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Development of dementia in older adults: the body-mind connection

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Ai miei genitori e a mio fratello

To my parents and my brother

"E questo ti sia sempre piombo a' piedi,
per farti mover lento com' uom lasso
e al sì e al no che tu non vedi"

"And lead shall this be always to thy feet,
To make thee, like a weary man, move slowly
Both to the Yes and No thou seest not"

Dante Alighieri
La Divina Commedia
Paradiso, Canto XIII, vv. 112-114

ABSTRACT

Over the past years, two major lines have emerged in the field of dementia research that are focused on: (1) The accurate and early prediction of dementia, and (2) The identification of modifiable factors for dementia prevention. This thesis has contributed to both. We explored the role played by the body-mind connection in cognitive aging by investigating whether motor functioning is a predictor of dementia and if different co-occurring diseases (i.e., multimorbidity [MM] patterns) are risk factors for dementia. We carried out four longitudinal studies, two for each research line, using 12 years of data from SNAC-K, a population-based study involving 3363 older adults, clinically assessed at regular intervals.

Study I. Participants with both cognitive and motor dysfunctions demonstrated the highest hazard of developing dementia. After gait speed was added to cognitive assessment, the area under the curve (AUC) increased from 0.69 to 0.83 among the oldest participants. This increase was driven by a reduction in the proportion of false negatives, while the number of false positives (high specificity) remained low. Adding gait speed did not improve the predictive power of the cognitive battery in identifying dementia among younger-old adults.

Study II. Individuals with concurrent cognitive and motor decline presented with a mixed and more rapidly evolving brain pathology on magnetic resonance imaging, affecting both gray and white matter. Adults experiencing only cognitive decline had a steeper hippocampal volume loss, whereas those exhibiting only motor decline displayed greater white matter hyperintensity burden.

Study III. Individuals belonging to the *neuropsychiatric*, *cardiovascular*, and *sensory impairment/cancer* MM-patterns had the highest hazards of dementia, among those with MM. Inflammation (high C-reactive protein levels) increased dementia hazard within these three patterns, whereas being an *APOE* ε4-carrier heightened dementia hazard for *neuropsychiatric* and *cardiovascular* MM-patterns.

Study IV. Exposure to air particulate matter ≤ 2.5μm [$PM_{2.5}$] was found to increase dementia hazard by up to 50%. The presence of heart diseases (heart failure and ischemic heart disease) further amplified the risk, whereas stroke mediated up to 50% of the $PM_{2.5}$-dementia association.

Conclusions. The findings from these four studies underline the relevance of the body-mind connection in dementia development. An easy-to-obtain motor marker (gait speed) improved the ability of the cognitive test to detect future dementia. This could be explained by the mixed brain pathology, which we found to develop in individuals with fast and concomitant cognitive and motor decline. Specific MM-patterns seemed to increase dementia risk, an effect that was further accentuated by the presence of inflammation and genetic predisposition. Finally, cardiovascular diseases could be important in explaining the relation between $PM_{2.5}$ and dementia risk. Further exploring the relation between body- and mind- related conditions could be essential in identifying at-risk populations and biomarkers for incipient dementia, and thus, in advancing our understanding of dementia in older adults.

Key words. Dementia, cognitive impairment, gait speed, brain MRI, multimorbidity patterns, air pollution, cardiovascular diseases.

RIASSUNTO

Nel corso degli ultimi anni due linee di ricerca principali sono emerse nel campo della demenza: (1) La predizione accurata e precoce della demenza; (2) L'identificazione di fattori modificabili, utili nella prevenzione della demenza. Questa tesi ha contribuito ad approfondire entrambe le linee. Abbiamo esplorato il ruolo della connessione mente-corpo nell'invecchiamento cognitivo, indagando, da un lato, se la funzione motoria possa essere un valido predittore di demenza e se, dall'altro, la presenza di diverse malattie nello stesso individuo (multimorbilità, MM) possa essere fattore di rischio per lo sviluppo di demenza. Abbiamo quindi condotto quattro studi longitudinali, due per ciascuna linea di ricerca, usando dati dello studio SNAC-K, uno studio di popolazione che include 3.363 persone di più di 60 anni, valutate clinicamente a intervalli regolari per 12 anni.

Studio I. Persone con deficit sia cognitivi, sia motori presentavano il più alto rischio di demenza. Quando la velocità del cammino veniva aggiunta alla valutazione neuropsicologica, l'area sotto la curva (AUC) per la predizione di demenza aumentava da 0.69 a 0.83, nella coorte più anziana (≥78 anni). Il miglioramento era largamente dovuto ad una riduzione nella proporzione dei falsi negativi, mentre il numero di falsi positivi (alta specificità) rimaneva basso.

Studio II. Individui con declino sia cognitivo, sia motorio mostravano alla risonanza magnetica cerebrale una patologia mista e in più rapida evoluzione, che interessava sia la sostanza grigia, sia quella bianca. I partecipanti con un esclusivo declino nella funzione cognitiva presentavano un maggiore danno a livello ippocampale, mentre coloro con un declino isolato nella funzione motoria evidenziavano un maggiore carico di iperintensità della sostanza bianca cerebrale.

Studio III. I pattern di MM neuropsichiatrica, cardiovascolare e disturbi sensoriali/cancro erano associati al più elevato rischio di demenza. La presenza di infiammazione (elevati livelli di proteina C reattiva) aumentava il rischio di demenza in tutti e tre i pattern, mentre essere portatori di almeno un allele *APOE* ε4 aumentava ulteriormente il rischio di demenza nei pattern di MM neuropsichiatrica e cardiovascolare.

Studio IV. Essere esposti al particolato atmosferico di dimensioni ≤ 2.5μm [$PM_{2.5}$] aumentava il rischio di demenza. La presenza di malattie cardiache (scompenso cardiaco e malattia cardiaca ischemica) amplificava ulteriormente tale rischio, mentre l'ictus mediava fino al 50% della associazione tra $PM_{2.5}$ e demenza.

Conclusioni. I risultati di questa tesi sottolineano la rilevanza della connessione mente-corpo nello sviluppo di demenza. L'ulteriore approfondimento di tale interazione sarà essenziale per identificare sia biomarcatori che predicano tale sviluppo, sia gruppi di popolazione a rischio. Questo studio in ultimo permetterà di accrescere le conoscenze relative alla demenza nelle persone anziane.

Parole chiave: demenza, disturbo cognitivo, velocita' del cammino, RMN cerebrale, pattern di multimorbilita', inquinamento atmosferico, malattie cardiovascolari.

SAMMANFATTNING

Under de senaste åren har två huvudsakliga inriktningar inom demensforskningen utkristalliserats: (1) tidig prediktion av demens och (2) identifiering av modifierbara faktorer för prevention av demens. Denna doktorsavhandling bidrog till båda dessa områden. Fyra longitudinella studier, två för vardera forskningsinriktningen, genomfördes baserade på data från befolkningsstudien SNAC-K, där 3 363 äldre stockholmare undersökts kliniskt med jämna mellanrum över en tolvårsperiod.

Studie I. Genom att addera gånghastighet till den neuropsykologiska bedömningen kan prediktionen av framtida demens förbättras. Området under kurvan (AUC) ökade från 0,69 till 0,83 bland de äldsta. Denna ökning drevs av en minskning av andelen falskt negativa fall samtidigt som andelen falskt positiva fall (hög specificitet) var fortsatt låg. Den prediktiva förmågan för identifiering av demens hos yngre vuxna förbättrades inte av att lägga till gånghastighet till det kognitiva standardbatteriet.

Studie II. De markörer som kännetecknar olika mönster av kognitiv och motorisk försämring identifierades genom magnetisk resonansavbildning av hjärnan. Individer med samtidig kognitiv och motorisk försämring uppvisade en mer blandad och snabbare utvecklande hjärnpatologi som involverade såväl grå som vit substans. Äldre personer som endast upplevde kognitiv försämring hade en brantare volymförlust i hippocampus, medan de med enbart motorisk försämring uppvisade en större hyperintensitet i vit hjärnsubstans.

Studie III. Effekterna av inflammation och *APOE*-genotyp inom olika multisjuklighetskluster undersöktes i relation till demensrisk. Individer som ingick i klustret neuropsykiatriska, kardiovaskulära och sensoriska funktionsnedsättningar/cancer uppvisade den högsta demensrisken. Inflammation (höga C-reaktiva proteinnivåer) ökade demensrisken inom dessa kluster. Att vara APOE ε4-bärare ökade demensrisken för neuropsykiatriska och kardiovaskulära multisjuklighetskluster.

Studie IV. Sambandet mellan luftföroreningar (dvs. partiklar ≤2,5µm, PM2,5 och kväveoxider, NO_X) och ökad demensrisk undersöktes, liksom i vilken utsträckning hjärt- och kärlsjukdomar kan förklara ett sådant samband. Exponering för PM2.5 ökade demensrisken med upp till 50 procent. Förekomsten av hjärtsjukdomar (hjärtsvikt och ischemisk hjärtsjukdom) förstärkte risken ytterligare, medan stroke förklarade upp till 50 procent av sambandet.

Slutsatser. Resultaten från de fyra studierna understryker betydelsen av sambandet mellan kropp och sinne i uppkomsten och utvecklingen av demens. Fortsatta studier av just förhållandet mellan kropps- och sinnesrelaterade tillstånd bidrar till en ökad förståelse för hur demenssjukdom hos äldre uppkommer och utvecklas.

Nyckelord: demens, förutsägelse, förebyggande, gånghastighet, hjärnas markörer, multisjuklighetskluster, luftföroreningar, kardiovaskulära sjukdomar

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. **Grande G**, Rizzuto D, Vetrano DL, Marseglia A, Vanacore N, Laukka JE, Welmer AK, Fratiglioni L. Cognitive and physical markers of prodromal dementia: A 12-year-long population study. *Alzheimers Dement*. 2020;16(1):153-161.

II. **Grande G**, Vetrano DL, Kalpouzos G, Welmer AK, Marseglia A, Fratiglioni L, Rizzuto D. Brain changes as the biological substrate of fast cognitive and motor decline: results from the SNACK-MRI study. *Submitted.*

III. **Grande G**, Marengoni A (co-first author), Vetrano DL, Roso-Llorach A, Rizzuto D, Zucchelli A, Qiu C, Fratiglioni L, Calderón-Larrañaga A. Multimorbidity burden and dementia risk in older adults: The role of inflammation and genetics. *Alzheimers Dement.* doi: 10.1002/alz.12237.

IV. **Grande G**, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. *JAMA Neurol*. 2020;77(7):801-809

OTHER SCIENTIFIC PAPERS RELATED TO THE TOPIC OF THIS DOCTORAL THESIS

Grande G, Qiu C, Fratiglioni L. Prevention of dementia in an ageing world: Evidence and biological rationale. *Ageing Res Rev*. 2020 Mar 19:101045. doi: 10.1016/j.arr.2020.101045.

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Marseglia A, Darin-Mattsson A, Kalpouzos G, **Grande G**, Fratiglioni L, Dekhtyar S, Xu W. Can active life mitigate the impact of diabetes on dementia and brain aging? *Alzheimers Dement*. 2020 Jul 27. doi: 10.1002/alz.12142.

Grande G, Haaksma ML, Rizzuto D, Melis RJF, Marengoni A, Onder G, Welmer AK, Fratiglioni L, Vetrano DL. Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: Systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2019 Dec;107:96-103.

Grande G, Triolo F, Nuara A, Welmer AK, Fratiglioni L, Vetrano DL. Measuring gait speed to better identify prodromal dementia. *Exp Gerontol*. 2019 Sep;124:110625.

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LIST OF ABBREVIATIONS

APOE	Apolipoprotein E
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CIND	Cognitive impairment, no dementia
CRP	C-reactive protein
CVDs	Cardiovascular diseases
DALYs	Disability-adjusted life years
DTI	Diffusion tensor imaging
HR	Hazard ratio
MCI	Mild cognitive impairment
MM	Multimorbidity
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NOx	Nitrogen Oxides
NPV	Negative predictive value Randomized
O/E	Observed/Expected
OR	Odds ratio
$PM_{2.5}$	Particulate matter $\leq 2.5\mu m$
PPV	Positive predictive value
RCT	Randomized Controlled Trial
SD	Standard devation
SES	Socioeconomic status
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
WHO	World Health Organization

1 INTRODUCTION

1.1 COGNITIVE AGING

The world's older population has grown at an unprecedented pace. According to the World Health Organization (WHO), approximately two billion people will be older than 65 years in 2050 [1]. In high-income countries, population aging has been a result of decreased fertility rates as well as increased life expectancy, due to prevention and improved treatment of chronic diseases. A longer life comes with increased opportunities, as it enables the individual to carry out (new) activities and actively take part in the society. However, to a certain extent, these benefits are restrained by the progressive deterioration of seniors' physical and mental health, and consequently, their increased need for medical and social care [2].

Worldwide, a great proportion of disease burden is due to non-communicable disorders and account for more than 80% of all years lived with disability and more than 70% of all deaths worldwide [3]. Neurological disorders play an increasing role—in Europe they were ranked as third after cardiovascular diseases and cancer, being responsible for approximately 13% of total disability-adjusted life years (DALYs) and 20% of total deaths. Dementia, stroke, and headache accounted for the greatest share of DALYs in Europe [4, 5].

Dementia is clinically featured by a progressive deterioration in multiple cognitive domains, severe enough to interfere with daily activities and social functioning. Dementia impacts not only the affected individual, but also their relatives and society as a whole [6]. The annual global cost of dementia was estimated to be 1 trillion USD [7]. The WHO and Alzheimer's disease International deem dementia to be a global public health priority [8, 9]. In 2018, nearly 50 million people worldwide were affected by Alzheimer's disease and other dementias—and this number is projected to double approximately every 20 years.

In spite of this "dementia epidemic" and the urge for effective curative or disease-modifying treatments for Alzheimer's disease, a sizable number of clinical trials have tried, and failed, to identify drugs for dementia or Alzheimer's disease [10-12]. Among other reasons for these failures, the complex pathophysiology of the disease and the inclusion of patients with advanced stages of cognitive impairment in randomized clinical trials may have limited the efficacy of the tested treatments [13, 14].

For these reasons, epidemiological and clinical research has increasingly focused on two major research lines:

1. **Identifying accurate predictors for an earlier diagnosis of dementia.** Diagnosed dementia cases are just the 'tip of the iceberg' of a long and progressive pathological process that begins several years, or even decades, before disease detection [15]. This long preclinical phase represents a window of opportunity to implement preventive and/or therapeutic strategies to slow down the pathological process and delay the onset of the disease [16].

2. **Identifying modifiable risk and protective factors for cognitive decline and dementia prevention.** Findings from projection studies have suggested that prevention delays dementia onset, and therefore, reduces its prevalence [17, 18]. Notably, several population-based studies in both Europe and the United States have suggested that dementia incidence may be declining [19-21], primarily due to a reduction in cardiovascular risk factors, improved treatment of heart-related diseases, and higher educational attainment [22]. This evidence supports the idea that prevention is a key strategy in halting, or at the very least, delaying, cognitive deterioration in old age [10, 23].

1.2 THE COGNITIVE CONTINUUM AND EARLY DEMENTIA DETECTION

As individuals age, their cognitive function progressively declines [24]. The pace of such decline varies widely and depends on a number of internal and external factors. Dementia is characterized by an insidious onset of symptoms that gradually progress over time. Thus, it can be challenging to differentiate the early stages dementia from physiological or mild memory impairments that are expected with aging. The cognitive continuum from intact cognition to dementia (see **Figure 1**) also includes a stage characterized by mild cognitive disturbances, which do not yet affect everyday life activities, and thus, do not meet the dementia diagnostic criteria [25].

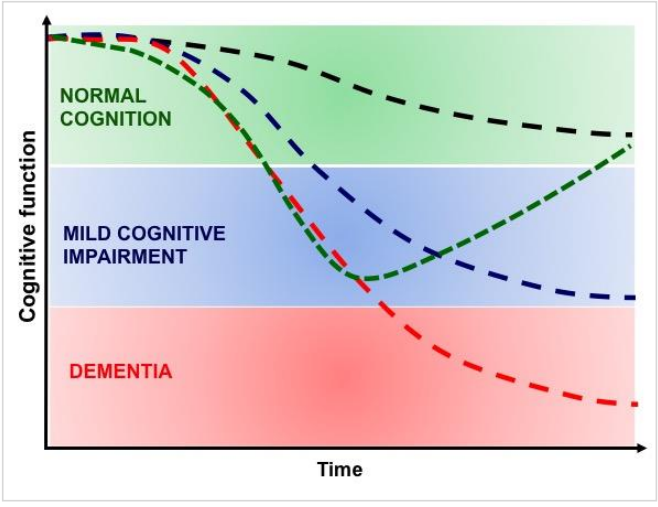


Figure 1. The cognitive continuum

As shown in **Figure 1**, older individuals may follow different cognitive trajectories. Some may experience a slight decline in cognitive performance, which can be expected with passing time, but with no further impact on daily functioning. Other subjects face a steeper cognitive decline, yet not severe enough to impact their daily functioning, and thus, do not meet the diagnostic criteria for clinical dementia. Finally, some individuals experience a steep and more severe cognitive decline that limits their daily functioning and leads to dependence, which constitute the threshold for diagnosing dementia.

1.2.1 Cognitive impairment, no dementia

In the last 20 years, the focus in the field of cognitive disorders has gradually shifted from recognizing overt dementia to identifying its prodromal, and even preclinical, stages. The importance of tracing cognitive trajectories in prodromal phases is well established [15, 26]. However, the operationalization of clinical constructs that can capture the different pre-diagnostic phases of dementia is still debated. Various definitions have been proposed in the context of different study settings (population-based vs. clinical setting), creating a challenging heterogeneity. This has led to poor comparability across different studies and limited applicability in clinical practice. However, despite this variability in the operationalizations, there is a consistent core concept within each of these constructs: the presence of an impairment in cognition without fulfilling the diagnostic criteria of dementia.

In 1997, Graham et al. proposed the concept of cognitive impairment, no dementia (CIND) [27]. CIND entails the presence of objective cognitive impairments, clinically detectable using a neuropsychological assessment that does not meet the criteria for dementia. Similar to CIND, mild cognitive impairment (MCI) is seen as an intermediate stage between normal cognition and dementia (**Figure 1**) that also involves abnormal objective cognitive performance for the individual's age but does not impact functional independence [28]. Unlike CIND, MCI also requires a subjective cognitive complaint and the ability to perform the basic activities of daily living, allowing for only minimal impairment in more complex instrumental activities of daily living (**Table 1**). According to the recent literature [29, 30], the MCI criterion of a subjective cognitive complaint seems to be predictive of dementia in the context of a memory clinic, where subjective complaint often triggers the referral itself and represents an indicator of cognitive impairment severity [31]. In contrast, in community-based studies researchers explicitly ask participants questions regarding their own perception of memory performance, somewhat eliminating the red flag represented by the spontaneous reporting of cognitive complaints. Thus, by capturing subjective cognitive complaints across all severity levels, a higher number of false positive cases is likely to be reported in community-based studies.

Table 1. Differences between CIND and MCI diagnostic criteria

	CIND [27]	**MCI** [28]
Presence of objective cognitive impairment	✓	✓
Absence of dementia	✓	✓
Subjective cognitive complaint		✓
Essentially preserved activities of daily living		✓

Although CIND occurrence increases with age, estimates of its prevalence vary largely depending on the study setting, ranging from 5 to 30% [32-34]. Similar to MCI, CIND is associated with a higher risk of incident dementia, with an annual rate of progression ranging from 5 to 15% [35]. Both CIND and MCI have been the focus of investigations attempting to detect early clinical and pathophysiological changes that would allow for a timely dementia diagnosis. However, there are several related issues in terms of the progression from CIND and

MCI to dementia. Notably, up to 30% individuals with CIND/MCI remain cognitively stable over time or revert to a normal state of cognition [36] (see green line in **Figure 1**). A large bodyof literature has in fact indicated that reversion to intact cognition is a common outcome, making CIND and MCI a heterogeneous and dynamic condition [37-39].

Research has focused on identifying neuropsychological [40-43], as well as biological [44], markers to allow for a more reliable prediction of impending dementia [45]. In 2018, the National Institute on Aging – Alzheimer's Association (NIA-AA), in the United States, proposed a research framework for the diagnosis of Alzheimer's disease, focused on a biological definition of the disease [46]. The main proposed biological markers were the cerebro-spinal fluid (CSF) tau [47] and Aβ-42, amyloid PET images [48, 49], and brain magnetic resonance imaging. This approach has led to promising results. However, some asymptomatic individuals with cerebral amyloidosis never—or very slowly-—progress to dementia, whereas some individuals with advanced tauopathy rarely exhibit significant clinical symptoms [50, 51]. A longitudinal study of 600 cognitively intact individuals in Australia found that, out of the participants who were PET amyloid-positive, more than 80% did not develop cognitive impairment/dementia over the eight-year observational period [52]. This suggests that amyloid status does not predict a clinically relevant impairment in a timeframe that can represent a useful prognostic window. As stated in the Report of the Lancet Commission 2020 on dementia prevention, intervention, and care "there is now reasonable evidence that amyloid and tau measured by PET or in fluid indicate increased risk for development of cognitive impairment in older adults but, at the individual level, prognostication is not possible as most cognitively normal people with these markers do not develop dementia within a clinically relevant timeframe" [10]. Moreover, these findings indicate that some underlying compensatory mechanisms might exist even in the presence of high neuropathological burden. While these biomarkers appear to be promising in providing targets for interventions and in opening new research avenues in the field of Alzheimer's disease [53, 54], their costly nature and requirement of a specialist setting limit their applicability in the general population [55, 56]. Finally, non-Alzheimer dementias, which account for a large proportion of dementia in older people, are not fully captured in this framework.

1.2.2 Gait speed as a "window to the brain"

The identification of reliable, easy-to-obtain, and non-invasive clinical markers to improve dementia prediction has been highly advocated. This is particularly true when it comes to population-based settings, where utilizing invasive and costly biomarkers is oftentimes not possible. Among others, markers of motor function have been largely studied in relation to various health-related outcomes, including cognitive function [57-59]. Impaired motor function, including gait slowing, is commonly observed in elderly patients and is usually more pronounced in people with cognitive impairment compared to those who are cognitively intact [60]. Motor changes including motor impairments and slowing may precede the onset of MCI; in fact, studies have shown that gait speed decline can appear up to 12 years before the MCI diagnosis [61]. As shown in **Figure 2**, several studies have investigated the role of slow gait

speed in adverse cognitive outcomes and the majority of the studies have pointed toward a positive association.

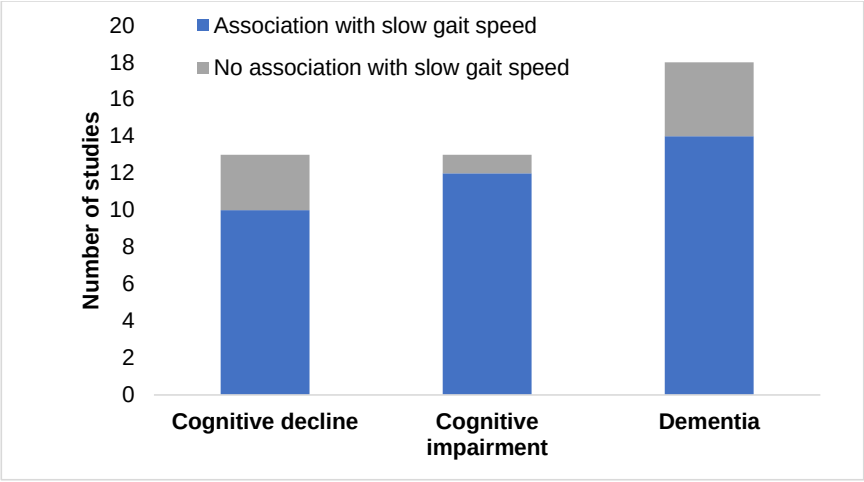


Figure 2. Number of longitudinal studies reporting an association or no association between slow gait speed and different cognitive outcomes

Source: Grande G et al, Measuring gait speed to better identify prodromal dementia. Exp Gerontol. 2019 Sep; 124:110625 [62]

Although largely consisting of automatic movements, gait is a complex function requiring the integration and synergy of several organs and systems (e.g. respiratory, cardiovascular, musculoskeletal systems) [63], the fine control of peripheral and central nervous systems, and the support of a number of sensorial functions [64] (**Figure 3**).

As such, gait speed captures clinical and subclinical disorders across organs and systems, with a change in gait speed and/or pattern potentially indicative of damage in different brain areas [65, 66]. Neuroimaging studies have demonstrated that motor control and some cognitive functions share common neural substrates, including the prefrontal, parietal and temporal areas [67]. Indeed, executive function, attention, and memory are crucial for the correct execution of a motor task [68].

A bidirectional association between motor and cognitive function and their shared neuroanatomical substrates has been demonstrated in studies showing that higher levels of amyloid β are associated with slower gait speed in cognitively intact individuals [69-71]. In addition to neurodegeneration, the cerebral vascular system has been largely implicated in the alteration of motor function [72]. In fact, patients with vascular dementia often display gait slowing earlier than Alzheimer's disease patients. Finally, studies have observed a close

relationship between increased burden in white matter vascular lesions and decline in gait abilities [73].

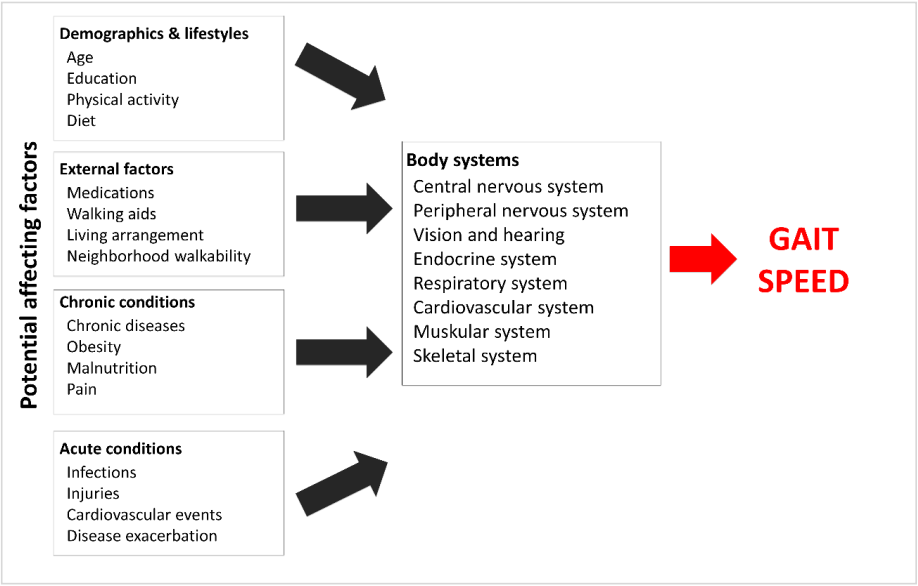


Figure 3. Systems involved in the maintenance of gait speed and potential affecting factors

1.2.3 Co-occurring cognitive and motor impairments as a distinct at-risk profile for dementia?

Although typically studied as separate entities, cognitive and physical impairments frequently co-occur. They are closely interrelated and affect each other, which results in the development of complex health profiles [74]. In recent years, expanding research has focused on the health consequences of co-occurring cognitive and motor dysfunction, with the majority of the studies reporting an increased risk of adverse outcomes, such as disability and shorter survival [75]. A study from our group used data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) and found that older individuals who concurrently had CIND and slow gait speed presented the greatest increase in disability (**Figure 4**) and had five times higher the mortality rate (95%CI: 3.5-7.4) than those free from these conditions.

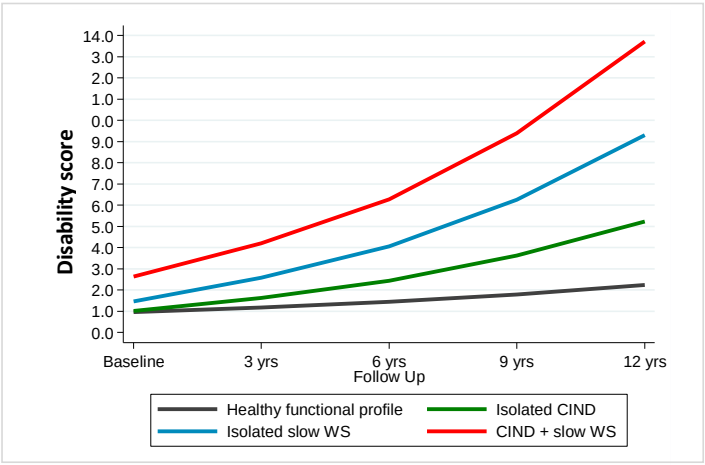


Figure 4. Trajectories with 95% confidence intervals of disability over 12 years of follow-up by functional profiles

Abbreviations: CIND: cognitive impairment, no dementia; WS: walking speed

Source: Grande G et al, Disability trajectories and mortality in older adults with different cognitive and physical profiles. Aging Clin Exp Res. 2020 Jun;32(6):1007-1016 [75].

Several studies have investigated the association between co-occurring cognitive and physical impairments with dementia development, see below **Table 2**. Some of these studies have used subjective cognitive complaints rather than objective cognitive deficits. The *Motoric Cognitive Risk syndrome* (MCRS), described by Verghese et al in 2014, captures individuals with slow gait speed and cognitive complaints [76, 77]. This syndrome was found to be a strong predictor of incident cognitive impairment and dementia. Similarly, other syndromes have been suggested, such as *Gait and cognitive syndrome* [78] and the so-called *Cognitive frailty* [79]. These conditions are characterized by impaired cognition—captured by the Montreal Cognitive Assessment (MoCA) or the Clinical Dementia Rating (CDR) scale—coexisting with either slow gait speed or physical frailty. Overall, these studies produced inconsistent associations of co-occurring cognitive and physical decline with impending dementia (**Table 2**). Also, they have different lengths in the follow-up time, and it was not assessed whether the simultaneous cognitive and motor dysfunction is associated with dementia during the short or long follow-up.

The study of cognitive and motor domains is not limited to the presence of impairments, but has recently expanded to investigate their longitudinal changes [80]. Studying cognitive and motor trajectories in older age is justified by the fact that a single assessment is unlikely to sufficiently capture the complex deterioration in health. Multiple intra-individual evaluations are of great clinical relevance and as they would improve our prediction of dementia in at-risk groups. A study by Montero-Odasso [80] observed that those who declined both in gait speed and cognition were at the highest dementia risk. Recently, a multi-cohort meta-analysis, involving six cohort studies from the United States and Europe (including the SNAC-K cohort),

found that those who concurrently declined in gait speed and memory presented with a pooled hazard ratio (HR) for dementia of 6.3 (95% CI: 4.6-8.6), compared to the "usual agers" (those who exhibited no decline) [81]. In all six cohorts, dementia risk was much more robustly associated with changes in memory performance and gait speed, rather than with the baseline levels of these variables. These results indicate that physical and cognitive changes over time provide important insight into the understanding of dementia risk that is not captured by a one-time assessment.

However, we still lack research concerning the biological basis of the parallel and fast decline in both cognition and motor function. We do not know whether it occurs as result of common or different underlying mechanisms of motor and cognition decline. One way of understanding the mechanisms is by investigating the brain burden related to isolated (or concurrent) decline in gait and cognition through brain magnetic resonance imaging (MRI) studies. Few cross-sectional studies have explored the brain structural correlates of the MCRS and found that it was associated with smaller gray but not white matter volumes [82, 83]. It was shown that MCRS adults had smaller prefrontal cortex, supplementary motor area, and insula, but not greater white matter hyperintensities [84]. One longitudinal study, published in 2020, used data from the Baltimore Longitudinal Study on Aging to explore brain MRI correlates in relation to dual decline in memory and gait speed [85]. The study found that individuals experiencing dual decline exhibited more gray matter loss in specific areas, including the superior frontal gyrus, superior parietal gyrus, precuneus, thalamus, and cerebellum. It is unknown whether these brain correlates are different in those experiencing isolated cognitive or motor decline.

Table 2. Main characteristics and findings of longitudinal studies investigating the co-occurrence of slow gait speed and cognitive impairment in relation to cognitive decline and dementia development

Study	Clinical marker definition & criteria	Population sample N	Mean follow-up time	Mean age (% female)	Association with	
					Cognitive decline	Dementia
Doi et al, 2018 [86]	MCI (cognitive tests) + slow GS	3937	43 months	74 (53)	n/a	YES
Hooghiemstra et al, 2017 [87]	Cognitive tests+ slow GS and impaired grip strength	309	2.1 ± 1.2 years	70 (35)	YES	NO
Montero-Odasso et al, 2016* [78]	MoCA + physical frailty [88]	252	5 years	77 (63)	n/a	YES
Montero-Odasso et al, 2017* [89]	MCI (cognitive tests) + slow GS	112	6 years	76 (49)	n/a	NO
Verghese at al, 2013 [77]	Cognitive complaints (CERAD) + slow GS	997	9 years	80 (60)	n/a	YES

*: Clinical based; n/a: non-applicable; GS: gait speed; MoCA: Montreal Cognitive Assessment; CERAD: 15-item Consortium to Establish a Registry for Alzheimer's Disease questionnaire

1.2.4 Knowledge gaps addressed in this thesis (I)

Studies on the co-occurrence of cognitive and motor impairments and their association with dementia are limited to few reports characterized by inconsistent findings. It is still debated whether the simultaneous presence of cognitive and motor impairments represents a distinct, at-risk profile compared to having only one, or none, of these deficits.

In addition, the following questions remain unanswered:

1. Can we consider gait speed as a valid and useful complement to the standard neuropsychological assessment in the detection of prodromal dementia?
2. Does the discriminative power of gait speed remain stable over time?
3. Is the parallel decline in both motor and cognitive function a result of shared or distinct underlying biological mechanisms?

1.3 DEMENTIA PREVENTION: THE ROLE OF SOMATIC DISORDERS

As the most common type of dementia, Alzheimer's disease is responsible for approximately 70% of all dementia cases [90]. The pathological hallmarks of Alzheimer's disease are the extracellular deposition of amyloid-β, as well as the intracellular accumulation of hyperphosphorylated tau (p-tau) protein [91]. However, these features do not usually present in isolation; they frequently occur alongside micro- and macro-vascular dysfunction, disintegration of the neurovascular interface, and a certain degree of neuroinflammation [92, 93]. These observations have changed our understanding of dementia aetiology, particularly in the oldest old persons [94].

Autopsy and neuroimaging studies have shown that most dementia cases present with brain lesions of both degenerative and vascular nature, especially in individuals older than 75 years [95, 96]. Growing evidence also indicates that many cardiovascular risk factors and diseases are associated with Alzheimer's pathology and accelerated brain atrophy [97]. Similarly, in post-mortem studies, a certain degree of vascular pathology, including lacunes, microbleeds, and brain infarcts has been observed in up to 80% of individuals with a diagnosis of Alzheimer's dementia [98-102]. Finally, recent studies have demonstrated that vascular dysfunction appears early in the pathological process leading to Alzheimer's disease and dementia, further contributing to neurodegeneration.

Considering the above-mentioned evidence, it is plausible to hypothesize that dementia is a multifactorial disorder and that genetic susceptibility, environmental factors, and their interplay over the lifespan, contribute to the underlying brain pathology, as well as the clinical manifestation of the disease. Several reviews have already been published on this topic, with all [6, 10, 23, 103] discussing modifiable risk factors linked to vascular burden, including cardiometabolic disorders and health-related behaviours (smoking, alcohol abuse, physical inactivity, diet, and obesity). In addition, a recent review concluded that the evidence coming from a number of well-conducted observational studies is robust enough to indicate that stimulating psychosocial and lifestyle factors (such as education, as well as engagement in mental, physical, and social activities) are protective against dementia, as they promote resiliency against accelerated cognitive decline [104].

1.3.1 Disease-burden and dementia

A number of chronic conditions are well-established risk factors for dementia. Both cardiovascular diseases and dementia are common in older adults and they share similar, if not the same, risk factors such as hypertension, smoking, obesity, and dyslipidemia [105]. People with heart diseases (e.g. atrial fibrillation, heart failure, coronary heart disease) are both at an increased dementia risk and have poor prognosis following the diagnosis. In a study from our group, using data from the SNAC-K cohort, it was observed that individuals with atrial fibrillation experienced steeper cognitive decline and were at greater risk for dementia than those without atrial fibrillation [106]. This association could be explained by the occurrence of cerebrovascular lesions, likely due to thromboembolism, which is commonly observed in those

with atrial fibrillation. However, increased dementia risk was also detected in the absence of stroke, suggesting that alternative pathways are at play, such as silent brain infarcts, systemic inflammation, platelet activation, and cerebral hypoperfusion [107, 108] (**Table 3**). Altered cardiac output, due to atrial fibrillation, and the presence of micro-embolic pauci, or even asymptomatic phenomena (micro-embolic events), might predispose older individuals to chronic brain damage and subsequent cognitive dysfunction. Cerebral small vessel diseases, such as lacunar infarcts, white matter hyperintensities, and microinfarcts, are associated with a disruption in the blood-brain barrier and altered brain connectivity, which are critical mechanisms linked to impaired cognitive function [105, 109].

Table 3. Somatic disorders associated with increased dementia risk and possible biological mechanisms

	Biological mechanisms		
	Neurodegeneration	**Vascular damage**	**Neuroinflammation**
Atrial fibrillation	C	A	B
Heart failure	C	A	B
Ischemic heart disease	C	A	B
Diabetes mellitus	B	A	B
Mid-life hypertension	B	A	B
Systemic and cerebral atherosclerosis	C	A	A

***Legend**: A: Strong evidence (i.e. evidence from meta-analyses, RCTs, well designed cohort studies with consistent findings); B: emerging evidence; C: Limited evidence (i.e. limited number of studies)*
Table modified from: Grande G et al, Prevention of dementia in an ageing world: Evidence and biological rationale. Ageing Res Rev. 2020 Mar 19:101045 [94]

Cognitive impairment and dementia are also frequently detected among older adults with heart failure and metabolic conditions such as diabetes mellitus (hereafter diabetes) [110, 111]. Diabetes nearly doubles dementia risk, and approximately 3% of Alzheimer's disease cases worldwide have been attributed to its presence in the general population [112]. Typically, diabetes clusters with other cardiovascular diseases [113, 114]. The co-occurrence of diabetes, heart diseases, and stroke has been associated with a four-fold increase in the risk of dementia compared to the absence of these disorders [115]. Diabetes induces systemic atherosclerosis, whereas heart diseases affect cerebral blood flow; eventually leading to brain hypoxia, thromboembolism, and ultimately, dementia [116] (**Table 3**).

1.3.2 Cluster of somatic diseases and dementia

Many, if not all, of the above-mentioned diseases are often comorbid with other chronic conditions in older age. Indeed, it is the exception, rather than the rule, to be affected by one single disease after the age of 75, with 55-90% of adults aged 60+ suffering from two or more chronic diseases, a condition referred to as multimorbidity [117]. Wang et al, found that relative to those with zero cardiometabolic conditions, the hazard ratio of dementia increased progressively with the number of co-occurring cardiometabolic conditions: it was 1.41 (1.07-

1.86) for one condition, 2.38 (1.58-3.59) for two, and 4.76 (2.04-11.13) for three, suggesting that a dose-response relationship might exist when more diseases co-occur [115].

In fact, when more than one chronic disease are present, they tend to interact and further complicate a person's health status [118]. Also, the co-occurrence of several chronic conditions results in complex drug regimens, challenging care management, and negative effects that exceed the sum of the individual diseases [119-121]. Notably, a large collaborative study including more than 1 million persons reported that a combination of cardio-metabolic diseases negatively impacted on survival [122].

Chronic diseases do not appear at random but tend to cluster in a person following specific disease patterns [123-125]. This systematic clustering may be due to the fact that some conditions share similar pathophysiological mechanisms and/or risk factors. Such homogeneity within disease-clusters could also stem from the fact that a number of diseases may belong to the same pattern and receive the same pharmacological treatment.

Different disease combinations have been studied in relation to a number of health-related outcomes including disability, functional decline, and shorter survival [126]. A SNAC-K study [118] including 2,385 older adults found that different patterns of cardiovascular and neuropsychiatric morbidity led to different trajectories of functional decline over a 9-year follow-up. Neuropsychiatric diseases were strong determinants of dependence, while cardiovascular multimorbidity was associated with mobility decline.

The association between clusters of somatic diseases and dementia has never been studied to date. In 2020, the Lancet commission on dementia prevention, intervention and care highlighted, for the first time, the importance of considering combinations of different cardiovascular risk factors in relation to dementia incidence [10]. As reported by the commission, several studies have focused on single vascular risk factors, neglecting their frequent co-occurrence in the same individual. A study in the United Kingdom, including 7,899 middle aged individuals, demonstrated that a combination of behavioral (smoking, diet, physical activity, BMI) and biological (hyperglycemia, dyslipidemia, hypertension) risk factors was associated with increased dementia risk [127]. Notably, individual risk factors alone, did not show significant associations with dementia in the same sample. Again, this supports the importance of considering diseases as they co-occur, rather than as isolated entities, in relation to dementia.

1.3.3 Air pollution, cardiovascular disorders, and dementia

More recently, there is growing evidence concerning exposure to ambient air pollution as a risk factor for brain pathology. Notably, the Lancet Commission on dementia prevention, intervention and care 2020 included air pollution in its list of modifiable risk factors related to dementia onset. In fact, a growing number of recent studies have related exposure to air pollution with brain pathology including neurodegeneration, excessive oxidative stress, and neuroinflammation [128, 129]. In addition, several studies, conducted in various regions

(United States, Canada, Europe, and Taiwan), have consistently pointed toward an association between exposure to air pollution and incident dementia (**Table 4**).

These findings are of considerable importance since exposure to air pollution is universal and substantial [130]. Even if the association is of moderate effect size, actions at a global level would translate into sizable public health achievements in the field of dementia prevention.

Table 4. Main characteristics and findings of longitudinal studies investigating the association between air pollution exposure and dementia development

Study	Country	Population sample, N	Age (years)	Air pollutant(s)	Association with dementia
Andersson et al (2018) & Oudin et al. (2019) [131, 132]	Sweden	1721	≥55	NOx	YES
Cacciottolo M et al (2017) [133]	USA	3647	65-79	$PM_{2.5}$	YES
Carey IM et al (2018) [134]	England	13 0978	50-79	$PM_{2.5}$, NO_2, O_3	YES
Cerza F et al (2019) [135]	Italy	350 844	74.5±8.8	NOx, NO_2, $PM_{2.5}$, PM_{10}, O_3	YES
Chen et al (2017) [136, 137]	Canada	2 165 286	66.8±8.2	$PM_{2.5}$, NO_2	YES
Jung et al (2015) [138]	Taiwan	97 627	≥65	PM_{10}, O3	YES
Kioumourtzoglo MA et al (2016) [139]	USA	9.8 million	75.6±7.6	$PM_{2.5}$	YES
Ilango SD et al (2019) [140]	Canada	34 391	Mean age: 59	NO2, $PM_{2.5}$	YES
Shi L (2020) [141]	USA	63 038 019	≥65	$PM_{2.5}$	YES
Yuchi W et al (2020) [142]	Canada	678 000	45-84	PM2.5, Black Carbon, NO2, NO	YES

The mechanisms by which air pollution may impact the brain are still largely unknown. We know that increased cardiovascular morbidity and mortality have been associated with different components of air pollution [143, 144]. Given the close relationship between cardiovascular burden and dementia [105], it is plausible to hypothesize that air pollution may affect the brain through its impact on cardiovascular morbidity. If our hypothesis is confirmed, we will add a new perspective on the relevance of the body-mind connection in dementia development.

1.3.4 Knowledge gaps addressed in this thesis (II)

A number of single chronic diseases have been associated with higher dementia risk, but in older adults, diseases tend to cluster together in the same individual. The association between disease clusters and dementia incidence has never been explored to date. In addition, factors that might play a role in such an association are unknown. Based on the current knowledge, it is plausible to hypothesize that a) systemic inflammation may accelerate the progression of neurodegeneration and vascular pathology in the brain; and b) the combination of specific multimorbidity patterns and the *APOE* ε4 allele puts individuals at an even greater risk of dementia development.

Recent evidence is growing concerning exposure to air pollution and associated brain pathology, particularly dementia. Although the underlying mechanisms linking air pollution and dementia remain unknown, it is plausible to hypothesize that cardiovascular diseases play a role, considering the heart-brain connection in dementia development, and given that air pollution is a well-established risk factor for cardiovascular morbidity and mortality.

2 RESEARCH AIMS

2.1.1 Overall aim

The overall aim of the present thesis was to explore the relevance of the body-mind connection in cognitive aging by investigating physical functioning as a possible predictor of incipient dementia, and different somatic conditions as potential risk factors for dementia in older adults.

2.1.2 Specific aims

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

Study I. To quantify the hazard of dementia in relation to isolated cognitive impairment, isolated slow gait speed, and their combination over a 12-year period and to test whether adding gait speed to the neuropsychological assessment improves the predictive power of cognitive impairment for incident dementia.

Study II. To investigate the association between brain volume changes and lesion accumulation over six years and different patterns of decline in cognition and motor function.

Study III. To quantify the impact of specific patterns of multimorbidity on dementia risk over 12 years, while also exploring the role played by inflammation and *APOE* genotype in such association.

Study IV. To test whether exposure to air pollutants ($PM_{2.5}$ and NOx) is associated with greater dementia incidence, and whether cardiovascular diseases may mediate or strengthen that association.

3 MATERIALS 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) [145], an ongoing longitudinal population-based study including community-dwelling and institutionalized individuals, aged 60 or older, residing in the Kungsholmen district of Stockholm, Sweden. Between March 2001 and June 2004, a random sample of residents, stratified across 11 age cohorts, was invited to participate in the baseline assessment (**Figure 5** below). The two youngest and four oldest age cohorts were oversampled to account for the likelihood of a high attrition rate in these groups. Of the 5,111 individuals who were initially randomly selected, 521 were not eligible (e.g. death before the study start, no contact information, moved out of Kungsholmen, or not Swedish-speaking). Among the remaining 4,590 living persons, 3,363 (response rate: 73.3%) were assessed. Due to higher attrition rates and more rapid health changes experienced by those in older cohorts, follow-ups were conducted every three years for participants ≥78 years (78, 81, 84, 87 and ≥90 years) and every six years for those <78 years. Home visits (at baseline n=717) were conducted for those who agreed to participate but were unwilling or unable to visit the research center.

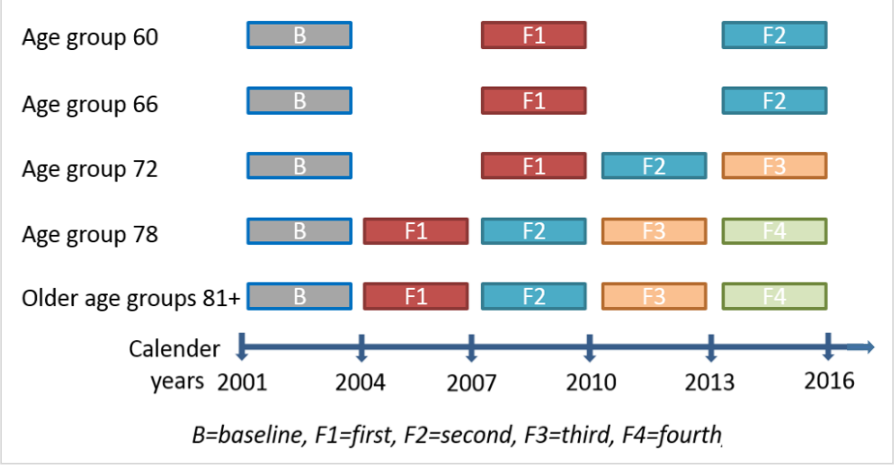


Figure 5. SNAC-K cohorts (2001-2016)

Non-institutionalized SNAC-K participants who were free from disability and dementia were invited to undergo structural brain magnetic resonance imaging (MRI) between September 2001 and October 2003. Overall, 555 SNAC-K participants were scanned at baseline. Those 78 or older repeated the brain MRI every three years and those aged <78 repeated it every six years.

3.1.2 Study samples

All studies included in the present thesis has a longitudinal design. Four different study samples were selected from the original SNAC-K population to answer the specific research questions. The SNAC-K MRI subsample was used for *Study II*.

3.2 DATA COLLECTION

At each study visit, data on demographics (age, sex, education), lifestyle (e.g. smoking, alcohol consumption, physical activity), medical history, and current medication use were collected via face-to-face interviews, clinical examinations, and cognitive and laboratory tests. The study visits include three parts: a physician examination, nurse interview, and psychological evaluations conducted by qualified staff who received *ad-hoc* training aimed at standardizing the procedures. Participants were examined for five to six hours at each wave. Additionally, the SNAC-K study was linked to primary care and hospital discharge registers, which increased the coverage of diagnostic episodes.

3.2.1 Cognitive assessment

An extensive neuropsychological battery was performed by trained psychologists at each wave, typically lasting two hours. There are three versions of the test battery and two test orders. All testing was conducted in Swedish.

To measure global cognition, the Mini Mental State Examination (MMSE) [146] was administered during the medical examination, together with the clock-drawing test. The MMSE is a 30-point questionnaire that covers a range of cognitive abilities, such as orientation in time and space, attention and calculation, recall, language, ability to follow written and verbal commands, and visuospatial abilities.

A battery of ten cognitive tests was administrated in a fixed order to assess the following five domains:

1. **Episodic memory** was assessed using a word list of 16 unrelated nouns. Words were visually presented individually every five seconds. To assess *free recall*, a two-minute recollection task was presented immediately after the word list and the number of correctly remembered words was recorded.
2. *Letter and category fluency* tests were used to assess **verbal fluency**. For letter fluency, the participant had to list as many words as possible starting either with the letter "F" or with the letter "A" within 60 seconds. For category fluency, they had to generate as many words as possible that belonged to the categories 'animals' and 'professions'. Verbal fluency was then calculated by averaging the total number of words produced within each cognitive test.
3. Two tests (digit cancellation and pattern comparison) were used to assess **perceptual speed**. *Digit cancellation* included 11 rows of random digits. Participants were asked to mark the number (4) whenever they encountered it during a 30 second time period. *Pattern comparison* consisted of pairs of basic line constructs and the participant had

to mark, within 30 seconds, whether the pair was the "same" or "different". The average number of correct answers was calculated from two trials.

4. **Executive function** was measured using the *Trail Making Test part B*, TMT-B. The participant has to connect circles with numbers and letters on both numeric and alphabetic order, alternating between the two categories (1-A, 2-B, etc.). Time were only recorded for those who completed the task correctly. The number of correct answers was used in this thesis.
5. **Visuospatial ability** was assessed by means of the *Mental Rotations* test. In this test the participants have to look at a figure and match the same, but rotated, figure (e.g. the figure might be shown from a different angle). The total number of correct identifications was recorded for the final score.

Cognitive impairment, no dementia (CIND) was operationalized using the neuropsychological battery as objective impairment in cognition that did not meet the diagnostic criteria for dementia [27]. To calculate age-specific cognitive norms we first standardized the raw scores into *z* scores using the age-specific baseline mean and standard deviation (SD). When more than one cognitive test was available, we averaged test *z* scores, creating the cognitive domain. Participants were identified as having CIND if they scored more than 1.5 SDs below the age-specific mean in at least one cognitive domain. The same procedure was used to identify CIND at follow-up visits, using the baseline means and SD.

3.2.2 Gait speed

In *Study I* and *Study II*, gait speed was used as an indicator of motor function [63]. Participants walked at usual pace over 6 meters or, alternatively, 2.4 meters if the space was restricted (e.g. during home visits), or if the individual had a limited walking capacity [147]. When the participant was unable to walk, a value of zero was recorded. Gait speed is reported in meters per second (m/s). In *Study I*, a cut-off of <0.8 m/s was used to define slow gait speed (we also considered a cut-off of 1.0 m/s in sensitivity analyses). In *Study II*, the rate of decline in gait speed was used.

3.2.3 Disease assessment

Several sources have been linked to make the clinical diagnoses. Participants were interviewed about clinical conditions during the medical evaluation, their medical journals were reviewed, and proxy information was obtained, if applicable. In addition, we also used clinical and laboratory paratmeters, information related to medication utilization, and physicians' assessments during the medical examination to define the disease. All drugs were classified in accordance with the Anatomical Therapeutic Chemical (ATC) classification. Medication use was further verified by inspecting drug prescriptions and containers. For participants with cognitive impairment, a proxy was interviewed instead. For individuals living in nursing homes, medical records were used to gather information. All diseases were coded in accordance with the International Classification of Diseases 10th revision (ICD-10). The Swedish National Patient Register, which includes data on inpatient and outpatient registers, was also used. Once

informed consent was obtained from participants, SNAC-K data were linked with the inpatient and outpatient registers through personal identification numbers.

Chronic diseases were classified into 60 disease categories in accordance with a clinically driven methodology [117], which was developed by researchers from our group and described in details elsewhere.

3.2.4 SNAC-K MRI protocol

A 1.5 Tesla MRI scanner (Philips Intera, The Netherlands) was used at baseline and during the follow-up. The protocol included an axial 3D T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle [FA] 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94 × 0.94 mm, no gap, matrix 256 × 256) and an axial turbo fluid-attenuated inversion recovery sequence (FLAIR; TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90 × 0.90 mm, gap 1 mm, matrix 256 × 256). A diffusion tensor imaging (DTI) scheme with six non-collinear diffusion-weighted gradient directions was used to determine the diffusion tensor set [148].

Brain volumes. Gray matter, white matter, and cerebrospinal fluid volumes were derived after segmentation of T1 images in SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA, USA), using the improved unified segmentation algorithm that employs an extended set of tissue-probability maps [149]. The "light cleanup" option was used to further remove odd voxels from the images. To obtain the total brain tissue volume, we summed gray and white matter volumes. Hippocampal volume was obtained with automated segmentation of the T1 images, performed with the Freesurfer 5.1 image-analysis suite (http://surfer.nmr.mgh.harvard.edu/) [150, 151]. A neuroimaging expert manually assessed the load of white matter hyperintensities on FLAIR images [152]. Gray, white matter, and cerebrospinal fluid were summed to calculate total intracranial volume. All MRI volumetric measurements were normalized by the total intracranial volume.

Diffusion tensor imaging data (DTI) and metrics of white matter diffusion. The DTI images were pre-processed using an iterative optimization algorithm for the diffusion tensor calculation. Fractional anisotropy (FA) and mean diffusivity (MD) were derived on a voxel-by-voxel basis. To obtain mean FA and MD, seven tracts of interest in each brain hemisphere were extracted, including the cingulate gyrus part of cingulum, the portion of the cingulum that extends to the hippocampus, the corticospinal tract, the forceps major, the forceps minor, the inferior fronto-occipital fasciculus, and the superior longitudinal fasciculus [153, 154].

3.2.5 Air pollution data

Data on air pollution since 1990 are available in SNAC-K. The levels of air pollutants were estimated at the participants' residential addresses using dispersion models [155]. The annual average of air pollution levels was computed using emission inventories from traffic and non-traffic sources for the years 1990, 1995, 2000, 2005 and 2011. Two main air pollutants were

studied: Nitrogen Oxides (NO_x) and Fine Particles with diameters 2.5 micrometers and smaller ($PM_{2.5}$). NO_x were used as a proxy for exhaust emissions from road traffic, whereas $PM_{2.5}$ consists of combustion particles from residential wood burning, exhaust and wear particles from road traffic. To allow for high resolution in the vicinity of the roads, a quadtree receptor grid was used and 95% of the grid squares were 60x60m^2 or smaller in Kungsholmen (the area from which SNAC-K participants were rectuited). A linear interpolation over four years was used to obtain the annual average levels of $PM_{2.5}$ and NO_x for the entire observation period 1990−2011.

3.2.6 Dementia diagnoses

Dementia diagnoses were ascertained at each study wave in accordance with the DSM-IV criteria [156]. The clinical and cognitive assessments performed during the medical examination were used to make the diagnosis.The assessments involved several cognitive tests, including the MMSE [146]; the Clock Drawing test [157]; counting forward and backward; and questions on problem solving, abstract thinking, self- and time-space orientation, and general knowledge. If applicable, the interview with the proxy was also taken into account.

In SNAC-K, the diagnosis was made following a three-step procedure. First, a preliminary diagnosis was made by the examining physician, followed by a second preliminary diagnosis made by the reviewing physician who was involved in data collection. The physicians were blinded to each other's diagnoses. In the case of discordance between the two diagnoses, a neurologist external to the data collection process, made the final determination.

For those participants who died between two follow-up assessments, the diagnoses of dementia were complemented by: 1) linking the SNAC-K database with the Swedish National Cause of Death Register and, 2) reviewing the clinical charts and medical records.

Diagnoses of dementia subtypes included: Alzheimer's diseases in accordance with standard criteria in *The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [158]*, and vascular dementia (VaD) in keeping with the standard criteria in the *Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences [159]*.

3.2.7 Other variables considered in the thesis

Highest level of education was obtained from the nurse interview and categorized as elementary school, high school, and university or above. Body mass index (BMI) was obtained by dividing participants' weight by their squared height (kg/m^2). A BMI <18.5 kg/m^2 was used as a proxy for malnutrition [160]. Serum C-reactive protein (CRP) was measured at the Karolinska Hospital lab, Stockholm, Sweden and obtained through a low-sensitive assay. The CRP cut-off used in this thesis (*Study III*) was 5 mg/L; this was dictated by the assay's lower detection limit, in line with previous literature [161]. Socioeconomic position derived from the longest held occupation was used as a measure of socioeconomic position and was categorized into three groups:1) blue collar workers; 2) white collar workers; 3) entrepreneurs. Early

retirement was defined as retirement before 65 years. Smoking status was categorized as current, former, or never smoker. Physical activity level was based on a questionnaire assessing activity frequency and intensity. Marital status was assessed during the nurse interview and further categorized into partnered, widowed, unmarried, or divorced. DNA was extracted from peripheral blood samples and the Apolipoprotein E (*APOE*) alleles were genotyped. Participants were categorized as ε4-carriers (at least one ε4 allele) and ε4-non-carriers. Dates and causes of death were derived from the death certificates provided by the Swedish national statistics agency (Statistics Sweden).

3.3 STATISTICAL ANALYSES

Each study included in the present thesis reported participants' characteristics as absolute number and proportion (%) or mean ± standard deviation (SD), as appropriate. All analyses were carried out with Stata 15 (Stat-Corp. LP, TX, USA). Specific analytical approaches were adopted in each of the four studies, as reported below and summarized in **Table 5.**

Study I. The association between functional profiles and dementia was assessed through Cox regression models, using age as the time scale, and adjusting for potential confounders. Four mutually exclusive functional profiles were defined based on the presence of CIND and slow gait speed: (1) healthy functional profile: without CIND and with a gait speed ≥ 0.8 m/s (reference group), (2) isolated CIND, (3) isolated slow gait speed, and (4) both CIND and slow WS. The functional profiles were considered both only at baseline and as time-changing variables. Diagnostic accuracy measures [sensitivity, specificity, positive and negative predictive values (PPV, NPV), positive and negative likelihood ratios (LR+, LR-) and area under the curve (AUC) and their 95% CI] were obtained for each functional profile, using the clinical diagnosis of dementia as a reference standard within the first six years of follow-up.

Study II. In this study, we first operationalized the rate of cognitive and motor decline for each individual using linear mixed models, where MMSE and gait speed were the dependent variables, and the intercept and follow-up time provided the fixed and random effects. The rates of decline were categorized according to the quartile and the study participants were subsequently assigned to one of these four mutually exclusive groups. Fast decliners in both MMSE score and gait speed were identified as those persons belonging to the top quartile of decline, whereas the slow-/non-decliners (reference), belonged to the lower three quartiles of decline.

Second, we estimated the association between the four profiles of MMSE/gait speed decline (i.e. no/slow decliners, isolated motor decliners, isolated cognitive decliners and cognitive and motor decliners) and the rate of change in brain MRI volumes by the means of linear mixed models, considering several potential confounders. For DTI images, we used adjusted linear regression models to test the association between baseline DTI measures and patterns of decline.

Study III. Clusters of older adults sharing patterns of chronic diseases were identified at baseline using a fuzzy c-means cluster analysis algorithm. The fuzzy c-means

algorithm assigns a probability of cluster membership for all individuals. Participants were later allocated to the cluster in which they had the highest membership probability. To characterize the clusters of multimorbid individuals, we calculated the frequency of diseases in each cluster. Observed/expected 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 included in the cluster over the total number of participants with the disease, was also calculated. Diseases with both observed/expected ratio ≥2 and exclusivity ≥25% in a particular cluster were deemed to characterize that cluster. The association between multimorbidity clusters and dementia was tested using Cox regression models using calendar time as time scale; adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained. Interactions between *APOE* genotype, CRP levels, and multimorbidity patterns, in relation to dementia risk, were tested and stratified analyses were conducted.

Study IV. Cox models using age as the time scale were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia in relation to time-varying 5-year averages of $PM_{2.5}$ and NO_x exposure. Departure from linearity was analyzed using restricted cubic splines with 3 knots (2 degrees of freedom) at fixed percentiles (10th, 50th, 90th) of its distribution. The role of cardiovascular diseases (CVDs) in this association was tested through stratified and mediation analyses. The mediating effect was analyzed using generalized structural equation models using logistic regression.

Table 5. Analytical approach used in the four studies included in the thesis

Study	Exposure	Outcome	Confounders	Analytical approach
Study I	Functional profiles (CIND and slow gait speed) at baseline and as time-varying variables	Incident dementia	Education, sex, malnutrition*, chronic diseases*, marital status* and *APOE* genotype. *: covariates considered also as time-varying	Cox regression models (age as time scale)
			No adjustments for the prediction models	Diagnostic accuracy measures (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and area under the curve)
Study II	6 years brain MRI volumes	12 years cognitive and motor decline	Age, sex, education, cardiovascular diseases (atrial fibrillation, heart failure, ischemic heart disease, cerebrovascular diseases), depression and *APOE* genotype.	Linear mixed models
	Baseline DTI measures		Age, sex, education, white matter hyperintensities	Linear regression models
Study III	Multimorbidity clusters	Incident dementia	Age, sex, education, civil status, malnutrition, CRP, *APOE* genotype, and baseline MMSE score.	Cox regression models Stratified analyses by CRP and *APOE* genotype
Study IV	Air pollutants ($PM_{2.5}$ and NOx)	Incident dementia	Age, sex, education, smoking, physical inactivity, SES, early retirement, BMI, depression, baseline MMSE and cardiovascular risk factors.	Cox regression models Stratified analyses by CVDs Mediation analyses

Abbreviations: CIND: cognitive impairment, do dementia; MRI: magnetic resonance imaging; $PM_{2.5}$: particulate matter≤2.5 micrometers; NOx: Nitrogen Oxides; CRP: C-reactive protein; MMSE: Mini Mental State Examination; CVD: cardiovascular diseases

3.4 ETHICAL CONSIDERATIONS

This thesis is based on data collected in the SNAC-K study. The Ethics Committee at Karolinska Institutet, Stockholm, Sweden, and the Regional Ethical Review Board in Stockholm approved all the SNAC-K phases and the use of Patient Register data. The following are the registration numbers: 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.

In keeping with the ethical principles for medical research involving humans (World Medical Association's Declaration of Helsinki) we obtained written informed consent from all SNAC-K participants at each assessment. For those individuals with cognitive impairment, consent was acquired from the next of kin (family members or caregivers).

Two weeks before the visit, the participant was informed by a detailed letter about the purpose of the study and the duration and interview process. Participation was completely voluntary and participants could withdraw at any time and with no explanation. During the face-to-face evaluations the 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 any discomfort from the participant, the test/evaluation was stopped and, if agreed, rescheduled. The same protocol is applied to blood test sampling: we collect the minimum necessary blood amount, and participants can deny undergoing the procedure. If the participants agree, they will be informed about the results of the tests. If any abnormal data is detected, the participant is referred to the general practitioner or to the emergency services if necessary. Furthermore, if any suspicion regarding participant's cognitive status arises during the medical examination, they are offered to undergo specialized clinical assessment in a memory clinic in Stockholm.

All data that are collected are anonymized once they are digitalized from the questionnaires. All researchers working with the dataset follow the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

4 RESULTS

This section reports the main results of the thesis. For additional details, please refer to the published papers and the manuscripts included in the thesis.

4.1 CHARACTERISTICS OF THE STUDY POPULATION

At baseline, the mean age of the 3,363 SNAC-K participants was 74.6 ± 11.2, 64.9% were female, 32.4% had a university-level education, and 5.7% lived in an institution. The participants who took part in the MRI sub-project (n=555) were younger, more likely to be female, and more educated than those who did not undergo an MRI scan.

4.2 COGNITIVE AND PHYSICAL IMPAIRMENTS AS MARKERS OF PRODROMAL DEMENTIA (STUDY I)

At baseline, out of the 2,546 included participants, 17.3% (n=441) presented with isolated CIND, 10.0% (n=255) with isolated slow gait speed, and 9.3% (n=237) with both CIND and slow gait speed (**Figure 6**). The isolated presence of slow gait speed and the co-occurrence of CIND and slow gait speed were more frequent among older participants (78+) and women.

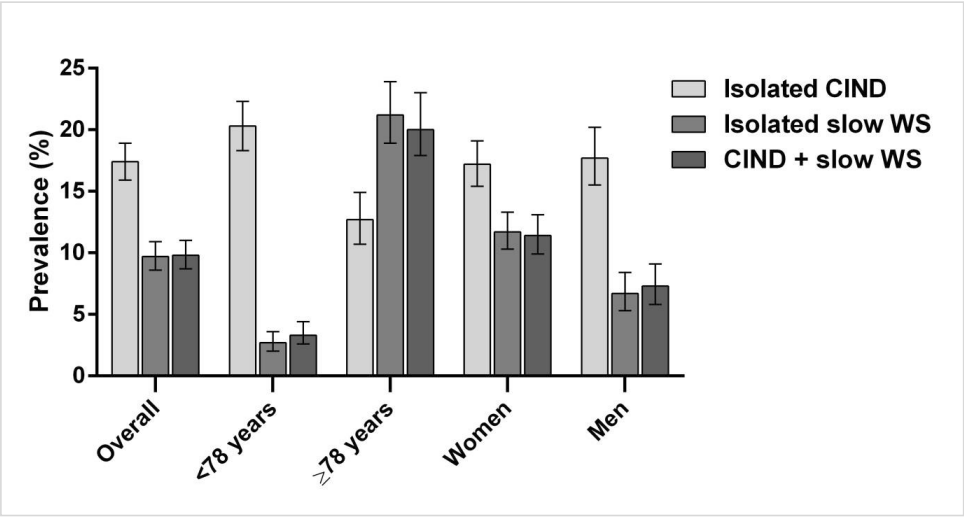


Figure 6. Prevalence per 100 participants of functional profiles at baseline in the entire population and by age and gender

Abbreviations: CIND: cognitive impairment, no dementia; WS: walking speed

During 8.5 years (±4.0) of follow-up, 310 incident dementia cases were detected. The simultaneous presence of CIND and slow gait speed was associated with more than three times higher hazard of dementia (HR: 3.4; 95%CI: 2.5−4.8), compared to having none of these conditions. Consistent results were obtained when we considered the profiles as time-varying variables (HR for co-occurring CIND and slow gait speed: 4.9; 95% CI: 3.1-8.1) (**Figure 7**).

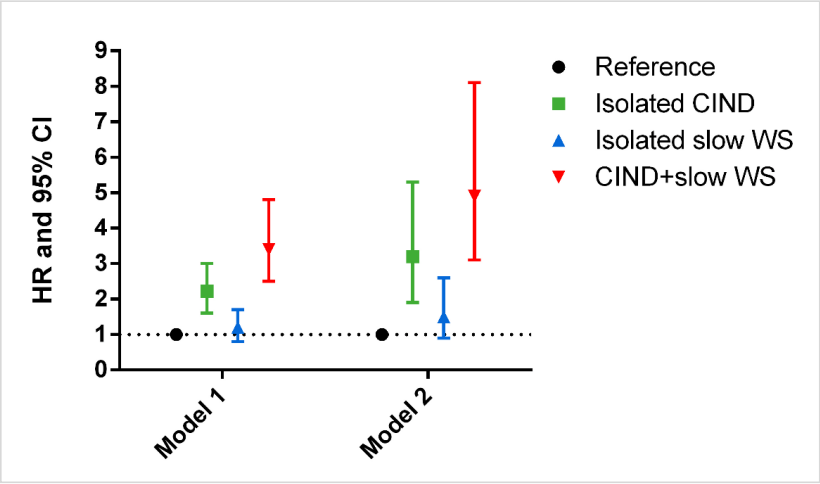
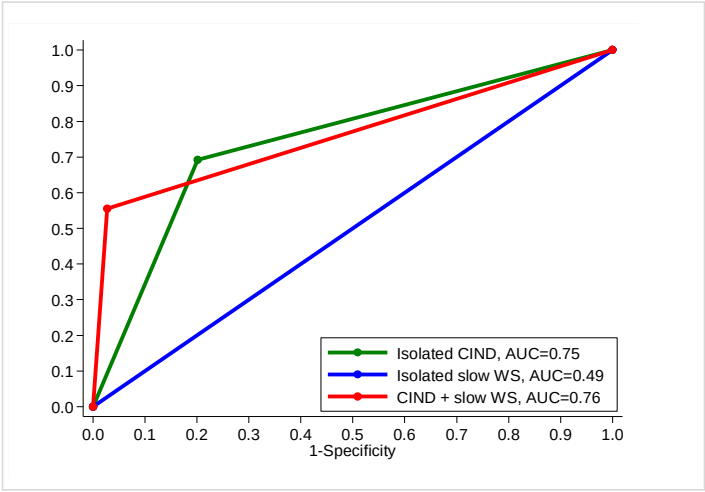


Figure 7. Association between functional profiles and incident dementia
Hazard models consider age as the time scale. Adjustments for sex, education, malnutrition, chronic diseases, marital status and APOE genotype.
Abbreviations: CIND, Cognitive impairment, no dementia; HR: hazard ratio; CI: confidence interval
Model 1: Functional profiles and covariates at baseline only.
Model 2: Functional profiles and covariates as time varying variables.
Source: Grande G et al, Cognitive and physical markers of prodromal dementia: A 12-year-long population study. Alzheimers Dement. 2020;16(1):153-161 [162]

When CIND and slow gait speed were combined, the best area under the curve (AUC) was obtained (**Figure 8**). The analyses stratified by age (above and below 78 years) showed that isolated CIND was more accurate in predicting incident dementia among the younger individuals (AUC: 0.78; 95%CI: 0.61-0.88), whereas the AUC for isolated CIND in the older group was 0.70 (95%CI: 0.62-0.77). When CIND and slow gait speed were considered together in the younger cohort, we observed a minor improvement in the AUC (0.76; 95%CI: 0.59-0.94). Conversely, in the older cohort, we detected a higher AUC when CIND and slow gait speed were combined (AUC: 0.82; 95%CI: 0.76-0.87). This increase reflects a significant improvement in the PPV (from 10% to 51%), with an equally high level of the NPV (over 98%).

PANEL A: YOUNGER-OLD COHORT



PANEL B: OLDER-OLD COHORT

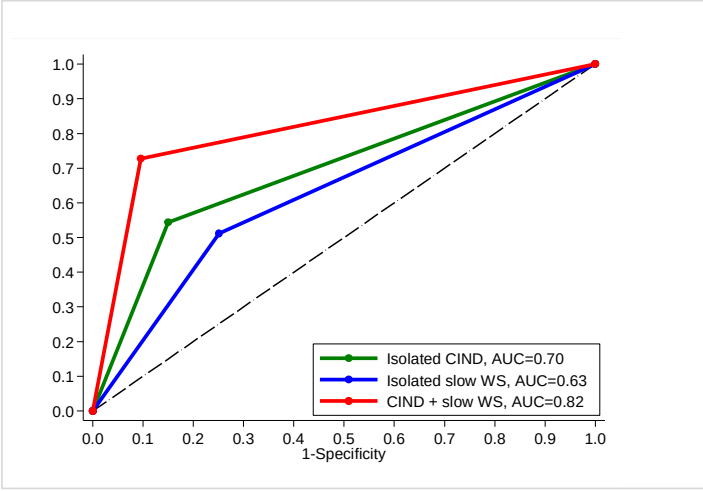


Figure 8. Area under the curve (AUC) for dementia by functional profile, by age group

Abbreviations: CIND: cognitive impairment, no dementia; WS: walking speed

Source: Grande G et al, Cognitive and physical markers of prodromal dementia: A 12-year-long population study. Alzheimers Dement. 2020;16(1):153-161 [162]

4.3 BRAIN CHANGES RELATED TO FAST COGNITIVE AND MOTOR DECLINE (STUDY II)

Overall, 385 individuals who participated in the brain MRI were included in *Study II*. Over the follow-up (mean: 10.0 ± 2.61 years), 50 (13%) of them belonged to fastest quartile of decline in both cognition and motor function.

At baseline, individuals who declined in both MMSE and gait speed presented with smaller total brain tissue volumes (average difference: -26.3 mL), larger ventricles volumes (average difference: 10.7 mL), smaller hippocampal volume (average difference: 0.27 mL) and a larger volume of white matter hyperintensities (average difference: +4.43 mL), compared to those in the reference group (no/slow decliners). Similar results were obtained in the longitudinal analyses: participants with both motor and cognitive decline experienced the most rapid loss of total brain tissue volumes (average annual decline: -12.3 mL), the greatest enlargement of ventricles volumes (average annual increase: +2.07 mL), the greatest hippocampal volume loss (average annual decline: -0.25 mL), and the steepest accumulation of white matter hyperintensities (average annual increase: +1.61 mL). See **Table 6**.

Participants who declined in both cognition and motor function had worse baseline mean diffusivity (MD) values (mean difference: 2.17; 95%CI: 0.78-3.54) compared to those who did not experience decline. Similar coefficients for fractional anisotropy (FA) were observed in those who declined in both cognition and motor function (mean difference: 0.96; 95%CI: -1.79-0.11).

Table 6. β-coefficients and 95% confidence intervals (95% CI) for the association of different patterns of decline with baseline brain volumes and lesions (intercept) and annual brain volumes and lesions changes (slope) over six years, from multivariable mixed-effect models

	β (95% CI)			
	Total brain tissue	**Ventricles volume**	**Hippocampal volume**	**White matter hyperintensities**
Decliners profiles (intercept)				
Slow/No decliners (Ref.), N=238	Ref.	Ref.	Ref.	Ref.
Isolated motor decliners, N=46	-16.5 (-34.1; 1.21)	2.94 (-1.99; 7.87)	-0.13 (-0.34; 0.08)	1.97 (-0.86; 4.82)
Isolated cognitive decliners, N=50	-24.8 (-42.9; -6.72)	5.21 (0.16; 10.26)	-0.25 (-0.47; -0.04)	-0.48 (-3.37; 2.41)
Cognitive and motor decliners, N=50	-26.3 (-45.2; -7.51)	10.74 (5.47; 16.01)	-0.27 (-0.51; -0.04)	4.43 (1.42; 7.44)
Decliners profiles (slope)				
Slow/No decliners (Ref.)	Ref.	Ref.	Ref.	Ref.
Isolated motor decliners	-3.39 (-8.41; 1.62)	1.17 (-0.02; 2.36)	-0.09 (-0.17; -0.02)	0.73 (-0.20; 1.67)
Isolated cognitive decliners	-10.78 (-16.3; -5.31)	1.92 (0.61; 3.23)	-0.17 (-0.25; -0.08)	0.69 (-0.32; 1.70)
Cognitive and motor decliners	-12.3 (-18.2; -6.38)	2.07 (0.67; 3.47)	-0.25 (-0.34; -0.16)	1.61 (0.54; 2.68)

Models are adjusted for age, sex, education, cardiovascular diseases (intended as atrial fibrillation, heart failure and ischemic heart disease), depression and APOE genotype. Brain volumes (mL) were adjusted for intracranial volume.

4.4 CLUSTERS OF DISEASES AND INCIDENT DEMENTIA (STUDY III)

In *Study III*, we identified a cohort of 2,622 dementia-free persons affected by multimorbidity (2+chronic diseases; MM) at baseline. The following MM patterns were identified: *neuropsychiatric* (7.6%), *cardiovascular* (9.5%), *sensory impairment/cancer* (14.8%), and *respiratory/metabolic/musculoskeletal* (20.8%). The remaining 47.3% of the population were grouped in a cluster in which no diseases were overexpressed, termed as "*unspecific"* MM-pattern. The *unspecific* MM-pattern was considered to be the reference group.

Compared with individuals in the *unspecific* cluster, the hazard of dementia was: 66% higher for those with *neuropsychiatric* MM-pattern (HR:1.66; 95%CI: 1.13-2.42), 61% higher for those with *cardiovascular* MM-pattern (HR:1.61; 95%CI: 1.17-2.29), and 32% higher for those with *sensory impairment/cancer* MM-pattern (HR: 1.32; 95%CI: 1.10-1.71). No association was found between the *respiratory/metabolic/musculoskeletal* MM-pattern and dementia development (**Figure 9**).

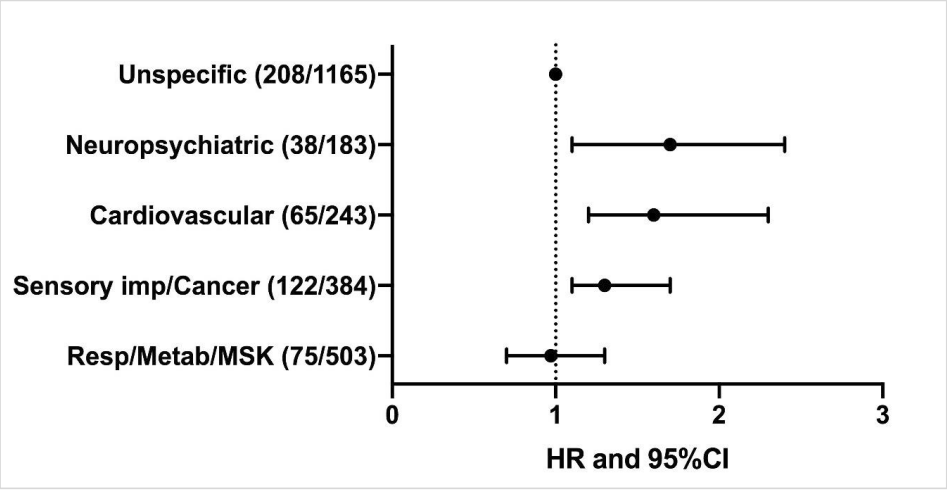


Figure 9. Adjusted hazard ratios (HRs) of dementia with 95% confidence intervals (CIs) by baseline multimorbidity patterns (N=2,478)

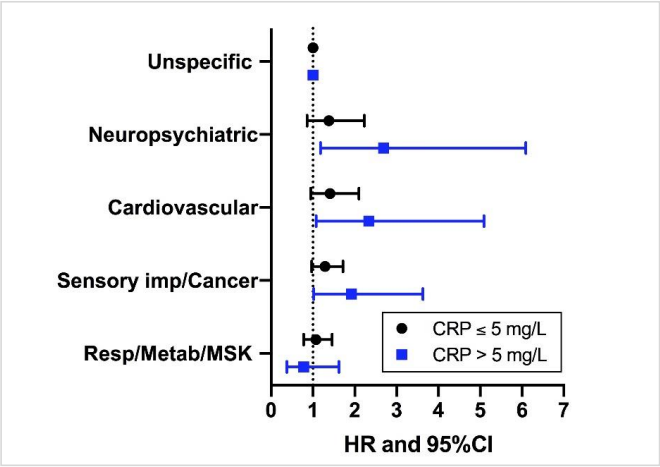
Cox models are adjusted for age, sex, education, civil status, malnutrition, C-reactive protein levels, APOE genotype, and baseline Mini-Mental State Examination score.

The association between the *neuropsychiatric*, *cardiovascular*, *and sensory impairment/cancer* MM-patterns and dementia was even stronger in the group with high levels of CRP (HR: 2.69; 95% CI: 1.19-6.09; HR: 2.34; 95% CI: 1.08-5.09; HR: 1.92; 95% CI: 1.02-3.63, respectively). No association was detected between the *respiratory/metabolic/musculoskeletal* MM-pattern and dementia development in either of the CRP level groups (**Figure 10 Panel A**).

In the analyses stratified by *APOE* genotype, we detected a stronger association between the *neuropsychiatric* (HR: 2.79; 95%CI: 1.43-5.43) and *cardiovascular* (HR: 2.58; 95% CI: 1.39-

4.76) MM-patterns and dementia development in ε4-carriers (**Figure 10, Panel B**). No association with dementia development was detected for either the *sensory impairment/cancer* or the *respiratory/metabolic/musculoskeletal* MM-pattern in *APOE* ε4-carriers.

PANEL A: BY CRP LEVELS



PANEL B: BY *APOE* GENOTYPE

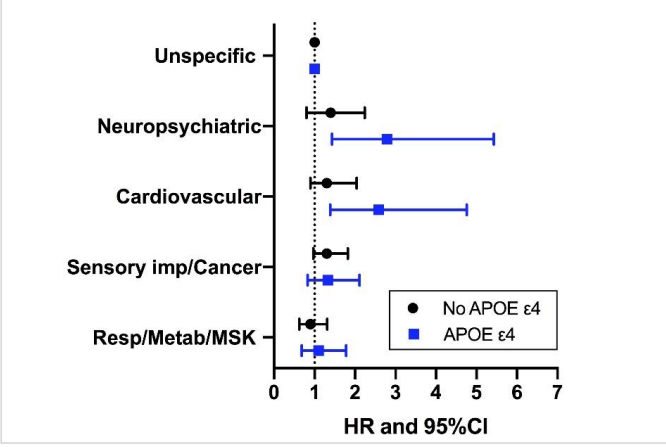


Figure 10. Associations between baseline multimorbidity pattern and incident dementia according to serum CRP levels and *APOE* genotype

*Hazard ratios (HRs) and 95% confidence intervals (CI) are derived from Cox regression models adjusted for: **Panel A**: age, sex, education, civil status, malnutrition, and baseline Mini-Mental State Examination score, and APOE ε4 allele. **Panel B**: age, sex, education, civil status, malnutrition, and baseline Mini-Mental State Examination score, and CRP levels.*

4.5 AIR POLLUTION, CARDIOVASCULAR DISEASE AND DEMENTIA (STUDY IV)

During the 6.1 (±2.56) years of follow-up, 364 incident dementia cases were identified among the 2927 participants. A higher hazard of dementia was found per interquartile range (IQR) difference of $PM_{2.5}$ (HR=1.54, 95% CI: 1.33−1.78, IQR=0.88 μg/m^3) and NO_x (HR=1.14,95% CI:1.01−1.29, IQR=8.35 μg/m^3) during the five years preceding the event. The concentration-response curve (**Figure 11**) showed a linear association at levels below the mean pollutant level (8.4 μg/mm^3). Above the average level, we observed no further increase in dementia hazard.

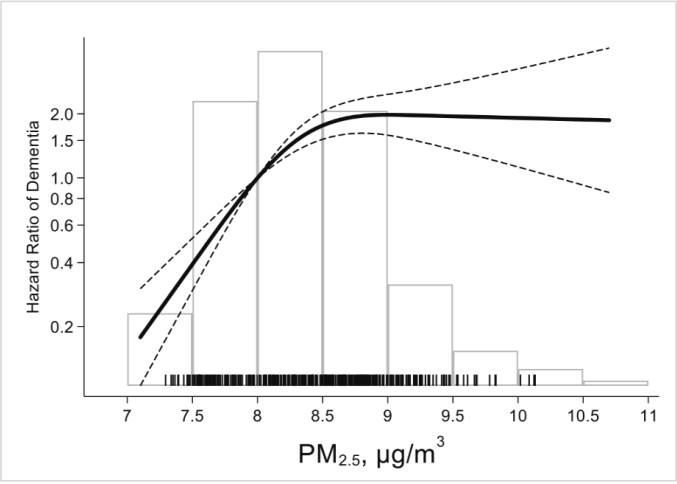


Figure 11. Hazard ratios (HR) of dementia with 95% confidence intervals by $PM_{2.5}$

Estimates are hazard ratios derived from Cox proportional hazard models by $PM_{2.5}$. Air pollutants were modeled using restricted cubic splines. Models were adjusted for sex, age at baseline, year of assessment, education, smoking, socio-economic status, early retirement, physical activity, depression, baseline MMSE score, diabetes, BMI, hypertension, and dyslipidemia. The exposure window was between 0 and 5 years before the event. The reference group was set as the mean exposure level in the entire population. Bars represent distribution of the exposure levels in the entire population and black dashes above the X-axis represent the dementia cases.

Concerning dementia subtypes, higher hazard of VaD was found per IQR difference for $PM_{2.5}$ (HR:1.66; 95%CI:1.38–1.99). No associations were detected for Alzheimer's disease.

In the analyses stratified by CVDs, we observed an overall higher risk of dementia associated with exposure to $PM_{2.5}$ and NO_x in persons with heart failure and – to a lesser degree – in those with ischemic heart diseases, in comparison to those without these conditions (**Figure 12**). We did not observe any risk differences for those affected by stroke and atrial fibrillation.

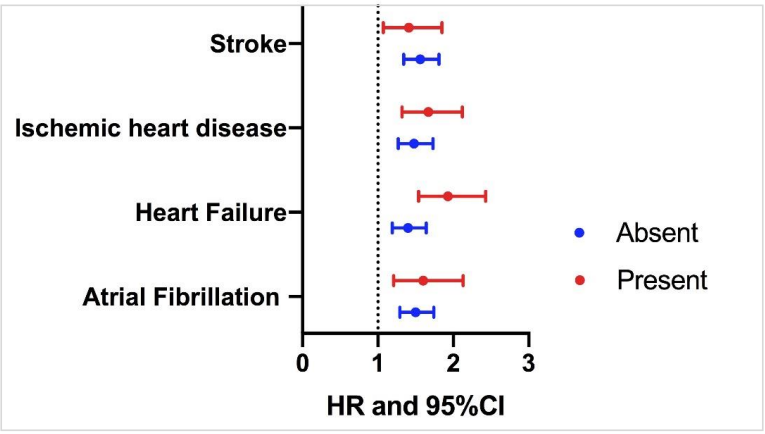


Figure 12. Hazard ratios (HR) of dementia with 95% confidence intervals by $PM_{2.5}$, stratified by cardiovascular diseases

Estimates are hazard ratios derived from Cox proportional hazard models according to $PM_{2.5}$. Age is considered as the time scale. Models are adjusted for sex, age at baseline, year of assessment, education, smoking, socio-economic status, early retirement, physical activity, BMI, baseline MMSE score, depression, hypertension, dyslipidemia and diabetes. The time exposure period is between 0–5 years before the event.

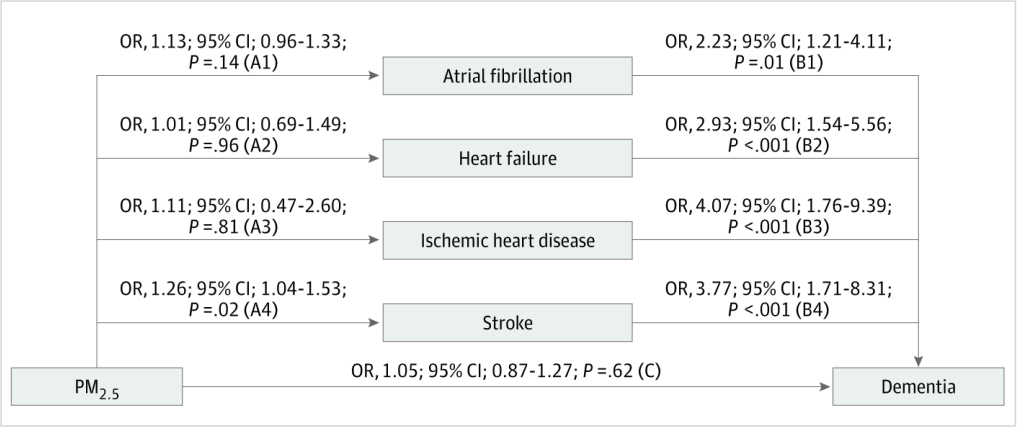


Figure 13. Association between $PM_{2.5}$ and dementia, with heart diseases and stroke as mediators

Models are adjusted for sex, age at baseline, year of assessment, educational attainment, smoking status, socioeconomic status, early retirement, physical activity, baseline Mini-Mental State Examination score, body mass index, depression, hypertension, dyslipidemia, and type 2 diabetes. OR indicates odds ratio Abbreviations: OR: odds ratio; $PM_{2.5}$: particulate matter≤2.5 micrometers.
Source: Grande G et al, Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. JAMA Neurol. 2020;77(7):801-809 [163]

In the mediation analysis (**Figure 13**), half of the association between $PM_{2.5}$ and dementia was explained by the preceding stroke (49.4%). Higher levels of $PM_{2.5}$ were found to be associated with a 26% higher odds of stroke per IQR, and stroke was associated with more than 3.5 times higher odds of subsequent dementia. $PM_{2.5}$ was also associated with CVDs other than stroke, albeit non-significantly, and each of them exhibited strong associations with dementia. Only a fraction of the total association between $PM_{2.5}$ and dementia was estimated to be through a direct effect. No statistically significant mediation effect by CVDs was found in the association between NO_X and dementia.

5 DISCUSSION

5.1 MAIN FINDINGS

This doctoral thesis explored the role of the body-mind connection in the development of dementia in older individuals by investigating 1) the predictive value of motor function in detecting prodromal dementia and the biological substrates underlying simultaneous cognitive and motor decline; and 2) the impact of different somatic conditions on dementia risk and their role in dementia development.

The main findings of the thesis can be summarized as follows:

1. People experiencing co-occurring cognitive and physical impairments have the highest hazard of developing dementia over time. Adding an easy-to-perform measure of physical function—such as gait speed—to a standard cognitive battery can help clinicians identify patients who will develop dementia [162] (**Study I**).
2. A rapid decline in both cognition and motor function is accompanied by brain damage that involves both gray and white matter. Isolated cognitive and motor decline seem to exhibit brain damage characterized by qualitatively different features (**Study II**).
3. Older adults with neuropsychiatric and cardiovascular conditions experience the highest dementia risk, followed by those with sensory impairments and cancer. The presence of systemic inflammation seems to amplify this risk in all three MM-patterns, whereas the presence of *APOE* ε4 appears to increase dementia risk only in the neuropsychiatric and cardiovascular MM-patterns [164] (**Study III**).
4. Exposure to $PM_{2.5}$ is associated with increased dementia risk. Cardiovascular diseases amplify the harmful effect of air pollution. In particular, stroke seems to be an important intermediate condition between air pollution and dementia [163] (**Study IV**).

5.2 ASSESSING MOTOR FUNCTION TO BETTER PREDICT PRODROMAL DEMENTIA (STUDY I)

Several conclusions can be drawn from **Study I**. First, the simultaneous presence of cognitive and motor deficits represents an at-risk condition for future dementia. The related dementia hazard was found to be even stronger when this profile (co-occurring cognitive and motor deficits) was considered as a time-varying variable. This indicates that assessing cognitive and motor functions longitudinally allows for a more refined risk stratification than what can be estimated when considering only a single timepoint.

To assess the prognostic value of cognitive and motor markers in detecting impending dementia, we computed accuracy measures and AUC curves. Importantly, we assessed accuracy separately in individuals < 78 and ≥ 78 years, while also differentiating between short- and long-term predictions (0-6 vs. 6-12 years of follow-up). The combination of cognitive and motor impairment dramatically improved our ability to predict future dementia in the older group (78+) within the first six years of observation. This increase was primarily due to a

significant improvement in the positive predictive power (from 10% to 51%), with the negative predictive power remaining at a high level (over 98%). In other words, among older individuals, adding gait speed to the neuropsychological battery led to a reduction in the proportion of false negatives and the low number of false positives (high specificity) remained low. Conversely, adding gait speed to the standard cognitive battery did not improve the predictive power for dementia identification among younger-old adults.

These results have important clinical implications for the routine care and management of older patients with cognitive problems, indicating that adding an easy-to-perform, non-invasive, and inexpensive motor test to the neuropsychological battery would improve its ability to predict dementia [165]. This was recently acknowledged in a paper, by Montero-Odasso and colleagues, which recommended "testing gait speed in patients with cognitive complaints/impairments if time and recourses are available" with a 1B level of evidence [166]. Our finding of age group differences calls for interesting aetiological speculation. In older adults, cognitive impairment is frequently a result of complex and interrelated factors, such as the presence of multiple chronic conditions and poor contextual factors (e.g. social deprivation) [167]. Gait speed is a valid measure of biological age and a good indicator of several clinical and subclinical impairments that are frequently associated with accelerated aging [62, 63]. As such, assessing gait speed in the context of a cognitive assessment might capture some non-neurological aspects that contribute to the onset and the progression of cognitive symptoms in the oldest persons.

5.3 MIXED BRAIN PATHOLOGY UNDERLYING SIMULTANEOUS COGNITIVE AND MOTOR DECLINE (STUDY II)

The results from **Study II** are in line with recent accumulating evidence that cognitive and motor domains both play a major role in dementia development. Here, we advanced this evidence by exploring whether motor and cognitive dysfunctions have independent contributions to dementia, or if their effects are rather due to shared brain correlates.

We found that individuals who experience a steep joint decline in cognition and memory function are characterized by several brain pathological markers that involve both gray and white matter. These individuals present with smaller total brain volumes and larger ventricles, but also smaller hippocampal volumes and greater white matter hyperintensity lesions. This last observation was further supported by the sub-analyses, which included DTI measures and showed that co-occurring cognitive and motor decline is accompanied by greater microstructural white matter damage. Interestingly, we were also able to detect qualitative brain MRI differences when we studied cognitive and motor decline in isolation. Individuals with isolated cognitive decline experienced steeper hippocampal volume loss, whereas those with isolated motor decline presented with a greater white matter hyperintensity burden.

These findings may help us to better understand the neurobiological mechanisms underlying the interplay between cognitive and motor function in dementia. First, as expected, our results indicate that older adults who rapidly decline in both cognition and motor function exhibit pathological neuroimaging correlates involving both gray and white matter. As shown in

Figure 14, this supports the idea that the underlying pathology behind the decline in both domains is complex and mixed and derives from damages to both the brain and the body.

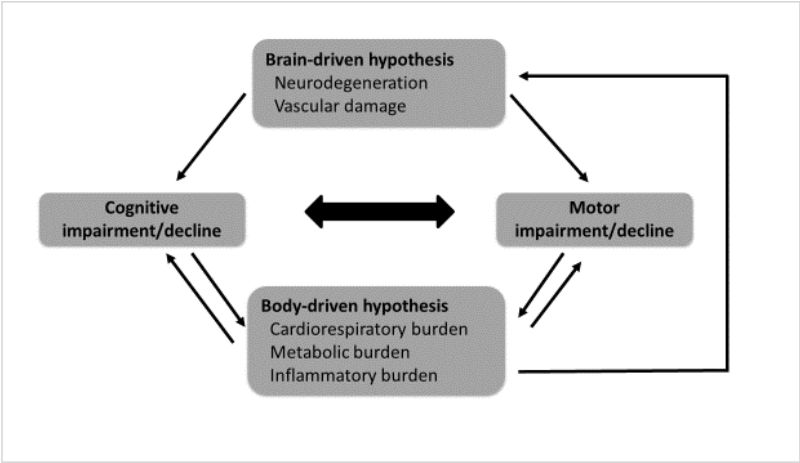


Figure 14. Determinants and interplay between cognitive and motor domains

Figure adapted from: Grande G et al. Measuring gait speed to better identify prodromal dementia. Exp Gerontol. 2019 Sep;124:110625 [62].

Interestingly, when cognitive and motor decline occurred in isolation, they were featured by qualitatively different brain damages. While the differences between the groups were not statistically significant due to smaller group sizes, we still observed a greater loss in hippocampal volume in individuals with an isolated decline in cognitive function, and greater accumulation of white matter hyperintensities in those with isolated motor function decline. In addition, there was a certain degree of loss in the hippocampus volume when isolated motor decline occurred, which is in line with previous findings that had identified the hippocampus as a possible shared brain area for both cognitive and motor function [68, 168, 169]. Gait speed decline, in isolation, or accompanied by cognitive decline, was characterized by greater white matter damage. As previously mentioned in the discussion of *Study I*, this indicates that slow gait speed may be a result of several clinical and subclinical dysfunctions, or, in other words, a reflection of systemic vulnerability.

5.4 SPECIFIC MM-PATTERNS INCREASE DEMENTIA RISK (STUDY III)

According to the findings of **Study III**, *neuropsychiatric* and *cardiovascular* MM-patterns confer the highest dementia risk throughout 12 years, followed by the *sensory impairment and cancer* MM-pattern. Systemic inflammation, assessed with serum CRP, amplified dementia risk in all three MM-patterns, whereas the presence of *APOE* ε4 only increased the risk in the *neuropsychiatric* and *cardiovascular* MM-patterns.

The focus of *Studies I and II* was on function, both cognitive and physical, as a predictor of incipient dementia. In *Study III*, we shifted our attention to the impact of clusters of somatic

diseases on dementia development. The role played by specific diseases in accelerating dementia onset, or increasing dementia risk, has been extensively studied. However, ours was the first study to measure dementia risk arising from several chronic conditions that share similar pathophysiological characteristics among multimorbid individuals.

In line with previous studies, we further confirmed that cardiovascular diseases have a detrimental effect on the brain [105]. This evidence indicates the existence of an intricate interplay between the heart and the brain in dementia development [170]. Furthermore, we detected increased dementia risk among individuals with neuropsychiatric diseases. The relation between depression and dementia is extremely complicated, as neuropsychiatric symptoms are a common feature in patients with dementia, and because depression may be regarded as a prodromal sign, rather than a risk factor for dementia. A large study of 28 years of follow up and involving 10,189 participants, found that those who reported depressive symptoms in midlife, even when chronic/recurring, were not at increased dementia risk later in life [171]. However, those with chronic/recurrent depressive symptoms in late life (on average 10 years before dementia diagnosis) did have a 67% higher dementia risk. Our results align with this study, as we detected a similar increased dementia risk over a similar time frame (12 years). Depression and dementia share pathophysiological pathways, including neurodegeneration, inflammation, and dysregulation of the hypothalamic-pituitary-adrenal axis that leads to prolonged exposure to glucocorticoids and subsequent hippocampal atrophy [172, 173].

Both inflammation and the presence of the *APOE* ε4 allele increased the risk of dementia in people belonging to the *cardiovascular* and *neuropsychiatric* MM-patterns. Older individuals are frequently characterized by a low-grade chronic proinflammatory state (i.e. *inflammaging*) [174, 175], and such imbalance between pro and anti-inflammatory cytokines might be the basis for the accumulation of somatic disorders and ultimately can affect the brain [176]. Unsurprisingly, the presence of the *APOE* ε4 allele—the strongest recognised genetic risk factor for late-onset dementia [177]—amplified the dementia risk of individuals in these two MM-patterns. *APOE* has also been linked to accelerated atherosclerosis and is implicated in the modulation of proinflammatory and anti-inflammatory cytokines [178].

Interestingly, in our cohort, sensory impairment and cancer clustered together. This could be explained by different mechanisms: (1) A bidirectional association between cancer and sensory impairment has been previously established. Persons with visual impairment have increased cancer risk [179] and, likewise, age-related macular degeneration occurs more frequently among smokers, increasing the risk of different types of cancer [180]. (2) Many cancer treatment regimens combine multiple ototoxic medications [181]. (3) Finally, these two conditions might co-occur as they are expressions of biological degenerative changes occurring with age. In our cohort this was further supported by the fact that those belonging to this cluster were the oldest, more likely to be women and malnourished, and had lower levels of cognitive performance. Hence, this profile identifies a frail proportion of the older population at increased risk of several adverse health-related outcomes, including dementia [74]. The dementia risk was further increased in the presence of high CRP levels but not the *APOE* ε4 allele, suggesting

that systemic health deterioration is a possible feature of dementia development among individuals with sensory impairment/cancer MM pattern.

In conclusion, the findings from this study indicate the existence of a somatic contribution to the development of dementia among older multimorbid individuals.

5.5 CARDIOVASCULAR DISEASES PLAY A MAJOR ROLE IN THE ASSOCIATION BETWEEN AIR POLLUTION AND DEMENTIA (STUDY IV)

Two major conclusions can be derived from the results of **Study IV**. First, exposure to $PM_{2.5}$ and NOx, particularly in the five years before dementia onset, is associated with increased dementia risk. Second, cardiovascular diseases appear to amplify the detrimental effects of air pollution, whereas stroke, in particular, emerges as a likely mediator of air pollution's influences on dementia.

Several recent longitudinal epidemiological studies have investigated the association between air pollution and dementia, finding consistent results [182]. However, very few explored the mechanisms behind this association and were mostly based on animal models. According to these studies, several hypotheses have been put forward in the attempt to explain brain damage related to air pollution exposure. First, the inhaled ultrafine particles and particulates cross the lung-blood barrier and enter the circulatory system, after which they may: (1) trigger systemic inflammation with consequent platelet activation and increased thrombotic risk [183]; and/or (2) damage the blood-brain barrier and activate the microglia [184]. In addition, evidence from toxicological studies indicates that exposure to high levels of air pollution leads to damage of the olfactory mucosa, olfactory bulb, and frontal cortex region, with greater deposition of amyloid-β [185].

Based on our findings, an indirect link between air pollution and dementia is plausible, with cardiovascular diseases playing a crucial role in this association. Indeed, this thesis has established that a close link between the heart and brain exists, and that the presence of cardiovascular diseases accelerates the onset and worsens the progression of dementia. Air pollution is an established risk factor for cardiovascular morbidity and mortality [130, 186]. As such, a close link between air pollution exposure/cardiovascular diseases/dementia is plausible. In our study, stroke mediated half of the association between air pollution and dementia. The fact that a vascular pathway was in place in the association between air pollution and dementia was further corroborated by the fact that we found an association between air pollution and vascular dementia and not Alzheimer's disease. However, since we lacked biomarkers for Alzheimer's disease, we were unable to further investigate the possible role played by neurodegeneration and amyloid deposition in relation to air pollution exposure.

These findings support the relevance of the heart-brain connection in dementia development, as they identify stroke to be mediator of the air pollution-dementia association. This possible pathway further highlights the need to optimize the treatment of concurrent cardiovascular diseases, as well as risk factor control, particularly for those living in the most polluted areas of our cities.

5.6 METHODOLOGICAL CONSIDERATIONS

5.6.1 Study design

All studies included in this thesis were derived from a population-based cohort and followed a longitudinal design. Apart from the inclusion criteria of being 60+ (which is in place because we are interested in an aging population), very few exclusion criteria have been applied in SNAC-K (e.g. inability to speak Swedish was an exclusion criterion). The random sampling from 11 age cohorts, and very few exclusion criteria are aspects of SNAC-K that make it a representative cohort of older Swedish adults living in an urban area.

5.6.2 Random error

In any observational study, two major sources of random error exist: one related to sample variance and, the other, to measurement error.

Sampling error. The ultimate goal of sampling is to obtain the lowest number of observations that is still representative of the original population. Due to the heterogeneity of the population, a degree of discrepancy will always exist between the sample statistics and the population statistics (e.g. mean, median). A larger sample size might help to minimize the sampling error and improve the precision of the estimates.

Measurement error. Measurement error is non-systematic error introduced by random variations in measurement. For example, in SNAC-K, some measures were assessed only once at each study wave; this could have led to measurement error by the assessor and/or participant, who might not have fully understood the task. A way to control for this type of error is to collect, and then average, several assessments for each individual. Examples of this kind of measurement error in SNAC-K are gait speed, laboratory tests, and cognitive tests. However, gait speed has been shown to be a robust measure even when assessed only once [147, 187]. In addition, SNAC-K staff is trained and follow standard procedures, which further minimizes the risk of random measurement error.

5.6.3 Systematic error

Systematic errors are common issues in every research study. They are derived from any systematic error in designing, conducting, and/or analyzing the study and may lead to biased results. Three main categories of systematic error exist: selection bias, information bias and confounding.

Selection bias. Selection bias may occur for several reasons. One occurs when certain persons that were selected randomly are more likely to refuse to participate in the study. When refusal to participate is more likely in some individuals as opposed to others, there is a possibility that systematic error will be introduced in the derived estimates. In SNAC-K, out of the 4950 initially invited persons, 1227 declined to participate, leaving a study sample of 3363 older individuals (participation rate: 73.3%). A high participation rate (above 70%) was observed for all 11 age cohorts and for both women and men. Those who declined to participate were more likely to die soon after the start of the study than those who participated [188]. This implies

that SNAC-K participants were healthier than the overall Kungsholmen population, which is likely to lead to an underestimation of the associations between the exposures and the negative outcomes. Similar issues could have affected the SNAC-K MRI subsample, which included individuals who were non-institutionalized, non-disabled, dementia-free, and, overall, younger and healthier than the larger SNAC-K cohort.

Another source of selection bias might be introduced by the presence of missing values for variables included in the analyses. Missing data can be accounted for through imputation models, as performed in *Study IV*.

Attrition refers to the loss of participants over time due to refusal or death. Attrition due to death is of extreme importance in longitudinal studies including older individuals, especially when looking at outcomes like dementia. We addressed this issue in several ways. First, in SNAC-K we have the unique opportunity to complement the dementia diagnosis obtained during the in-person examination by: (1) linking the SNACK database with the Swedish National Cause of Death Register; and (2) reviewing the clinical charts and medical records of the participants who died between two follow-up assessments. Despite these measures, some milder cases might not be captured [189], which can lead to an underestimation of the association. We tried to mitigate this by adjusting for baseline cognitive performance, whereas in *Study I* and *Study IV*, where dementia was the outcome, we also repeated the analyses by implementing the Fine and Gray competing risk model, considering dying without dementia as the competing event.

Attrition rate due to refusal is relatively low in SNAC-K, at approximately 20% for all age groups during the 12 years of observation. Certain variables included in this thesis were differentially distributed between dropouts and non-dropouts. To mitigate the effect of dropouts due to refusal, we adjusted each of the analyses for these variables (e.g. age, sex, educational level, number of chronic diseases) that were associated with a probability of non-participation at follow-up waves.

Information bias. This type of error can occur when information is collected by the assessor, reported and/or recalled from the participant, and/or noted by the assessor. Two types of information bias exist: differential and non-differential misclassification. Differential misclassification occurs when the proportion of misclassification is differentially distributed across study groups, which biases the association estimates. Non-differential misclassification occurs when different groups in the study have the same probability to be misclassified which decreases the study power with increased type II error.

Virtually any variable is subject to misclassification, however, although misclassification is more likely when self-reported measures are used. The four studies in this thesis all used objective measures: seven cognitive tests and/or the MMSE to define cognitive impairment, measured gait speed, diseases (collected and defined during the interview, but coupled with clinical examinations, instrumental and laboratory tests, medication-use, and patient register data), and dementia (following a three-step procedure).

Confounding. When the association between two variables is attributed to the effects of the third variable that is 1) causally related to both exposure and outcome and 2) unavailable for researchers to adjust for in the model, confounding bias can arise. We aimed to address this bias by adjusting the analyses for several covariates that could be considered as potential confounders. Despite extensive adjustment in all four studies, residual confounding cannot be entirely ruled out in any observational study.

5.6.4 Generalizability

Epidemiological research attempts to produce generalizable results, which means that the findings can be applied to a broader/other population, or ultimately, to human beings in general. SNAC-K is derived from a healthy and affluent population, living in a central district of Stockholm. As such, caution is always recommended before generalizing the results from SNAC-K to other populations, although they are likely valid for populations with similar socio-economic characteristics.

In most cases, the generalizability of a result depends upon the plausibility of the biological mechanisms responsible for the observed associations (and the biological basis of the associations observed in the present thesis are rather strong), rather than the representativeness of the sample itself.

6 CONCLUSIONS

Co-occurring cognitive and motor impairments represent a specific at-risk profile for dementia. Adding a measure of motor function, like gait speed, to a neuropsychological assessment improves our ability to detect impending dementia, especially among the older individuals (**Study I**).

Individuals who experience joint decline in cognitive and motor function present with a complex and mixed brain pathology that involves gray and white matter alterations. Isolated cognitive and motor decline seem to exhibit brain damage with qualitatively different features (**Study II**).

Persons with neuropsychiatric, cardiovascular, and sensory impairment/cancer MM-patterns are at increased risk for dementia. Such risk is further amplified by the presence of the *APOE ε4* allele and systemic inflammation (**Study III**).

Exposure to $PM_{2.5}$ is associated with increased dementia risk. Cardiovascular diseases appear to amplify the detrimental effects of air pollution, whereas stroke, in particular, emerges as a likely mediator of air pollution's influences on dementia. (**Study IV**).

These findings highlight the relevance of the body-mind connection in the development of dementia. In conclusion, further exploring the relation between body- and mind- related conditions may greatly advance our understanding of dementia development in older adults, allowing us to identify biomarkers for incipient dementia and at-risk populations

7 RELEVANCE AND IMPLICATIONS

The growing number of persons living with dementia and cognitive disorders, along with the failure of clinical trials to identify a curative treatment for these disorders, have led to two major clinical, research, and public health challenges: (1) Finding reliable and accurate predictors for early dementia detection, and (2) Identifying modifiable risk and protective factors for dementia prevention. In the present thesis, we aimed to contribute with research related to both these challenges.

First, we aimed to identify a reliable clinical marker that can improve our ability to detect future dementia. Our results indicate that adding gait speed to the standard neuropsychological battery may refine risk stratification and improve dementia prediction. Biomarkers for Alzheimer´s disease have the potential to be useful, but they are costly, and their invasive nature requires specialist settings [55]. As such, motor makers might be most suitable in the context of general populations where they can be used as a filter to assist clinicians in the management and care of persons with cognitive problems.

Second, we found that several somatic disorders, as well as exposure to $PM_{2.5}$, were associated with increased dementia risk. Identifying older adults affected by specific patterns of chronic diseases might help in tailoring interventions for dementia prevention and targeting individuals who would benefit most from such interventions [103, 190]. Furthermore, we found that cardiovascular diseases play a major role in the development of dementia related to air pollution. This finding calls for optimizing the treatment of concurrent cardiovascular diseases, specifically in persons living in the most polluted areas of our cities.

Overall, we observed that a body-mind connection exists in the development of dementia in older individuals, both in terms of the interplay between cognitive and motor function as well as with respect to the burden of cardiovascular and neuropsychiatric diseases. The neuroimaging study further supported this finding, showing a mixed and rapidly evolving brain pathology in persons experiencing parallel cognitive and motor decline.

Collectively, these results demonstrate that dementia in older adults is a complex and multifactorial disorder, in which somatic dysfunctions play an important role. Integrating these aspects in the study of dementia will undoubtedly advance our understanding of the pathophysiology of the disease and will enable the identification of effective therapeutic and preventive strategies.

8 FUTURE DIRECTIONS

The present thesis has contributed to a better understanding of dementia with the identification of predictors and risk factors. However, future research is needed to extend our knowledge of this disorder.

First, the added value of a motor marker in detecting impending dementia requires further confirmation in different settings, particularly the clinical environment (e.g. memory clinic). Second, our dataset lacks neuroimaging and biological markers that define Alzheimer's disease in-vivo. Thus, future studies including more specific markers of Alzheimer's disease pathology, such as Aβ and tau deposition, are needed. Third, more fine and sensitive markers (e.g. TNFα and specific interleukins) are critical to unpack the role of systemic inflammation in further increasing the dementia risk associated with specific MM-patterns. Fourth, to thoroughly understand the biological pathways at play in the association between somatic disorders and dementia, subtypes of dementia must be comprehensively characterized. This would also allow for more comprehensive investigations into the specific biological mechanisms that lead to different subtypes of dementia

Our knowledge on the occurrence, clinical manifestations, and biology of dementia in older adults has greatly expanded in the last decades. However, the number of persons suffering from dementia worldwide is increasing and no curative treatment has been identified. Given that a somatic component appears to be involved in the development of dementia, a more profound understanding of the biological underpinnings of this complex disease is crucial to complement our clinical and epidemiological knowledge. Combining these aspects will be the essential as we move forward in the field of dementia research.

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