The Effect of Sociodemographic and Clinical Predictor Variables on Depression and Anxiety of Recruited Participants (n=847)

Predictor Variables	PHQ9			GAD7		
	Odds Ratio^	**95% CI^**	**p-value^**	**Odds Ratio^**	**95% CI^**	**p-value^**
Age						
<55 years old	REF			REF		
55-64 years old	1.29	0.57,2.94	0.55	0.87	0.44,1.73	0.70
65-74 years old	1.08	0.46,2.51	0.86	0.68	0.33,1.42	0.30
≥75 years old	1.47	0.53,4.07	0.46	1.02	0.40,2.63	0.96
Sex						
Male	REF			REF		
Female	0.95	0.59,1.53	0.84	1.24	0.78,1.99	0.37
Ethnicity						
Chinese	REF			REF		
Non-Chinese	1.02	0.33,3.12	0.98	0.73	0.26,2.03	0.54
First Language						
English	REF			REF		
Mandarin	0.90	0.46,1.79	0.77	0.68	0.36,1.27	0.22
Chinese Dialects	1.17	0.55,2.50	0.69	0.56	0.26,1.21	0.14
Others	1.92	0.60,6.13	0.27	1.70	0.58,4.99	0.34
Marital Status						
Married	REF			REF		
Single/Separated/Divorced/Widowed	2.05	1.19,3.55	**0.01***	1.66	0.95,2.90	0.08
Education Level						
No Formal Education	REF			REF		
Primary	1.05	0.56,1.98	0.87	1.26	0.65,2.47	0.50
Secondary	0.74	0.36,1.52	0.41	0.63	0.29,1.35	0.23
Post-Secondary	0.59	0.22,1.54	0.28	0.88	0.35,2.17	0.77
Housing Type						
HDB 1/2/3 Room	REF			REF		
HDB 4 Room	0.76	0.43,1.32	0.33	0.78	0.43,1.42	0.41
HDB 5 Room/HUDC	0.71	0.36,1.41	0.33	1.40	0.73,2.69	0.31
Private Housing	0.67	0.27,1.67	0.39	0.79	0.32,1.98	0.61
Ownership Status of Current Housing						
Owner	REF			REF		
Non-Owner	0.88	0.48,1.61	0.67	0.80	0.42,1.52	0.50
Monthly Household Income						
<SGD2,000	REF			REF		
SGD2,000 – SGD3,999	1.11	0.59,2.10	0.74	1.56	0.85,2.86	0.16
SGD4,000 – SGD5,999	1.01	0.42,2.41	0.98	0.90	0.40,2.06	0.81
≥SGD6,000	1.73	0.78,3.82	0.18	1.28	0.57,2.86	0.55
Income not disclosed	0.55	0.30,1.02	0.06	0.78	0.43,1.45	0.44

^Odds ratio, 95% CI and p-values were obtained from logistic regression; REF – reference group; *p<0.05 is considered statistically significant.

Table 1A: The Effect of Sociodemographic and Clinical Predictor Variables on Depression and Anxiety of Recruited Participants (n=847) (continued)

Predictor Variables	PHQ9			GAD7		
	Odds Ratio^	**95% CI^**	**p-value^**	**Odds Ratio^**	**95% CI^**	**p-value^**
Body Mass Index (BMI)	0.96	0.90,1.01	0.13	1.00	00.94,1.05	0.87
Chronic Disease Control Score (CDCS)						
1	REF			REF		
2	1.33	0.77,2.30	0.31	1.12	0.64,1.96	0.69
3	0.91	0.46,1.78	0.78	1.10	0.58,2.09	0.78
4	0.48	0.13,1.73	0.26	0.69	0.22,2.20	0.53
Additional Disease Count – Self Reported (ADC-SR)						
0	REF			REF		
1	1.35	0.82,2.23	0.24	0.98	0.59,1.61	0.93
2+	2.86	1.53,5.34	**0.001***	2.08	1.10,3.91	**0.024***
Additional Disease Count – Electronic Medical Records (ADC-EMR)						
0	REF			REF		
1	0.99	0.54,1.83	0.99	0.55	0.32,0.96	**0.034***
2+	1.02	0.53,1.95	0.95	0.62	0.34,1.12	0.11
Chronic Medication Count (CMC)	1.06	0.95,1.19	0.31	1.06	0.95,1.19	0.30

^Odds ratio, 95% CI and p-values were obtained from logistic regression; REF – reference group; *p<0.05 is considered statistically significant.

Table 1B: The Effect of Sociodemographic and Clinical Predictor Variables on Quality of Life of Recruited Participants (n=847)

Predictor Variables	EQ5D-UI					EQ5D-VAS				
	Unadjusted Mean (SD)	**Adjusted Mean (SE)**	**Beta Coefficient^**	**95% CI^**	**p-value^**	**Unadjusted Mean (SD)**	**Adjusted Mean (SE)**	**Beta Coefficient^**	**95% CI^**	**p-value^**
Age										
<55 years old	0.900 (0.186)	0.870 (0.018)	REF			71.3 (17.1)	73.1 (1.8)	REF		
55-64 years old	0.907 (0.156)	0.877 (0.013)	0.007	-0.031,0.046	0.71	72.6 (14.7)	73.8 (1.3)	0.010	-0.037,0.058	0.67
65-74 years old	0.908 (0.151)	0.876 (0.013)	0.007	-0.033,0.047	0.74	74.3 (15.4)	74.7 (1.3)	0.023	-0.026,0.072	0.37
≥75 years old	0.869 (0.173)	0.837 (0.018)	-0.039	-0.090,0.013	0.15	75.5 (14.2)	75.3 (1.8)	0.030	-0.032,0.091	0.34
Sex										
Male	0.922 (0.142)	0.880 (0.013)	REF			72.0 (14.4)	73.3 (1.3)	REF		
Female	0.877 (0.178)	0.849 (0.012)	-0.036	-0.061,-0.012	**0.004***	75.3 (16.1)	75.2 (1.3)	0.025	-0.004,0.054	0.09
Ethnicity										
Chinese	0.908 (0154)	0.863 (0.013)	REF			73.5 (15.0)	72.8 (1.3)	REF		
Non-Chinese	0.868 (0.186)	0.866 (0.019)	0.003	-0.050,0.057	0.91	73.7 (16.4)	75.6 (2.0)	0.038	-0.028,0.103	0.26
First Language										
English	0.927 (0.138)	0.876 (0.016)	REF			71.3 (15.1)	74.3 (1.6)	REF		
Mandarin	0.909 (0.156)	0.880 (0.017)	0.005	-0.027,0.037	0.77	74.1 (14.5)	75.7 (1.7)	0.019	-0.021,0.059	0.35
Chinese Dialects	0.893 (0.162)	0.872 (0.018)	-0.004	-0.043,0.034	0.82	74.6 (15.5)	73.9 (1.8)	-0.004	-0.051,0.042	0.85
Others	0.850 (0.197)	0.830 (0.020)	-0.053	-0.112,0.006	0.08	73.9 (17.1)	73.0 (2.0)	-0.017	-0.087,0.054	0.65
Marital Status										
Married	0.913 (0.150)	0.883 (0.012)	REF			73.3 (15.1)	74.8 (1.2)	REF		
Single/Separated/Divorced/Widowed	0.859 (0.191)	0.846 (0.014)	-0.042	-0.073,-0.011	**0.009***	74.1 (16.0)	73.7 (1.4)	-0.015	-0.051,0.022	0.43
Education Level										
No Formal Education	0.892 (0.152)	0.878 (0.017)	REF			80.5 (16.3)	81.7 (1.8)	REF		
Primary	0.876 (0.187)	0.845 (0.014)	-0.039	-0.074,-0.004	**0.03***	72.6 (16.0)	73.5 (1.5)	-0.106	-0.146,-0.067	**<0.0001***
Secondary	0.922 (0.133)	0.874 (0.014)	-0.005	-0.042,0.033	0.80	71.9 (13.4)	72.1 (1.3)	-0.124	-0.168,-0.081	**<0.0001***
Post-Secondary	0.919 (0.160)	0.861 (0.016)	-0.019	-0.066,0.027	0.41	70.6 (13.9)	70.1 (1.6)	-0.153	-0.209,-0.097	**<0.0001***
Housing Type										
HDB 1/2/3 Room	0.889 (0.176)	0.851 (0.015)	REF			73.2 (15.2)	72.7 (1.5)	REF		
HDB 4 Room	0.891 (0.161)	0.854 (0.013)	0.004	-0.027,0.035	0.81	73.8 (14.8)	74.0 (1.3)	0.018	-0.019,0.055	0.33
HDB 5 Room/HUDC	0.910 (0.159)	0.863 (0.014)	0.014	-0.022,0.050	0.45	73.7 (16.5)	75.3 (1.4)	0.035	-0.008,0.078	0.11
Private Housing	0.940 (0.127)	0.891 (0.018)	0.046	0.002,0.091	**0.04***	72.6 (14.5)	75.0 (1.9)	0.031	-0.024,0.085	0.27

^Beta coefficient, 95% CI and p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 are considered statistically significant

Table 1B: The Effect of Sociodemographic and Clinical Predictor Variables on Quality of Life of Recruited Participants (n=847) (continued)

Predictor Variables	EQ5D-UI					EQ5D-VAS				
	Unadjusted Mean (SD)	Adjusted Mean (SE)	Beta Coefficient^	95% CI^	p-value^	Unadjusted Mean (SD)	Adjusted Mean (SE)	Beta Coefficient^	95% CI^	p-value^
Ownership Status of Current Housing										
Owner	0.910 (0.148)	0.865 (0.012)	REF			73.3 (14.7)	73.9 (1.2)	REF		
Non-Owner	0.866 (0.206)	0.864 (0.015)	-0.001	-0.034,0.033	0.97	74.6 (17.4)	74.6 (1.5)	0.010	-0.029,0.049	0.62
Monthly Household Income										
<SGD2,000	0.900 (0.168)	0.877 (0.013)	REF			75.4 (15.1)	75.6 (1.3)	REF		
SGD2,000 – SGD3,999	0.903 (0.135)	0.862 (0.016)	-0.017	-0.051,0.017	0.33	71.7 (14.8)	72.7 (1.6)	-0.039	-0.081,0.002	0.06
SGD4,000 – SGD5,999	0.936 (0.135)	0.878 (0.018)	0.002	-0.038,0.043	0.92	74.5 (13.5)	76.5 (1.9)	0.012	-0.037,0.061	0.63
≥SGD6,000	0.913 (0.162)	0.849 (0.019)	-0.032	-0.075,0.011	0.14	72.8 (14.9)	75.3 (2.0)	-0.004	-0.056,0.048	0.88
Income not disclosed	0.884 (0.173)	0.857 (0.014)	-0.023	-0.053,0.007	0.14	72.0 (16.3)	71.1 (1.4)	-0.061	-0.097,-0.025	**0.001***
Body Mass Index (BMI)	NA	NA	-0.003	-0.006,0.000	**0.023***	NA	NA	-0.002	-0.006,0.001	0.20
Chronic Disease Control Score (CDCS)										
1 (All 3 conditions optimally controlled)	0.894 (0.171)	0.854 (0.014)	REF			72.7 (15.1)	72.6 (1.4)	REF		
2 (1 condition sub-optimally controlled)	0.914 (0.149)	0.866 (0.012)	0.014	-0.014,0.042	0.33	73.8 (15.4)	74.5 (1.2)	0.030	-0.004,0.064	0.09
3 (2 conditions sub-optimally controlled)	0.875 (0.179)	0.843 (0.014)	-0.014	-0.048,0.02	0.43	74.0 (15.0)	75.6 (1.4)	0.040	0.000,0.081	0.05
4 (3 conditions sub-optimally controlled)	0.939 (0.101)	0.895 (0.023)	0.047	-0.006,0.100	0.08	73.4 (15.8)	74.1 (2.4)	0.021	-0.045,0.086	0.54
Additional Disease Count – Self Reported (ADC-SR)										
0	0.934 (0.136)	0.914 (0.013)	REF			73.8 (15.4)	74.7 (1.2)	REF		
1	0.885 (0.164)	0.871 (0.013)	-0.048	-0.073,-0.023	**<0.0001***	73.4 (15.3)	74.2 (1.3)	-0.007	-0.037,0.023	0.64
2+	0.817 (0.201)	0.811 (0.017)	-0.119	-0.159,-0.079	**<0.0001***	72.8 (14.6)	73.8 (1.7)	-0.012	-0.057,0.032	0.59
Additional Disease Count – Electronic Medical Records (ADC-EMR)										
0	0.924 (0.122)	0.869 (0.015)	REF			73.4 (15.5)	74.4 (1.5)	REF		
1	0.911 (0.162)	0.869 (0.013)	0.000	-0.029,0.029	0.99	74.1 (15.1)	74.8 (1.3)	0.006	-0.029,0.041	0.75
2+	0.875 (0.179)	0.854 (0.013)	-0.017	-0.050,0.015	0.29	72.9 (15.3)	73.5 (1.3)	-0.012	-0.051,0.026	0.53
Chronic Medication Count (CMC)	NA	NA	-0.004	-0.009,0.002	0.24	NA	NA	-0.008	-0.015,-0.001	**0.024***

^Beta coefficient, 95% CI and p-values were obtained from linear regression with log link function; REF – reference group; *p<0.05 is considered statistically significant

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CHAPTER FIVE

General Discussions and Conclusions

1 Introduction

The major gaps in multimorbidity research concern the immaturity of the different measurements of multimorbidity: prevalence, levels of morbidity burden, and outcomes. Therefore, this thesis aimed to narrow these gaps by providing a uniform definition for multimorbidity in order to define the prevalence of multimorbidity in the primary care population in Singapore, identifying a list of instruments to measure the levels of multimorbidity and exploring some patient-reported outcomes and their association with different levels of multimorbidity.

Three studies were conducted to achieve the above aims. Chapter Two reported the first study on the prevalence and patterns of multimorbidity: the title is 'The Prevalence and the common patterns of multimorbidity in Singapore: An Epidemiological Study based on Administrative Data' (PESAD); Chapter Three reported the systematic review and the title is 'A Systematic review on the Instruments used for measuring the level of multimorbidity' (SIM); Chapter Four reported the study of the outcomes of multimorbidity and the title is 'Multimorbidity and its association with depression, anxiety and quality of life' (MDAQ).

The thesis has met these aims. In Chapter Two (PESAD) on prevalence and patterns of multimorbidity, the study compared the standardised prevalence rates of multimorbidity based on two different multimorbidity lists (CDMP and Fortin lists) with two different cut-points, and identified the Fortin list with 'three or more' chronic conditions as a better definition of multimorbidity in the primary care population. The systematic review, Chapter Three (SIM), found 33 different instruments reported since January 2010 to August 2018 that were used to measure the levels of multimorbidity for specific outcomes in the primary care and general population. Finally, Chapter Four (MDAQ), a study of outcomes of multimorbidity, found that the outcomes depressive symptoms, anxiety symptoms, and quality of life of patients with multimorbidity were associated with different levels of multimorbidity.

Section 2 of this concluding chapter will elaborate further on these results and synthesise what was learnt from the findings reported in Chapters Two, Three and Four. Section 3 discusses the importance of considering age, sex and ethnicity when studying multimorbidity. Based on all the findings reported in Chapters Two, Three and Four, some new insights are shared in

Sections 4, 5 and 6 where the future directions in the conceptualisation of multimorbidity, future directions in multimorbidity research, and future directions in clinical practice will be discussed.

2 The measurement of multimorbidity

2.1 Defining multimorbidity

The fundamental reason for a wide variety of prevalence rates among multimorbidity studies is the contentious issues related to the definition of multimorbidity. On top of using reporting guidelines like RECORD[1] for Chapter Two (PESAD) on the prevalence and patterns of multimorbidity and STROBE[2] for Chapter Four (MDAQ) for the cross-sectional study on the outcomes of multimorbidity, five components of the definition of multimorbidity were also identified and included in both chapters. These five components were:

a) the types of conditions selected to form the multimorbidity list;
b) the total number of conditions considered in the multimorbidity list;
c) the data sources of the chronic conditions;
d) the cut-points used to define multimorbidity; and
e) the reference population.

When data were extracted for the included articles for the systematic review in Chapter Three (SIM), the provision of these five components were purposefully searched from each article. Only 34.3% of the included studies provided at least a brief statement of what a chronic condition was. The total number of conditions considered in the multimorbidity list ranged from seven to 147 diseases in this review but only slightly more than half of them, i.e., 56.7% of the studies, provided a full list of the conditions. Finally, only 34.3% of the studies stated clearly the cut-points they used to define multimorbidity. In total, only 20.9% of the studies included all three components, i.e., the definition of chronic condition, list of conditions and cut-points used to define multimorbidity. The data sources of the chronic conditions and the reference population were the only two components that were stated in all the included studies.

In Chapter Two (PESAD), different definitions of multimorbidity for determining the prevalence of multimorbidity in the Singapore primary care population were explored and it

was found that Fortin's list with a cut-off of 'three or more' conditions was clinically more meaningful. However, using 'three or more' conditions as a cut-off was not commonly used in multimorbidity studies. For the included studies in the systematic review in Chapter Three (SIM) where the cut-points was mentioned, only two studies used the cut-off of 'three or more' conditions[3-5]. The MDAQ study reported in Chapter Four used a cut-off of three specific chronic conditions as the inclusion criteria.

2.2 Measuring multimorbidity

Lefevre et al.[6] listed four common methods of measuring multimorbidity as described in Chapter One. They are: by simple counts of chronic diseases from a list of individual conditions (i.e., disease count), by grouping chronic diseases into dyads or triads (i.e., dyad and triad patterns), by identifying homogeneous groups of people with common disease and characteristics (i.e., non-random association patterns), and by using an index of variable complexity (i.e., weighted indices). However, this classification does not clearly explain the different purposes of measuring multimorbidity[7].

It is important to establish the purpose of measuring multimorbidity and to note that the same instrument can serve different purposes[8]. According to de Vet et al.[8], the three main purposes of measurement in medicine are for diagnosis, evaluation of intervention and prediction of outcome. Discriminant measurement is for diagnosis, evaluation measurement is for evaluation after an intervention, and predictive measurement is to predict a specific outcome. The studies conducted in this thesis have improved on the terminology of measuring multimorbidity based on Lefevre et al.'s[6] classification. Therefore, it is proposed that explicitly described measurements of multimorbidity should be upfront in all multimorbidity studies and should include the purpose, i.e., discriminant, evaluative or predictive, using de Vet et al.'s[8] framework. As the studies in this thesis did not involve intervention studies, the types of measurement of multimorbidity described in this thesis were mainly discriminant and predictive measurements. These two types of measurements are described below.

2.2.1 Discriminant measurement

Measuring the prevalence of multimorbidity is a discriminant measurement and using disease count is a common practice as used in Chapter Two (PESAD). For understanding the patterns of multimorbidity, 'dyads and triads' of combinations and random associations of chronic conditions are frequently used, and these are also discriminant measurements. 'Dyads and triads' was used in Chapter Two (PESAD) and distinct differences in patterns of multimorbidity between the different ethnic/sex groups were found.

Multimorbidity is common. Comparing the outcomes between patients with multimorbidity and no multimorbidity has already been well-established as described in Chapter One (*Section 4.1 to 4.3 p5-6*). However, in this thesis, measuring different levels of multimorbidity in Chapters Three (SIM) and Four (MDAQ) were also done. The frequent instruments used for measuring the level of multimorbidity include disease count, weighted indices of varying complexity, case-mix, and drug counts as reported in the systematic review. Chronic disease control score, additional disease count-self-reported, additional disease count-electronic medical records, and chronic medication count were used in Chapter Four (MDAQ). In de Vet et al.'s[8] framework, these instruments are also discriminant measurements as they distinguish among the different levels of multimorbidity.

Out of the four different instruments used in Chapter Four (MDAQ) that comprises of chronic disease control score (CDCS), additional disease count-self-reported (ADC-SR), additional disease count-electronic medical records (ADC-EMR), and chronic medication count (CMC), only CDCS was not found in the list of instruments identified in the systematic review in Chapter Three (SIM).

2.2.2 Predictive measurement

Chapters Three (SIM) and Four (MDAQ) also looked at the specific outcomes that were predicted******** by the different levels of multimorbidity. In this case, the different levels of multimorbidity were used as predictive measurements for specific outcomes like depressive

******** The term 'predicted' is used here to mean 'associated with' as the MDAQ study is a cross-sectional study whereby causal relationships cannot be ascertained.

symptoms, anxiety symptoms and quality of life in Chapter Four. However, when focusing on the independent variables, the differentiation of multimorbidity into different levels is a discriminant measurement as mentioned in Section 2.2.1 above.

Four different instruments in Chapter Four (MDAQ) were used to predict the outcomes of patients with multimorbidity in primary care using an observational interviewer-administered questionnaire. The study found that poorer disease control was associated with a better quality of life which was contrary to the hypothesis. It was postulated that when patients worked hard to keep all the three clinical parameters for each of the chronic diseases optimally controlled, the resultant treatment burden imposed on them led to a poorer quality of life. Conversely, those patients who chose not to be restrained by the treatment burden resulting in sub-optimal control of their clinical conditions experienced a better quality of life before illness burden became overbearing. This finding was interpreted based on the conceptual framework of minimally disruptive medicine that is described further in Section 4 later.

In summary, the work done in this thesis has improved the description and terminology of measurements of multimorbidity based on Lefevre et al.'s[6] classification. Authors should make it clear to readers whether investigators are discriminating between patients with multimorbidity or no multimorbidity, or among patients with different levels of multimorbidity. The same instrument, i.e., disease count, can be used as a prediction instrument for specific outcomes, or an evaluation instrument if there were an intervention. De Vet et al.[8] suggested to speak of discriminative, predictive or evaluative applications than of instruments because the same instrument can be used for different purposes.

2.3 Disease count by self-report or electronic medical records

In Chapter Three (SIM), out of the 33 instruments identified in the systematic review for measuring the level of multimorbidity, 21 of them were obtained from administrative or medical records, 12 of them were self-reported by participants of the studies, and two of the studies obtained data from both medical records and self-reports of participants. Despite the different sources of data on chronic conditions in these studies, the outcomes associated with the different levels of multimorbidity were all aligned.

However, in the study of outcomes of multimorbidity in Chapter Four (MDAQ), additional disease count-self reported (ADC-SR) and additional disease count-electronic medical record (ADC-EMR) were associated in different directions for the patient-reported outcome of anxiety symptoms. A higher number of ADC-SR was associated with a higher level of anxiety, but a higher number of ADC-EMR was associated with a lower level of anxiety. (*Chapter Four Table 4-12 p199*).

Additionally, there was, at the most only, moderate agreement between the two data sources for 15 chronic conditions. The one exception was for the condition 'stroke' where there was substantial agreement. The patient-reported outcomes (depressive symptoms, anxiety symptoms, and quality of life) associated with ADC-SR were aligned with the findings of the systematic review in Chapter Three (SIM) but not ADC-EMR. The implications of this disparity are discussed further in Section 4.

3 Age, sex and ethnicity

This section looks at the significance of considering age, sex and ethnicity when studying multimorbidity especially in a multi-ethnic society of Singapore that comprises the three main ethnic groups of Chinese, Malay and Indian.

3.1 Age

Age was related to the standardised prevalence rates of multimorbidity in Chapter Two (PESAD) in much the same way as in the literature[9-16] with a rise in the prevalence rates with advancing age. Similarly, in Chapter Four (MDAQ), it was found that being in the oldest age group was associated with a lower quality of life (EQ-5D utility index) compared to those less than 55 years old, which was consistent with previous literature[17,18].

3.2 Sex

Although the evidence of an association between multimorbidity and sex has not been consistent across studies[19], investigators who conducted multimorbidity studies in primary care found no sex differences in the prevalence of multimorbidity[20-24]. Similarly, in Chapter

Two (PESAD), no sex differences in the standardised prevalence rates of multimorbidity was found. Sex was also not found to be associated with depressive symptoms, anxiety symptoms, or quality of life in the MDAQ study (*Chapter Four*).

3.3 Ethnicity

The literature on race or ethnic group in relation to multimorbidity is sparse as shown by the systematic review in Chapter Three (SIM) finding that only two[25,26] of 22 studies using prognostic models included race. Therefore, the addition this thesis makes to the literature is somewhat original and potentially important. In the descriptive study on the prevalence and patterns of multimorbidity in Chapter Two (PESAD), the standardised prevalence rates were not found to be clinically different among the three major ethnic groups of Singapore (Chinese, Malay, and Indian) for those age from 0 to 99. However, different distinct patterns of dyads and triads of multimorbidity were noted between the different ethnic/sex groups for those ages 45 years old and above. The latter finding indicates how potentially important it will be for future studies in multi-ethnic communities to identify any clinically important differences in the patterns of dyads and triads, to prepare clinicians to provide appropriate care, hopefully using relevant guidelines developed for the unique communities of patients. Ethnicity was not found to be associated with depressive symptoms, anxiety symptoms, or quality of life in Chapter Four (MDAQ).

4 Future directions in the conceptualisation of multimorbidity

Chapter One introduced two concepts/frameworks of relevance to multimorbidity: the Patient-Centred Clinical Method (PCCM); and Minimally Disruptive Medicine (MDM). The thesis findings resonate well with PCCM because the variable that was the most strongly associated with patient-reported outcomes was the patient self-reported count of chronic conditions. In other words, the patient's perspective, i.e., the measure of patients' self-reported conditions, was the most valid in terms of its relationship with outcomes. Once again, as has been found before in the literature, patient perceptions are the key to patient outcomes[27].

Minimally disruptive medicine (MDM) emphasises the importance of balancing the capacity of patients with the workload experienced by patients with multimorbidity. The workload of

such patients is imposed both by the treatment rendered by the health care providers (treatment burden) and the demands of life which are outside the control of health care providers[28]. The concept of MDM was used to explain the unexpected finding in the MDAQ study reported in Chapter Four where patients with multimorbidity that have poorer disease control were associated with a better quality of life. Buffel du Vaure et al.[29] reported that the potential workload for patients with multimorbidity in applying different clinical practice guidelines was too arduous and not practical for patients and inevitably induced poor adherence, wasted resources and poorer outcomes[29]. Similarly, the capacity of coping with multimorbidity was overwhelmed by the treatment burden imposed such that poorer surrogate outcomes (i.e., control of individual chronic conditions) were observed in patients who chose not to adhere to the clinical advice and therefore reported better quality of life.

While both concepts PCCM and MDM have been used to interpret the findings in Chapter Four (MDAQ), the prevalence study in Chapter Two (PESAD) highlighted the importance of individual chronic conditions that when combined, constituted the phenomenon of multimorbidity. The literature supports considering multimorbidity as an entity of interdependent parts which the PCCM advocates in its language about understanding the whole person. Cassel talks of this interdependence[30] and Koestler[31] described the 'wholes' that simultaneously are 'parts' of other 'wholes' as 'holons'. Single conditions are the 'parts' of multimorbidity ('whole'), and the same multimorbidity is also a 'part' or 'holon' of the overall health ('whole').

The new insights obtained from looking at how multimorbidity is formed from single conditions suggested that multiple conditions within an individual, are not necessarily caused by independent mechanisms[32]. A common underlying physiological disease process(es) may be at play. These underlying process(es) affect the whole individual across the molecular, personal and social domains of life and physiologically lead to a new state of objective and subjective adaptation. Recognising that multimorbidity reflects an underlying disturbance in a network of interlinked neuroendocrine, immunological and cellular processes allows clinicians and scientists to view an individual with multimorbidity as both a 'whole' and a 'part' of the bigger scheme of life.

Future directions should consider the notion of 'interdependence with an underlying unifying mechanism' together with PCCM and MDM in the conceptualisation of multimorbidity.

5 Future directions in multimorbidity research

The results of this thesis have led to the recognition of two important directions for multimorbidity research: involvement of patients in multimorbidity research; and the creation of the most appropriate data sources for the measurement of multimorbidity.

Involving the individuals with multimorbidity in priority setting and preferences in a resource-scarce climate in healthcare is both rational and ethical. The finding in this thesis, that patient self-reported measure of multimorbidity was the most highly associated with outcomes, supports this thrust. Besides, research into patients' perspectives on how multimorbidity affects their health, well-being, and clinical care is pertinent lest one falls into the McNamara fallacy†††††††† of focusing on certain metrics of measuring multimorbidity and neglecting the less easily quantifiable attributes of health care such as self-management behaviour and treatment burden[33]. The shift to involve patients in multimorbidity research will encompass abandoning a linear, reductionist view of the world to an integrated understanding of the complexity of multimorbidity and its management moving from 'what is the matter?' to 'what matters?'[34] to the patient.

The lack of a 'gold standard' data source in obtaining accurate medical conditions is a hurdle in multimorbidity research. There have been advocates in the scientific community to adopt real-world data (RDW) such as electronic medical records and administrative data for the evaluation of epidemiology and burden of disease, treatment patterns, adherence, persistence, and health outcomes of different treatments[35]. However, there are also concerns about their use[36,37], with similar apprehensions being echoed from findings in this thesis. Fundamentally, the problem lies in the messy evolvement of our medical records that have grown cumbersome for serving too many purposes[38]. A re-conceptualisation and further research work on how we document chronic conditions for patient care and clinical research is urgently needed. Until issues related to the re-conceptualisation of our current documentation of chronic conditions

†††††††† "*The first step of McNamara's fallacy is to measure whatever can easily be measured. This is OK as far as it goes. The second step is to disregard that which can't be easily measured or to give it an arbitrary quantitative value. This is artificial and misleading. The third step is to presume that what can't be measured easily really isn't important. This is blindness. The fourth step is to say that what can't be easily measured really doesn't exist. This is suicide."* (O'Mahony S. Medicine and the McNamara fallacy. *J R Coll Physicians Edinb* 2017;47(3):281-87.)

are addressed such that the documentation truly captures patients concerns, chronic conditions self-reported by patients would be the preferred data source for multimorbidity research for now.

Finally, researchers studying multimorbidity should aim to make their work reproducible by reporting their work transparently to allow direct and conceptual replication. All the work done for multimorbidity to improve the body of knowledge on the subject should be incremental and useful to the world literature. In preparing this thesis, it was found that most researchers were not as transparent as they should be, making it difficult to achieve the above aim. This is an area of improvement in multimorbidity research that should not be trivialised.

6 Future directions in clinical practice

System-level rationing is the norm in the current model of care where ageing and multimorbidity threatens the sustainability of many health care systems[40]. The findings in this thesis point to paying closer attention to the patients' perceptions of their morbidity as these are the measures that were related to the outcomes of interest and therefore the best solution for sustainability at the patient, clinician, and system level.

Care is better when it recognises what patients' defined problems are rather than focusing only on what the diagnoses are[41]. Health care providers should aim to provide minimally disruptive medicine by not focusing solely on improving clinical parameters as recommended by individual clinical practice guidelines[42]. The overall aim is to provide patient-centred care as described by Stewart et al.[43], the 'willingness to become involved in the full range of difficulties individuals bring to their doctors, and not just their biomedical problems'. However, medical education in the last few decades has concentrated on the latter and promoted reductionism, specialisation, mechanistic models of disease, and faith in a definitive cure[44]. The way we deliver caregiving will have to be revamped in both undergraduate, postgraduate training and daily practice especially in our management of individuals with multimorbidity.

Although there were no clinically significant differences in the prevalence rates of multimorbidity between the different sexes and among the different ethnic groups, but importantly distinct patterns of multimorbidity were identified in the different ethnic and sex

groups in our population. Kastner et al.'s systematic review on effective interventions for managing multimorbidity in older adults also found the occurrence of commonly occurring diseases dyads like diabetes and cardiovascular diseases, and urged researchers to investigate the potential impact of interventions on these clusters of chronic conditions[45]. As such, primary care physicians should partake in the development of guidelines for the most common combinations of chronic conditions that are personalised to each subgroup. Ideally, the payoff time framework‡‡‡‡‡‡‡‡ should be included in the guidelines and preferably in electronic form individualised to each patient[46].

7 Conclusion

The research work undertaken in this thesis has added to the body of knowledge on the definition of multimorbidity and suggested the most appropriate data source for multimorbidity research pertaining to patient-reported outcomes in a multi-ethnic country. The thesis has also helped to improve on the terminology used in measuring multimorbidity and provided an updated list of instruments for measuring the level of multimorbidity in community-dwelling adults with multimorbidity bearing in mind that the same instrument may have several applications.

Developing strategies to manage individuals with multimorbidity on what truly matters to them will need further work. These will include the identification of the unifying underlying mechanism(s) in the development of multimorbidity, involvement of patients in multimorbidity research, and development of multimorbidity clinical practice guidelines targeting specific sex/ethnic groups for health care providers.

‡‡‡‡‡‡‡‡ The earliest time when cumulative incremental benefits attributable to a clinical guideline exceed cumulative incremental harms attributable to that guideline.

8 References

1. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885
2. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007;4(10):e297. doi: 10.1371/journal.pmed.0040297
3. Boeckxstaens P, Vaes B, Legrand D, et al. The relationship of multimorbidity with disability and frailty in the oldest patients: a cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. *Eur J Gen Pract* 2015;21(1):39-44. doi: 10.3109/13814788.2014.914167
4. Boeckxstaens P, Vaes B, Van Pottelbergh G, et al. Multimorbidity measures were poor predictors of adverse events in patients aged >/=80 years: a prospective cohort study. *J Clin Epidemiol* 2015;68(2):220-7. doi: 10.1016/j.jclinepi.2014.08.010
5. van den Bussche H, Schon G, Kolonko T, et al. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC geriatr* 2011;11:54. doi: 10.1186/1471-2318-11-54
6. Lefevre T, d'Ivernois JF, De Andrade V, et al. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. *Rev Epidemiol Sante Publique* 2014;62(5):305-14. doi: 10.1016/j.respe.2014.09.002
7. de Vet HCW, Terwee CB, Mokkink LB, et al. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
8. de Vet HCW, Terwee CB, Mokkink LB, et al. Chapter 3 - Development of a measurement instrument. Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press 2011.
9. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population attending primary care in Portugal: a cross-sectional study. *BMJ Open* 2015;5(9):e009287. doi: https://dx.doi.org/10.1136/bmjopen-2015-009287
10. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2
11. van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014;15:61. doi: 10.1186/1471-2296-15-61
12. Glynn LG, Valderas JM, Healy P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28(5):516-23. doi: 10.1093/fampra/cmr013
13. Laux G, Kuehlein T, Rosemann T, et al. Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project. *BMC Health Serv Res* 2008;8:14. doi: 10.1186/1472-6963-8-14
14. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011;61(582):e12-21. doi: https://dx.doi.org/10.3399/bjgp11X548929
15. Harrison C, Britt H, Miller G, et al. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014;4(7):e004694. doi: 10.1136/bmjopen-2013-004694

16. Schafer I, Hansen H, Schon G, et al. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. *BMC Health Serv Res* 2012;12:89.
17. Liddy C, Blazkho V, Mill K. Challenges of self-management when living with multiple chronic conditions: systematic review of the qualitative literature. *Can Fam Physician* 2014;60(12):1123-33.
18. Hunger M, Thorand B, Schunk M, et al. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. *Health Qual Life Outcomes* 2011;9:53. doi: 10.1186/1477-7525-9-53
19. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS ONE* 2014;9(7):e102149. doi: 10.1371/journal.pone.0102149
20. Britt HC, Harrison CM, Miller GC, et al. Prevalence and patterns of multimorbidity in Australia. *Med J Aust* 2008;189(2):72-7.
21. Brett T, Arnold-Reed DE, Popescu A, et al. Multimorbidity in patients attending 2 Australian primary care practices. *Ann Fam Med* 2013;11(6):535-42. doi: 10.1370/afm.1570
22. Ashman JJ, Beresovsky V. Multiple chronic conditions among US adults who visited physician offices: data from the National Ambulatory Medical Care Survey, 2009. *Prev Chronic Dis* 2013;10:E64. doi: 10.5888/pcd10.120308
23. Rizza A, Kaplan V, Senn O, et al. Age- and gender-related prevalence of multimorbidity in primary care: the Swiss FIRE project. *BMC Fam Pract* 2012;13:113. doi: 10.1186/1471-2296-13-113
24. Harrison C, Britt H, Miller G, et al. Prevalence of chronic conditions in Australia. *PLoS ONE* 2013;8(7):e67494. doi: https://dx.doi.org/10.1371/journal.pone.0067494
25. Saver BG, Wang CY, Dobie SA, et al. The central role of comorbidity in predicting ambulatory care sensitive hospitalizations. *Eur J Public Health* 2014;24(1):66-72. doi: 10.1093/eurpub/ckt019
26. Sullivan PW, Ghushchyan VH, Bayliss EA. The impact of co-morbidity burden on preference-based health-related quality of life in the United States. *Pharmacoeconomics* 2012;30(5):431-42. doi: 10.2165/11586840-000000000-00000
27. Stewart M, Brown JB, Donner A, et al. The impact of patient-centered care on outcomes. *J Fam Pract* 2000;49(9):796-804.
28. Leppin AL, Montori VM, Gionfriddo MR. Minimally Disruptive Medicine: A Pragmatically Comprehensive Model for Delivering Care to Patients with Multiple Chronic Conditions. *Healthcare (Basel)* 2015;3(1):50-63. doi: 10.3390/healthcare3010050
29. Buffel du Vaure C, Ravaud P, Baron G, et al. Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: a systematic analysis. *BMJ Open* 2016;6(3):e010119. doi: https://dx.doi.org/10.1136/bmjopen-2015-010119
30. Cassel EJ. The nature of suffering and the goals of medicine. *N Engl J Med* 1982;306(11):639-45. doi: 10.1056/nejm198203183061104 [published Online First: 1982/03/18]
31. Koestler A. The ghost in the machine. London: Hutchinson & Co (Publishers) Ltd 1967.
32. Sturmberg JP, Bennett JM, Martin CM, et al. 'Multimorbidity' as the manifestation of network disturbances. *J Eval Clin Pract* 2017;23(1):199-208. doi: 10.1111/jep.12587
33. O'Mahony S. Medicine and the McNamara fallacy. *J R Coll Physicians Edinb* 2017;47(3):281-87. doi: 10.4997/JRCPE.2017.315

34. Bayliss EA, Bonds DE, Boyd CM, et al. Understanding the context of health for persons with multiple chronic conditions: moving from what is the matter to what matters. *Ann Fam Med* 2014;12(3):260-9. doi: 10.1370/afm.1643
35. Mahajan R. Real world data: Additional source for making clinical decisions. *International journal of applied & basic medical research* 2015;5(2):82. doi: 10.4103/2229-516x.157148 [published Online First: 2015/06/23]
36. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J Med* 2016;375(23):2293-97. doi: 10.1056/NEJMsb1609216
37. Kim HS, Kim JH. Proceed with Caution When Using Real World Data and Real World Evidence. *J Korean Med Sci* 2019;34(4):e28. doi: 10.3346/jkms.2019.34.e28
38. Sinsky CA, Beasley JW, Simmons GE, et al. Electronic health records: design, implementation, and policy for higher-value primary care. *Ann Intern Med* 2014;160(10):727-8. doi: 10.7326/M13-2589
39. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. *Pharmacoepidemiol Drug Saf* 2017;26(9):1018-32. doi: 10.1002/pds.4295
40. Stange KC. A science of connectedness. *Ann Fam Med* 2009;7(5):387-95. doi: 10.1370/afm.990
41. Starfield B. Primary Care and Equity in Health: The Importance to Effectiveness and Equity of Responsiveness to Peoples' Needs. *Humanity & Society* 2009;33(1-2):56-73. doi: 10.1177/016059760903300105
42. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *Bmj* 2009;339:b2803. doi: 10.1136/bmj.b2803
43. Stewart M, Brown JB, Weston WW, et al. Patient-Centered Medicine: Transforming the Clinical Method. Third ed. Oxford, UK: Radcliffe Publishing 2014.
44. Grumbach K. Chronic illness, comorbidities, and the need for medical generalism. *Ann Fam Med* 2003;1(1):4-7.
45. Kastner M, Cardoso R, Lai Y, et al. Effectiveness of interventions for managing multiple high-burden chronic diseases in older adults: a systematic review and meta-analysis. *Cmaj* 2018;190(34):E1004-E12. doi: 10.1503/cmaj.171391
46. Braithwaite RS. Can life expectancy and QALYs be improved by a framework for deciding whether to apply clinical guidelines to patients with severe comorbid disease? *Med Decis Making* 2011;31(4):582-95. doi: 10.1177/0272989X10386117

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