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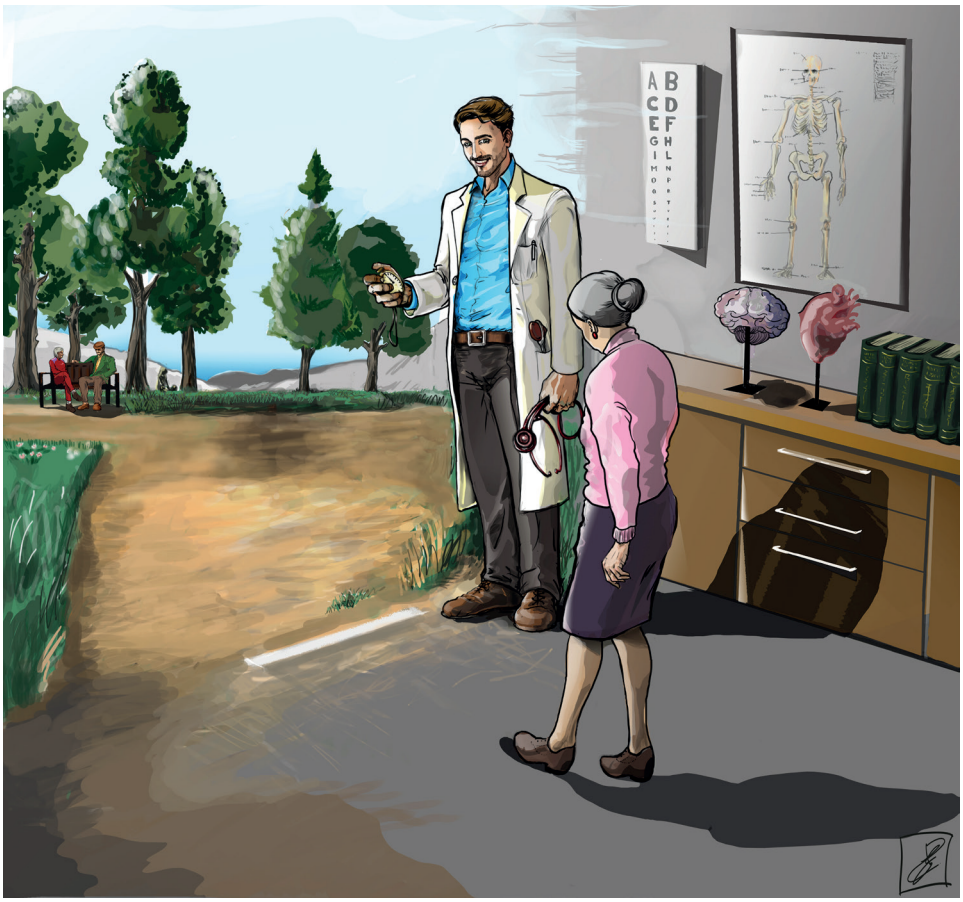
Impact of Cardiovascular and Neuropsychiatric Multimorbidity on Older Adults' Health



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IMPACT OF CARDIOVASCULAR AND NEUROPSYCHIATRIC MULTIMORBIDITY ON OLDER ADULTS' HEALTH

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Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health

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To my brother, Dario

To my parents, Francesca and Vincenzo

ABSTRACT

Multimorbidity, the presence of two or more chronic diseases in one person, is common in older people, and associates with a number of negative outcomes. In this thesis, we propose a methodology to assess and measure multimorbidity in older individuals. We use it to describe the longitudinal evolution and prognosis of multimorbidity clusters, and to investigate the extent to which clusters of cardiovascular and neuropsychiatric multimorbidity impact and interact with physical function. Data are from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), a population-based study including 3,363 community-dwelling and institutionalized individuals aged ≥60 years.

Study I. We provided a clinically driven list of 60 chronic diseases for the assessment of multimorbidity in older adults. After applying this methodology to the 3,363 SNAC-K participants, we found that 88.6% of them had two or more diseases, 73.2% had three or more diseases, and only 11.4% had zero or one single disease. Given the ceiling effect associated with the use of a cutoff, multimorbidity should be rather be considered as a continuous metric, which better reflects the progressive accumulation of diseases starting in early aging and continuing up to very late life.

Study II. We identified and traced the evolution of multimorbidity clusters over 12 years of 2,931 SNAC-K participants with two or more diseases. At baseline, 51.3% of participants were included in one of five clusters; the rest were part of an unspecified group, given that no disease patterns could cluster them. Cardiometabolic risk factors, the evolution of several diseases, and death may have steered most of the longitudinal transitions among the multimorbidity clusters we described over a period of 12 years.

Study III. We investigated the association of cardiovascular and neuropsychiatric multimorbidity with 9 years of change in walking speed and intact basic activities of daily living in 2,385 SNAC-K participants. Neuropsychiatric disease, alone or combined with cardiovascular disease, showed the strongest detrimental impact on functional decline. Cardiovascular multimorbidity showed an association solely with decline in walking speed.

Study IV. We studied the interplay between cardiovascular multimorbidity and functional impairment, as well as between neuropsychiatric multimorbidity and functional impairment, on all-cause and cause-specific mortality in 3,241 SNAC-K participants. Slow walking speed provided additional prognostic information in terms of all-cause and cause-specific mortality beyond the number of both cardiovascular and/or neuropsychiatric diseases.

Conclusions. The use of a standardized methodology to assess chronic disease and multimorbidity may enhance comparability across studies, settings, and geographical regions. Studying the natural evolution of multimorbidity in older individuals may help to better hypothesize about underlying mechanisms and provide important prognostic information. In this regard, multimorbidity clusters including cardiovascular and neuropsychiatric disease emerge as major determinants of functional decline and higher mortality rate. Finally, the adoption of a simple and easy-to-use measure of functional impairment such as walking speed may help health-care professionals identify older people affected by specific groups of chronic disease with similar needs, health trajectories, and prognoses.

Key words. Multimorbidity; multimorbidity clusters; chronic disease; walking speed; disability; older people; mortality; personalized medicine.

SAMMANFATNING

Multisjuklighet, närvaron av minst två kroniska sjukdomar hos en individ, är vanligt bland äldre och associerat med flera negativa hälsorelaterade utfall. I den här doktorsavhandlingen föreslår vi ett sätt att mäta och bedöma multisjuklighet hos äldre individer, metoden används för att förklara den longitudinella utvecklingen och prognosen för olika kluster av multisjuklighet. Vi undersöker till vilken grad olika kluster av kardiovaskulära och neuropsykiatriska sjukdomar påverkar och interagerar med fysisk funktion. Det här projektet baseras på data från the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), en befolkningsstudie med 3,363 hemmaboende och institutionaliserade individer från 60 år och uppåt.

Studie I. Vi skapade en kliniskt förankrad lista med 60 kroniska sjukdomar för att bedöma multisjuklighet hos äldre. Bland de 3,363 SNAC-K-deltagarna fann vi att 88.6% hade två eller fler kroniska sjukdomar, 73.2% hade tre eller fler kroniska sjukdomar och endast 11.4% hade ingen eller en kronisk sjukdom. Multisjuklighet borde ses som en pågående process av kroniska sjukdomars ackumulering som startar tidigt i åldrandet och fortsätter upp till mycket hög ålder.

Studie II. Vi identifierade och följde utvecklingen av olika kluster av multisjuklighet över 12 år för 2,931 SNAC-K-deltagare. Vid första mättillfället inkluderades 51.3% av deltagarna i ett av fem kluster, de resterande tillhörde en ospecificerad grupp eftersom de inte passade in i något sjukdomsmönster. Longitudinella övergångar mellan de kluster av multisjuklighet vi såg under 12 år berodde till stor del på kardiometaboliska riskfaktorer, utvecklandet av flera sjukdomar och mortalitet.

Studie III. Vi undersökte sambandet mellan kardiovaskulär och neuropsykiatrisk multisjuklighet med förändringar av gånghastighet och förmågan av aktiviteter i dagligt liv (ADL) hos 2,385 SNAC-K-deltagare över 9 år. Neuropsykiatrisk sjukdom, ensam eller i kombination med kardiovaskulär sjukdom, försämrade funktionen mest. Kardiovaskulär multisjuklighet var enbart associerat med en försämring i gånghastighet.

Studie IV. Vi studerade samspelet mellan kardiovaskulär multisjuklighet och nedsatt funktion, samt mellan neuropsykiatrisk multisjuklighet och nedsatt funktion i relation till dödlighet (alla orsaker och orsaks-specifik) hos 3,241 SNAC-K-deltagare. Långsam gånghastighet ger ytterligare prognostisk information om dödlighet (alla orsaker och orsaks-specifik), utöver antalet av kardiovaskulära och/eller neuropsykiatriska sjukdomar.

Slutsats. En standardiserad metod för att bedöma kroniska sjukdomar och multisjuklighet kan förbättra jämförelsebarheten mellan studier, miljöer och geografiska regioner. Att studera utvecklingen av multisjuklighet bland äldre kan bidra till bättre hypoteser om underliggande mekanismer och ge viktig prognostisk information. Kluster av multisjuklighet som innefattar kardiovaskulära och neuropsykiatriska sjukdomar är viktiga bestämmande faktorer för försämrad funktion och högre dödlighet. Användandet av en enkel och lätt mätning av nedsatt funktion, såsom gånghastighet, kan hjälpa hälsovårdspersonal att identifiera äldre personer med specifika kluster av kroniska sjukdomar med liknande behov, hälsoutveckling och prognos.

Nyckelord: multisjuklighet; kluster av multisjuklighet; kronisk sjukdom; gånghastighet; nedsatt funktion; äldre; dödlighet; personcentrerad vård.

RIASSUNTO

La multimorbilità, la presenza di due o più malattie nello stesso individuo, è una condizione frequente negli anziani, e si associa a numerosi eventi avversi. Nella presente tesi proponiamo una metodologia per la valutazione della multimorbilità nelle persone anziane, e impieghiamo la stessa per descrivedere l'evoluzione e la prognosi di diversi clusters di multimorbilità, nonchè per valutare in che misura cluster di malattie cardiovascolari e neuropsichiatriche impattino sulla funzione fisica. I dati derivano da uno studio di popolazione, lo Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), che include 3,363 persone di 60 anni o più, che vivono al proprio domicilio o in istituzione.

Studio I. In questo studio proponiamo l'utilizzo di una lista di 60 malattie croniche, selezionate su base clinica, per la valutazione della multimorbilità negli anziani. Applicando tale metodologia nei 3,363 partecipanti di SNAC-K, l'88.6% e il 73.2% di essi risultava affetto rispettivamente da due o più e da tre o più malattie. Solo l'11.4% presentava zero o una malattia. Alla luce della facile saturazione di questi cutoff sarebbe preferibile considerare la multimorbilità come una misura continua che rispecchia l'accumulo di malattie che ha inizio in età adulta e continua sino ad età avanzate.

Studio II. 2,931 partecipanti di SNAC-K sono stati suddivisi in cluster, in funzione dei pattern di multimorbilità espressi, e seguiti per 12 anni. Al baseline, 51.3% dei partecipanti è stato incluso in uno dei cinque cluster identificati. I restanti sono stati definiti come "non classificabili" poichè non caratterizzabili sul piano del pattern di malattie. Diversi fattori di rischio cardiovascolare, l'evoluzione e la complicazione delle stesse malattie, così come la morte, potrebbero essere responsabili della maggior parte delle transizioni tra cluster osservate durante i 12 anni di follow-up.

Studio III. Abbiamo valutato in 2,385 partecipanti di SNAC-K la associazione della multimorbilità cardiovascolare e neuropsichiatrica con la variazione della velocità del cammino e il numero delle attività del vivere quotidiano intatte durante 9 anni. Le malattie neurospichiatriche, da sole o in combinazione con le cardiovascolari, esprimono rispetto ad altre il più forte impatto negativo sulla funzione. La multimorbilità cardiovascolare è associata selettivamente con la velocità del cammino.

Studio IV: Abbiamo studiato come le malattie cardiovascolari e neuropsichiatriche interagiscono con la ridotta velocità del cammino nell'associazione con la mortalità in 3,241 partecipanti di SNAC-K. La ridotta velocità del cammino sembra conferire un valore prognostico aggiuntivo, in termini di mortalità, alla conta delle delle malattie cardiovascolari e/o neuropsichiatriche, ed in particolare rispetto alla mortalità per cause cardiovascolari.

Conclusioni. L'utilizzo di una metodologia standardizzata per la valutazione delle malattie croniche e della multimorbilità può aumentare la comparabilità tra diversi studi, setting e regioni geografiche. Studiare l'evoluzione naturale della multimorbilità in persone anziane può aiutare a generare nuove ipotesi sui possibili meccanismi coinvolti e a fornire importanti informazioni di tipo prognostico. I cluster di malattie cardiovascolari e neuropsichiatriche emergono come un importante determinante di declino funzionale e mortalità. Infine, l'impiego di un semplice strumento per la valutazione della funzione fisica, quale la velocità del cammino, permette di identificare omogenei gruppi di individui che condividono simili traiettorie di salute e prognosi.

Keywords: multimorbilità, cluster di multimorbilità, malattie croniche, velocità del cammino, disabilità, anziani, mortalità, medicina personalizzata.

摘要

多重慢性疾病被定义为在同一人中存在两种或以上的慢性疾病；它在老年人群中很常见，并伴有许多不良后果。在本论文中，我们提出了一种在老年人群中评估和测量多重慢性疾病的方法，并以此来描述慢性疾病群的演变和预后，以及研究心血管性和神经精神性多重慢性疾病对身体机能的影响。我们使用的数据来自Swedish National Study on Aging and Care in Kungsholmen （SNAC-K）队列。此队列是一个基于3363名年龄60岁及以上居住在社区或收容机构的老年人的人群研究队列。

课题一：我们基于临床上60种慢性疾病对老年人中的多重慢性疾病进行了评估。在3363名SNAC-K参加者中，我们发现88.6%的人患有两种或以上慢性疾病，73.2%的人患有三种或以上慢性疾病，而只有11.4%的人未患任何或只患有一种慢性疾病。因此，多重慢性疾病应被视为一个，始于衰老早期至生命晚期的慢性疾病的持续积累的过程。

课题二：我们用2931名患有两种或以上慢性疾病的SNAC-K参加者的12年随访数据，分析并追踪了多重慢性疾病群的演变过程。在基线时，51.3%的参加者属于五个疾病群中的任意一个，而剩余的参加者都属于一个非特定疾病群体，由于没有任何一种疾病模式能够将他们划分在一起。心脏代谢风险因素、几种疾病的演变、以及死亡可能在12年随访间驱使了大部分多重慢性疾病群的演变。

课题三：我们用2385名SNAC-K参加者的数据研究了心血管性多重慢性疾病和神经精神性多重慢性疾病与9年随访中步行速度变化和日常生活活动之间的相关性。单独或伴有心血管疾病的神经精神疾病对身体机能衰退有最为不利的影响。心血管性多重慢性疾病仅与步行速度下降相关。

课题四：我们用3241名SNAC-K参加者的数据研究了心血管性多重慢性疾病与身体机能障碍的交互作用，以及神经精神性多重慢性疾病与身体机能障碍的交互作用，对全因死亡率和死因别死亡率的影响。我们发现，除心血管和/或神经精神疾病数量以外，较慢的步行速度能为全因死亡率和死因别死亡率提供额外的预后信息。

结论：使用标准化方法评估慢性疾病和多重慢性疾病可以提高不同研究、人群、和地理区域间的可比性。研究老年人群种多重慢性疾病的自然演变可助于更好地研究潜在机制并提供重要的预后信息。心血管和神经精神疾病在内的多重慢性疾病群是身体机能衰退和高死亡率的主要决定因素。最后，采用简单易用的身体机能测量方法（如步行速度）可以帮助专业医疗人员在老年人群中识别具有相似的需求、健康轨迹、和预后的慢性疾病患者。

关键词：多重慢性疾病；多重慢性疾病群；慢性疾病；步行速度；失能；老年人；死亡率；个性化医疗

LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the following original papers, which will be referred to in the text as studies I, II, III, and IV.

I. Calderón-Larrañaga A, **Vetrano DL (co-first author)**, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfí A, Pisciotta MS, Angleman S, Melis RJF, Santoni G, Mangialasche F, Rizzuto D, Welmer AK, Bernabei R, Prados-Torres A, Marengoni A, Fratiglioni L. Assessing and measuring chronic multimorbidity in the older population: A proposal for its operationalization. J Gerontol A Biol Sci Med Sci. 2017 Oct 1;72(10):1417–1423.

II. **Vetrano DL**, Roso-Llorach A (co-first author), Fernández S, Guisado-Clavero M, Violán C, Onder G, Fratiglioni L, Calderón-Larrañaga A, Marengoni A. Twelve-year clinical trajectories of multimorbidity in older adults: A population-based study. *Submitted.*

III. **Vetrano DL**, Rizzuto D, Calderón-Larrañaga A, Onder G, Welmer AK, Bernabei R, Marengoni A, Fratiglioni L. Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: A Swedish cohort study. PLoS Med. 2018 Mar 6;15(3):e1002503.

IV. **Vetrano DL,** Rizzuto D, Calderón-Larrañaga A, Onder G, Welmer AK, Qiu C, Bernabei R, Marengoni A, Fratiglioni L. Walking speed drives the prognosis of older adults with cardiovascular and neuropsychiatric multimorbidity. *Submitted*.

OTHER SCIENTIFIC PAPERS RELATED TO THE TOPIC OF THIS DOCTORAL THESIS - SELECTED

Marengoni A, **Vetrano DL**, Calderón-Larrañaga A, Onder G. Multimorbidity and patient-centered care in the 3D trial. Lancet. 2019 Jan 12;393(10167):127–128.

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Zucchelli A, **Vetrano DL (co-first author)**, Marengoni A, Grande G, Romanelli G, Calderón-Larrañaga A, Fratiglioni L, Rizzuto D. Frailty predicts short-term survival even in older adults without multimorbidity. Eur J Intern Med. 2018 Oct;56:53–56.

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Calderón-Larrañaga A, Santoni G, Wang HX, Welmer AK, Rizzuto D, **Vetrano DL**, Marengoni A, Fratiglioni L. Rapidly developing multimorbidity and disability in older adults: Does social background matter? J Intern Med. 2018 May;283(5):489–499.

Vetrano DL, Calderón-Larrañaga A (co-first author), Marengoni A, Onder G, Bauer JM, Cesari M, Ferrucci L, Fratiglioni L. An international perspective on chronic multimorbidity: Approaching the elephant in the room. J Gerontol A Biol Sci Med Sci. 2018 Sep 11;73(10):1350–1356.

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
B-ADL	Basic Activities of Daily Living
BMI	Body Mass Index
CI	Confidence Interval
CNS	Central Nervous System
CV	Cardiovascular
DALYs	Disability-Adjusted Life Years
ESPEN	European Society for Clinical Nutrition and Metabolism
HR	Hazard Ratio
IANA	International Academy on Nutrition and Aging
I-ADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
MMSE	Mini Mental State Examination
MSK	Musculoskeletal
N	Number
NPR	National Patient Register
NP	Neuropsychiatric
O/E	Observed/Expected
OR	Odds Ratio
RERI	Relative Excess Risk Due to Interaction
RCT	Randomized Controlled Trial
SD	Standard Deviation
SNAC-K	Swedish National Study in Aging and Care in Kungsholmen
TAME	Targeting Aging with Metformin
WHO	World Health Organization
WS	Walking Speed

1 INTRODUCTION

1.1 HEALTH AND AGING

1.1.1 The aging population

Individuals live longer than in past decades as a result of improvements in the biomedical sciences and public health, and the development of modern preventive strategies and medical treatments. Together with dropping fertility rates, this has resulted in a dramatic increase in the absolute number and prevalence of older adults (2). By 2050, the percentage of the world's population over 60 years of age will nearly double, compared with 2015, increasing from 12% to 22%. In Sweden, by the same year, people older than 60 years will represent 30% of the population (3).

This massive expansion, especially of those older than 85 years, coupled with the contraction of the active-age population, poses a series of challenges for worldwide public financial, welfare, and health-care systems. Changes in the way health care is delivered and human and economic resources are allocated will soon be required (2). In this scenario, a strategy toward sustainability includes improving older adults' health, thus promoting their continued vitality and active participation in society for as long as possible.

1.1.2 Defining health in older age

If living longer was the main accomplishment of the past century, living healthier as long as possible is the current goal. Personal attitudes change during life, making people value different activities and aspirations at different ages. Older adults value the following capabilities: maintaining mobility, tightening relationships, coping with basic needs, being able to make decisions, and contributing actively to society. According to the World Health Organization (WHO), health in older age is a holistic attribute that enables older individuals to achieve goals that are important to them. Rather than the mere absence of disease, it is the ability to preserve and enhance those aspects of life that defines a good perception of health in older adults (2, 4).

Hence, the maintenance of physical and mental functions is essential to accomplishing life goals in all ages (4). However, older people are more likely to experience circumstances that undermine their functioning and limit their ability to fully carry out everyday activities, potentially leading to disability. Several conditions, including disease and socioeconomic disadvantage, contribute to accelerating the progressive functional decline experienced by older people. Buffering the negative impact of these factors on function, and compressing disability to the very last period of life, are the main goals of medical and public health interventions aimed at improving older adults' health (2, 4).

1.1.3 Health heterogeneity and complexity

Aging is a dynamic, multifaceted, and complex phenomenon, and its effects are reflected in the phenotypic heterogeneity of older people and their health (5). Lifelong exposure to combinations of intrinsic and environmental factors set the pace of aging (6). The aging process is accompanied by the accumulation of biological deficits that undermine the homeostatic balance of the organism, progressively leading to physical and cognitive impairment. Such impairment characterizes disadvantageous phenotypes predisposed to develop disability and

earlier mortality (7). This process is characterized by varied health trajectories and proceeds at varied speeds in different individuals. The concept of *frailty* identifies the tendency of phenotypically old persons to develop adverse outcomes and experience rapid changes in their health status (8). Chronic disease is among the most important determinants of frailty. To a certain extent, and with exceptions, disease may be thought of as the result of accrued biological impairment that, beyond certain thresholds, configures precise nosological entities (9). Notably, in older people, to be affected by multiple chronic diseases (*multimorbidity)*—rather than a single disease—represents the norm.

At an older age, many individuals enjoy good physical and mental functioning; others, however, may require assistance to accomplish daily basic activities at a younger age than their counterparts. Interestingly, frailty can occur also in the absence of a high disease burden (5, 10-13). One meta-analysis has shown that at least seven in ten frail older people suffer from multimorbidity, but less than two in ten older people with multimorbidity also exhibit frailty (9). On the one hand, these findings support the idea that a higher disease burden is associated with higher frailty. On the other, they confirm that most people with multimorbidity remain well functioning even in older ages. Understanding the determinants of frailty and functional impairment in the absence of overt disease and multimorbidity represents an interesting research question for future studies.

Assessing the health and care needs of older persons requires taking into consideration not only the burden of specific diseases but also the extent to which they interact and impact on function (2, 4, 14, 15). This holistic approach—as opposed to the unidimensional assessment of disease status—is the cornerstone of geriatric medicine, and is shown to better predict survival and other health-related outcomes in older adults (5). Health-care models that consider and manage the complex needs of older age in a multidimensional and integrated way have been shown to be more effective than services tailored merely to individual diseases (16-18).

The complexity and multidimensional features of health in older people represent major sources of uncertainty at several levels of the clinical decision process, especially when facing multimorbidity, frailty, or approaching end of life (19-22). A health system centered on the treatment of single diseases and the lack of guidelines tailored to patients with multifaceted needs drive this uncertainty (23). Currently, clinicians have limited scientific support in approaching complex patients and explaining the potential benefit and harm of treatments (1). In the era of personalized medicine, the identification of clinically relevant health profiles may help care systems build personalized preventive and intervention care paths (23-26). As hypothesized later in this thesis, clusters of multimorbidity may help detect groups of people with similar care needs and prognoses. Untangling the relationship between disease and function and investigating their prognostic meaning ultimately represents a step toward personalized medicine (1).

1.2 THE DISEASE BURDEN IN OLDER AGE

1.2.1 Epidemiology of multimorbidity

The concurrent presence of multiple diseases in the same individual defines the condition of *multimorbidity* and is usually considered a distinctive syndrome of aging. Depending on the sample population and its operationalization, multimorbidity prevalence ranges from 55% to 98% in older people (27). In the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), source of the present thesis, the prevalence of multimorbidity (i.e., two or more diseases) is as high as 89% (***figure 1***). This makes multimorbidity a more common condition than any other single disease and consequently the most frequently encountered one in clinical practice, including primary care (27, 28). According to projections, 26% of the total United States population will live with multimorbidity by 2030 (29). In recent decades, both the amount and prevalence of the population with multimorbidity increased, with the sharpest increment in more recent generations of older adults (30). These demographic shifts, along with the application of more sensitive diagnostic tools and procedures, are the main drivers of this phenomenon (31).

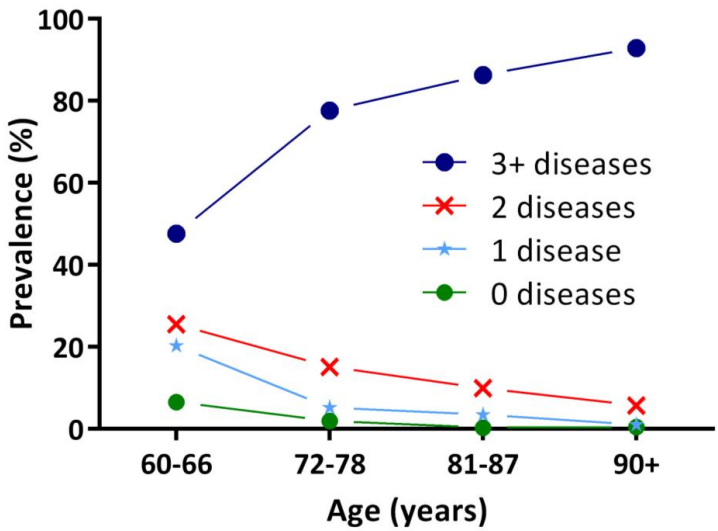

Figure 1. Percentage distribution of the number of chronic diseases by age group in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; N = 3363). *Data source: Journals of Gerontology: Medical Sciences 2017 (1).*

Multimorbidity is associated with a number of negative health-related outcomes, including poor quality of life and an intense utilization of health-care services (12, 27, 32). According to a meta-analysis of 26 observational studies, having two or more diseases, or three or more diseases, was associated with a pooled relative hazard ratio for mortality of 1.73, and 2.72, respectively. On average, each additional disease increased the mortality rate by 40% (33). The result of the interaction of multiple coexisting illnesses is hard to predict and may lead to completely new clinical phenotypes (e.g., geriatric syndromes) (1, 34). The negative outcomes related to multimorbidity are often more significant than the simple sum of the effects of single diseases. In a large study involving 1.2 million participants, the negative impact on surviving

co-occurring cardiometabolic diseases was found to be multiplicative (35). Several studies showed an association between multimorbidity and clinical and functional outcomes, such as hospitalization, poorer quality of life, shorter survival, disability, physical and psychological distress, and higher health-related costs (5, 10, 12, 27, 36).

1.2.2 Aging and multimorbidity

Age, female sex, socioeconomic deprivation, and low educational attainment represent the most important known risk factors for multimorbidity (31, 37). However, the development of multimorbidity cannot be entirely explained by individuals' sociodemographic traits, which indeed are more likely to be proxies of underlying phenomena, directly or indirectly linked to multimorbidity. In this regard, a handful of sparse, longitudinal, epidemiological studies identified a group of clinical risk factors for the development and progression of multimorbidity (31).

Obesity has been associated with an earlier onset of multimorbidity, both in males and females (38). Several mechanisms may explain such association. Overweight and obesity may affect people's functional abilities and fitness, reducing mobility and promoting social isolation. At the same time, adipose tissue is a source of inflammatory cytokines and promotes insulin resistance, both of which represent risk factors for the onset of cardiovascular and noncardiovascular diseases (39). Interestingly, in obese older adults, unintentional weight loss has also been linked with multimorbidity. The development of anemia and kidney dysfunction partially explains such association (40). In several studies, a low level of physical activity and a sedentary lifestyle have been associated with the incidence of a number of age-related diseases, including cardiovascular diseases, dementia, depression, and cancer (41). Our grasp of risk factors for multimorbidity is probably incomplete, given the paucity of studies on the topic, and further studies are needed to shed light on such mechanisms (31).

The aging process and multimorbidity share the same foundation. This is supported by the epidemiological observation that age is the most important risk factor for the development of multimorbidity (7, 30, 31, 42). Age is the signature of the stochastic damage—and subsequent activation of compensatory mechanisms—that accumulates over an entire life. Disease may be seen as the phenotypic manifestation of such accrued damage and depletion of reserves. Aging and multimorbidity mutually interact, speeding each other's progression (1, 31). In this regard, a faster accumulation of chronic disease has been proposed as a model of accelerated aging (30, 43).

Insight into the putative biomolecular causes of aging and multimorbidity is enhanced by emerging evidence that highly circulating levels of inflammatory cytokines, a condition of chronic low-grade inflammation known as inflammaging, has been associated with multimorbidity both cross-sectionally and longitudinally (30, 44). Inflammation and multimorbidity result from the damages accumulated over time in organs and physiological systems. Such damage challenges individuals' biological reserve capacity and resilience to stressors (30, 43). Diseases are typically recognized when organ and system dysfunction, and the underlying molecular determinants, exceeds a clinically relevant threshold. These changes lead to cellular damage and are usually referred to as the hallmarks of aging (***figure 2***). Such hallmarks may be grouped into primary (gene and protein instability, telomere attrition, epigenetic changes), secondary (nutrient sensing dysregulation, mitochondrial dysfunction,

cellular senescence), and integrative (stem cell exhaustion and impaired intercellular communication) mechanisms (45). Primary hallmarks thus represent the initial underlying damages responsible for the aging process, secondary hallmarks are compensatory responses to the initial damage, and integrative hallmarks contribute directly to aging-related phenotypes, including multimorbidity (43, 45). Interestingly, defect accumulation is not only the foundation of the aging process and the fertile ground from which diseases arise, but is also integral to the "frailty syndrome" concept, which will be addressed later in this thesis (8).

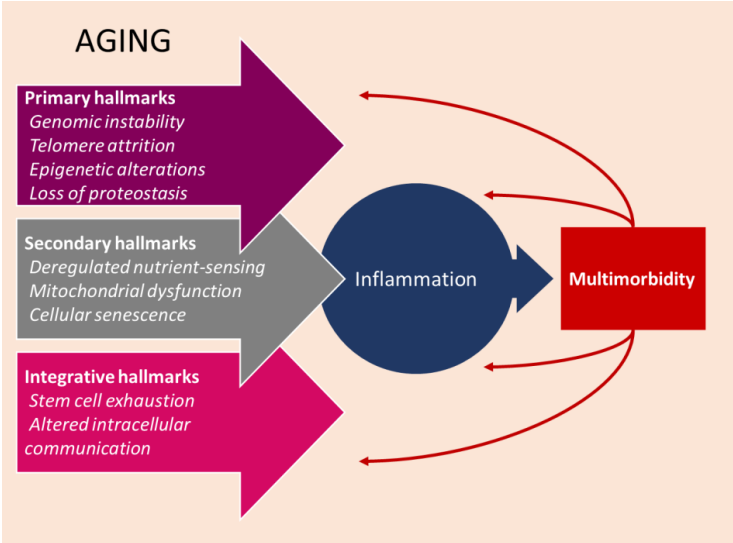

Figure 2. Underlying hallmarks of aging and multimorbidity.

Experimental studies have demonstrated that an extended life-span may be reached by delaying the onset and progression of multiple diseases and the subsequent functional decline (46, 47). It is therefore plausible that postponing or preventing the onset of multimorbidity could slow down the functional decline associated with aging. At the same time, intervention focused on the underlying mechanisms of aging could reduce the number of chronic conditions and the speed of their accumulation, resulting in a significant improvement in people's health (47). Caloric restriction and multidomain intervention suggest promising strategies in this regard (48, 49). In particular, a regimen of caloric restriction coupled with proportionate nutrient intake was shown to protect against central obesity and reduce the incidence of diabetes, hypertension, and cardiovascular events (50). Notably, the Targeting Aging with Metformin (TAME) trial will be the first randomized controlled trial (RCT) that will test the effectiveness of a drug, metformin, to slow the aging process. In the TAME trial, the accumulation in time of age-related diseases was identified as the outcome of interest (46).

1.2.3 Clusters of multimorbidity

While earlier studies in multimorbidity considered the pure count of concurrent diseases, with or without the use of cutoffs, more recent efforts converge on the study of a more systematic and homogeneous combination (that is, patterns) of chronic conditions, or *associative*

multimorbidity (51). Epidemiological studies consistently show that chronic diseases tend to cluster in a person according to specific patterns. As many as 97 specific clusters of chronic diseases have been identified in a systematic review published in 2014 (51). Most consistently detected are cardiovascular, neuropsychiatric, and musculoskeletal disorders (51). The systematic clustering of chronic diseases may be related to common pathophysiological mechanisms or risk factors. On the one hand, this could indicate genuine etiological links between the conditions, opening up new research avenues. On the other hand, some clustering could be spurious, attributable mainly to a methodological pitfall, namely, the way diseases have been assessed and clustered in an individual study (1, 52). Another explanation of the inconsistency across studies may be that multimorbidity clusters are likely not to be static, but rather to evolve over time, and are conditioned by the modifying pressure of contextual factors and death. Indeed, very few studies have investigated multimorbidity clusters from a longitudinal perspective, and most of them were compromised by the use of administrative data sources or self-reported diagnoses, restricted lists of chronic diseases, and short observation periods (53-58). Notably, all these studies focused on clusters of chronic diseases, instead of clusters of people characterized by specific multimorbidity patterns. Focusing on people instead of diseases is more in line with the principle of patient-centered care and may provide information that would help physicians and health-care systems to move faster toward models of personalized medicine (23, 24, 26).

In the present thesis we have focused our attention on the clusters of multimorbidity featured by cardiovascular and neuropsychiatric chronic disease. Cardiovascular and neuropsychiatric disease is the most prevalent and burdensome chronic condition in the older population and is among the major determinants of the global burden of disability-adjusted life years (DALYs) (59). Cardiovascular and neuropsychiatric diseases account respectively for 30% and 7% of the years that older people spend with disability (59). Beyond being the most prevalent condition encountered in this age group, cardiovascular and neuropsychiatric disease share common risk factors, stem from the same pathophysiological pathways, and may influence each other (both in terms of etiology and severity). An indirect proof of such cluster-specific homogeneity is that different diseases are often treated with the same medication. For instance, angiotensin-converting enzyme inhibitors, widely prescribed in older adults, find multiple indications in cardiovascular medicine. This is attributable to their pleiotropic properties, which encompass the ability to lower blood pressure, slow myocardial remodeling in heart failure and ischemic heart disease, and reduce the recurrence of atrial fibrillation (60).

Beyond cluster specificity, cardiovascular and neuropsychiatric diseases are likely to interact with each other. For instance, mental disorders may stem from heart disease, as in the case of dementia in people with heart failure and atrial fibrillation (61, 62). Similarly, heart disease can be triggered by mental conditions, as in the case of arrhythmias that are more frequently diagnosed in people with anxiety and related disorders. Finally, there is sparse evidence of an interplay among diseases of different systems; better understanding of the body-mind interaction has the potential to uncover novel preventive and prognostic strategies.

1.2.4 Clinical challenges of multimorbidity

Available guidelines for the treatment and management of specific chronic diseases are exclusively based on the results of randomized controlled trials carried out in selected sample

populations. Complex older people, affected by multiple diseases and with social and physical frailty are either severely underrepresented, or outright absent, in these studies (63, 64). As a consequence, a huge gap exists between official recommendations provided by the scientific community and the real-world clinical complexity encountered every day by clinicians and other health-care professionals (23, 24, 26, 64, 65).

Recent attempts have been made to provide official guidelines for people with multimorbidity (66-69). The primary focus of these guidelines has been on patients' quality of life rather than increasing survival or the accomplishment of disease-specific targets, such as reaching optimal blood pressure or cholesterol values. Moving the aim away from the treatment of a single disease and toward a more holistic approach, these recommendations recognize the role not only of health-care professionals but of patients with multimorbidity and caregivers. Five key principles have been identified in systematic review and expert consensus on available guidelines for the management of multimorbidity and polypharmacy in complex older adults: (a) identifying the target population; (b) assessing the interactions of disease and medication; (c) taking into account patients' preferences, priorities, and goals; (d) individualizing the intervention; and, (e) monitoring and following up patients over time (17, 66). Given the risk factors involved in developing multimorbidity and that the biological bases of the condition are far to be fully understood, guidelines for the actual treatment and prevention of multimorbidity are nonexistent; thus far, only indications for its management have been provided.

Multimorbidity poses a number of managerial and therapeutic challenges (68). *Polypharmacy*, usually defined as the use of five or more medications, is the direct result of the application of single-disease guidelines to individuals suffering from multiple chronic diseases (***figure 3***) (70-74). Polypharmacy has been associated with an increased risk of developing iatrogenic illness and functional decline (both physical and cognitive), which further increases the level of clinical complexity in people with multimorbidity (65). Overlooking the possibility of triggering drug-disease interaction is one of the most relevant threats of prescribing medication to multimorbid older people (64). Pharmacokinetics and pharmacodynamics are affected by the aging process and may strongly vary between patients affected by one disease and complex patients presenting multimorbidity (75). Beyond drug-disease interactions, drug-drug interactions are also a consequence of polypharmacy.

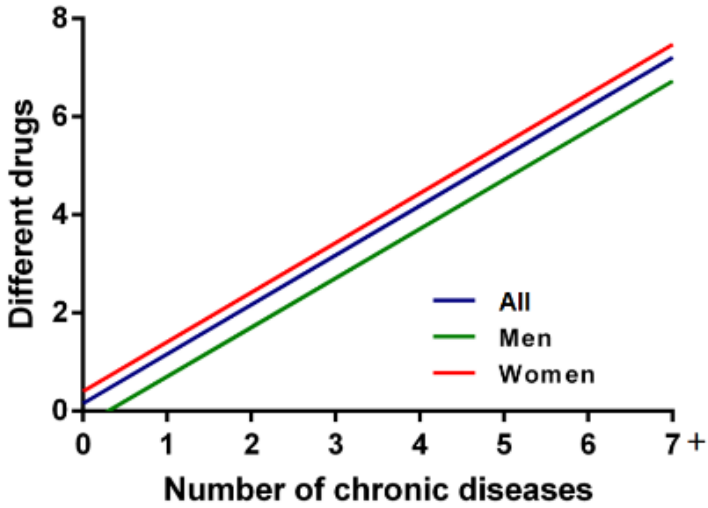

Figure 3. Association between number of chronic diseases and number of drugs in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; N = 3363). *Data modified from Journals of Gerontology: Medical Sciences 2017 (1).*

The side effect of a given medication is often interpreted as a new symptom, and is then treated with additional medication, generating a vicious circle referred to as a prescribing cascade. Medication review and deprescribing are two important components of managing older people with multimorbidity (76). Unfortunately, little evidence has been produced thus far to support such practices (77). Some studies show that involving a clinical pharmacist and using a computerized prescription support system during medication review and reconciliation for older patients with multimorbidity can be crucial to improving the quality of prescription and patients' experience (19, 78).

In 2018, the results of the largest pragmatic RCT on the management of people with multimorbidity were published. In this study, the authors tested the efficacy of a patient-centered approach, based on the assessment of several health dimensions, depression, and medication—a so-called 3D approach—carried out in 33 United Kingdom primary-care practices. Overall, 1,546 adults with three or more chronic conditions were randomized to receive either the 3D intervention or the usual care. After 15 months of the randomization, the authors could not demonstrate any improvement in patients' quality of life, chosen as the primary outcome of the study (79). Several factors may explain the negative result. First, the threshold of three diseases may not be clinically relevant. Several studies have shown that older people can experience a good quality of life despite a high disease burden (5, 10, 36, 80). Second, targeting multimorbidity is probably not enough. In this regard, a more holistic and multidimensional approach toward complex patients may improve the identification of the at-risk population. The simultaneous assessment of dimensions including frailty, physical functioning, cognitive status, and social disadvantage could help in identifying subgroups of patients with multimorbidity who are more susceptible to the intervention (1, 9, 34, 81, 82).

1.2.5 Public health challenges of multimorbidity

Multimorbidity is among the major triggers of intense health-care-service utilization. Health-care systems nonetheless fail to address complex older adults with multimorbidity, because robust scientific evidence that can guide new models of care is lacking (2). Consequently, health-care spending keeps increasing, but the clinical needs and preferences of frail and multimorbid patients remain largely unattended (1).

National health-care systems are currently designed to respond to acute health episodes, neglecting that the health status of older adults fluctuates over time, strongly influenced by socioeconomic and other nonclinical domains. Nowadays, medicine tends to prioritize the use of technology and increasingly heads toward hyperspecialization. This directly contradicts the strengthening of primary and highly coordinated care, which has been recently advocated for the effective management of the increasing number of people with multimorbidity. Finally, despite many clinicians knowing that effective care of older people with multimorbidity cannot disregard a person-centered approach, the real-world gap between practice and patient is growing. Health-care models are left with expensive, burdensome, or unclear benefits and potential harm and are economically unsustainable (83).

Several steps need to be taken to build effective care paths for people with multiple chronic diseases. The steps recommended for the clinical management of older people with multimorbidity may also promote the implementation of high-performance health-care systems. Based on patient-centered medicine that detects older adults' care needs in a timely fashion, they take into account the complexity of the clinical picture, empower patients and their families, and guarantee continuity of care (17).

1.2.6 Methodological aspects of multimorbidity assessment

Recent decades have produced extensive literature on the topic of multimorbidity, yet a number of methodological weaknesses limit the generalizability—and sometimes the interpretation—of these findings. While there is strong agreement on the definition of *multimorbidity* as the presence of two or more chronic diseases in the same person, it remains unclear which diseases should be assessed, how many diseases should be included in the count, and how diseases should be assessed. The lack of indication depends on the vast methodological heterogeneity encountered in these studies. According to a systematic review published in 2011 of 39 articles, the number of diseases assessed in the retrieved studies ranged from 4 to 102, most of them based on self-reported information (84). The diseases considered in these studies were usually identified according to predefined criteria, such as prevalence in the older population, risk of adverse health-related events, or likelihood to be treated. Finally, it is not uncommon that researchers choose a list of candidate diseases for pragmatic reasons, such as the availability of information in a given data set. The heterogeneity of the methodology is reflected primarily in the wide range of multimorbidity prevalence estimates reported, from 55% to 98% in the abovementioned systematic review. In addition, as mentioned earlier in this chapter, the varied ways in which diseases are assessed may be responsible for the high number of unique multimorbidity clusters identified in the literature (51).

In addition to the challenges of selecting specific diseases, their counts, or data sources, the actual definition of chronic disease and the level of aggregation and categorization of chronic

conditions for the operationalization of multimorbidity impose additional limitations. In most studies of multimorbidity in older people, a univocal definition of chronic disease is missing. Characteristics such as duration, reversibility, course, treatment, and consequences are usually considered in the definition of chronic condition, yet these features are used in a sparse and inconsistent fashion across studies. It is not uncommon for studies to categorize the diseases of interest differently, whereby the same nosological entity may either be considered individually (e.g., atrial fibrillation) or operationalized as part of a more comprehensive category (e.g., heart disease). These elements of variability further contribute to affect the clinical, pathophysiological, and epidemiological interpretation of such studies (1).

Developing ad hoc indications for the operationalization of multimorbidity in older adults, both in clinical and research settings, represents a priority of this research area. Such a tool will enable high quality and comparable research, which will assist physicians and health-care systems in improving the prognosis, diagnostic paths, treatment, and care of older people with multimorbidity.

1.2.7 Knowledge gaps antecedent to this thesis

In the last two decades, a high number of studies have investigated the occurrence of multimorbidity and its impact on different health-related outcomes. Unfortunately, very few have contributed solid evidence based on a sound methodology with a clear definition of chronic disease and, most importantly, a robust and reliable, clinically driven operationalization of multimorbidity. Consequently, findings from different studies are hardly comparable and often contradict each other. The establishment of rigorous and scientifically valid recommendations for the appraisal of multimorbidity in older adults may help answer many of the questions remaining open or dubious in this field.

Another important research gap arises from the scarce relevance given until now to the longitudinal evolution of multimorbidity, and the subsequent effects of such changes on older individuals' health. Multimorbidity is a dynamic phenomenon, and describing it through static (i.e., cross-sectional) snapshots may run the risk being too reductionist in mapping its underlying complexity. Longitudinal studies that describe the evolution of multimorbidity over time, with its potential driving factors, can improve understanding of the pathophysiology of multimorbidity, eventually increasing the potential of preventive strategies.

1.3 FUNCTION IN OLDER AGE

1.3.1 Functional decline with aging

Preserving the ability to move around and carry out daily activities are two of the most valued goals of older adults. The integrity of mental and physical functioning is essential to accomplishing these tasks. When either one or both of these functions are impaired beyond a certain threshold, people are no longer able to maintain their independence, with consequences at personal, familial, and societal levels (5, 10, 36, 80, 85, 86).

Aging is associated with a decline in most physiological systems that culminates in limiting physical capacity. Muscle strength and physical performance peak in an early stage of adulthood, usually between the third and fourth decades of life, as a result of the developmental plasticity of humans evident during the first decades of life. During the fourth decade, these functions start their progressive decline (87). According to an Italian-Taiwanese collaborative study involving community-dwelling adults, muscle strength, measured through the handgrip test, and physical performance, assessed by the chair stand test, start to decline at the age of 45, after reaching a plateau, in both women and men (88). To a certain extent, this decline may be physiological, although a fast decline in physical function can also be considered a sign of the accelerated aging that precedes several negative health outcomes (86, 89). If death does not occur, disability and dependence in the activities of daily living are usually the results of the decline in cognitive and physical function.

1.3.2 Functional assessment

Several measures have been proposed to assess physical function in older adults, including strength tests (e.g., handgrip strength), balance tests (e.g., one-leg balance test), performance tests (e.g., walking speed), or combinations thereof (e.g., short physical performance battery). All these measures have been consistently shown to predict adverse outcomes in older adults and perform well in detecting at-risk individuals, also in clinical settings. Among the suggested tests, walking speed appears to be the most convenient and informative measure of physical performance in older adults, both in research and clinical practice.

1.3.2.1 Walking speed

Walking speed is a comprehensive and commonly used measure of mobility. It can be easily assessed in clinical settings and is highly predictive of a number of health-related outcomes. In accordance with the International Academy on Nutrition and Aging (IANA), the assessment of *usual gait speed* represents a “single, more reliable, valid, sensitive (not necessarily specific), cheap, safe, quick, and simple tool” able to identify older people at risk of negative events (90). Older people with impaired walking speed, and those experiencing a more rapid decline in walking speed, exhibit more care needs, incident disability, and higher mortality rates (89-92). Interestingly, impaired walking speed is also associated with faster cognitive decline and higher incidence of dementia. Thus, walking speed can be considered a relevant metric and determinant of health in older age (5, 10).

In older people, walking speed is the result of one’s genetic predisposition and its interaction with lifelong exposure to internal and external factors. Walking is an energy-demanding activity that requires a fine command of the central nervous system (CNS), the integrity of a

number of body systems and organs (e.g., cardiovascular and musculoskeletal), and the support of several sensorial functions (e.g., vision and hearing; ***figure 4***). Walking speed decline is the result of both clinical and subclinical impairment accumulating across the abovementioned structures and functions. For these reasons, it is deemed a reliable summary measure of biological age, and its faster decline is a sign of accelerated aging and frailty (31, 91, 93).

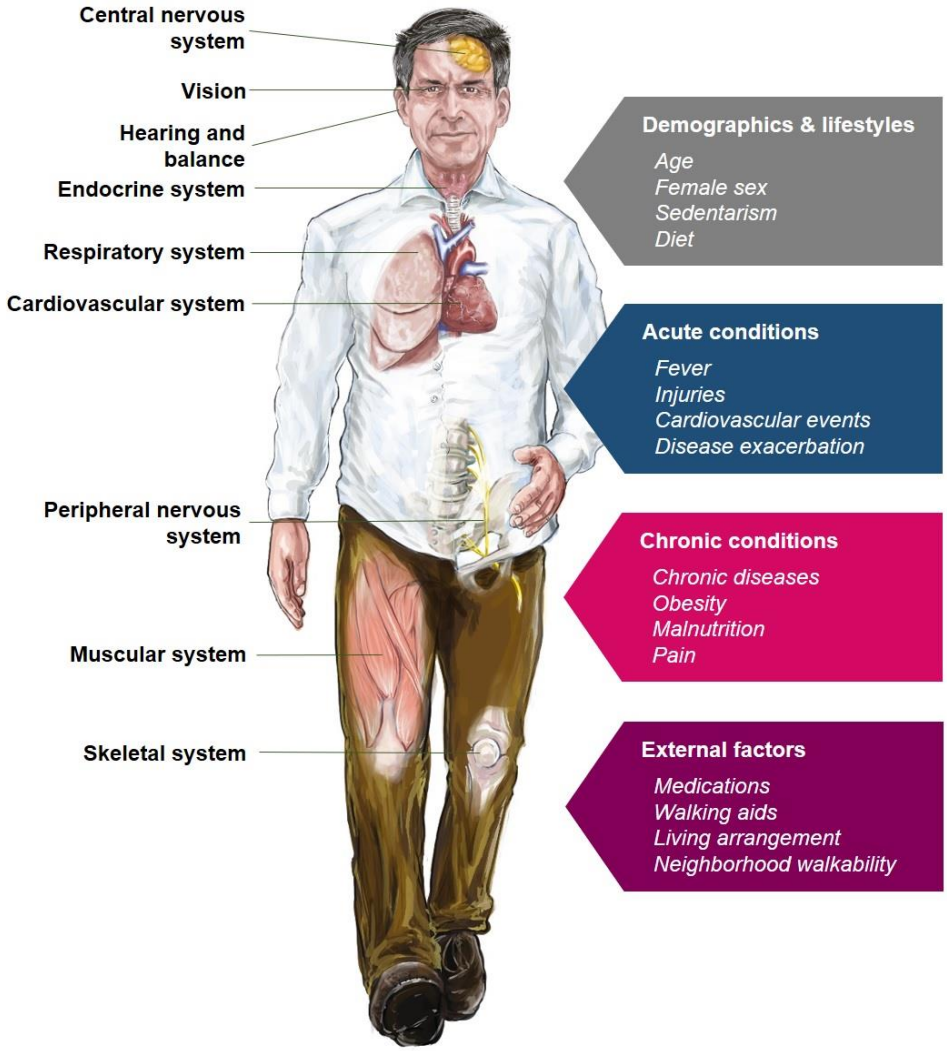

Figure 4. Body systems involved in the maintenance of gait speed and possible determinant factors. *Data modified from Experimental Gerontology 2019 (in press).*

Several factors may affect walking speed. First, demographic and lifestyle-related conditions, such as female sex and sedentarism, may affect walking speed (94-96). Second, both acute and chronic conditions may impair walking. These include systemic (e.g., fever, pain) or organ-specific conditions (e.g., cardiovascular events, osteoarthritis) (93, 97-99). Finally, a number of external factors may affect gait speed, including medication (e.g., anticholinergics) or the use of walking aids (100-106). Untangling the role played by each of these conditions remains challenging.

Several cutoffs have been suggested to define slow walking speed. Among them, cutoffs of 0.8 m/s and 1.0 m/s are the most frequently used. Studenski et al., in a large study (N = 34,485) of nine cohorts of community-dwelling older adults, showed that walking speed exceeding 0.8 m/s was associated with an increase in life expectancy above median levels (91). Interestingly, as shown in the Health, Aging and Body Composition Study, a more rapid decrease in walking speed is associated with shorter survival, independent of baseline status (89).

1.3.2.2 Disability

The most common way to assess disability is by evaluating the impairments an individual has accumulated in six basic activities of daily living (B-ADL) and in eight instrumental activities of daily living (I-ADL) (107). B-ADL relate to the ability to move around, eat, and take care of personal hygiene. Older adults are usually able to maintain B-ADL until late life, and start to lose them as severe physical and mental impairments occurs. On the other hand, I-ADL relate to more complex activities, encompassing the ability to go out independently, manage finances, and take care of the house. In contrast to B-ADL, I-ADL become impaired earlier in old age, and require the integrity of more complex cognitive functions and fitter physical functions. Impaired B-ADL and I-ADL are highly predictive of a number of negative health-related outcomes, including hospitalization, institutionalization, and shorter survival. Finally, people with disabilities consume most social care services (108).

1.3.3 Complementarity of measures of physical function

Walking speed and other parameters of physical function, including measures of disability, follow different trajectories for different individuals during the life course. Timely detection of the modifiable risk factors that lead to a faster functional decline may help prevent disability later in life, eventually improving quality of life of older adults. According to a Swedish population-based study, and in line with previous studies, walking speed starts to decline at a constant pace from midlife until very old age (10, 89, 109). Dependency in I-ADL and in B-ADL, however, starts to become evident only after ages 80 and 85, respectively (10). This suggests that walking speed may help to detect further development of disability at an early stage. In other words, as the discriminative power of each of these metrics changes with age, their assessment may provide different information during different periods of life (5). Above all, assessing more than one of these metrics will provide a broader overview of one's functional status and prognosis.

1.3.4 Frailty

Although investigating the role of frailty as a determinant of health in older people was not among the aims of this thesis, its multiple points of contact with both multimorbidity and functional ability demand an introduction. *Frailty* is defined as a condition of increased susceptibility to internal and external stressors, and reflects the faster aging of multiple organs and systems (8, 110). The concept of frailty as a measure of biological age appeared in geriatric medicine during the last two decades and soon obtained consensus from both clinicians and researchers. Frailty is a common finding in older adults. A systematic review of 21 community-based studies published in 2012 that encompassed more than 60 thousand individuals found that the prevalence of frailty in the general population varied between 4.0% and 59.0%, depending on the study population and operationalization of frailty. The review reported an overall weighted prevalence of frailty of 10.7%, which increased with older age and in women (111).

Despite wide agreement on the theoretical definition of frailty, less consensus exists on its operationalization. This lack of consensus has led to a multitude of different tools for the screening and assessment of frailty. Some researchers assert that a reliable operationalization of the concept of frailty should be founded on its ability to predict both the natural history of older adults' health and the response to specific therapeutic interventions (8). So far, the two most successful models of frailty have been the frailty phenotype, proposed by Fried et al., and the frailty index, proposed by Rockwood et al.

Fried et al. proposed a conceptual framework and an operationalization of physical frailty for the first time in 2001. In this proposal, physical frailty is diagnosed in the presence of at least three of the following items: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength (112). Older people exhibiting one or two of these criteria are considered prefrail, and those with none are identified as robust. Using the data from the Cardiovascular Health Study, according to Fried et al., 7% of the study sample was considered frail, 47% prefrail, and 46% robust. In longitudinal analyses, both in this and other studies, the frailty phenotype was shown to reliably predict increased risk of several negative health outcomes, including hospitalization, disability, and shorter survival (113-115).

Conceptually different from the construct of physical frailty, the Rockwood's frailty index is based on the ratio between the number of deficits expressed by an individual and the number of those assessed. The frailty index assumes values between zero (no frailty) and one (100% of deficits present). In the original proposal, 70 deficits, including symptoms, signs, abnormal lab tests, diseases, and disabilities, were used to compute the score (116). This model of frailty is clinically attractive, given that it allows consideration of frailty on a continuum rather than as a binary outcome (117, 118). The ability of the frailty index to predict negative health outcomes has been demonstrated in numerous studies (113).

While many tools assess frailty, the prognostic value of the concept has been repeatedly demonstrated across populations and instruments. The multidimensional and comprehensive assessment of function embedded in each of these tools may explain this. However, one of the main obstacles to translating research findings to clinical practice is the difficulty of including complex and time-consuming assessments in daily clinical practice. For this reason, many agree that the measurement of walking speed may be a practical and exhaustive way of

assessing frailty. In several clinical studies it allowed a reliable stratification of the clinical risk of specific conditions related to procedures and interventions (119-121) .

1.3.5 Multimorbidity and functional decline

Apart from a few exceptions (122), the association between multimorbidity and poor physical function in older adults was demonstrated in several cross-sectional and longitudinal studies (12, 123, 124). According to a population-based study by Aarts et al., functional impairment from multimorbidity persists over time and often shows further worsening (125). Jindai et al. showed that, in older individuals, the association between multimorbidity and functional limitation is strengthened in older age (>75) and in females. If the modifier effect of older age is expected, given the reduced resilience of the oldest old individuals, the effect of the sex of the individual requires further investigation (126).

Sparse evidence suggests that, in older individuals, specific clusters of chronic disease exert a differential impact on physical function and disability (27). Some combinations of disease may be more detrimental than others in their effect on physical function as the result of mechanisms stemming from the dysfunction of various bodily systems (127, 128). Given the focus here on the health impact of cardiovascular and neuropsychiatric multimorbidity, published evidence of cardiovascular and neuropsychiatric clusters of multimorbidity and functional decline in older adults is reported. Beyond one of the constituent papers of this thesis, four studies investigated the association between multimorbidity clusters and disability. Jackson et al. reported that, in a sample of 7,270 older women participating in the Australian Longitudinal Study on Women's Health, cardiovascular and neuropsychiatric clusters of chronic disease—but not musculoskeletal—were significantly associated with more dependence in B-ADL and I-ADL (129). Koller et al., in a study based on administrative data from 115,203 older individuals, reported a significant association between all the main multimorbidity patterns identified in the study and dependency. Notably, the cluster including neuropsychiatric diseases showed the strongest association with dependency (130). Quiñones et al., using longitudinal data from the United States on nearly 9,000 older individuals, found that the multimorbidity cluster composed of symptoms of depression, arthritis, and hypertension predicted disability better than other multimorbidity clusters (131). This result was replicated in another study based on 4,000 older adults from the Medicare database in which the copresence of physical and mental disorders (especially cognitive impairment and dementia) was linked with a higher likelihood of disability, relative to reporting several exclusively physical conditions (132).

The abovementioned studies provide several insights into the association between multimorbidity clusters and function in older people. First, cardiovascular and neuropsychiatric diseases represent the most common conditions in older adults and feature as recognizable clusters of multimorbidity. Second, these two disease groups are independent predictors of poor functioning. Third, neuropsychiatric diseases show a stronger impact than cardiovascular diseases on functional outcomes. Finally, the presence of neuropsychiatric diseases seems to exacerbate the negative consequences of other individual conditions, suggesting the existence of a biological interaction among such morbidities.

However, several issues inhibit the generalizability of the results of these studies, limiting the possibility of drawing definitive conclusions about the relationship between cardiovascular and neuropsychiatric multimorbidity and functional decline. First, those studies relied on ad hoc

and not comprehensive lists of chronic diseases. Second, the multimorbidity patterns were developed according to data-driven—not clinical—principles. Third, the dynamic and evolving nature of multimorbidity and other measures was not considered.

1.3.6 Knowledge gaps antecedent to this thesis

Despite many studies showing an independent impact of multimorbidity on several negative outcomes, some failed to demonstrate an independent association. On the one hand, this may be attributed to methodological inconsistencies in the way multimorbidity was operationalized. On the other hand, the scarce specificity implicit in the definition of multimorbidity—the co-occurrence of two or more diseases—may lead to heterogeneous and unexpected results. In this regard, reducing the heterogeneity of the exposure and assessing more homogeneous clusters of multimorbidity can help to identify groups of chronic disease selectively associated with specific outcomes.

Finally, several studies clearly showed that many older individuals are able to live a satisfying life in spite of the presence of multiple chronic diseases. Rather, the concurrent development of functional impairment is widely believed to drive the negative consequences of multimorbidity. Notably, only a handful of studies investigated the interplay between multimorbidity and functional impairment, and none of them assessed the role played by specific multimorbidity clusters. Understanding the effect of the interplay between multimorbidity and functional impairment in older adults may improve the detection of groups of individuals with more intense health-care needs and poor prognoses, in line with the principles of patient-centered care.

2 AIMS

2.1 OVERALL AIM

The overall aim of the present thesis was to propose a clinically driven methodology to assess multimorbidity in older individuals, to describe multimorbidity evolution over time, and to investigate the impact that cardiovascular and neuropsychiatric clusters of multimorbidity exert on older individuals' health.

2.2 SPECIFIC AIMS

The specific aims addressed in four individual studies are summarized below.

1. To propose a novel clinically driven approach for assessing and measuring multimorbidity, and to examine its applicability in a population-based cohort of older adults.

2. To identify multimorbidity clusters in a population-based cohort of older adults, trace the evolution of the clusters over 12 years, and follow the clinical trajectories of the individuals as they moved between clusters or to death over time.

3. To examine if multimorbidity clusters, defined by the copresence of cardiovascular and neuropsychiatric conditions, have a differential influence on the longitudinal evolution of function in older individuals.

4. To explore the effect of cardiovascular multimorbidity and functional impairment, as well as the effect of neuropsychiatric multimorbidity and functional impairment, on all-cause and cause-specific mortality.

3 MATERIAL AND METHODS

3.1 STUDY POPULATION

3.1.1 The SNAC-K study

This thesis is based on data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) (133), which is an ongoing longitudinal population-based study of individuals aged 60 years or older residing at home or in an institution in the Kungsholmen area of Stockholm, Sweden. A random sample stratified across 11 birth cohorts born between 1892 and 1939 was invited to participate (***figure 5***). Those accepting (N = 3,363; participation rate 73%), were examined for the first time in 2001–2004. Individuals from the oldest as well as the youngest birth cohorts were oversampled. Participants who were <78 years at baseline were followed up every 6 years and participants ≥78 years every 3 years.

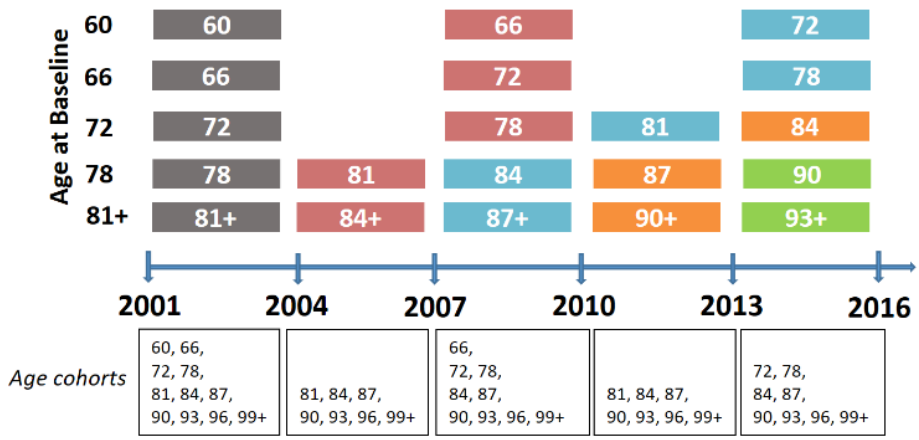

Figure 5. SNAC-K cohorts (2001–2016). Grey boxes indicate baseline assessment, red boxes 1st follow-up, light-blue boxes 2nd follow-up, orange boxes 3rd follow-up and green boxes 4th follow-up.

3.1.2 Study designs and selection criteria

With the exception of Study I, which has a cross-sectional design, all the other studies included in the present thesis have a longitudinal design. A literature review and a consensus of experts were also part of Study I. Four different study samples were selected from the SNAC–K population in order to answer the research questions (that is, Studies I–IV). In Study I, information on the entire SNAC-K population was used (N = 3,363). In Study II, only participants that had two or more diseases at baseline were included (n = 2,931). In Study III, only participants with at least two valid assessments over a period of nine years were included

in the analyses (n = 2,385). Finally, in Study IV, only participants with baseline valid information on walking speed and chronic disease were selected (n = 3,241).

3.1.3 Data collection

Data collection included information on participants' current status and past history. Information was collected through interviews, clinical examinations, and specific tests. Staff components (nurses, psychologists, and physicians) received ad hoc training aimed at standardizing any procedure. At each wave, each individual was examined for an average of six hours. The examination included a biographic assessment and a measurement of physical functioning by a nurse (two hours); clinical examination by a physician for the geriatric, neurological, and psychological assessment (two hours); and cognitive evaluation by a psychologist (two hours).

3.2 DISEASE ASSESSMENT

3.2.1 Information source and collection

In SNAC-K, clinical diagnoses were made on the basis of participants' self-reported information, review of medical journals, anamnestic data, and information obtained from participants' proxies. Further clinical and lab parameters, and information related to medication utilization, complemented physicians' assessments of specific diseases. All drugs used by SNAC-K participants were noted and coded based on the Anatomical Therapeutic Chemical (ATC) classification. Participants were asked to provide a list of currently used medications. For participants with cognitive impairment, a proxy was asked instead. For participants living in a nursing home, medical records were consulted to gather information on medication utilization. All diseases were coded in accordance with the International Classification of Diseases 10th revision (ICD-10).

For the studies included in this thesis, the Swedish National Patient Register (NPR) was also consulted for five years preceding the baseline and twelve years following the baseline. All in-patient visits in Sweden since 1987 have been recorded in the. Starting in 2001, specialized outpatient visits, including day surgery and psychiatric care from both private and public providers, have been reported to the NPR. Once informed consent was obtained from the participants, the SKAC-K data were linked with the NPR through personal identification numbers. The ICD-10 codes used for identifying chronic diseases were based either on the primary diagnosis or on any of the nine secondary diagnoses recorded in the NPR.

3.2.2 Disease categorization

Building a clinically driven list of chronic diseases for the operationalization of multimorbidity was the main purpose of Study I. Five geriatricians and two general practitioners from Sweden, Italy, and Spain were involved in this process. The first step consisted of the classification as chronic or nonchronic of all ICD-10 codes, in accordance with a definition of chronic disease agreed on by the authors of the study. The second step consisted of classifying the identified chronic diseases into broader categories. For this, the following principles were considered:

pathophysiology, pharmacological and nonpharmacological treatment, prognosis, and prevalence. While we aimed to preserve the original structure of the ICD-10 codes, some modifications were made. First, some disorders, given their high prevalence or in light of their highly specific clinical characteristics, management, and prognosis, were isolated from the rest of the nosographic group, thereby becoming a separate disease category (e.g., diabetes [separate from metabolic], multiple sclerosis [separate from autoimmune], or inflammatory bowel disease [separate from colitis-related diseases]). Second, a series of diseases were removed from the original category and placed into a different nosographic group in light of their greater clinical homogeneity with the new group (e.g., chronic viral hepatitis was removed from "Chronic infectious diseases" and aggregated with "Chronic liver diseases"). Third, new disease categories were generated aggregating a range of infrequent codes involving common body organ/system pathophysiology (e.g., "Ear, nose and mouth disorders" or "Other neurological conditions"). Finally, some disease codes were placed in multiple categories when their labels specified multiple disease entities. (Spondylosis with myelopathy was included, for example, once in the group "Dorsopathies" and another time in the group "Other neurological disorders.") As reported in the results section, this procedure led to the composition of 60 homogeneous categories of chronic disease.

3.2.3 Cardiovascular and neuropsychiatric diseases

In Study I and Study II, all 60 disease categories were considered for the analyses. Conversely, Study III and Study IV focused on the prognostic role of cardiovascular and neuropsychiatric disease. Overall, seven chronic cardiovascular-disease groups were considered: atrial fibrillation, bradycardias and conduction disease, cardiac valve disease, heart failure, ischemic heart disease, peripheral vascular disease, and other cardiovascular disease. Similarly, twelve chronic neuropsychiatric disease groups were of interest: cerebrovascular diseases; dementia; depression and mood diseases; epilepsy; migraine and facial pain syndromes; multiple sclerosis; neurotic, stress-related and somatoform diseases; Parkinson and parkinsonisms; peripheral neuropathy; schizophrenia and delusional diseases; other neurological diseases; and other psychiatric diseases.

With the aim of exploring the associations of specific disease patterns on trajectories of physical function, Study III participants were grouped based on the baseline number of cardiovascular and neuropsychiatric diseases (i.e., zero, one, or two or more). This categorization resulted in seven mutually exclusive groups (***figure 6***) that allowed us to investigate the impact on trajectories of function of (a) cardiovascular morbidity and multimorbidity, (b) neuropsychiatric morbidity and multimorbidity, and (c) mixed multimorbidity (i.e., one cardiovascular and one neuropsychiatric disease) and complex multimorbidity (two or more cardiovascular diseases plus two or more neuropsychiatric diseases, and vice versa).

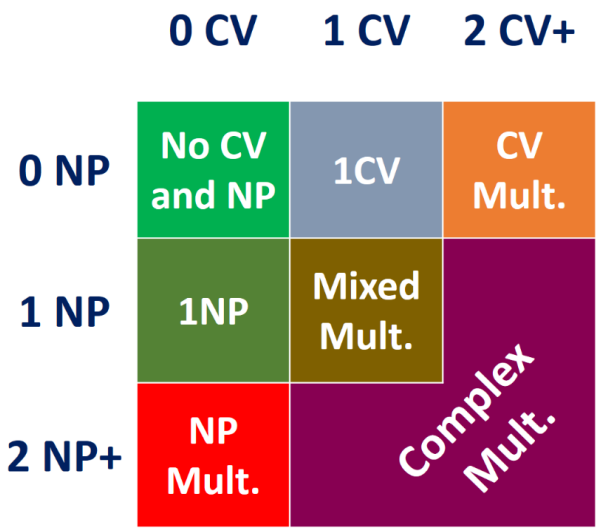

Figure 6. Participants' categorization applied in Study III, based on the presence of zero, one, or two or more cardiovascular (CV) and neuropsychiatric (NP) diseases.

In Study IV, in order to investigate the interplay between chronic disease and functional status, participants were categorized into six mutually exclusive groups derived from the combination of the number of cardiovascular and neuropsychiatric diseases (zero, one, or two or more) with the presence of slow walking speed (see definition below).

3.3 FUNCTIONAL ASSESSMENT

3.3.1 Walking speed

In Study III and Study IV, walking speed was used as an indicator of physical function, as an outcome, and as an effect modifier, respectively. Walking speed was assessed by asking SNAC-K participants to walk 6.0 meters at their usual speed or, if not feasible (if participants had limited walking capacity to begin with or space was limited, for instance, in an institution), to walk 2.4 meters instead. Walking speed was measured in meters per second (m/s). In Study IV, a cutoff of 0.8 m/s was used to define slow walking speed in main analyses and 1.0 m/s in sensitivity analyses.

3.3.2 Independency

In Study III, independency was assessed by the ability to independently perform the following six B-ADL: bathing, dressing, toileting, continence, transferring from bed, and eating. The B-ADL score was obtained by summing the number of intact items; change over 9 years was considered one of the outcomes of the study.

3.4 MORTALITY DATA

All-cause mortality at three and five years was the main outcome in Study IV. In a secondary analysis, we examined cardiovascular causes of mortality (ICD-10 I00-I79) and noncardiovascular causes of mortality separately to explore whether specific clinical profiles were selectively associated with fatal cardiovascular events. To this end, only the underlying cause of death—and no secondary causes—was considered. Dates and causes of death were derived from death certificates provided by Statistics Sweden, the Swedish national statistics agency.

3.5 COVARIATES

Information on age, sex, education, and living arrangement was gathered by questionnaire. Age was used as a continuous variable for model adjustment and categorized as <75 and ≥75 years for stratifying analyses. Education was measured as the total years of formal schooling and categorized as elementary (<8 years), high school (8–13 years), and university or higher (>13 years). Living arrangement was categorized as living in institution or not. In keeping with the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), malnutrition was defined as having a body mass index (BMI) <18.5 kg/m^2 (134). The number of drugs used at the moment of the assessment was obtained by summing up retrieved ATC codes. Global cognition was assessed through the 30-item Swedish version of the Mini-Mental State Examination (MMSE). MMSE is a questionnaire covering cognitive functions such as orientation to time and space, attention and calculation recall, language, ability to follow written and verbal commands, and visual construction (135).

3.6 STATISTICAL ANALYSES

In the four studies included in the present thesis, participants' characteristics were reported as absolute numbers and proportion (%), or mean ± standard deviation (SD), or 95% confidence intervals (95% CI), as appropriate. A P value of <0.05 was considered statistically significant in all analyses. All analyses were carried out with Stata® 14.0 and Stata 15.0 (StataCorp LP) for Microsoft Windows®, and with R 3.5.1. Specific analytical strategies were adopted in each of the four studies (summary in ***table 1***).

3.6.1 Study I

Age- and sex-specific weights were applied to chronic-disease prevalence figures in order to account for the SNAC-K sampling method. In order to verify if categorization into 60 homogeneous groups of chronic disease led to an underestimation of specific conditions, and consequently multimorbidity, we calculated the number of people with two or more differing ICD-10 codes within the same disease category.

3.6.2 Study II

Clusters of older adults who shared patterns of multimorbidity were independently identified using the fuzzy c-means cluster analysis at baseline, six, and twelve years. Through this

technique, we obtained clusters of individuals and a membership matrix that indicated the degree of participation of each individual in each cluster. Different degrees of fuzzification and several validation indices were considered to estimate the optimal number of clusters. We based our evaluation of the consistency and significance of the final solution on clinical criteria. To characterize the clusters of multimorbidity that corresponded to each cluster of individuals, we calculated the frequency of chronic diseases in each cluster. Observed-to-expected (O/E) ratios were calculated by dividing the prevalence of a given disease within a cluster by its prevalence in the overall population. Disease exclusivity, defined as the fraction of participants with the disease in the cluster over the total number of participants with the disease, was also calculated. We considered a disease to be associated with a given cluster of individuals when the O/E ratio was ≥2 or the exclusivity was ≥25%. To evaluate the most likely clinical trajectories of the participants as they moved between clusters over time, a hard cut of fuzzy c-means assigned each individual to the cluster with the highest membership score at each time point (136, 137). Shifts between clusters were computed by cross-tabulating individuals between each wave (baseline to six-year follow-up and six- to twelve-year follow-up). Frequencies (%) of participants who changed from one cluster to another were computed to assess the overlap between waves. Mortality and dropout status were considered as fixed clusters in both six- and twelve-year follow-ups. Logistic regression models were used to estimate the association between clusters and mortality. Odd ratios (OR) and 95% CI were adjusted for age, sex, and education. All comparisons were adjusted for multiplicity.

3.6.3 Study III

Mixed-effect linear regression models were used to draw trajectories of walking speed and B-ADL over nine years across seven different combinations of cardiovascular and neuropsychiatric disease. Participants without cardiovascular and neuropsychiatric disease served as reference. Follow-up time was modelled through unrestricted cubic splines. In a second analysis, the association between the seven disease combinations and the outcomes was tested in mixed-effect linear regressions including both the exposure and the adjustment variables (i.e., number of prescribed drugs, malnutrition, and institutionalization) as time-varying covariates. Interaction between clinical patterns on one side and sex and age on another was tested, and further stratified analyses were performed. A series of sensitivity analyses were carried out. First, we re-estimated all models, after excluding the most common cardiovascular and neuropsychiatric diseases one disease at a time from the total count of the respective multimorbidity clusters. Second, we repeated all analyses, using a subsample of known survivors, who neither died nor were lost to follow-up. Finally, we re-estimated all models, after removing incontinence from the list of B-ADL impairments.

3.6.4 Study IV

Three- and five-year mortality rates (per 100 person years) were provided for each clinical profile. Cox regressions were used to test the association between the clinical profiles built by combining baseline walking speed (<0.8 m/s and ≥0.8 m/s) and the number of cardiovascular or neuropsychiatric diseases and three- and five-year all-cause mortality. Participants with a

walking speed of ≥0.8 m/s and without cardiovascular or neuropsychiatric disease were the reference group. We tested multiplicative and additive (relative excess risk due to interaction, RERI) interactions between walking speed and cardiovascular and neuropsychiatric multimorbidity. Fine-Gray competing risk regression models were used to test the association between clinical profiles and cause-specific (cardiovascular and noncardiovascular) mortality. In a sensitivity analysis, the analyses were repeated, taking participants without cardiovascular or neuropsychiatric disease and a walking speed of <0.8 m/s as the reference group. In a second sensitivity analysis, a walking speed cutoff of <1 m/s was used. Finally, the association between the number of cardiovascular and neuropsychiatric diseases and mortality was tested in Cox regression models, adjusted and not for walking speed, as a continuous—instead of an indicator—variable. For these models, the Harrell's C statistic was obtained. Finally, the predicted values of the hazards of mortality were plotted against walking speed as a continuous variable (with a walking speed of 0.8 m/s as reference).

Table 1. Analytical approach of the four studies included in the thesis.

Study	Outcome	Exposures	Potential confounders	Analytical approach
Study I	Chronic disease Chronic disease categories to operationalize multimorbidity	–	–	Expert consensus Descriptive analyses
Study II	Multimorbidity clusters Mortality	Multimorbidity clusters	Age, sex, and education	Fuzzy C-means cluster analysis Logistic regression models
Study III	Nine-year changes in walking speed and B-ADL score	Seven patterns of chronic disease based on the presence of zero, one, or two or more cardiovascular and neuropsychiatric diseases	Age, sex, education, malnutrition, institutionalization, and number of medications	Mixed-effect linear regression models including and not including time-varying exposure and covariates
Study IV	Three- and five-year mortality (all-cause, cardiovascular, and non-cardiovascular)	Six clinical profiles built by combining a baseline walking speed (<0.8 m/s and ≥0.8 m/s) and the number of cardiovascular and neuropsychiatric diseases (zero, one, or two or more)	Age, sex, education, malnutrition, institutionalization, number of medications, MMSE, and number of cardiovascular or neuropsychiatric diseases (as appropriate)	Cox regression models Fine-Gray competing risk regression models

3.7 ETHICAL CONSIDERATIONS

This dissertation was based on data collected in the SNAC-K study. All SNAC-K phases and the use of Patient Register data were approved by the Ethics Committee at Karolinska Institutet, Stockholm, Sweden, and the Regional Ethical Review Board in Stockholm (Dnrs: KI 01-114, 04-929/3, Ö26-2007, 2009/595-32, 2010/447-31/2, 2013/828-31/3, and 2016/730-31/1).

Written informed consent was obtained from all SNAC-K participants. For individuals with cognitive impairment at baseline or during follow-up visits, consent was obtained from the next of kin (family members or caregivers).

Study participants were assessed in a friendly and comfortable environment. Each test and examination was performed in accordance with the participants' willingness to undergo the procedure. Every time the assessors perceived some kind of distress for the participants, the test was stopped and eventually rescheduled. The same applied to blood test sampling: the minimum necessary blood amount was sampled, and participants could refuse consent to the procedure. Subjects were asked if they wanted to be informed of any condition detected during the examination. If any test results were abnormal, participants were referred to their general practitioner or emergency room, if necessary. Finally, the main results of research conducted on SNAC-K data were disseminated to participants through annual seminars held by the researchers, booklets of scientific results, and popular science publications.

All collected data were anonymized once they were digitalized from the questionnaires. An artificial ID was given to each participant and all personal data removed. All researchers working with the data set respected and followed the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

4 RESULTS

4.1 CHARACTERISTICS OF THE STUDY POPULATION

At baseline, the mean age of the 3,363 participants in SNAC-K was 74.6 ± 11.2, 64.9% were female, and 5.7% lived in an institution. Over nine years of observation, 38.7% participants died, and 15.2% dropped out. Dropouts occurred when the participant or her or his relative refused, contact with the participant was lost, or the participant moved from the Stockholm area. As previously mentioned, specific inclusion criteria were applied to Study II, Study III, and Study IV; sample characteristics are reported in the corresponding articles.

4.2 CHRONIC DISEASE DEFINITION AND CATEGORIZATION (STUDY I)

Based on expert consensus, a disease was considered *chronic* if it had a prolonged duration and either (a) left residual disability or worsening quality of life, or (b) required a long period of care, treatment, or rehabilitation. After revising all the ICD-10 codes, 918 were classified as chronic and further categorized into 60 homogeneous groups (***table 2***). Of all 3,363 SNAC-K participants and 60 disease groups, 13 participants showed a prevalence >10%, 35 had a prevalence between 1% and 10%, and 12 <1%. Overall, only 3.2% of the participants had zero diseases, 8.2% had one disease, 88.6% had two or more diseases, and 73.2% had three or more diseases. For both males and females, the number of chronic diseases increased with age (***figure 7***). The three most frequent diseases were hypertension (69%), dyslipidemia (46%), and chronic kidney disease (38%). Finally, we found that the proportion of people with two or more different ICD-10 codes within a given disease category was <1% of all participants in that category.

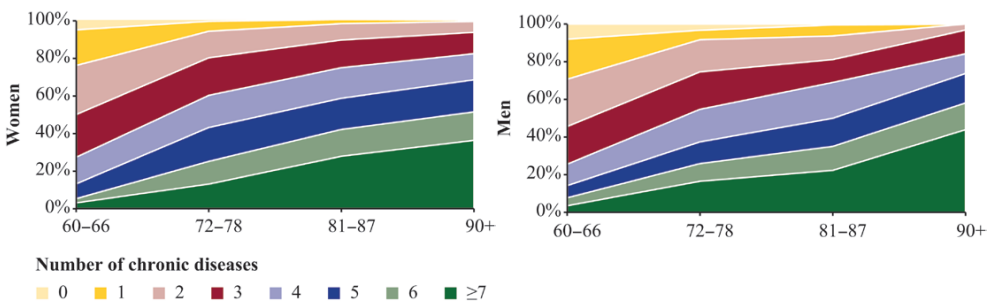

Figure 7. Percent distribution of chronic disease categories by age and sex in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; N = 3363). *Data source: Journals of Gerontology: Medical Sciences 2017 (1).*

Table 2. Age and sex-standardized prevalence (%) and 95% confidence interval (CI) of chronic disease categories (N = 3,363).

Chronic disease	%	95% CI	Chronic disease	%	95% CI
Hypertension	68.8	67.1-70.4	Other cardiovascular diseases	3.7	3.1-4.5
Dyslipidemia	45.8	44.1-47.6	Neurotic, stress-related and somatoform diseases	3.2	2.6-3.9
Chronic kidney disease	37.5	35.9-39.1	Other genitourinary diseases	2.8	2.2-3.5
Ischemic heart disease	16.7	15.4-18.1	Cardiac valve diseases	2.7	2.1-3.3
Anemia	13.7	12.5-15.1	Migraine and facial pain syndromes	2.5	2.0-3.1
Osteoarthritis and other degenerative joint diseases	13.2	12.0-14.5	Other psychiatric and behavioral diseases	2.3	1.8-2.9
Colitis and related diseases	13.2	12.0-14.5	Other neurological diseases	1.9	1.5-2.5
Deafness, hearing impairment	12.3	11.2-13.5	Sleep disorders	1.9	1.5-2.4
Heart failure	11.7	10.6-12.9	Bradycardias and conduction diseases	1.9	1.4-2.4
Obesity	11.2	10.1-12.3	Peripheral vascular disease	1.8	1.3-2.4
Thyroid disease	11.1	10.0-12.3	Other metabolic diseases	1.7	1.3-2.3
Dementia	10.5	9.5-11.6	Peripheral neuropathy	1.6	1.2-2.2
Atrial fibrillation	10.3	9.2-11.4	Chronic pancreas, biliary tract and gallbladder diseases	1.5	1.1-2.0
Depression and mood diseases	9.4	8.4-10.5	Allergy	1.4	1.1-1.9
Solid neoplasms	9.0	8.0-10.1	Parkinson and parkinsonism	1.3	0.9-1.8
Diabetes	8.9	7.9-10	Other respiratory diseases	1.1	0.8-1.6
Cerebrovascular disease	8.5	7.5-9.6	Chronic ulcer of the skin	1.0	0.7-1.5
Osteoporosis	7.6	6.7-8.7	Epilepsy	1.0	0.7-1.4
Other musculoskeletal and joint diseases	7.1	6.2-8.2	Ear, nose, throat diseases	0.9	0.6-1.3
Dorsopathies	6.6	5.8-7.6	Inflammatory bowel disease	0.9	0.6-1.3
Glaucoma	6.5	5.6-7.5	Hematological neoplasms	0.8	0.5-1.2
Cataract and other lens diseases	6.3	5.4-7.2	Venous and lymphatic diseases	0.8	0.5-1.2
Asthma	6.0	5.2-6.9	Schizophrenia and delusional diseases	0.7	0.5-1.1
Other eye diseases	5.4	4.6-6.3	Blood and blood forming organ diseases	0.5	0.3-0.9
COPD, emphysema, chronic bronchitis	5.2	4.4-6.0	Other digestive diseases	0.5	0.3-0.8
Autoimmune diseases	4.8	4.1-5.7	Chronic infectious diseases	0.3	0.2-0.6
Blindness, visual impairment	4.5	3.8-5.3	Chronic liver disease	0.2	0.1-0.4
Esophagus, stomach and duodenum diseases	4.5	3.8-5.3	Multiple sclerosis	0.1	0.0-0.2
Prostate diseases	4.3	3.6-5.1	Other skin diseases	0.1	0.0-0.2
Inflammatory arthropathies	4.1	3.5-4.9	Chromosomal abnormalities	0.0	---

The Swedish population was used to standardize disease-category prevalence.

4.3 TRAJECTORIES OF CLUSTERS OF MULTIMORBIDITY (STUDY II)

In the analytical sample of Study II, including 2,931 individuals with two or more diseases at baseline, the mean age was 76.1 ± 11.0, and 66.6% were females. Five clusters of people were identified at baseline: those with *psychiatric and respiratory disease* (5.4%), *heart disease* (9.3%), *respiratory and musculoskeletal disease* (15.7%), *cognitive and sensory impairment* (10.6%), and *eye disease and cancer* (10.7%). However, half of the people (48.7%) were grouped in an *unspecified* group, as they were affected by prevalent diseases of which the occurrence did not exceed the expected. At baseline, demographic, clinical, and functional characteristics were differentially distributed across the clusters.

Participants in the *cognitive and sensory disease*, the *eye disease and cancer*, and the *heart disease* clusters were the oldest. Participants in the *heart disease*, the *eye disease and cancer*, and the *psychiatric and respiratory disease* clusters presented the greatest number of chronic diseases. Participants in the *heart disease* and *psychiatric and respiratory disease* clusters and those in the *cognitive and sensory impairment* cluster used the highest number of drugs. Moreover, individuals included in the *heart disease*, the *eye disease and cancer*, and the *cognitive and sensory impairment* clusters presented the highest prevalence of disability and slow walking speed. Those clusters, together with the *psychiatric and respiratory disease* cluster, showed the lowest MMSE scores. The *unspecified* group of participants was characterized by the lowest mean age, the lowest number of chronic disease and drugs, and better functional status. Yet it had a high prevalence of hypertension, diabetes, dyslipidemia, and obesity.

Five clusters were identified at six and twelve years. At follow-ups, those diseases characterizing the baseline clusters were regrouped into different multimorbidity clusters. In spite of varied clustering, a similar clinical distribution was observed for the different types of disorders. ***Figure 8*** depicts the longitudinal evolution of multimorbidity clusters over twelve years and includes both the change over time of disease patterns (the diseases that characterize a specific cluster of individuals) and the migration of participants from one cluster to another.

Over the twelve years, 1,290 (44%) deaths occurred. At baseline the *heart disease*, the *cognitive and sensory impairment*, and the *psychiatric and respiratory disease* clusters were significantly associated with the highest six-year mortality compared with the people who were not part of any cluster. These clusters accounted for 51% of deaths. At first follow-up, the *heart and vascular disease*, the *heart disease*, and *neuropsychiatric and respiratory disease* clusters had the highest OR for six-year mortality when compared with the *unspecified* group. These clusters accounted for 57% of deaths in the following six years.

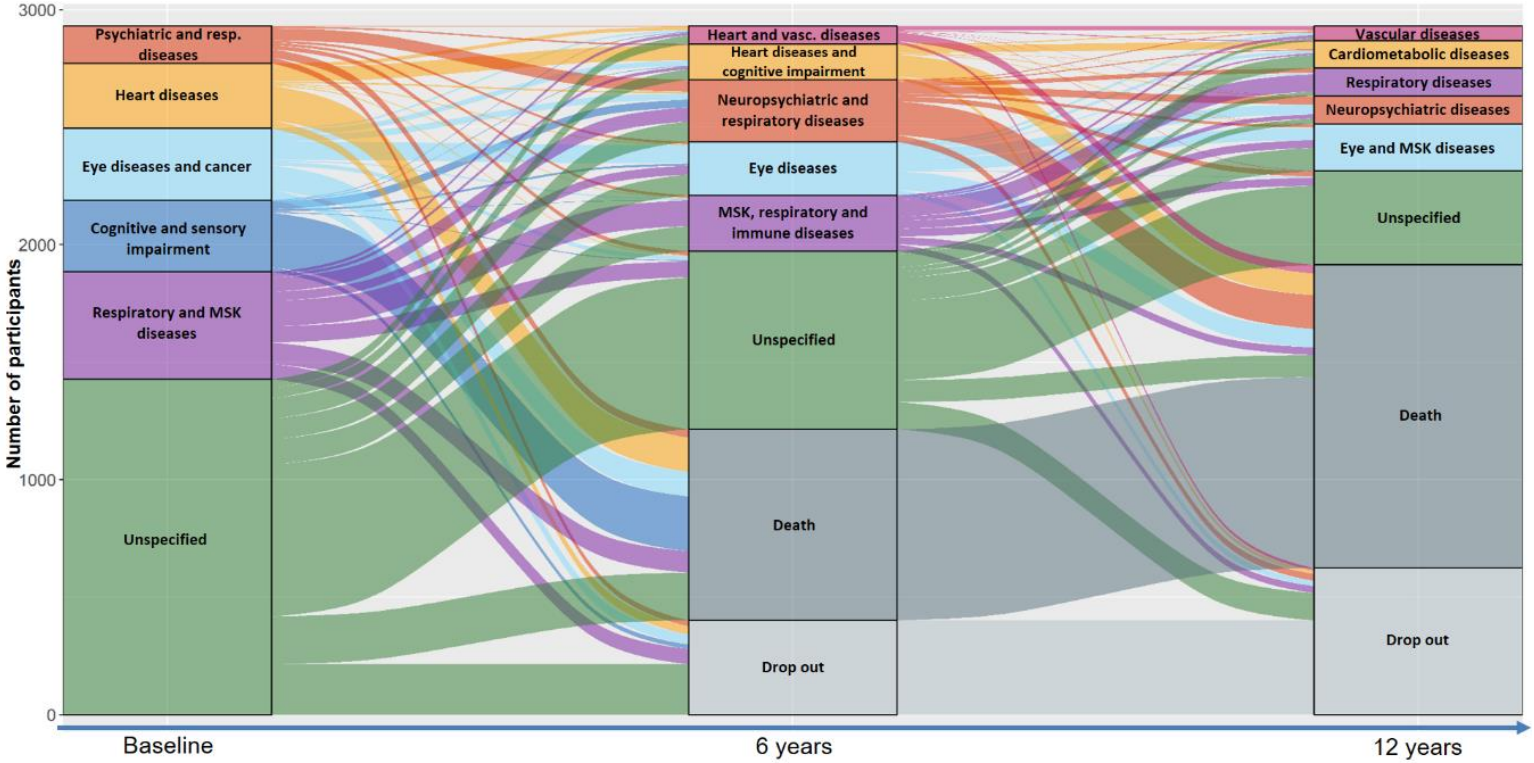

Figure 8. Evolution of multimorbidity clusters and clinical trajectories of older adults with multimorbidity over 12 years. The height of the boxes and the thickness of the stripes are proportional to the amount of people belonging to the cluster and moving from the cluster, respectively. MSK = musculoskeletal.

4.4 CARDIOVASCULAR AND NEUROPSYCHIATRIC MULTIMORBIDITY AND PHYSICAL FUNCTION (STUDY III)

In the analytical sample of Study III, including at baseline 2,385 participants with at least two valid assessments over nine years, the mean age was 72.9 ± 10.3 years, and 65% were females. ***Figure 9*** depicts the distribution in the study sample of the chronic disease patterns based on the number of cardiovascular and neuropsychiatric diseases.

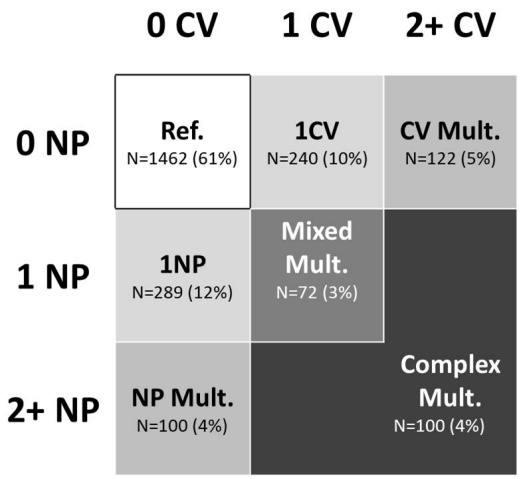

Figure 9. Participant categorization used in Study III, based on the presence of zero, one, or two or more cardiovascular (CV) and neuropsychiatric (NP) diseases.

Figure 10 shows the trajectories of walking speed and B-ADL score predicted for the disease-load clusters over nine years of follow-up. Irrespective of the presence or not of cardiovascular diseases, those with several neuropsychiatric diseases experienced the most drastic drop in walking speed as well in the number of preserved B-ADL. Individuals with cardiovascular multimorbidity experienced steeper deterioration in walking speed over time, relative to those in the reference group, although such effect was not present for disability trajectories. Individuals with a copresence of multiple cardiovascular and neuropsychiatric conditions experienced the largest drop in walking speed (up to 0.7 m/s; $p < 0.001$) and B-ADL (up to 3 B-ADL, $p < 0.001$) over nine years, relative to the control group.

In additional analyses, in which both disease patterns (exposures) and adjustment variables were considered as time-varying covariates, the negative association between walking speed and having just one cardiovascular disease became only marginally statistically significant ($\beta = -0.03$; 95% confidence interval [CI] −0.07 to 0.00). Importantly, all other clinical patterns preserved their negative statistically significant association with walking speed, with the strongest one being that involving neuropsychiatric multimorbidity ($\beta = -0.20$; 95% CI −0.24 to −0.16) and complex multimorbidity ($\beta = -0.21$; 95% CI −0.25 to −0.18). Regarding the disability trajectories, all patterns involving at least one neuropsychiatric condition (characterizing 25% of the study population) were associated with a faster decline in B-ADL,

and mixed multimorbidity and complex multimorbidity exhibited the largest association estimates (β = −0.20; 95% CI −0.30 to −0.11; β = −0.27; 95% CI −0.34 to −0.19, respectively). Generally, functioning was reduced between 5% and 20% in those with the most complex clinical patterns, relative to the reference group. Older age and female sex generally exacerbated the negative association between the clinical patterns and disability and walking speed. The pattern of the associations remained intact after excluding individuals with the most prevalent cardiovascular and neuropsychiatric diseases.

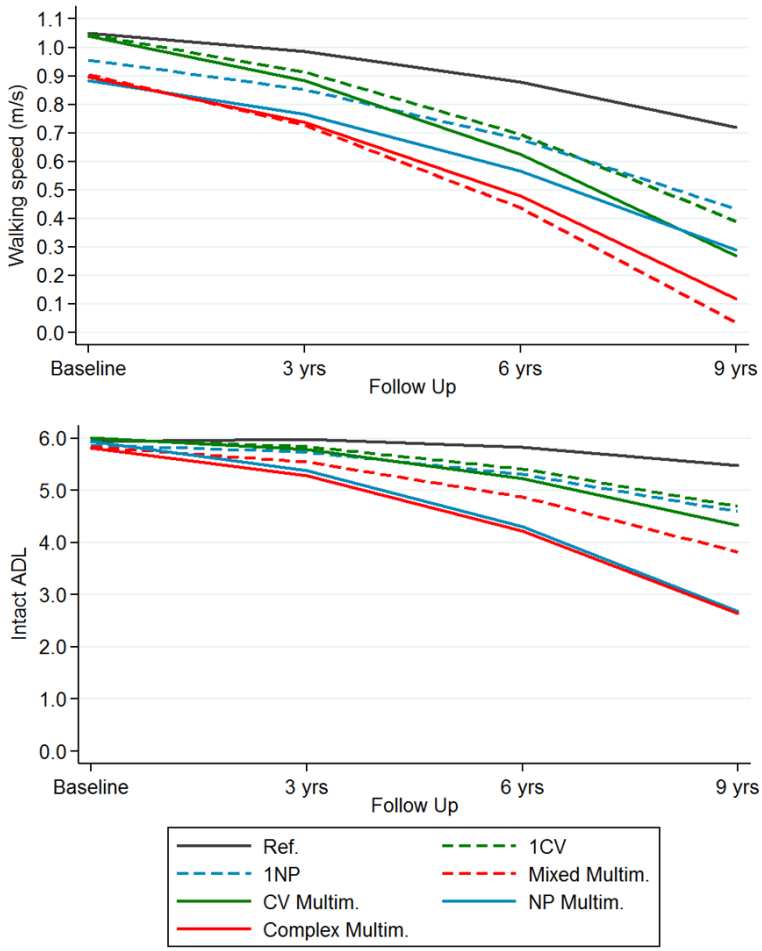

Figure 10. Trajectories of walking speed and ADL impairment over nine years by clinical patterns. Trajectories derived from mixed-effect linear regressions adjusted for baseline age, sex, education, malnutrition, institutionalization, and number of medications. Reference group: participants free from cardiovascular and/or neuropsychiatric diseases. CV = cardiovascular; NP = neuropsychiatric.

4.5 PROGNOSTIC ROLE OF WALKING SPEED (*STUDY IV*)

In the analytical sample of Study IV, including 3,241 participants with valid baseline measurements of walking speed, the mean age was 74.3 ± 11.0 years, and 64.4% were females. One third of baseline participants reported a walking speed of <0.8 m/s. By the three-year follow-up, 411 participants (12%) were deceased: 174 (5%) from cardiovascular causes and 237 (7%) from other causes. A further 682 (21%) individuals died by the time of the five-year follow-up: 287 (9%) of cardiovascular and 395 (12%) of other causes. According to the findings in table 3, a greater cardiovascular burden was associated with an elevated three-year mortality risk only in the presence of slow walking speed (reference group: preserved walking speed and no cardiovascular disease). The pattern of results was similar for five-year mortality, although this time, even in the presence of preserved walking speed, having one or two cardiovascular conditions was associated with greater risk of death. An increasing burden of neuropsychiatric disease was associated with greater three-year mortality among individuals with slow walking speed, relative to participants with intact walking speed and no neuropsychiatric disease (***table 3***). When looking only at individuals with slow walking speeds, the crude excess risk of three-year mortality was 18.4/100 person-years in those with two or more cardiovascular diseases and 17/100 in those with two or more neuropsychiatric diseases (reference: intact walking speed). While some minor attenuation of results was observed for the five-year follow-up, the pattern remained consistent. Quantifying the joint effect of multimorbidity and walking speed on mortality using additive interaction revealed that 42% and 34% of the relative excess risk of death was attributable to the effect of slow walking speed and cardiovascular and neuropsychiatric multimorbidity, respectively.

Table 3. Association between cardiovascular and neuropsychiatric multimorbidity by walking speed.

3-year mortality				
Cardiovascular diseases	*No. Diseases*	*Deaths/ No. at risk*	IR per 100/person year	HR (95% CI)
WS > 0.8 m/s	0	59/1860	1.1	1.00 (Ref.)
	1	18/287	2.1	1.17 (0.68-2.01)
	2+	12/124	3.4	1.47 (0.78-2.80)
WS ≤ 0.8 m/s	0	113/505	8.3	1.88 (1.29-2.74)
	1	98/237	17.3	3.85 (2.60-5.70)
	2+	111/228	21.8	5.18 (3.45-7.78)
Neuropsychiatric diseases	*No. Diseases*	*Deaths/ No. at risk*	IR per 100/person year	HR (95% CI)
WS > 0.8 m/s	0	61/1872	1.1	1.00 (Ref.)
	1	24/316	2.6	2.09 (1.30-3.37)
	2+	4/83	1.6	1.29 (0.47-3.55)
WS ≤ 0.8 m/s	0	118/492	9.0	2.88 (2.03-4.08)
	1	129/306	17.8	3.36 (2.31-4.89)
	2+	75/172	18.6	3.68 (2.43-5.59)

WS = walking speed; IR = incident rate; HR = hazard ratio; CI = confidence interval

Figure 1 shows the hazard ratios (HRs) for three-year all-cause mortality across walking speed (continuous variable), depending on the number of cardiovascular and neuropsychiatric diseases. Participants with a speed of <0.8 m/s had a higher mortality (dashed line). Mortality was exacerbated in the presence of one or more cardiovascular or neuropsychiatric diseases. Individuals with two or more neuropsychiatric diseases did not differ in mortality risk from those with one neuropsychiatric disease. The pattern of results was unchanged at five years.

Focusing exclusively on individuals who died of cardiovascular causes, cardiovascular diseases were associated with a greater relative risk of three-year mortality, irrespective of walking speed. Examining those who died of causes other than cardiovascular disease revealed that a higher burden of cardiovascular diseases was associated with a greater change in three-year mortality only in individuals with slow walking speeds. These findings remained consistent after a five-year mortality follow-up, as well as in the analysis of neuropsychiatric conditions. An alternative cutoff of <1 m/s to define slow walking speed did not affect the pattern of the associations presented.

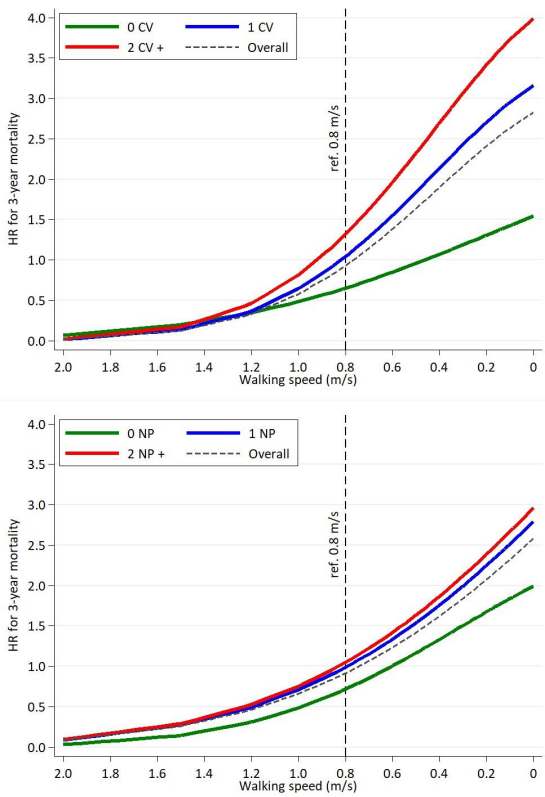

Figure 11. Estimated hazard ratio (HRs) of 3-year all-cause mortality for different values of walking speed (reference 0.8 m/s) in the overall population (centering the number of diseases on their average number) and in participants with 0, 1, or 2+ cardiovascular and neuropsychiatric diseases.

5 DISCUSSION

5.1 MAIN FINDINGS

In this doctoral thesis, a methodology was proposed to assess and measure multimorbidity in older individuals, describe the longitudinal evolution and prognosis of multimorbidity clusters, and investigate the extent to which clusters of cardiovascular and neuropsychiatric multimorbidity impact and interact with physical function.

The main findings of the project can be summarized as follows.

1. When applying a comprehensive and clinically driven methodology to its assessment, multimorbidity—the presence of two or more diseases in a single person—is present in nine out of ten individuals aged 60 years and older (Study I).

2. Clinical trajectories of older adults with multimorbidity are characterized by great dynamism and complexity but can still be tracked over time. Over 12 years, changes in cluster composition, participants' transitions from one cluster to another, and participant mortality generated a dynamic but well-defined clinical picture (Study II).

3. Different combinations of cardiovascular and neuropsychiatric disease exert a differential impact on independence and walking speed in older adults, with neuropsychiatric diseases (alone or combined with others) showing the strongest association with functional decline (Study III).

4. In older adults, the assessment of walking speed provides further prognostic information to the association of cardiovascular morbidity with mortality, and neuropsychiatric morbidity with mortality (Study IV).

5.2 ASSESSING CHRONIC DISEASES AND MULTIMORBIDITY IN OLDER ADULTS

As previously stated, despite general agreement on multimorbidity defined as the concurrent presence of two or more diseases, and as the most frequent chronic condition encountered in older people, less unanimity characterizes studies reporting the prevalence of multimorbidity in the older population (55% to 98%) (27). The greater part of such discordance is driven by methodological pitfalls related to the way multimorbidity is assessed (1, 52). In fact, the lack of a standard and clinically driven list of chronic diseases, both for clinical and research purposes, has led several authors to rely on discretional criteria (52). The first inconsistencies that emerged from the literature concerned the inclusion of both chronic and acute conditions (e.g., pulmonary embolism) in the measurement of multimorbidity, as well as the different weight given to some of the aspects defining a chronic disease (e.g., duration, treatment). In this regard, the first output of Study I was to reach consensus on the definition of what in older people can be reliably considered a *chronic disease*—namely a condition that has a prolonged

duration and, either (a) leaves residual disability or worsening quality of life, or (b) requires a long period of care, treatment, or rehabilitation. With this definition, 918 ICD-10 codes could be classified as chronic. Another issue was the varying number of conditions assessed in previous studies, ranging from a few to more than hundred diseases (1, 52). This mainly depended on the level of aggregation of nosological entities included by other authors. For example, sometimes atrial fibrillation is counted as an individual condition, while in other cases atrial fibrillation is included in the wider category of heart disease. In Study I, after selecting 918 chronic ICD-10 codes, we reduced them to 60 homogeneous categories of chronic disease, taking into account pathophysiologic, treatment-related, prognostic, and prevalence criteria. The result, upon applying this list of chronic conditions, was that 88.6% of SNAC-K participants were affected by chronic multimorbidity. Such prevalence is among the highest reported in the literature (27). Two main reasons may explain this finding. First, this is one of the most comprehensive lists of chronic disease provided so far. Beyond the most prevalent diseases, a number of conditions were included that were characterized by a low prevalence, even in older adults. Note that 12 out of 60 diseases had a prevalence <1% within the SNAC-K population. Those conditions, such as epilepsy, inflammatory bowel disease, and chronic liver disease, despite being rare, exert an undeniable negative burden on older individuals' health and survival. Second, in SNAC-K, the detection of chronic disease is based on a comprehensive clinical and instrumental assessment carried out by physicians, nurses, and psychologists, minimizing the underdetection of several conditions. Moreover, the linkage of the SNAC-K database with the Swedish National Patient Register further improves disease detection.

5.3 QUESTIONING THE "TWO OR MORE" CONCEPT

That 9 in 10 older individuals have two or more diseases (Study I) when a thorough assessment is performed makes it a threshold of uncertain relevance (52). In fact, based on the given definition of multimorbidity, physicians would consider it to "affect" almost 100% of their older patients, epidemiologists would struggle to see multimorbidity as a valuable prognostic tool, and public health experts would find it hard to identify 9 in 10 as a population at risk. It is not surprising that the studies that defined multimorbidity as a mere dichotomous metric failed to demonstrate an association with several health-related outcomes, especially when function and disability have been taken into consideration (12). That such a threshold is applied to a disease count, independently of the type of disease encountered, further weakens the construct. Indeed, many would agree that a person with dementia plus heart failure should have a completely different prognosis than a person with allergy plus prostate hypertrophy—despite both being affected by multimorbidity.

Two different ways of operationalizing the concept of multimorbidity have emerged in recent years. The first is the concept of *associative multimorbidity*, based on the observation that chronic diseases cluster within the same individual according to specific patterns reflecting their pathophysiological commonalities (36). This approach has a strong clinical valence, given that similar risk factors, prognoses, and treatments may be identified across diseases belonging

to the same pattern (1, 51, 93). An alternative way to study the phenomenon of multimorbidity is through its development and progression over time, namely the speed *of accumulation of chronic diseases* in a single person. This approach is rooted in the gerontological significance of multimorbidity, establishing a close relationship between the speed of accumulation of diseases and the pace at which the aging process advances (85). Studies II, III and IV focused on the description of the occurrence and prognosis of multimorbidity clusters in older adults.

5.4 THE DYNAMIC NATURE OF MULTIMORBIDITY CLUSTERS

In Study II, using a flexible cluster analysis method, we described the occurrence and the evolution of multimorbidity clusters across 12 years in the SNAC-K population. The main advantages and the novelty of this study are represented by the use of a method that (a) identifies clusters of individuals, not diseases and (b) does not force participants to belong to a cluster but attributes them a probability of belonging to a cluster. The approaches previously used to study patterns of multimorbidity in older individuals include the estimation of O/E ratios and ORs of the most commonly coexisting couples or triads of chronic disease, as well as cluster and factor analysis (27). However, the limitations of these analytical strategies restrict their interpretation and clinical relevance. The need for large samples, the issue of multiple comparisons, and the forcing of diseases into single clusters according to similarity or dissimilarity measures represent some of these limitations. Another important limitation of previous studies is their cross-sectional design (51). Given that a dynamic evolution of multimorbidity clusters is expected over time, their assessment at a single time point may be reductionist and biased.

According to our analytical approach, only half of the SNAC-K participants with two or more diseases could be grouped at baseline into one of five multimorbidity clusters. The rest were not sorted into any cluster and were characterized by having a younger age, lower numbers of co-occurring diseases and drugs, good functional and cognitive abilities, and a high percentage of cardiovascular risk factors. This *unspecified* group, despite not identifying any specific cluster at baseline, contributed to several clusters identified at the six-year follow-up with a proportion varying from 29% to 49%, and to the clusters identified at the twelve-year follow-up with a proportion varying from 16% to 50%. The most relevant contribution was observed toward those clusters characterized by cardiovascular, eye, respiratory, and musculoskeletal diseases. This finding reflects the fact that cardiometabolic conditions such as diabetes, obesity, dyslipidemia, and hypertension are important risk factors for the development of several cardiovascular and noncardiovascular diseases (138).

Over 12 years, the evolution of cluster composition, participants' transitions from one cluster to another, and mortality generated dynamic but well-defined clinical paths. The first remarkable trajectory has been mentioned and involved the *unspecified* cluster that includes individuals at their first stage of the multimorbidity process. The second relevant trajectory was driven by the high mortality of individuals in clusters characterized by cardiovascular and neuropsychiatric disease, which, despite representing only 25%, 28%, and 29% of the participants at baseline, 6 years, and 12 years, respectively, accounted for 51% and 57% of

deaths during the first and second follow-up periods, respectively. In Study IV, the relationship between cardiovascular and neuropsychiatric multimorbidity was further investigated. A final group of trajectories from one cluster to another could have been driven by several mechanisms. For example, one disease may result from another. This may explain why a large number of people in the *heart disease* cluster at baseline became part of the *heart disease and cognitive impairment* cluster at 6 years. The association between heart disease and cognitive decline may be supported by different mechanisms such as emboli, ischemic events, small vessel disease, cerebral hypoperfusion, and hypoxia (62, 139). Another possible pathway is represented by iatrogenic events, as when a disease results from the pharmacological or surgical treatment of another condition. For example, an association that was part of the *neuropsychiatric and respiratory disease* cluster and remained over the entire course of study may be linked to the steroid treatment of respiratory diseases, which can cause neurotic symptoms and depression (140). Finally, overlapping symptomatology may result in diseases being misdiagnosed in an initial phase. This may be the case of some baseline psychiatric conditions in the *psychiatric and respiratory diseases* cluster, which at 6 or 12 years may have evolved into, or been correctly classified as, cognitive impairment and dementia, justifying the *cognitive impairment, psychiatric, and respiratory disease* cluster (141).

Only a handful of studies addressed the issue of the longitudinal development of multimorbidity. The study with comparable methodology was carried out in Spain and found at baseline six multimorbidity clusters: musculoskeletal, endocrine-metabolic, digestive/respiratory, neuropsychiatric, cardiovascular, and an unspecified group. These clusters showed less variation over six years than those identified in Study II. The shorter follow-up and use solely of primary-care electronic records may contribute to the differences (53, 142). Beyond the abovementioned report, three others from the Netherlands, Denmark, and Australia investigated the longitudinal accrual of diseases, leading to results only partially concordant with the results of this thesis. Once again, sample selection, the lack of clinical assessment of disease, the use of electronic information, and different analytical approaches make comparison difficult (55, 56, 58).

5.5 ASSOCIATION AND INTERPLAY BETWEEN CHRONIC DISEASE AND FUNCTION

In this thesis, both the association between multimorbidity and functional decline and the interplay between the two have been investigated. Given the prevalence and burden of cardiovascular and neuropsychiatric conditions in the older population, and considering that such disease characterizes most of the multimorbidity clusters previously identified in the literature, the focus here is on these two disease groups (51). Findings from Study III show that multimorbidity patterns combining cardiovascular and neuropsychiatric diseases are differentially associated with walking speed and B-ADL decline in older individuals (93). The pattern that includes multiple cardiovascular and neuropsychiatric diseases is associated with the worst trajectory in both walking speed and B-ADL, compared with people without cardiovascular and neuropsychiatric disease, suggesting that the interplay among diseases

belonging to different body systems is stronger than diseases with similar pathophysiology that belong to the same group. This is in line with two studies from Quiñones et al. that describe how multimorbidity patterns including a combination of mental and somatic diseases are more often associated with the worst functional trajectories (131, 132). Interestingly, neuropsychiatric diseases, independently of cardiovascular diseases, are shown in this thesis to be the major determinants of functional decline. Isolated cardiovascular multimorbidity is only associated with changes in walking speed. This contrasts with a study by Jackson et al. including only women, in which both cardiovascular and neuropsychiatric multimorbidity were independently and significantly associated with a steeper development of disability (129). A number of characteristics differentiate this from previous studies, challenging any direct comparison. First, the assessment of chronic disease and multimorbidity is based on the comprehensive and clinically driven methodology proposed in Study I. Second, multimorbidity patterns are not defined by data-driven procedures, but rather considered from all cardiovascular and all neuropsychiatric conditions listed. Finally, this is the first study that includes time-varying information related to multimorbidity, thus including the dynamic nature of this condition, as shown in Study II.

In Study IV, this knowledge is expanded by investigating the interplay of cardiovascular and neuropsychiatric multimorbidity with functional ability, in association with mortality. Walking speed was found to provide additional prognostic information on mortality at three and five years, beyond the number of both cardiovascular and neuropsychiatric diseases. For SNAC-K participants with a slow walking speed, the association with all-cause and cardiovascular mortality was stronger for cardiovascular diseases. While the number of cardiovascular diseases has a discriminative power for mortality in individuals walking at slow speed, the same strong differential association cannot be found for neuropsychiatric diseases. An explanation of this finding may be that, given the strong association between neuropsychiatric disease and functional decline observed in Study III, slow walking speed may act more as a mediator than an effect modifier, buffering the direct effect that neuropsychiatric diseases may exert on mortality (93). Such consideration remains to be tested in further longitudinal studies. No comparison with other studies is possible as, to the best of our knowledge, ours is the first addressing the relationship between walking speed and multimorbidity.

5.6 METHODOLOGICAL CONSIDERATIONS

5.7 STUDY DESIGN

For all the studies included in this thesis we used the population-based cohort of individuals participating in the SNAC-K study. A few exclusion criteria were applied at baseline: age <60 years, nonproficiency in the Swedish language, and residency outside the Kungsholmen district in Stockholm. The final participants resulted in a healthier and wealthier group of individuals, compared not only to nonparticipants but also to the Swedish population.

5.7.1 Random error

Two types of random error from sample variance and measurement error are commonly observed in research.

5.7.1.1 Sampling error

The aim of sampling a population is to operate with a smaller number of observations while preserving the representativeness of the whole population. However, a certain level of discrepancy between the obtained estimates and the true ones can always be expected. Randomly sampling the population and increasing the sample size may help to address this variation and improve the precision of the estimates.

5.7.1.2 Measurement random error

Random error can be also attributed to measurements' imprecision. For instance, in SNAC-K, walking speed is assessed only once at each study wave, increasing the likelihood of measurement error by either the assessor (not following the exact procedure) or the participant (not understanding the task). A way to control for this type of error is to collect multiple assessments per individual and average them. Nevertheless, gait speed has shown to be a fairly robust measure when assessed only once, despite a lack of repeated assessments (143). SNAC-K assessors are trained in clinical assessment and data collection, and standardized protocols are used, with the aim of reducing measurement errors.

5.7.2 Systematic error (bias)

Systematic errors are common issues in every study design as well. Any systematic error that arises in designing, conducting, or analyzing the study and results in an error in the estimate is defined as bias.

5.7.2.1 Selection bias

The first type of selection bias potentially encountered in the SNAC-K study is the one arising during baseline sample selection. Although based on random sampling, selection bias may arise because someone accepts to participate to the study and someone else does not. Out of 5,111 people initially invited to participate to SNAC-K, 521 were not eligible (200 died, 262 had no contact information, and 59 were deaf, moved away, or were not Swedish speakers). Out of the remaining 4,590, 1,227 declined to participate, leaving a study population of 3,363 people (participation rate 73%). Participation rates were above 70% in all age groups and were similar among males and females. On the one hand, decliners may be older, less educated, affected by more chronic diseases, or disabled, all characteristics that could prevent them from participating in the study. In our studies, this could have led to an underestimation of the association between exposure and outcome. On the other hand, decliners may be younger, be still working, and not have time to be part of the study. This latter scenario could have led to an overestimation of the association. The proportion of people living in institutions was significantly higher among participants (6%) than among nonparticipants (<1%). For age cohorts 60 through 87, shorter time to death after the beginning of the study was associated with a higher likelihood of nonparticipation. Nonparticipants were also older. Thus, in our project the first scenario is more likely to have occurred.

Another type of selection bias of study participants arises from longitudinal attrition when individuals die or decline to participate further. Like sample selection, attrition can affect the study estimates in longitudinal studies, leading to biased results, particularly because of missing data. In Study III, for example, disability was an outcome; we could have underestimated the association between exposure and disability because people might have died before experiencing disability. However, in sensitivity analyses, using joint regression models, we accounted for the competing effect of death, modelling our outcomes (walking speed and B-ADL score) together with mortality data.

5.7.2.2 Information (measurement) bias

This systematic error occurs when the assessment of participants' characteristics is vitiated by factors dependent either on the assessors or the participants themselves. Namely, the way specific information is measured, asked for, reported, and noted may cause a misclassification of the participants. Misclassification may be differential or nondifferential. In the first case, the proportion of misclassification is differentially distributed across different study groups, and potentially biases the estimations. Conversely, nondifferential misclassification results are randomly distributed across the groups of interest and may dilute the extent of the effect.

Virtually all the variables considered in our studies may be subject to information bias. Chronic disease, for instance, when self-reported, is susceptible to both overreporting and underreporting and can be responsible for a differential misclassification of participants. To overcome this problem in the present thesis, we maximized the sensitivity of disease detection

by gathering information from several sources, including clinical examination, instrumental tests, blood tests, medication, and both inpatient and outpatient data. The prevalence of multimorbidity we obtained by applying this methodology is among the highest reported in the literature. Similarly, the assessment of the outcomes (excluding mortality) and several covariates may be biased by the abovementioned factors. However, the use of a rigorous and validated methodology, like the one applied in SNAC-K, is expected to minimize such possibility.

5.7.2.3 Confounding

A problem common to epidemiological studies is to observe an association between two measures that should actually be explained by the distribution across groups of a third variable, a *confounder*. Potential confounders are typically risk factors for the outcome, are associated with the exposure but are not surrogates of it, and usually precede (temporally) the exposure. We handled the problem in the data analyses by either stratifying or adjusting the analyses for confounders. Although the analyses in all four papers of this thesis were adjusted for a number of factors we deemed to be potential confounders, also considering their variation over time (i.e., Study III), we cannot completely rule out the presence of residual confounding.

5.7.3 Generalizability

One of the aims of research is to produce generalizable results, namely the possibility of applying the findings of a study to other populations, or to all human beings. However, all the abovementioned types of bias contribute to affect the generalizability of a given study, and in general it is considered impossible to exactly reproduce the characteristics of the whole population through a subset of it. For example, as mentioned, the SNAC-K sample population resulted in a healthier and wealthier sample, compared with the actual population living in the Kungsholmen district of Stockholm, and such differences are likely to be even more accentuated if the comparison is made with the rest of the Swedish or European population. For these reasons, caution is recommended when the results of our studies are generalized to other settings. However, if this is true when attempting to generalize prevalence and incidence figures (or other descriptive statistics) from one setting to another, it is less of a problem when examining associations for findings with a strong biological plausibility and clear or well-known underlying biological mechanisms. Knowing the biological bases of the observed phenomena helps us to better design a study and to account for specific confounders. In other words, what makes generalizability possible in most cases is good biological plausibility and knowledge of the underlying mechanisms, not only a representative sample.

5.8 CONCLUSIONS

1. We provided a clinically driven list of 60 chronic diseases for the study of multimorbidity in older adults. Upon applying the methodology to a population-based cohort of individuals aged 60 years or older, 9 in 10 of them were found to be affected by two or more diseases. The use of a standardized methodology to assess chronic disease and multimorbidity may enhance the comparability across studies, clinical settings, and geographical regions.

2. Clinical trajectories of older adults with multimorbidity are characterized by great dynamism and complexity but can still be tracked over time. The presence of several cardiometabolic risk factors, the evolution and consequences of several diseases, as well as death, steer most of the longitudinal transitions among the multimorbidity clusters we identified over a period of 12 years. Studying the natural evolution of multimorbidity in older individuals may help to better hypothesize underlying mechanisms and provide important prognostic information.

3. Patterns of multimorbidity combining cardiovascular and neuropsychiatric diseases are differentially associated with walking speed decline and disability in older adults. Neuropsychiatric disease, alone or combined with cardiovascular disease, exterts the strongest detrimental impact on functional decline. Cardiovascular multimorbidity shows an association solely with decline in walking speed. Accounting for specific combinations of chronic diseases may provide important prognostic information related to the speed of physical function decline in older individuals.

4. In older individuals, slow walking speed, a marker of motor impairment, provides additional prognostic information in terms of all-cause and cause-specific mortality, beyond the number of both cardiovascular and/or neuropsychiatric diseases. The adoption of a simple and easy-to-use measure of functional impairment such as walking speed may help health-care professionals identify older people affected by specific groups of chronic disease with similar needs, health trajectories, and prognoses.

6 RELEVANCE AND IMPLICATIONS

The rapid growth in the number and proportion of older adults demands that societies worldwide take action and find sustainable ways to promote and maintain seniors' health. In this regard, the epidemiological and biomedical research fields play a role of utmost importance. The first, describing the natural course of specific phenomena, help us recognize the common patterns upon which person-centered medicine can be built. The second, revealing the underlying mechanisms of such processes, provides the knowledge to implement effective preventive and curative strategies.

With the present thesis, we aimed to contribute mainly to the first issue. First, we provided a reliable and rigorous tool for the assessment of chronic disease and multimorbidity in the older population. The availability of an alphabet represents the first step toward the development of a common language. The lack of a shared methodology has strongly limited the comparability—and sometimes validity—of most studies to date in the field of multimorbidity, sometimes weakening the concept of multimorbidity itself. Our wish is to have contributed to reducing the methodological noise of future studies in this field.

Second, with this thesis we try to advance toward an alternative way of operationalizing multimorbidity, namely through the evaluation of multimorbidity clusters. Counting diseases independently from which diseases, and drawing a line between having zero or one and two or more diseases would appear to be reductionist and easily questionable approaches. The idea of multimorbidity clusters is backed up by strong biological plausibility and confers to the concept of multimorbidity the qualitative perspective that has been lacking. In addition, the approach in this thesis strives to recognize the expected dynamicity of multimorbidity clusters. Their natural evolution over time is described here for the first time through a novel methodology, and such dynamism is included in evaluating the impact of specific multimorbidity patterns on functional decline. In doing so, we hope to contribute to the identification of specific subgroups of older individuals characterized by similar health care needs and trajectories.

Finally, beyond studying the impact of cardiovascular and neuropsychiatric multimorbidity on functional decline, we investigated for the first time the interplay between multimorbidity clusters and function. We conclude that the complementary information gained from functional and morbidity status can be used to further select the share of the older population in higher need of clinical interventions and care.

7 FUTURE DIRECTIONS

The present thesis contributes to a better description of the occurrence, evolution, and prognosis of multimorbidity in older individuals. As a brick is part of a wall, however, it requires further support from other pieces of evidence and needs to be extended for a deeper knowledge of the phenomenon. First, the goodness of our clinically driven methodology for the assessment of multimorbidity requires further confirmation in other populations and settings (specifically, the clinical setting). One of our aims was to provide a flexible methodology that was rooted in the ICD-10 classification system and could be easily adapted or updated in the future. Second, our attempt to describe the longitudinal evolution of multimorbidity clusters is limited by the fact that our observations are left-censored at 60 years. In line with the life-course approach advocated today in aging research, studies of younger cohorts of individuals would shed further light on the phenomenon of multimorbidity. Third, the interplay between multimorbidity and functional impairment needs to be better understood. Such interplay may, to a certain extent, reflect an overlap between disease and function, rather than a synergistic effect. Longer observation periods, starting earlier in individuals' lives, may help to untangle this aspect.

Despite knowledge gleaned about the occurrence and prognosis of multimorbidity in older individuals in the last two decades, little is known about the biological mechanisms underlying the accumulation—and in particular the faster accumulation—of chronic disease. It is a common idea that disease accumulation is the signature of the aging process, and that the faster accumulation of disease in some individuals reflects their faster aging than other individuals. Multimorbidity may represent an optimal model for studying the secrets of the aging process in humans.

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10 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991–2019

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease.
Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.
Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.
Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)
Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.
Rehnman Jenny. The role of gender in face recognition. (Stockholm University)
Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?
Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)
Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.
Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.
Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.
Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)
Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.
Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.
Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.
Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.
Livner Åsa. Prospective and retrospective memory in normal and pathological aging.
Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.
Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.
Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.
Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.
Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.
Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence.

Berggren Rasmus. Cognitive development and educational attainment across the life span.

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