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THE EFFECT OF SOMATIC DISORDERS ON BRAIN AGING AND DEMENTIA

Findings from population-based studies

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To my extended family

ABSTRACT English

This doctoral thesis investigates the effect of somatic disorders on dementia, Alzheimer's disease (AD) and brain aging in late-life. The data for the studies are provided by the Kungsholmen Project (*Studies I and II*) and the Faenza Project (*Studies III and IV*). The Kungsholmen Project is a population-based longitudinal study on aging and dementia carried out on 75+ years old people, living in Stockholm, Sweden. The Faenza Project is a cross-sectional population-based study on dementia and cognitive impairment involving persons over 60 years, living in a wealthy area in Northern Italy. The major findings are summarized below.

Study I. The hypothesis that anemia may increase the risk of dementia and AD was investigated using three-year follow-up data. Subjects who fulfilled WHO criteria for anemia (hemoglobin < 130 g/L for men and < 120 g/L for women) were at higher risk of developing dementia (HR: 1.6, 95% CI: 1.1-2.4). In persons with good baseline cognition (Mini-Mental State Examination (MMSE) ≥ 26, n=1,139) the association was stronger, and still significant after adjustment for conditions potentially related to anemia and dementia such as chronic diseases, inflammatory markers, and indicators of nutritional status. Using different definitions for anemia, a dose-response relationship between low hemoglobin concentration and incident dementia was observed: the lower the cut-off, the higher the probability of dementia.

Study II. The relationship between body weight and dementia (or AD) was investigated using three-, six-, nine-year follow-up data. No association was detected between being underweight and dementia. Even after extensive adjustment, subjects with Body Mass Index (BMI) ≥ 25 had a lower risk of developing dementia over nine years (HR: 0.8, 95% CI: 0.6–0.96) than normal-weight subjects. These results were confirmed also when the analysis was restricted to the cases occurring between three and nine, or between six and nine years of follow-up. Severe changes in BMI between baseline and three years of follow-up were associated with incident dementia in the following three years.

Study III. The independent and combined effect of medical and social factors on cognitive status was investigated in the Faenza Project. A person was diagnosed with Cognitive Impairment No Dementia (CIND) if he/she scored two or more standard deviations lower than non-demented subjects on the adjusted MMSE. The diagnostic procedure identified 402 CIND cases (5.4%). Diabetes (OR: 1.6, 95% CI: 1.2-2.2), stroke (OR: 1.9, 95% CI: 1.4-2.6), and depressive symptoms (OR: 1.9, 95% CI: 1.4-2.7) were the most relevant associated medical comorbidities. The strength of the association increased when these conditions occurred in combination. Low education (OR: 1.8, 95% CI: 1.1-2.9), low socio-economic status (OR: 1.5, 95% CI: 1.1-2.1), and unmarried status (OR: 1.7, 95% CI: 1.2-2.5) were also independently associated with CIND. Medical and social factors had a strong synergistic effect. Persons with at least one medical and one social factor were six times more likely to be diagnosed as CIND.

Study IV. To investigate the relation between perceived cognitive decline and mental and somatic comorbidity we considered the non-demented, cognitively unimpaired cohort of the Faenza Project (n=6,825). According to the Global Deterioration Scale (GDS), 20.1 % and 8.3% of participants reported very mild or mild cognitive decline, respectively. Diseases significantly associated with perceived cognitive decline were stroke (OR: 1.8; 95% CI: 1.3-2.3), malignancy (OR: 2.7, 95% CI: 1.3-5.7), cardiovascular disorders (OR: 1.7, 95% CI: 1.2-2.3), diabetes (OR: 1.6; 95% CI: 1.2-2.2), and depressive and anxiety symptoms (OR: 3.7, 95% CI: 2.4-4.2; OR: 1.6, 95% CI: 1.2-2.1). Mental, cardiovascular, and respiratory diseases accounted for the discrepancy between perceived cognitive decline and cognitive performance.

Conclusions. The findings support the hypothesis that several somatic disorders might affect brain aging and dementia. This thesis suggests that late-life anemia is a risk factor for dementia, that diabetes, stroke, and depressive symptoms are clinical correlates of CIND, and that mental and somatic morbidity accounts for the discrepancy between perceived cognitive decline and cognitive performance. Finally, we do not confirm being overweight in late-life as a risk factor for dementia, but we suggest that weight loss is a good predictor of incipient dementia.

Key words. Dementia, Alzheimer's Disease, CIND, Perceived cognitive decline, Anemia, Hemoglobin concentration, BMI, Weight Loss, Multimorbidity, Comorbidity, Risk factors

SAMMANFATTING Svenska

Den här avhandlingen undersöker effekten av somatiska sjukdomar på hjärnans åldrande och utvecklingen av demens, särskilt Alzheimers sjukdom (AD). Studierna är baserade på två populationsbaserade material från Stockholm och norra Italien: Kungsholmsprojektet (uppföljningsstudie av 75+ gamla; studie I och II) och Faenzaprojektet (tvärsnittsstudie av 60+ gamla; studie III och IV).

Studie I. Hypotesen om att anemi kan öka risken för demens och AD undersöktes genom tre års uppföljningsdata. Deltagare som uppfyllde WHOs kriterium för anemi (män: mindre än 130 g/L, kvinnor: mindre än 120g/L) hade högre risk att utveckla demens (HR: 1.6, 95 % CI:1.1-2.4). Hos personer med en god kognition vid baslinjemätningen (Mini-Mental State Examination, MMT ≥ 26, n=1,139) var associationen starkare och fortfarande signifikant efter justering för tillstånd relaterade till anemi och demens: kroniska sjukdomar, inflammatoriska markörer, och indikatorer för näringsstatus.

Studie II. Relationen mellan kroppsvikt och demens undersöktes genom att använda tre-, sex-, nio års uppföljningsdata. Ingen association upptäcktes mellan undervikt och demens. Deltagare med övervikt (body mass index, BMI ≥ 25) hade en lägre risk att utveckla demens än normalviktiga deltagare under nio års uppföljning (HR: 0.8, 95% CI: 0.6-0.96), efter omfattande justering för potentiella störfaktorer. Ett liknande resultat erhölls när analyserna begränsades till fall som inträffade mellan tre och nio, eller mellan sex och nio års uppföljning. Dessa resultat var dock ej statistiskt signifikanta. En kraftig minskning av BMI under den första treårsperioden var associerad med ökad demensrisk under den följande treårsperioden.

Studie III. De oberoende och kombinerade effekterna av flera medicinska och sociala faktorer på kognitiv status undersöktes i Faenzaprojektet. Totalt 402 (5.4%) fall av kognitiv funktionsnedsättning (CIND) diagnostiserades (två eller fler standardavvikelser lägre än icke-demenda deltagare i den justerade MMT). Flera medicinska co-morbiditeter var associerade med CIND: diabetes (OR: 1.6, 95% CI: 1.2-2.2), depressionssymptom (OR: 1.9, 95% CI: 1.4-2.7) och stroke (OR: 1.9, 95 % CI: 1.4-2.6). Associationen var starkare för kombinationer av dessa tillstånd. Låg utbildning (OR: 1.8, 95% CI: 1.1-2.9), låg socio-ekonomisk status (OR: 1.5, 95% CI: 1.1-2.1), och att vara ogift (OR: 1.7, 95% CI: 1.2-2.5) var också oberoende associerade med CIND. Medicinska och sociala faktorer samverkade starkt. I jämförelse med deltagare som inte hade något medicinskt eller socialt ogynnsamt tillstånd, hade personer med minst en medicinsk eller social faktor sex gånger större sannolikhet att vara diagnostiserad med CIND. Kombinationen av medicinsk co-morbiditet och sociala faktorer stärkte ytterligare associationen (OR: 21.7, 95% CI: 9.4- 50.1).

Studie IV. För att undersöka relationen mellan upplevd kognitiv försämring och mental och somatisk co-morbiditet använde vi icke demenda, kognitiv funktionsnedsättande kohort av Faenzaprojektet (n=6,825). Mycket mild kognitiv försämring (enligt skalan för globala försämringsfaktorer; GDS), rapporterades av 20.1% av deltagarna och 8.3% rapporterade mild försämring. Sjukdomar som var signifikant associerade med upplevd kognitiv försämring var stroke (OR: 1,8, 95% CI: 1.3-2.3), malignitet (OR: 2.7; 95% CI: 1.3-5.7), kardiovaskulära sjukdomar (OR: 1.7, 95% CI: 1.2-2.3), diabetes (OR: 1.6, 95% CI: 1.2-2.2) samt depressiva och ångestsymptom (OR: 3.7, 95% CI: 2.4-42.; OR: 1.6, 95% CI: 1.2-2.1).

Slutsats. Fynden stödjer hypotesen att ett flertal somatiska sjukdomar kan påverka hjärnans åldrande och utveckling av demens. Resultaten i denna avhandling pekar på att anemi sent i livet är en riskfaktor för demens och att diabetes, stroke, och depressionssymptom är associerade med kognitiv funktionsnedsättning. Slutligen kan vi inte bekräfta att övervikt sent i livet är en riskfaktor för demens, men begynnande demens förefaller vara associerad med viktminskning.

Nyckel ord: Demens, Alzheimer's sjukdom, CIND, Upplevd kognitiv försämring, Anemi, Hemoglobin koncentration, Body Mass Index, Viktminskning, Multimorbiditet, Komorbiditet, Risk faktorer.

RIASSUNTO Italiano

Questa tesi si propone di studiare l'effetto della salute fisica e mentale sulla demenza, la Malattia di Alzheimer (AD) e l'invecchiamento cerebrale dell'anziano. Il Kungsholmen Project (*Studi I e II)* ed il Progetto Faenza *(Studi III e IV)* hanno fornito i dati per questa ricerca. Il Kungsholmen Project è uno studio epidemiologico longitudinale condotto su soggetti di età > 75 anni residenti a Stoccolma, Svezia. Il Progetto Faenza, invece, è uno studio epidemiologico dal disegno trasversale che ha coinvolto i cittadini ultrasessantenni di Faenza (Ravenna).

Studio I. L'ipotesi oggetto dello studio era che l'anemia potesse aumentare il rischio di demenza tra tempo zero e follow-up (tre anni dopo). Soggetti con anemia, ovvero con emoglobina <13 g/dL (uomini) e <12 g/dL (donne), avevano un rischio aumentato di sviluppare demenza (HR: 1.6, 95% CI: 1.1-2.4). In soggetti senza disturbi cognitivi al tempo zero (Mini-Mental State Examination, MMSE ≥ 26, n=1,139) l'associazione risultava più forte e rimaneva significativa anche dopo avere tenuto conto di possibili condizioni correlate ad anemia e demenza, quali malattie croniche, indici di infiammazione, indici di stato nutrizionale. Utilizzando definizioni di anemia alternative, si osservava una relazione dose-risposta tra bassa concentrazione di emoglobina ed incidenza di demenza: più basso era il cut-off, più alta la probabilità di demenza.

Studio II. Scopo dello studio era esaminare la relazione tra peso corporeo in età avanzata e demenza (o AD) nel tempo (ovvero tre, sei e nove anni dopo). Non veniva riscontrata alcuna associazione tra sottopeso e demenza ma i soggetti con Body Mass Index (BMI) ≥25 avevano un rischio ridotto di sviluppare demenza rispetto ai soggetti normopeso nel corso dei nove anni (HR: 0.75, 95% CI: 0.59-0.96). Questi risultati venivano confermati anche quando i casi verificatisi nei primi tre anni di follow-up non venivano considerati. Una severa riduzione del BMI, invece, si associava a sviluppo di demenza nei successivi tre anni.

Studio III. L'effetto combinato di fattori medici e sociali sulle funzioni cognitive è stato l'oggetto di questo studio condotto sulla popolazione di Faenza. Il Cognitive Impairment, No Dementia (CIND) ovvero un disturbo cognitivo di entità non sufficientemente grave da potere essere clinicamente diagnosticato come demenza, è stato definito in base a punteggi di due o più deviazioni standard inferiori rispetto alla media. Sono stati identificati 402 casi (5.4%) di CIND. Il diabete (OR: 1.6, 95% CI: 1.2-2.2), l'ictus (OR: 1.9, 95% CI: 1.4-2.6), ed i sintomi depressivi (OR: 1.9, 95% CI: 1.4-2.7) erano le condizioni mediche più importanti in questi soggetti. La bassa scolarità (OR: 1.8, 95% CI: 1.1-2.9), il basso stato socio-economico (OR: 1.5, 95% CI: 1.1-2.1), ed il non essere coniugati (OR: 1.7, 95% CI: 1.2-2.5) erano inoltre associati in maniera indipendente a CIND. Condizioni mediche e fattori sociali avevano un forte effetto sinergico. Confrontati con soggetti privi di condizioni mediche o sociali sfavorevoli, persone con almeno una malattia e un fattore sociale avevano una probabilità aumentata di sei volte di ricevere diagnosi di CIND; la combinazione di comorbidità medica e fattori sociali incrementava ulteriormente tale associazione.

Studio IV. Il 20.1% e l'8.3% dei soggetti studiati riferiva di percepire un deterioramento cognitivo molto lieve e lieve. Patologie associate in maniera significativa al deterioramento cognitivo percepito erano: ictus (OR: 1.8, 95% CI: 1.3-2.3), neoplasie (OR: 2.7, 95% CI: 1.3-5.7), malattie cardiovascolari (OR: 1.7, 95% CI: 1.2-2.3), diabete (OR: 1.6, 95% CI: 1.2-2.2), sintomi depressivi (OR: 3.72; 95% CI: 2.4-4.2); ed ansiosi (OR: 1.6, 95% CI: 1.2-2.1). Disturbi mentali insieme a malattie cardiovascolari e respiratorie erano responsabili della discrepanza tra percezione soggettiva di deterioramento cognitivo e punteggi ottenuti ai test cognitivi.

Conclusioni. L'ipotesi di un possibile effetto di alcune condizioni mediche sull'invecchiamento cerebrale e sulla demenza è supportata dai dati di questa tesi. L'anemia nell'anziano è un fattore di rischio per demenza. L'essere soprappeso, invece, non aumenta il rischio di demenza, mentre una severa perdita di peso può esserne un fattore predittivo. Diabete, ictus e sintomi depressivi sono le principali comorbidità del CIND. In soggetti senza compromissione cognitiva, disturbi somatici e psicologici possono essere responsabili della discrepanza tra la percezione soggettiva di difficoltà cognitive e la performance ai test cognitivi.

Parole chiave. Demenza, Malattia di Alzheimer, CIND, Percezione soggettiva di difficoltà cognitive, Anemia, Emoglobina, Body Mass Index, Multimorbidità, Comorbidità, Fattori di rischio.

LIST OF ABBREVIATIONS

AD	Alzheimer Disease
APOE	Apolipoprotein E
BMI	Body Mass Index
CI	Confidence Intervals
CIND	Cognitive Impairment, No Dementia
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GDS	Global Deterioration Scale
Hb	Hemoglobin
HR	Hazard Ratio
ICD	International Classification of Diseases
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders-Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation
SES	Socio-Economic-Status
VaD	Vascular Dementia
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

The present doctoral thesis includes the following four original articles, which are referred to in the text by their Roman numerals.

I. **Atti AR**, Palmer K, Volpato S, Zuliani G, Winblad B, Fratiglioni L. Anemia increases the risk of dementia in cognitively intact elderly. *Neurobiol of Aging* 2006; 27:278-284.

II. **Atti AR**, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life Body Mass Index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *J Am Geriatr Soc* 2008; 56:111-116.

III. **Atti AR**, Forlani C, De Ronchi D, Palmer K, Casadio P, Dal monte E, Fratiglioni L. Cognitive impairment after age 60: the role of medical and social conditions. The "Faenza Project". *Submitted.*

IV. **Atti AR,** De Ronchi D, Marengoni A, Palmer K, Scudellari P, Dal Monte E, Fratiglioni L. Perceived cognitive decline in relation to mental and somatic comorbidity in a cognitively intact population. *Manuscript*.

CONTENTS

“On such a full sea are we now afloat,
And we must take the current when it serves,
Or lose our ventures…”

William Shakespeare , Julius Caesar Act 4, scene 3

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1 INTRODUCTION

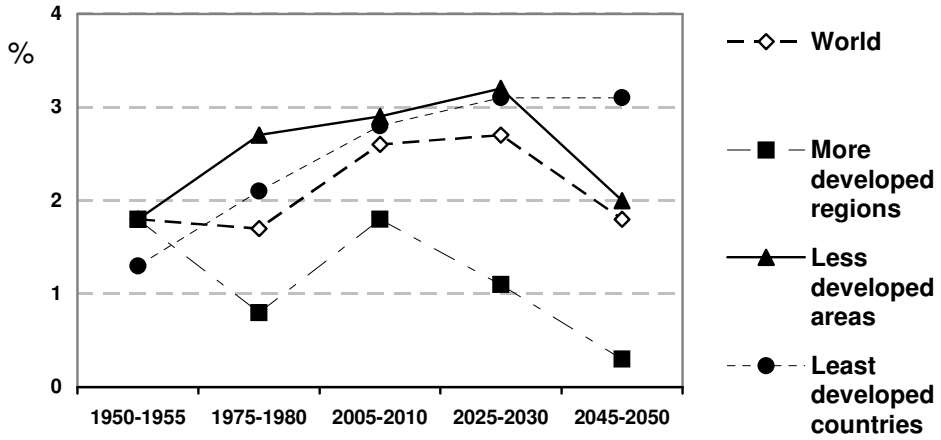
1.1 AGING IN THE 21st CENTURY

Thanks to social, technological, and medical advances occurring during the second half of the last century, population aging has become a worldwide phenomenon[1,2]. The high socio-economic impact of this demographic transition has recently stimulated a growing interest for research on the aging process, which has been approached from both a population and an individual perspective[3]. Besides economical, political, and social concerns[4], the worldwide aging phenomenon is, first of all, an indicator of improving global health. From this perspective, the World Health Organization (WHO) has highlighted that healthy older people might represent a resource for their families, communities, and economies, and has emphasized the need of more effective healthcare models for elderly people at the community-level aimed at promoting health, preventing diseases, and managing chronic illnesses[5].

1.1.1 Population perspective

The shift in the age structure of the population is a relatively recent phenomenon (Figure 1), which began in Western societies in the first half of the last century.

Figure 1. Average annual growth rate percent of population aged 60+ year.



Source: United Nation Departments of Economic and Social Affairs, Population Division "World Population Aging 2007" Chapter II, modified.

From being limited to developed countries, the aging of the population has nowadays become relevant also in low- and middle-income countries. In 1950-1955 the average annual growth rate of the number of persons aged 60 and over was similar all around the world (close to 1.8%). Since then, the growth rates of the older population have increased constantly only in the less developed regions. Currently, the average annual growth rate of the population aged 60 or above is 3% in less developed countries and 1.8% in the industrialized areas. This gap is expected to further increase. Indeed, by 2050 nearly 80% of the world's older population is expected to live in developing countries[4].

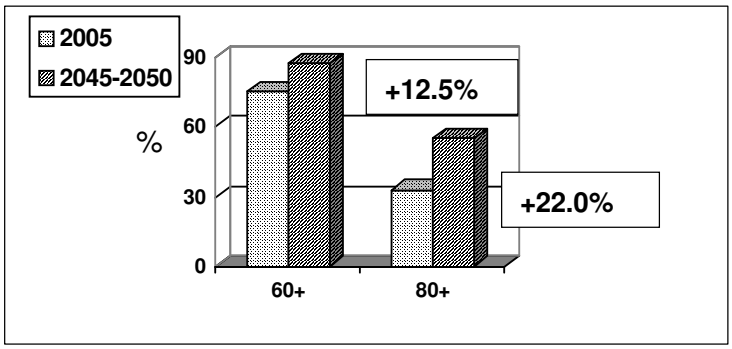
The principal causes of population aging are the sustained decline in fertility and the increased life expectancy that have occurred since 1950[6]. Almost all the developed countries are currently below the level needed to ensure a generational replacement (less than 2.1 children per woman). Although many disparities still exist between low- and high-income countries, a lower fertility rate is a worldwide phenomenon, and regional differences in fertility are expected to further decrease[7].

The decrease in all age mortality[8], resulted in a higher proportion of persons surviving until older ages. Assuming that current mortality conditions persist, approximately three out of every four newborns in the world are expected to survive to age 60, and one out of every three to age 80 years. In 2045-2050, almost seven out of every eight newborns are expected to reach age 60, and more than one out of two will reach age 80. In proportional terms, the increase in mean life expectancy is higher among older persons, and currently the older population is growing faster than the total population (Figure 2).

The mean life expectancy at age 65 is the number of further years a 65 year old person is expected to live[9]. Table 1 shows the secular trends in mean life expectancy at birth, at age 65 and at age 75 years. Persons born in 1944 had a life expectancy at birth of about 68 years, but if they did not die of infectious diseases when young or different accidents when adult, after reaching age 65, they can expect to live another 18.4 years. Therefore, the mean life expectancy of people born in 1944, nowadays, is not the same as it was at birth. Indeed, it is about six years longer than the current life expectancy at birth. Reaching age 75, life expectancy further increases[10].

To date, Europe is the area with the highest proportion of elderly persons aged 60+, which accounts for 21% of the population in 2007. This proportion is projected to reach 35% by 2050.

Figure 2. Proportion of persons surviving (2005) or expected to survive (2045-2050) until age 60+ or age 80+ years worldwide.



Source: United Nation Departments of Economic and Social Affairs, Population Division "World Population Aging 2007" Chapter II, modified

Within Europe, Italy and Sweden are among the countries with the oldest populations. In both countries the mean life expectancy at age 65 has increased between 1995 and 2003-2005, as shown in Figure 3. On average, after reaching age 65, women live three to four years longer than men.

Table 1. Life expectancy at birth, at age 65 and at age 75 in 1950, 1980 and 2003; Western countries.

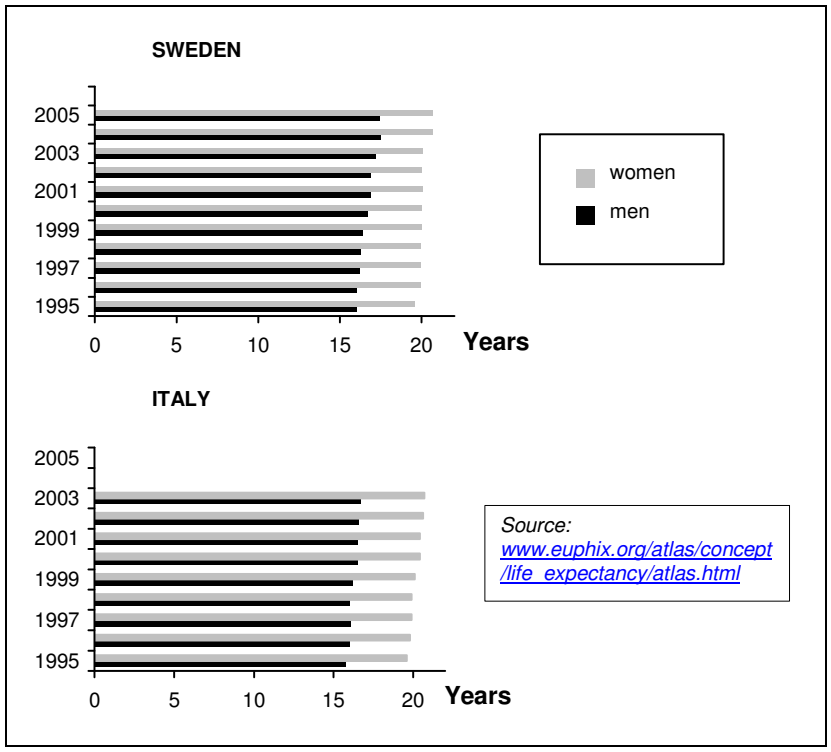
	Life expectancy		
	at birth	**at 65**	**at 75**
1950	68.2	78.9	Not available
1980	73.7	81.4	85.4
2003	77.5	83.4	86.8

Source: United Nation Departments of Economic and Social Affairs, Population Division "World Population Aging 2007"

1.1.2 Individual perspective

From an individual standpoint, life experience has changed dramatically over the last decades. In many countries persons spend a quarter of their lives over 65 years of age[11]. Furthermore, persons getting older in the 21st century face new challenges compared to their parents[10,12].

Figure 3. Mean life expectancy at age 65 by gender in Italy and Sweden.



Family household structure, for example, has largely changed. Increased mobility due to globalization leads to physical distance between first-degree relatives and to closeness with people with different socio-cultural backgrounds.

Marriages with a traditional gender-based division of tasks were the dominant pattern when today's older people started adult lives, especially in the middle classes[13].

This situation changed towards the end of the 1960s, when married women and mothers started entering the labor force in greater numbers than before. Elderly individuals are likely to experience the most severe effects of such changes. For example, the decreased number of children per family has led to a narrower parental and social network, and consequently elderly persons are likely to lose their main caregivers in the next future. However, nowadays, informal care still substitutes rather than complements formal care[14], even in countries with solid and well organized social and medical assistance. The New Haven Established Populations for the Epidemiologic Study of the Elderly (EPESE) shows that married older persons have about half the risk of nursing home admission than unmarried persons, and having at least one daughter or sibling reduces an older person's chance of admission by about one-fourth[15].

Technological advances are another challenge for elderly persons. Indeed, on one hand, the implementation of advanced technologies such as mobility devices, auditory equipment, and other technical aids, can help elderly persons to overcome disability and to reduce the risk of further impairment[16]. On the other hand, technological advances mean that elderly persons also have to learn new and unfamiliar skills, and cope with an increasing demand[17]. In the worst scenario, becoming dependent on an external device might contribute to reducing elderly self-esteem and produce feelings of loss of identity instead of being beneficial[18].

Psychologists have extensively investigated older age, especially in relation to bereavement, retirement, and loss of socially valued roles. Some authors suggest that people, because of depleted resources, become less effective as they age. Conversely, other authors hypothesize that people become better at managing stressful life events over time, having learned more effective strategies[19].

1.1.3 Health in aging

The aging process is a complex phenomenon where genetic, environmental, and biological factors are interacting with each other and with the socio-cultural context. Health represents one of the major issues in the aging of both individuals and populations. Indeed, on one side, technological and medical progress has increased survival from medical conditions that used to be deadly, leading to higher number of

diseases affecting each single person. On the other side, people's ability to cope with diseases has increased[20]. According to the "compression of morbidity" hypothesis, the decrease in old age mortality will reach a plateau and morbidity will be "compressed" into a few years at the end of life[21].

Conversely, according to other hypotheses, the augmented lifespan of persons with disabling conditions will lead to an "expansion of morbidity" in the age of degenerative disease[12,22]. In between these two alternative theories, a "dynamic equilibrium" has been proposed[23]. According to this theory, a decrease in the body's organ- and system-functioning will accompany the reduction in mortality. In other words, the population could be more diseased but at a lower severity level.

In the Kungsholmen Project the prevalence (95% Confidence Intervals) of morbidity (at least one medical condition) among 77+ years old elderly has been estimated to be 30.5% (27.8-33.2), whereas the prevalence of multimorbidity (2 or more diseases) was 54.8% (50.8-58.8). The prevalence of malignancy, respiratory, and musculoskeletal diseases was estimate to be below 10% in both the 77-84 and the 85+ year old individuals, whereas the prevalence of circulatory disease was around 57%. Noticeably, the prevalence of mental diseases, which was lower than 20% in the youngest age group, rose to 37% after age 84. At older ages, dementia was the most prevalent mental disorder (33.8%) and at all ages it was the second most prevalent medical condition after hypertension[24].

1.2 DEMENTIA

The history of dementia is probably as old as mankind itself[25], dating back to the ancient Greek and Roman philosophers and physicians. The etymological origin of the word *dementia* is Latin and means "being out of one's mind"[26]. A number of synonyms for the word "dementia" have been used to refer to diseased persons with a clear negative connotation[27]. Many elderly individuals have been institutionalized because the boundary between mental disorders and senile dementia has been unclear for many years. The description of the first case of Alzheimer's disease (AD) in 1906 represents the turning point for the understanding of this complex condition. After that time the

concept of senile dementia has evolved from a rather vague notion that "mental" decline occurs inevitably in old age to well-defined set of clinical and pathological features[26,27]. Currently, dementia is defined as a syndrome that includes acquired memory deficits and disturbances of other higher cortical functions, severe enough to interfere with daily functioning. Besides cognitive *core* symptoms, a certain degree of deterioration in emotional control, social behavior, or motivation might precede, co-occur, or complicate cognitive disturbances.

1.2.1 Causes of dementia

The dementia syndrome can be due to many different conditions as summarized in Table 2. AD is believed to be the most frequent dementia subtype, accounting for 60–70% of all dementia cases[28-31], whereas Vascular Dementia (VaD) accounts for 15–20% of the cases[32,33]. A few studies designed to estimate the distribution of dementia subtypes suggested that Dementia with Lewy Body and Frontotemporal Lobe Dementia are relatively common, accounting for 2.6-10.9% and 7.8% of all dementia cases, respectively[34,35]. Neuropathological, neuroimaging, and etiological studies have shown considerable overlap between neurodegenerative and vascular dementing disorders[36-39]. Since dementia subtypes often overlap in their clinical and pathological features, and more than one dementing disorder may contribute to dementia symptoms, in the present thesis we will consider the dementia syndrome as a whole entity, unless otherwise specified.

1.2.2 Diagnostic criteria

The most frequently used criteria to identify dementia are those provided by the American Psychiatric Association in the third edition revised of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, 1987)[40] and the fourth edition, text revision (DSM-IV-TR, 2000)[41]. Compared to the previous version, the DSM-IV criteria introduce the disturbances of executive functioning (e.g., the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behaviors) and cognitive decline from a previous level. The WHO has proposed its own criteria in the

International Classification of the Disease, tenth revision (ICD-10, 1992) (42). The ICD-10 guidelines specifically consider dementia as a chronic or progressive disorder, and require duration of symptoms of at least six months.

Table 2. Different dementia types according to the underlying disorders.

Dementia as the core symptomatology	*Dementia as a part of the core symptomatology*	*Dementia as a rare symptom of common disorders, or as a symptom of rare disorders*
Alzheimer's disease	Huntington's disease	Multiple sclerosis
Frontotemporal dementia/Pick's disease	Parkinson with dementia	Head trauma
Dementia with Lewy bodies	Amiotrofic Lateral Sclerosis-Parkinson-dementia complex	Primary and metastatic brain tumours
Alcoholic dementia	Progressive sopranuclear palsy	Subdural haematoma
Vascular dementia/ Multi-infarct dementia	Hydrocephalus	Mostly metabolic diseases
Binswanger's disease/ Subcortical VaD	Metabolic disorders (B_{12} deficiency, renal dialysis, hypothyroidism)	
Cerebral amyloid angiopathy		
Rare vasculopaties		
Subacute spongiform encephalopaties		
AIDS-dementia		
Chronic meningoencephalities (neurosyphilis)		

Source: Fratiglioni et al. In "Health Economics of Dementia", 2nd ed., edited by Wimo A, Jönsson B, Karlsson G, Winblad B. John Wiley & Sons, London, UK, 2008, modified.

Both DSM and WHO criteria agree on the fact that memory disturbances alone are not sufficient for a dementia diagnosis. Furthermore, other disorders causing cognitive disturbances such as delirium, amnestic disorder, mental retardation, and major

depression must be excluded. The Academy of Neurology defines these criteria as reliable and suggests their use routinely[43]. Although the presence of reliable criteria provides an essential support to the diagnostic procedure, it is not easy to make a dementia diagnosis, especially in the early stages of the disease. It requires good knowledge and clinical experience of the diagnosing physician. Taking a valid medical history, documenting characteristic findings, and conducting a clinical examination are crucial to carry out an appropriate differential diagnosis. The diagnostic difficulties increase with increasing age of the patient[44], because very old people reduce their social and work activities in a variable way depending more on family situation, personality, physical health status, and type of society than on their degree of cognitive impairment. Furthermore, multimorbidity is more common in very old ages, and could interfere in some way with cognitive functioning. In community-based epidemiological surveys, the diagnostic procedure is even more challenging, due to more limited contact with participants and their families. The revision of DSM criteria, currently ongoing, will hopefully provide solutions to some of the problems raised in the application of DSM and ICD-10 categories to elderly persons[45].

1.2.3 Prevalence and incidence

Using the Delphi consensus method, a systematic review of worldwide published studies on dementia estimated the numbers of people affected by dementia at 24.3 million in 2005. The number of people affected is predicted to double every 20 years, reaching 81.1 million by 2040. Most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040)[46]. The annual incidence of dementia is about 7.5 per 1,000 population[46]. The incidence rates of both AD and dementia increase almost exponentially with age[47], ranging from one every 1,000 person-years among persons aged 60-64 years up to 70 per 1,000 person-years in the 90+ year old subjects[48]. The issue of whether the rates continue to increase even in more advanced ages is still controversial[49]. The apparent decline found in some studies, however, is possibly due to survival effects or diverse response rates in these very old age groups[50]. Dementia incidence is similar in all continents and different regions of the world, even if a greater variability is observed among the oldest-old. Slight lower

rates detected in the North America in comparison with those in Europe are likely to be due to different study designs and ascertainment procedures[49].

1.2.4 Risk factors

The risk of dementia in late-life is considered to be a result of complex interactions of genetic susceptibility, biological factors, and environmental exposures experienced over the whole lifespan[12,51,52]. The description of risk and protective factors for dementia according to a life-course approach is especially useful to better understand the complexity of dementia syndromes and underlying diseases. For example, a condition at midlife that represents a risk factor for dementia might no longer be associated to an increased risk of dementia when the same factor occurs in late-life. The same factor may even have a protective effect. In the following paragraphs, we briefly summarize the current evidence on risk factors for dementia and AD according to the different lifetime periods.

Increasing age is the strongest determinant for all dementias[46], AD[53], and VaD[54]. Therefore, aging-related biological processes could be implicated in the etiopathogenesis of dementia. Further, the strong association of dementia with increasing age can be, at least partially, explained by a lifetime cumulative risk to different exposures. Female sex is often associated with an increased risk of AD, especially at the oldest-old age[48].

Genetic background

A few definite genetic mutations (amyloid precursor protein gene, presenilin 1, and presenilin 2 genes) cause some forms of familial AD, but they account merely for 1-5% of the total AD cases[55]. First-degree relatives of "sporadic" AD patients have a higher lifetime risk of developing AD than the general population or relatives of non-demented subjects. Both genetic and environmental factors contribute to the phenomenon of familial aggregation. Twin studies have shown that heritability of AD is about 58%, whereas other variance may be attributable to non-genetic factors[56]. Many other genes have been examined as possible candidates[57,58], but only the Apolipoprotein E (APOE) is clearly associated with AD. The effect of the APOE ε4

allele on AD risk, however, decreases with increasing age, and among persons 75+ years of age only 15-20% of AD cases are attributable to the APOE ε4 allele[59].

Early life - childhood

Strong evidence supports the hypothesis that illiteracy and low education increase the risk of dementia and AD[60-62]. The cognitive reserve hypothesis might provide an explanation for the protective effect of education, which could stimulate compensatory mechanisms in the brain[63]. In persons with higher cognitive reserve, more cerebral lesions are needed to clinically express dementia. It is otherwise possible that education is an indicator of other early life circumstances or a surrogate of intelligent quotient[64].

Young - Adult life

According to the vascular hypothesis, substantial evidence supports the role of the following factors on the development of all dementias:

- High blood pressure at midlife increases the risk of dementia and AD[65-67].
- Heavy alcohol intake at middle age is associated with an increased risk of late-life dementia, especially among APOE ε4 carriers[68].
- Smoking has been found to increase the risk of AD in some prospective studies[69,70] and in a meta-analysis[71]. The previously reported association of cigarette smoking with low dementia prevalence was probably due to survival bias, as the protective effect was no longer present studying incident cases.
- A strong protective effect of regular physical activity at middle age against dementia has also been reported, especially for APOE ε4 allele carriers[72].
- An association of midlife elevated cholesterol and increased risk of late-life AD disease was reported in some studies[65,73,74].
- High intake of saturated fats may be related to elevated risk of dementia[75] and AD[76-77], whereas high intake of fish and omega-3 polyunsaturated fatty acid may decrease the risk[75]. Fatty acids may affect dementia development through various mechanisms including inflammation. Indeed, some cohort studies found an association of inflammatory markers with dementia[78], and long-term use of nonsteroidal anti-inflammatory drugs was found to be associated with a lower risk of AD[79].

- Inflammation and the metabolic syndrome at mid-life are associated to cognitive decline later in life[80]

- Vascular risk factors often coexist and may act interactively to increase the risk of dementia. Several studies have consistently shown that the risk of AD and dementia increases with increasing number of vascular risk factors[65,81]. Vascular risk scores have been developed to quantify the risk of dementia associated with the clustering of multiple vascular factors[82], but the use of such scores in clinical practice is still limited due to low predictive values.

Adulthood - Late-life

- Evidence from longitudinal studies suggests that a poor social network or social disengagement is related to cognitive decline and dementia[51]. From a lifespan perspective, a decline in social engagement from middle age to late-life was also associated with a double risk of dementia[83]. Besides social engagement, a lower risk of dementia is observed in people participating in mental and physical activities[51]. In the Kungsholmen Project[84], a four-grade composite score to summarize activities according to their mental, social, and physical components was used. Persons with high scores in two or all three components had a substantial reduced risk of dementia.

- A systematic review of longitudinal studies also found that physical activity is related to a lower risk of dementia in six out of nine studies[51]. Regular exercise, even low-intensity activities such as walking, was also associated with a reduced risk of dementia and cognitive decline[85-87]. All these associations may be explained by the cognitive reserve hypothesis[88].

- The relevance of diet in cognitive aging is still controversial. Some longitudinal studies have shown a decreased risk of AD related to increasing dietary or supplementary intake of antioxidative vitamins E and C[89].

- Adherence to 'Mediterranean diet' (higher intake of fish, fruits, and vegetables rich in antioxidants) was associated with a reduced risk of AD independent of vascular pathways[89]. Clinical trials of vitamin E supplementation, however, failed to show any effect on cognitive decline[90]. A systematic review of randomized

trials found no effect of folate, vitamin B_6 or B_{12} supplementation on cognition, although folate plus vitamin B_{12} could reduce serum homocysteine[91]. Indeed, high serum homocysteine is associated with an increased risk of dementia, as reported in some cohort studies[92], but clinical trials did not consistently support the possible effect of lowering homocysteine by B vitamin intake on cognitive performance[93,94].

- The vascular hypothesis is supported by several investigations examining vascular risk factors in late-life including peripheral arterial disease, diffuse atherosclerosis, multiple cerebral infarcts, recurrent and strategic strokes, silent stroke, and white matter lesions detected on neuroimaging[95-97].
- Cerebrovascular lesions may interact with neurodegenerative lesions to produce the dementia syndrome in individuals who do not have sufficient neurodegenerative damage to clinically express dementia[98].
- Other hypotheses suggest a direct role in neurodegeneration [99,100] of vascular factors. For example, some longitudinal studies have detected not only an increased risk of both vascular and degenerative dementias in persons with diabetes[101-104], but also in persons with borderline diabetes[105], suggesting a direct effect of hyperglycemia or hyperinsulinemia on the Alzheimer-type pathology[106].
- Finally, according to the hypoperfusion hypothesis, very low blood pressure, rather than hypertension, is associated with dementia and AD risk among very old people[107]. This inverse association is not an exception in the dementia literature since the relationship between different vascular risk factors (e.g., blood pressure and total cholesterol) and dementia is age-dependent. It is also possible that low blood pressure may be a sign of impending illness rather than a risk factor. However, as studies with more than six years of follow-up confirm such an association, late-life low blood pressure and cerebral hypoperfusion[108] seem to play a causal role in the development of dementia[109]. In line with the hypoperfusion hypothesis, heart failure is also independently related to an increased risk of dementia. In the Kungsholmen Project, for example, heart failure was associated with a more than 80% increased risk of dementia and AD, but proper use of antihypertensive drugs might partially counteract the increased

risk[110]. The association between anemia and dementia might be explained by the hypoperfusion hypothesis too.

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1.2.5 Focus on anemia

Anemia can be most accurately defined as a reduction in the circulating red blood cells (RBC) mass. However, due to the difficulties in measuring cell mass it is more practical to define anemia in terms of reduced hemoglobin concentration[111]. Anemia reduces tissue and organ oxygenation that is manifested by fatigue, light-headedness, palpitations, and shortness of breath[112]. Currently, hemoglobin concentration below 12 g/dl for women and 13 g/dl for men are the cut-offs for defining anemia suggested by WHO[113]. These criteria were derived from average hemoglobin levels of adult participants in studies carried out in the sixties all around the world[113-116]. As those studies did not include persons older than 64 years, some concerns have been raised in relation to whether such cut-off points are valid also in older ages[117-118]. Indeed, in the elderly the detrimental effect of low hemoglobin concentration is relevant even above the cut-off set by WHO[117]. For that reason, some authors have proposed to move the anemia threshold to a higher level for the elderly[119,120]. This hypothesis is supported by the fact that the lowest levels of erythropoietin are present at a hemoglobin concentration of 14.3 g/dl, which is higher than the WHO cut-offs[121]. Most of the studies investigating anemia, however, apply the WHO criteria or establish alternative thresholds based on the hemoglobin distribution of the studied population.

Findings in the current literature agree on the fact that anemia prevalence increases with increasing age[122]. A pooled analysis of 45 studies published in the last 30 years estimates that 12% of community dwelling and 47% of nursing home residents have anemia[123]. On average, anemia occurs in four out of ten home dwelling elderly persons[124]. Anemia is a predictor of poor medical outcomes[120] as it is related to adverse health events[125] and is an independent risk factor for all-cause mortality[126]. In addition, anemia has been shown to influence quality of life[127] and physical performance including both lower extremity functions[128] and muscle strength[129].

Anemia and cognitive functioning

A search in PubMed was conducted to identify publications on elderly subjects describing the relationship between anemia and cognitive functioning. Search terms included: "Anemia/Anemia" OR "haemoglobin/hemoglobin" AND "dementia" OR "Alzheimer disease" OR "cognitive impairment". Limits were: human subjects, English language, and age 65+, 1980- April 2009. The search was supplemented by the revision of all relevant papers identified through a manual search of reference lists in all the retrieved and review articles previously found. This search strategy detected 199 articles (18 review articles were excluded *a priori*). After reading the titles and, in some cases the abstracts, most of the articles were rejected because they did not have a population-based design and/or because they were carried out in specific population such as persons with heart or renal failure, or cancer patients. None of the studies retrieved assessed the relationship between anemia and cognitive impairment, although some publications investigated the relationship between low hemoglobin concentration and performance on cognitive tests. Only three population-based studies had examined the relation between anemia and dementia or AD, with inconsistent results (Table 3).

Some issues need to be discussed. The first concern regards the time gap between assessments of anemia and outcome. Since anemia might be a clinical feature accompanying dementia syndromes, studies with a longer follow-up than those currently available in literature are needed to infer a causal relationship between anemia and dementia. The second concern addresses the disagreement about the definition of anemia criteria in the elderly. In hospitalized Italian elderly, for example, using alternative cut-offs to define anemia, a dose-response relationship with cognitive functioning has been detected[130]. In addition, a recent study[131] showed that both low and high hemoglobin concentration is associated with poor cognitive performance in a number of cognitive tests. If the association between anemia and dementia risk follows a "U–shape", it is possible that studies employing hemoglobin concentration as a continuous variable would miss or detect only a milder association.

In summary, there is limited evidence that anemia increases the risk of dementia, whereas the detrimental effect of low hemoglobin concentration on cognitive functioning is supported by stronger evidence[132-133].

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Table 3. Main population-based studies investigating the relationship between anemia and dementia.

Author Country	Type of study Population	Main outcome (Diagnostic criteria)	Exposure definition	Confounders	Results
Beard *et al,* 1997 Olmsted County, Mayo Clinic, USA (134)	Retrospective: 302 incident AD cases with matched controls	AD identified from Mayo Clinic linkage system (similar to DSM criteria)	Hb level from one year before dementia onset WHO criteria	Age, gender	Anemia increases risk of AD OR=1.9 (1.2-3.0) (All) OR=1.8 (0.8-4.4) (Men) OR=2.0 (1.1-3.5) (Women)
	Cohort study 618 people (65+) Follow-up: 5.1years	Medical records reviewed by nurses and confirmed by authors	A value below WHO criteria between 1985 & 1989	Smoking, age, serum creatinine and albumin plasmatic concentrations	No association between anemia and AD SIR=0.98 (0.67-1.37) (All) SIR=1.49 (0.79-2.56) (Men) SIR=0.79 (0.49-1.23) (Women)
Milward *et al,* 1999 Australia (135)	Cross-sectional Mean age 84.9±3.7	Probable AD (NINCDS-ADRDA) VaD (DSM-IV)	Hemoglobin measured within 14±5 months after medical assessment WHO criteria	Unadjusted	43.5% of VaD vs 17.1% of controls were anemic (p=0.005)
Pandav *et al*, 2004 Rural India (136)	Cohort study 605 participants aged 55 years+	Dementia (DSM-III-R) AD (NINCDS-ADRDA)	Hb continuous WHO criteria: Hb <130 (men), <120 (women) g/L	Age, gender, literacy, Hb X sex interaction term	Hb continuous: OR=0.7 (0.5-0.9) (Men) OR=0.8 (0.5-1.4) (Women) WHO criteria : OR=1.8 (0.8-4.1) (All)

Hb: hemoglobin concentration; OR: Odds Ratio; SIR: Standardized Index Ratio; WHO: World Health Organization; DSM: Diagnostic Statistic Manual

1.2.6 Focus on Body Mass Index

The Body Mass Index (BMI), defined as weight and height squared (Kg/m^2), is one of the most widely used measures of body mass and adiposity. It has several advantages together with specific limitations especially concerning its use in elderly populations. Indeed, beyond age 70, longitudinal studies showed an age-related decline in body mass and body fat[137-139]. A physiological loss of lean body mass - sarcopenia[140] - occurs with aging and seems to be even more pronounced than the loss of total mass[141]. It is intuitive that BMI cannot differentiate between fat and lean mass[142]. Other adiposity indices should be combined with BMI to provide a more realistic overview of elderly body composition. Nevertheless, BMI is largely used especially in epidemiological studies because it is easily measured and costless.

Some concerns are also raised by the used cut-offs for under-, normal-, over-weight, and obesity, which should take into account the effect of aging on BMI. Finally, since the association between BMI and mortality is "U-shaped", it is likely that the effect of BMI on other health outcomes is also nonlinear. This means that both low and high BMI are related to an increased risk of negative health events. Finally, according to a life-course approach to health epidemiology[143], it is also possible that the associations detected at middle age are reversed in late-life.

BMI and cognitive functioning

A Medline search in PubMed was implemented to identify publications on older persons describing the relationship between BMI and dementia. Search terms included: "Body Mass Index/BMI" OR "body weight" OR "adiposity" AND "dementia" OR "Alzheimer disease". Limits were: human subjects, English language, and age 65+, 1980- April 2009). After exclusion of 15 review articles and one meta-analysis, 187 publications were left. After reading the titles and the abstract, 34 articles of potential interest were found. Of these, 16 articles with a population-based design were examined. The main characteristics of those studies are reported in Table 4 and a summary of the findings in Figure 4.

Studies were different in terms of age at entry and length of follow-up (risk period). Out of seven studies examining midlife BMI, four[65,148,152,158] observed an increased risk of dementia and one[147] demonstrated a "J-shape" relationship. One study[141] found that

men, but not women, who subsequently developed dementia had a higher mean baseline BMI and, finally, one study did not detect baseline differences in BMI between persons who developed and who did not develop dementia at follow-up[149]. Out of seven studies with late-life BMI assessment, two studies[145,151] showed that high BMI was associated to an increased risk of dementia. In contrast, two studies[146,158] reported a relation between low BMI and higher dementia risk, consistent with other reports of a decreasing dementia risk with increasing BMI[150,153,155,157]. These paradoxal findings are more easily understandable considering BMI changes from midlife and late-life[149,158]. In the Honolulu-Asia Aging Study (HAAS)[149] an age- and education-adjusted weight loss was observed over 32 years of follow-up in the whole cohort. During the last six years of follow-up, however, weight loss was two-fold higher in persons who subsequently developed dementia compared to persons who did not. Weight loss has been suggested to be a sign of incipient dementia.

Figure 4. Number of studies in midlife and late-life reporting an association between BMI and dementia.

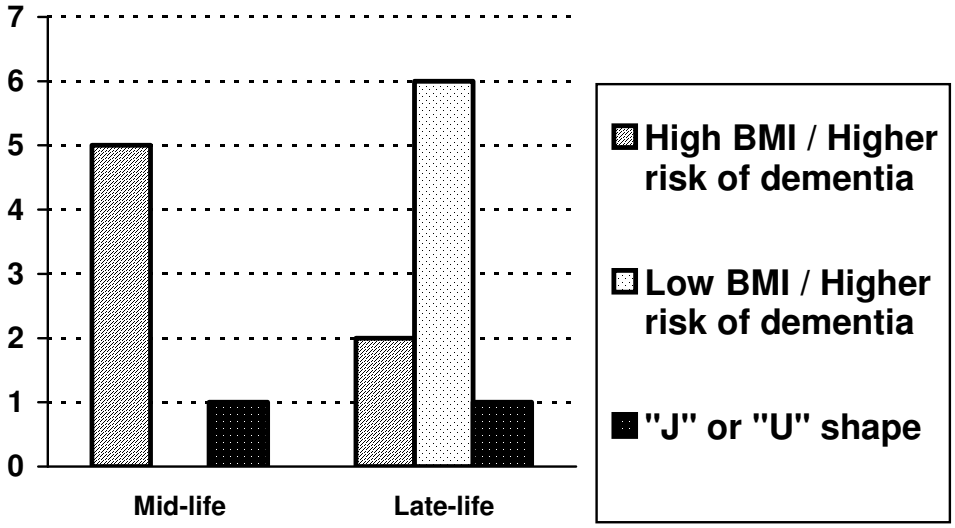


Table 4. Main population-based studies investigating the association between BMI (kg/m^2) and dementia / AD.

Author Year Country	Type of study Population Follow up	Main outcome (Diagnostic criteria)	Exposure definition	Confounders	Results
Barrett-Connor *et al*, 1996 (144) Rancho Bernardo Study, USA	50–79 years Follow-up: 20 years	AD (NINCDS-ADRDA)	Mean BMI=25.0 kg/m^2 BMI continuous	Age, education, weight	Mean baseline body weight higher in those who developed AD (men only) Greater decline in body weight (≥ 5 kg) in those who develop dementia
Gustafson *et al*, 2003 (145) H70, Sweden	70 years Follow-up: 18 years	AD (DSM-III)	25.8 ±3.8 kg/m^2 BMI continuous	Diastolic blood pressure, cardiovascular disease, smoking, socio-economic status, treatment for hypertension	Risk of dementia for each unit increase in BMI: RR = 1.13 (1.04–1.24) (at age 70 y) RR = 1.13 (1.04–1.24) (at age 75 y) RR = 1.15 (1.05–1.26) (at age 79 y)
Nourhashemi *et al,* 2003 (146) PAQUID Study, France	≥ 65 years Follow-up: 8 years	Dementia (DSM-III-R)	Mean BMI=24.6 ±3.9 kg/m^2 BMI<21 BMI=21-22 BMI=23-26 (ref.) BMI≥27	Sex, age, age*sex interaction, education, alcohol and smoking	No association for BMI 21-22, neither for BMI≥27 BMI<21: RR=1.48 (1.08–2.04), but the association was no longer present after exclusion of persons developing dementia within 5 years

Rosengren *et al,* 2005 (147) Primary Prevention Study, Sweden	47–55 years Men Follow-up: 28 years	Dementia (Hospital discharge diagnoses: ICD-8, ICD-9, ICD-10)	Mean BMI=25.5 ±3.3 kg/m^2 BMI=20-22.5 (ref)	Age, smoking, physical activity, occupational class, baseline diabetes, systolic blood pressure, serum cholesterol, stroke	BMI<20: RR=2.43 (1.10-5.29) BMI 27.5-30: RR=1.72 (1.03-2.88) BMI≥30: RR=1.98 (1.10-3.56)
Whitmer *et al,* 2005 (65) Kaiser Permanente, USA	40–45 years Follow-up: 27 years	Dementia (ICD-9)	BMI≥30 = 10%, BMI≥25-29.9 =36% BMI≥18.5-24.9 =53% (ref.) BMI<18.5 =1.3%	Hypertension, diabetes, cholesterol. In late-life (stroke, hypertension, diabetes, ischemic heart disease and hyperlipidemia)	BMI>30: RR=1.74 (1.34–2.26) BMI=25-29.9: RR=1.35 (1.14–1.60) BMI<18.5: RR=1.24 (0.70–2.21)
Kivipelto *et al*, 2005 (148) CAIDE, Finland	51 years Follow-up: 21 years	Dementia (DSM-IV) AD (NINCDS-ADRDA)	26.6 ±3.7 kg/m^2 BMI≤25 (reference)	Systolic and diastolic blood pressure, total cholesterol, smoking, APOE, diabetes, MI, stroke	BMI≥30: OR=2.44 (1.18–5.06) BMI=25-29.9: RR=1.05 (0.54–2.08) (age, sex, education adjusted) BMI≥30: OR=1.88 (0.76–4.63) BMI=25-29.9: RR=0.88 (0.47–2.15) (full-adjusted)
Stewart *et al,* 2005 (149) HAAS, USA	45–66 years Japanese American men Follow-up: 32 years	Dementia (DSM-III-R criteria) AD (NINCDS-ADRDA)	Mean BMI=23.9 ±2.7 kg/m^2 BMI continuous	Age, education, vascular factors, impaired physical functions, depression	No effect of baseline BMI Last 6 years of follow-up: weight loss two-fold higher for incident dementia cases compared to non-demented

Buchman *et al,* 2005 (150) Religious Order Study, USA	77.1 years Follow-up: mean 5.6 years	AD (NINCDS-ADRDA)	Mean BMI=27.4 ± 5.4 kg/m^2 1 unit of decline in BMI = about 10% of baseline BMI	CHD, stroke, diabetes, hypertension, thyroid diseases, head injury, cancer, smoking	RR=0.94 (0.91–0.98) per 1 unit decline in BMI RR=0.73 (0.63–0.85) by 1 unit less BMI Results confirmed when excluding those developing AD during first 4 years
Hayden *et al,* 2006 (151) Cache County study of Memory in Aging, USA	≥ 65 years Follow-up: 2–5 (mean 3.2) years	Dementia (DSM-III-R); AD (NINCDS-ADRDA); VaD: (NINDS-AIREN)	BMI ≥30 vs <30 kg/m^2	Sex, age, education, APOE, hypertension, high cholesterol, diabetes, stroke, cardiovascular diseases	All dementias: BMI≥30: RR=1.76 (1.03–2.88) AD: BMI≥30: RR=1.93 (1.05–3.36)
Whitmer *et al,* 2007 (152) Kaiser Permanente, USA	40–45 years Follow-up: 21–42 years	Dementia (ICD-9 criteria)	BMI ≥ 30 =10% BMI 25–29 = 36% BMI 18.5–24.9 = (55%)(ref.) BMI<18.5 = (1.3%)	Sex, age, education, and vascular factors	AD: BMI≥30: RR=3.10 (2.19–4.38) BMI=25–29: RR=2.09 (1.69–2.60) Vascular dementia: BMI≥30: RR=5.01 (2.98–8.43) BMI=25–29: RR=1.95 (1.29–2.96)
Luchsinger *et al,* 2007 (153) Washington Heights-Inwood community of New York City, USA	> 65 years Follow-up: 5 years	Dementia (DSM-IV) AD (NINCDS-ADRDA) VaD (after 3 months from a stroke)	Mean BMI=26.68 ±5.1 kg/m^2 BMI quartiles: I < 23.4 (ref) II = 23.4-26.2 III = 26.3–29.6 IV ≥ 29.7	Age, sex, education, ethnic group, APOE	All dementias: III quartile: RR=0.6 (0.40–0.90) U-shaped relationship between BMI and all dementias in those aged < 76 years Weight loss: Dementia: RR=1.9 (1.20–2.90) VaD: RR=4.9 (1.90–12.90)

Chiang *et al*, 2007 (154) MRMD & CSP Studies, Taiwan	≥ 30 years Follow-up: 8–20 years Case-control	Dementia (ICD-9 and DSM-IV)	BMI<20.5 BMI=20.5-22.9 (reference) BMI=23.0-25.4 BMI≥25.5	Age, sex, education, other vascular factors	J-shaped relationship between BMI and dementia: BMI<20.5: RR=1.84 (1.02-3.33) BMI=23.0-25.4: RR=1.87 (1.08-3.23) BMI≥25.5: RR=2.44 (1.39-4.28)
Knopman *et al,* 2007 (155) Rochester Epidemiology Project, USA	> 70 years Cases-controls Follow-up: 21–30 years	Dementia (DSM-IV criteria)	Weight in quartiles: IV quartile (ref)	Not reported	Odds of dementia for I quartile: All: OR=3.59 (1.51-8.55) Women: OR=3.42 (1.66-7.04) Men: OR=0.59 (0.17-1.98)
Dahl *et al*, 2008 (156) Finland	62-92 years Follow-up: 8 years	Dementia (DSM-IV)	BMI continuous	Sex, age, education, cardiovascular disease, smoking, alcohol	1 unit of increase in BMI: All: HR=0.92 (0.87-0.97) Men: HR=0.90 (0.84-0.96) Women: HR=0.95 (0.84-1.07)
West *et al*, 2009 (157) SALSA, USA	60-101 years Follow-up: > 8 years	Dementia (DSM-III-R and NINCDS-ADRDA) CIND (Clinically significant impairment in one or more cognitive domains)	BMI<25 (ref) BMI=25-29.9 BMI≥30 Waist circumference (WC) tertiles: I tertile (reference)	Age, sex, education, height BMI / WC	CIND+dementia: BMI=25-29.9: HR=0.52 (0.30-0.91) BMI≥30 HR=0.39 (0.20-0.78) WC II tertile: HR=1.8 (1.1–3.1) WC III tertile HR=1.9 (0.9–3.8) Result confirmed after exclusion of cases detected at first two follow-ups

Fitzpatrick *et al*, 2009 (158), CHS, USA	≥ 65years Mean age 74.7 Follow-up: 5.4 years	AD (NINCDS-ADRDA) VaD (State of California AD Diagnostic and Treatment Centers Criteria)	Self report at age 50, measured at age 65 BMI<20 BMI=20-25 (ref.) BMI=25-30 BMI>30	Model 1 (Age, sex, education) Model 2 (Sex, age, education, C-reactive protein level, interleukin 6 level, hypertension status, diabetes, coronary heart disease, total cholesterol level, ankle-arm index, smoking status, kilocalories expended per week, and APOE ε4 allele)	All dementias Midlife / model 1: BMI<20: HR=1.09 (0.64-1.85) BMI=25-30: HR=1.10 (0.90-1.35) BMI>30: HR=1.39 (1.03-1.87) Midlife / model 2: BMI<20: HR=1.20 (0.66-2.17) BMI=25-30: HR=1.01 (0.83-1.35) BMI>30: HR=1.36 (0.94-1.95) Late-life / model 1: BMI<20: HR=1.62 (1.10-2.39) BMI=25-30: HR=0.93 (0.76-1.15) BMI>30: HR=0.81 (0.61-1.07) Late-life / model 2: BMI<20: HR=1.62 (1.02-2.64) BMI=25-30: HR=0.92 (0.72-1.18) BMI>30: HR=0.63 (0.44-0.91)

H70= Gerontological and Geriatric Population Studies;
CAIDE: Cardiovascular Risk Factors, Aging, and Dementia,
PAQUID: Personnes Agees Quid, HAAS: Honolulu Asia Aging Study,
MRMD: Multiple Risk Factors for Major Diseases and CSP Cancer Screening Program Studies, Taiwan,
SALSA: Sacramento Area Latino Study on Aging,
CHS: Cardiovascular Health Study
MI=myocardial infarct; CHD=coronary heart disease

1.3 COGNITIVE DISORDERS OTHER THAN DEMENTIA

For many years, epidemiological research has devoted much attention to the dementia syndrome, as it is a highly disabling condition associated with many adverse outcomes. More recently, researchers have moved their focus to cognitive impairment without dementia. Indeed, many elderly people suffer from cognitive deficits although not severe enough to fulfill all criteria for a dementia diagnosis. Since activities of daily living are usually preserved, this condition appears to be less damaging than dementia. However, cognitively impaired non-demented persons are frequently worried about developing dementia and experience personal distress, which increases their need for attention and care.

1.3.1 Definitions and criteria

"Benign Senescent Forgetfulness"[159] was one of the first terms proposed to label cognitive symptoms with positive prognostic implications and to distinguish them from malignant ones. Then, different descriptive labels were suggested, such as "Age Associated Memory Impairment"[160], "Late-life Forgetfulness"[161], and "Age Associated Cognitive Decline"[162]. In addition, structured interviews or cognitive rating scales were introduced to define impairment. Among others, the term "very mild cognitive decline" was employed to identify persons with a score of 2 on the Global Deterioration Scale (GDS)[163], or the label "questionable dementia" was applied to subjects with Clinical Dementia Rating Scale (CDR) equal to 0.5[164].

Nowadays, Mild Cognitive Impairment (MCI) is often used in clinical settings[165]. According to the original proposal from Petersen et al[166], MCI refers to persons with preserved general cognitive functioning and memory loss (amnestic MCI). Later on, new subtypes, covering a broader range of cognitive disturbances, were added[167]. Originally, the MCI definition was created with the purpose of early identification of AD. This idea developed from the clinical observation that cognitive deficits are detectable up to ten years before AD diagnosis.

Conversely, Cognitive Impairment, No Dementia (CIND)[168-171] is one of the most frequently used definitions for cognitive impairment in population-based studies. In the

general population, CIND identifies non-demented persons with signs suggestive of global cognitive impairment, which are often operationalized as significant deficits in the Mini-Mental State Examination (MMSE)[172]. In other words, CIND is a broad definition suggestive of a cognitive syndrome of insufficient magnitude to warrant a diagnosis of dementia[173].

1.3.2 Cognitive Impairment, No Dementia

Different operational criteria for CIND have been suggested. Cases are frequently identified using the MMSE score with cut-offs of one[174] or two[175] standard deviations (SD) below the mean score derived from non-demented populations. Other studies defined CIND using both MMSE and other neuropsychological tests[176], or including persons with reported cognitive disturbances who did not fulfill all criteria for dementia[177]. As a consequence of the lack of uniformity in CIND definitions, the comparison of different studies on CIND is especially difficult. The term of CIND has been investigated in many countries, including Canada (CSHA[169], ACCORD[177]), Sweden (Kungsholmen Project[171]), Italy (Faenza Project[175], ILSA[174]) and Australia[176]. Unfortunately, none of the definitions used have a sufficient predictivity for future development of dementia at the community level.

Prevalence and incidence

Although figures of CIND prevalence and incidence vary depending on diagnostic criteria, CIND is a common condition in late-life and occurs even more frequently than dementia in younger elderly persons. In the Faenza Project, for example, the prevalence of CIND among persons aged 61-69 is 3-5%, whereas dementia occurs in 1-2% of persons. At age 80+ CIND occurs in 8-9% of people compared to a prevalence of dementia ranging from 15% to 50%[175]. Annual incidence rates vary from 15 per 1,000 among persons aged 75-79 years to 98 per 1,000 among nonagenarians[178]. Prevalence estimates are affected by high variability among different studies, and further population-based studies are needed to reach a more precise estimate of cognitive impairment. In addition, incidence studies have been sparse and only one has taken into account the possible underestimation of incidence estimates due to the effect of death

during follow-up. When incidence rates were corrected for attrition due to death, the observed incidence rates for CIND changed from 33.8 to 42.1[171].

Risk and protective factors

Few epidemiological studies have addressed protective and risk factors for CIND. High education seems to exert a protective effect against CIND[179] and CIND development[180], consistent with the cognitive reserve hypothesis. A risk effect of the APOE genotype in CIND has been documented by two studies[180,181] and it is not surprising that CIND shares a genetic background with dementia. From a life-long perspective, as for dementia, the longitudinal association between late-life hypertension and CIND is controversial[180], whereas midlife hypertension[180] increases the risk of cognitive impairment at older ages. Three long-term prospective studies showed that midlife elevated serum cholesterol[181], white matter hyperintensities[182], and alcohol drinking[68] were associated with an increased risk of cognitive impairment later in life. Cohort studies on persons aged 60+, with shorter follow-up durations, have identified vascular[183] and cerebrovascular diseases[184], as well as racial and constitutional factors[185] as risk factors for CIND. In the Kungsholmen Project, frailty-related factors such as history of hip fracture and high consumption of drugs, as well as neuropsychiatric conditions like history of psychoses and depressed mood, have been associated with incident CIND[186] independently of future development of dementia.

Natural History

Recently, most of the interest in psychogeriatric research has been focused on CIND evolution. Within the Kungsholmen Project, it has been estimated that two out of three persons affected by CIND would encounter an unfavorable outcome: 34% would develop dementia and 35% would die; 36% of CIND cases, however, would remain stable or even improve[187]. The detection of factors possibly associated with progression to dementia or AD, as well as the recognition of predictors in the earliest phase, is crucial. The predictive validity of cognitive impairment syndromes in identifying future dementia or AD cases is improved in the presence of anxiety and mood-related

depressive symptoms (dysphoria, suicidal ideation, etc), which might be related to some of the underlying neuropathlogical mechanisms of neurodegeneration.

However, research on cognitive impairment faces some challenging issues. First, cognitive decline is also present as a function of the normal aging process; second, several conditions other than AD may lead to cognitive disturbances in the elderly; and third, dementia-free patients with cognitive impairment observed in specialized clinical settings are different from cognitively impaired persons detected in the general population. These issues may partly explain the uncertainty of information about the epidemiology of cognitive impairment. Whether a categorical or a continuum model should be applied to the understanding of the aging process is still under debate. According to a categorical model, the aging process is either pathological or not. If this is the case, both quantitative and qualitative differences would distinguish normal aging and dementia. Conversely, hypothesizing a continuum, only quantitative differences would distinguish between different aging processes[188]. Not everyone will progress through all stages of this continuum, and the possibility of "successful aging" would also be possible.

2 AIMS

2.1 GENERAL AIM

The general aim of this doctoral thesis is to investigate the effect of somatic disorders on brain aging and dementia development under the hypothesis that several medical conditions have an unfavorable role on cognitive functioning.

2.2 SPECIFIC AIMS

The specific aims addressed in the four studies included in the thesis are as follows:

1. To examine the association between anemia and dementia taking into account the possible confounding effect of chronic diseases, inflammation, and nutritional status (*Study I*).

2. To explore the association between body weight and weight changes in relation to the occurrence of dementia during different time periods (*Study II*).

3. To investigate the independent and combined role of social factors, life habits, and medical conditions in CIND (*Study III*).

4. To investigate the relation between perceived cognitive decline and comorbidity in cognitively intact elderly, under the hypothesis that co-occurrence of mental and somatic diseases may account for the discrepancy between cognitive performance and perceived cognitive functioning (*Study IV*).

3 METHODS

The present thesis is based on data from two population-based studies: the Swedish Kungsholmen Project and the Italian Faenza Project.

3.1 THE KUNGSHOLMEN PROJECT (STUDIES I AND II)

3.1.1 Study Population

Kungsholmen is a district in central Stockholm. All inhabitants aged 75 and above who were living in this area on October 1st 1987 (prevalence day) were invited to take part in the survey. Out of 2,368 eligible subjects, 1,810 agreed to participate. The baseline survey was carried out between 1987 and 1989; then four follow-up waves were carried out, on average every three years. Study I uses baseline data in relation to three-year incident dementia. Study II investigates baseline data in relation to three-, six-, and nine-year incident dementia.

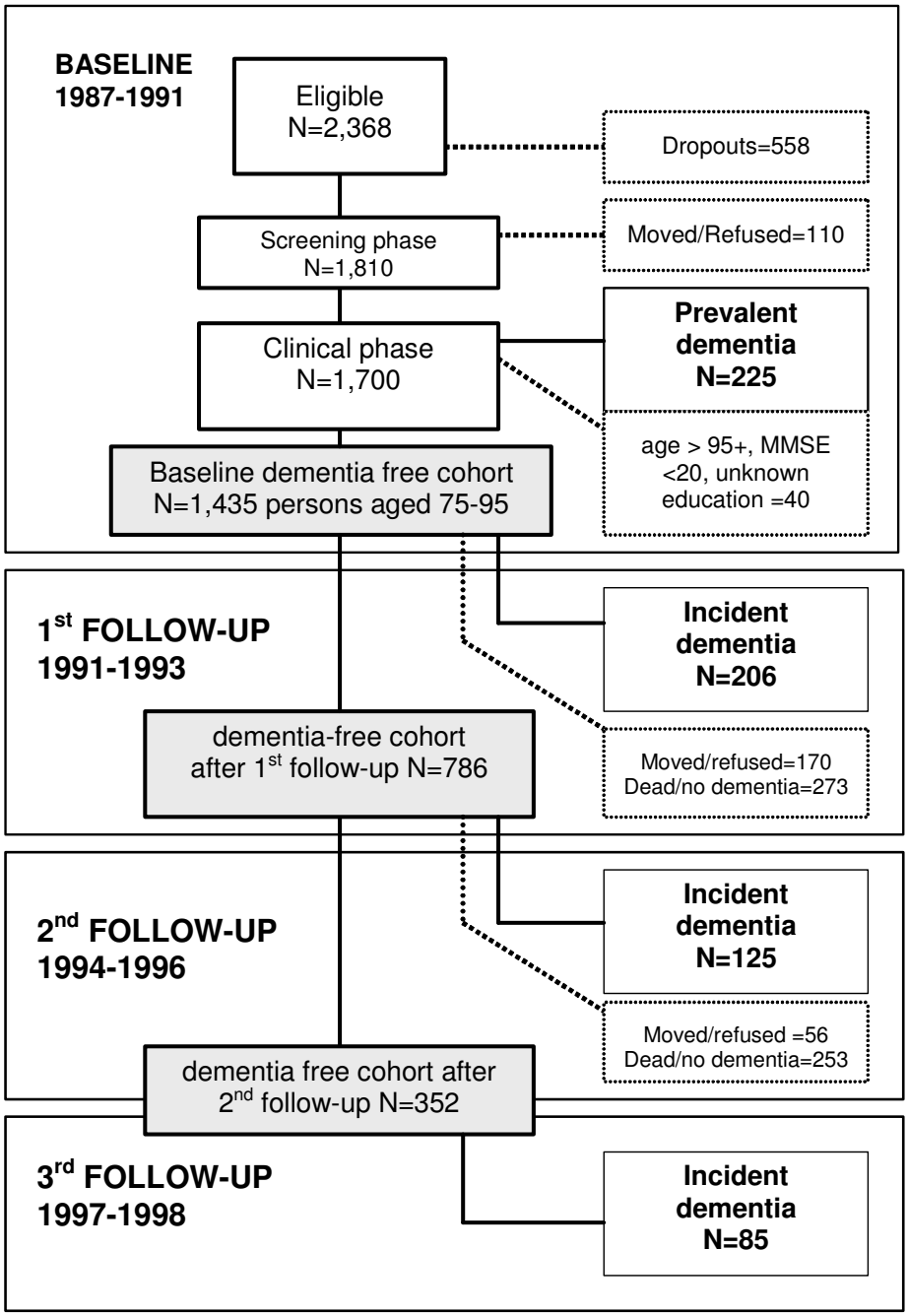
3.1.2 Assessment

At baseline, a two-step assessment consisting of a screening- and a clinical-phase was implemented. First, a structured interview was administered by trained nurses together with a cognitive screening test, the MMSE. Second, all participants who screened positive (MMSE score $\leq$23) and an age- and gender-matched sample of persons scoring above 23 were asked to undergo an extensive physical, neurological, and psychiatric examination conducted by trained physicians, and a detailed neuropsychological assessment by psychologists. At every follow-up wave, all participants underwent a clinical and psychological assessment using similar protocols as in the baseline clinical phase.

Figure 5 shows the study design of the Kungsholmen Project, reporting the number of participants, refusals, and deaths together with dementia-free cohort and the incident dementia cases for each follow-up. Out of 1,810 subjects who underwent the screening phase, 110 persons either refused or died before the clinical phase. After the clinical assessment, 225 prevalent cases of dementia were detected. Among the remaining

dementia-free individuals (n=1,475), we further excluded 40 persons because of age over 95 (n=11) or unknown level of education (n=9), or MMSE score <20 (n=20). Thus, the present thesis is based on a study population of 1,435 dementia-free subjects (75% women).

Figure 5. Study design of the Kungsholmen Project.



3.1.3 Data collection

Demographics

Information on age, gender, and education (maximum years of formal schooling) was collected by structured interview. On the basis of the education pattern present in Sweden when the cohort members were younger, participants were classified as low educated if they had attended less than eight years of schooling, and high educated when formal education was longer than seven years of schooling[189].

Comorbidities

Information concerning medical illnesses was retrieved from the Computerized Stockholm Impatient Registry System. The register records all discharge diagnoses (principal plus five additional diagnoses) for hospitalizations in the Stockholm area since 1969. Until 1986 all diagnoses were made according to the International Classification of Disease 8th Edition (ICD-8) [190], afterwards the 9th Edition (ICD-9) [191] was used. The specific codes used to identify diseases of interest are shown in Table 5.

Laboratory data

Blood samples taken at baseline and follow-up were used to measure different biochemical parameters including hemoglobin and B12 vitamin, folic acid, creatinine, and albumin. According to the WHO definition (3), anemia was defined as a hemoglobin concentration below 120 (men) or 130 (women) g/L. APOE allelic status was determined following a standardized procedure from DNA preparation.

Body Mass Index (BMI)

During the physical examination, weight and height were measured with the same standardized instruments with subjects wearing light clothes and no shoes. BMI was computed as the ratio of weight in kilograms to the square of height in meters (weight/(height)^2; kg/m^2). Based on standard cut-offs[192], participants were categorized as obese (BMI ≥30), overweight (BMI between 25 and 30) and normo-weight (BMI between 20 and 25, reference category). The threshold for being underweight was set at BMI=20, as only three subjects had BMI under 18.5 (cut-off suggested by WHO for being underweight).

Table 5. ICD codes for the diseases used in the four studies.

	KUNGSHOLMEN PROJECT (STUDY I & II)		FAENZA PROJECT (STUDY III AND IV)
Disease	**ICD-8**	**ICD-9**	**ICD-9**
Hypertension	400-404	401-405	401-405
Diabetes	250	250	250
Cerebrovascular dis.	430-438	430-438	433-434
Heart disease	427-428, 412-413	427-428, 410-414	390-398, 401-429, 440-459
Respiratory diseases	491-493	491-493	465-519
Malignancy		146-208	40-208
Gastrointestinal dis.		530-579	530-579
Parkinson's disease		332, 333	332
Hypothyroidism	243-244	243-244	
Chronic renal failure	582-584	585-586	
Respiratory infections		9-136, 460-491, 511, 513	
Psychiatric diseases		291-311	

3.1.4 Dementia diagnosis

Both at baseline and at each follow-up, participants underwent cognitive testing and clinical evaluation. Thereafter, dementia was diagnosed following DSM-III-R criteria using a validated procedure. First, the examining physician made preliminary diagnoses that were independently reviewed by a specialist. In case of disagreement, a third opinion was asked and the case was re-examined to reach a final diagnosis. Gradual onset, progressive deterioration and no evidence of other specific dementia causes were required for an AD diagnosis. On the contrary, abrupt onset, stepwise deterioration, history of stroke or focal deficits supported a diagnosis of VaD. The diagnostic criteria

were comparable to NINCDS-ADRDA criteria for probable AD, and the NIND-AIREN criteria for possible VaD.

For subjects who died during the follow-up periods, dementia diagnoses were made through thoroughly reviewing medical records and death certificates with the same three-step diagnostic procedure described above.

3.1.5 Ethical considerations

All eligible subjects were sent a personal letter, which explained the nature of the project and the importance of participation, emphasizing that participation was voluntary. Thereafter, all participants were contacted by phone to check their availability, and to book a date for their first visit. After explaining the aims of the project and assuring confidentiality, informed consent was obtained directly from the subject at the screening evaluation. In cases where the subject had severe cognitive impairment, consent was taken from a proxy, usually a next-of-kin or close relative. However, the examination or interview could be interrupted if the participant, in any way, expressed anguish or discomfort, regardless of whether the informed consent had been given by the subjects themselves or by a proxy. All phases of the Kungsholmen Project received approval from the Ethics Committee at the Karolinska lnstitutet, Stockholm, Sweden. All persons working with the Kungsholmen Project database follow the guidelines of the Swedish Council for Research in the Humanities and Social Sciences: the principles of autonomy and integrity, the rule of consent, and the demand for research.

3.2 THE FAENZA PROJECT (STUDIES III AND IV)

3.2.1 Study Population

Faenza is a wealthy municipality in Northern Italy. On 1st December 1991 (prevalence day) all inhabitants >60 years living in Faenza were invited to participate in a community-based study on brain aging and related disorders. Out of 12,743 eligible persons, 4,002 (31.4%) refused the interview, and 811 (6.4%) died before being

assessed, leaving 7,930 persons in the survey. Studies III and IV of this thesis are based on sub-samples derived from the original cohort as described in Figure 6.

3.2.2 Assessment

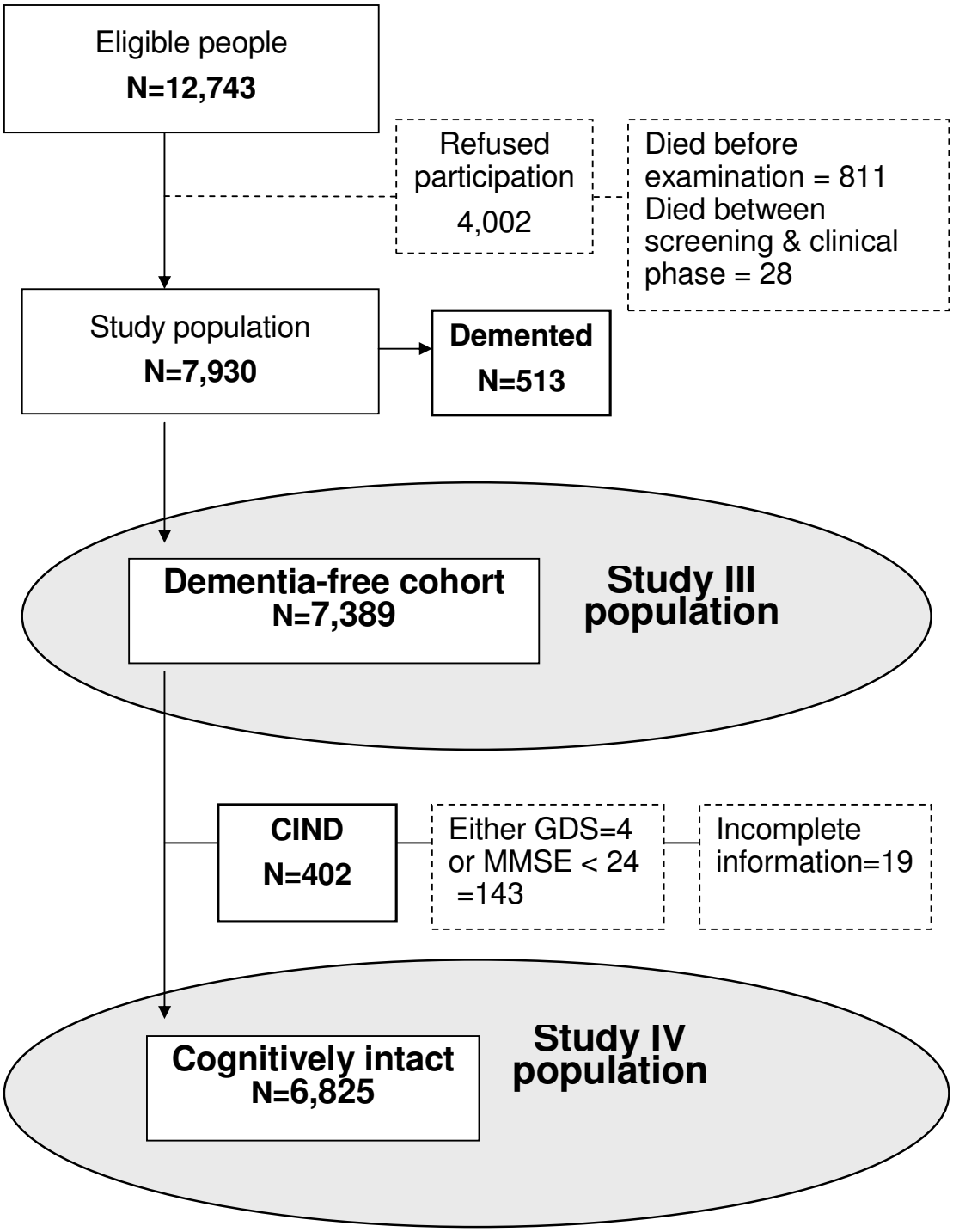
The Faenza Project has a two-phase study design. First, both the MMSE and the GDS were administered as screening instruments. In the second phase, persons with MMSE ≤28 and/or GDS ≥2 were further clinically evaluated by trained physicians in order to diagnose dementia. The ICD-9 was used to classify diseases identified in participants. The specific codes used to identify diseases of interest are shown in Table 5. Socio-demographic information and data concerning lifestyle habits were collected using a semi-structured interview. Mental and somatic comorbidities were assessed during the clinical examination; medical records were reviewed when needed. Further information was obtained directly from the cognitively intact participant and/or from an informant when the subject was cognitively impaired.

Diagnosis of Dementia and (CIND)

Dementia cases were diagnosed according to DSM-III-R criteria, using a standardized procedure. The preliminary diagnoses were made independently by two physicians who clinically examined the participants; a third opinion was requested in case of disagreement.

Cognitive impairment was defined using performance on the MMSE corrected for age and education according to Magni et al[193]. These authors provided normative scores derived from a large non-demented population in Northern Italy according to sixteen adjustment coefficients for four age intervals (every five years from 65 to 89), and four educational levels (0-4, 5-7, 8-12, and 13-17 years of schooling). Coefficients for subjects aged 61-64 and over 89 years were taken from the closest categories. A subject was classified as having cognitive impairment if he/she scored two or more standard deviations lower than the mean of the corrected MMSE score and was free of dementia.

Figure 6. Faenza Project Study design.



3.2.3 Ethical considerations

All eligible subjects were invited to participate by a personal letter explaining the aims of the project, assuring confidentiality and the possibility to interrupt the assessment whenever a participant would need. Thereafter, all subjects were contacted by phone to book a date for the first visit. Informed consent was obtained directly from the person at the first meeting with the staff of the project. In case of severely cognitive impaired persons, consent was taken from a proxy, usually a next-of-kin or a close relative. The Faenza Project received approval from the Ethics Committee of the Local Health Authority of Ravenna Province, Italy. In order to increase the participation rate, all Faenza's General Practitioners were informed of the ongoing project and were asked to support elderly participation. Studies III and IV were also approved by the Ethics Committee at Karolinska Institutet, Stockholm.

3.3 ANALYTICAL STRATEGIES (STUDIES I-IV)

The association between exposures and outcomes were estimated by binary or multinomial regression models in the case of cross-sectional analysis, whereas the estimates of the longitudinal associations were derived from Cox regression models. Dementia onset was assumed to be halfway between the date of assessment and the date of dementia diagnosis. All models were first constructed without any covariates, then each covariate was introduced separately, and then fully adjusted models were developed. When applicable, factors were introduced in the model first as continuous, then as indicator variables. In some analyses variables were also dichotomized and used to check statistical interaction. The covariates introduced in the model were all possible available confounders. A summary of the statistical techniques used in the four papers is reported in Table 7.

Table 7. Summary of the statistical analyses used in the four studies.

Studies	Statistical models	Exposure (definitions)	Outcome (diagnostic criteria)	Follow-up length
Study I	Cox proportional hazard	*Anemia* (WHO criteria; below the 5th or the 25th percentile of hemoglobin distribution)	Dementia/AD (DSM-III-R, NINCDS-ADRDA)	3 years
Study II	Cox proportional hazard	*BMI* (WHO criteria; quartiles) & *weight changes* (reference category changes within 5%)	Dementia/AD (DSM-III-R, NINCDS-ADRDA)	9 years
Study III	Binary logistic regression	*Medical conditions* (stroke, Parkinson disease, depressive symptoms, anxiety syndrome, hypertension cardiovascular disease, diabetes, BMI) & *Social factors* (age, gender, education, marital status, SES, smoking habits, alcohol consumption)	CIND (score ≥2 SD lower than the corrected MMSE mean, obtained by non-demented subjects)	Cross-sectional
Study IV	Binary and multinomial logistic regression	*Multimorbidity* & *specific diseases* (stroke, Parkinson disease, gastrointestinal disease, respiratory disease, malignancy, hypertension, diabetes, cardiovascular disease, depressive symptoms, anxiety symptoms)	GDS decline Poor performance on MMSE Disagreement between GDS and MMSE	Cross-sectional

4 RESULTS

The main characteristics of the dementia-free cohort of the Kungsholmen Project and the Faenza Project are reported in Table 8. Mean age and mean MMSE score were similar between the two populations, whereas education and SES were lower in the Italian cohort.

Table 8. Main features of the Kungsholmen Project and Faenza Project dementia free cohort.

		Kungsholmen Project N=1,435	Faenza Project N=7,389
Female Gender	*n (%)*	1,081 (75%)	4,408 (59.7)
Age	*mean (SD)*	81.3±4.8	71.9 ±7.7
MMSE	*mean (SD)*	26.9 ±1.9	28.0 ±2.6
Education (< 8 years)	*n (%)*	842 (58.6)	6532 (88.4)
SES (Low)	*n (%)*	522 (56)	4582 (66.3)

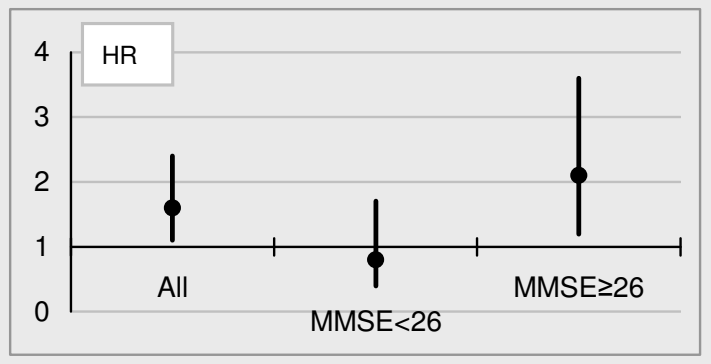
4.1 ANEMIA AND INCIDENT DEMENTIA (STUDY I)

In the baseline dementia-free cohort of the Kungsholmen Project, anemia - defined by WHO criteria –occurred in 15.7% of men and 7.3% of women ($p < 0.01$). Sex-, age-, and education-adjusted Hazard Ratio (HR) and 95% Confidence Intervals (95% CI) for dementia in relation to anemia was 1.6, 95% CI: 1.1-2.3. When baseline MMSE score was included in the model, the association was no longer significant. Therefore, stratified analysis by baseline cognitive performance was implemented (Figure 7).

The analysis on cognitively impaired elderly (MMSE <26; n=296) did not show any statistically significant association whereas among cognitively unimpaired subjects (MMSE ≥26: n=1,139) anemic persons had a twofold higher risk of developing dementia. Supplementary analysis demonstrated that this association persisted also when AD was considered as outcome (HR, 2.1 95% CI: 1.1-4.2).

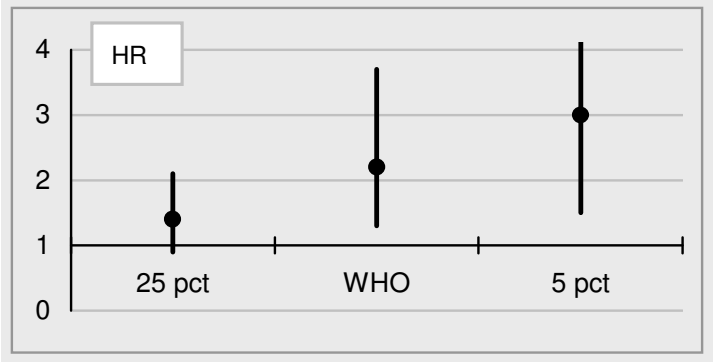
Among cognitively intact persons, the association between anemia and dementia was further explored by using alternative cut-off points to define anemia: the lower the hemoglobin concentration, the higher the probability of dementia (Figure 8).

Figure 7. Hazard ratios (HR) and 95% confidence intervals for dementia due to anemia in different strata of the study population.



Noticeably, persons with hemoglobin below the 25th percentile – which is above the WHO cut-off –still had a higher probability to develop dementia. Further analysis confirmed a risk effect associated to anemia even after multiple adjustment.

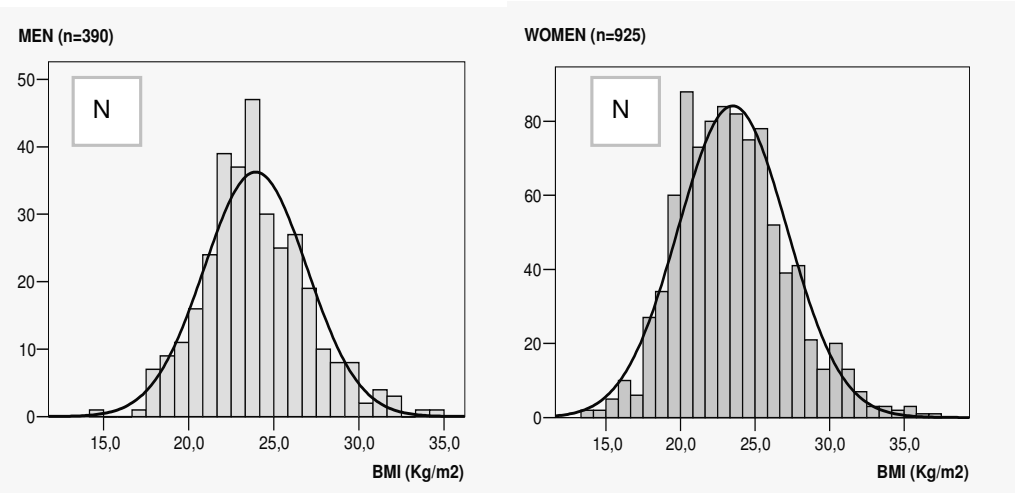
Figure 8. Cognitively intact persons: Hazard ratios (HR) and 95% confidence intervals for dementia according to different cut-offs of anemia (25th and 5th percentiles, and WHO criteria).



4.2 BMI AND INCIDENT DEMENTIA (STUDY II)

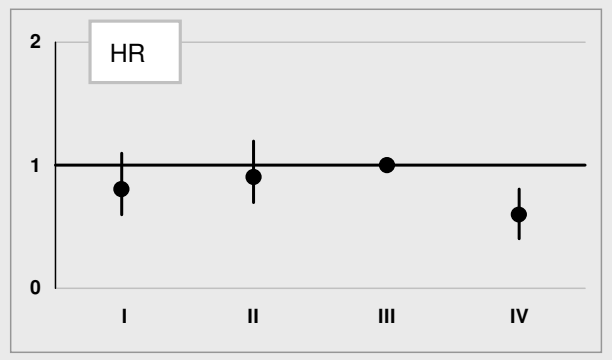
Among the 1,255 non-demented elderly aged 75-95, mean BMI was 23.4 ± 3.5 Kg/m^2. BMI distribution in men and women is reported in Figure 9. Mean BMI was higher in men than in women. The estimates for the association between gender specific BMI quartiles and dementia development are reported in Figure 10.

Figure 9. BMI distribution by gender.



The HR for dementia in persons with BMI higher than 25.6 (IV quartile) compared to persons with BMI between 23.5 and 25.6 was 0.6, 95% CI: 0.4-0.8. Results were confirmed when only AD cases were considered, as well as when analysis was run only among survivors. A similar pattern was observed for both men and women.

Figure 10. Baseline BMI (quartiles) and nine-year incident dementia: Hazard ratios (HR) and 95% confidence intervals.

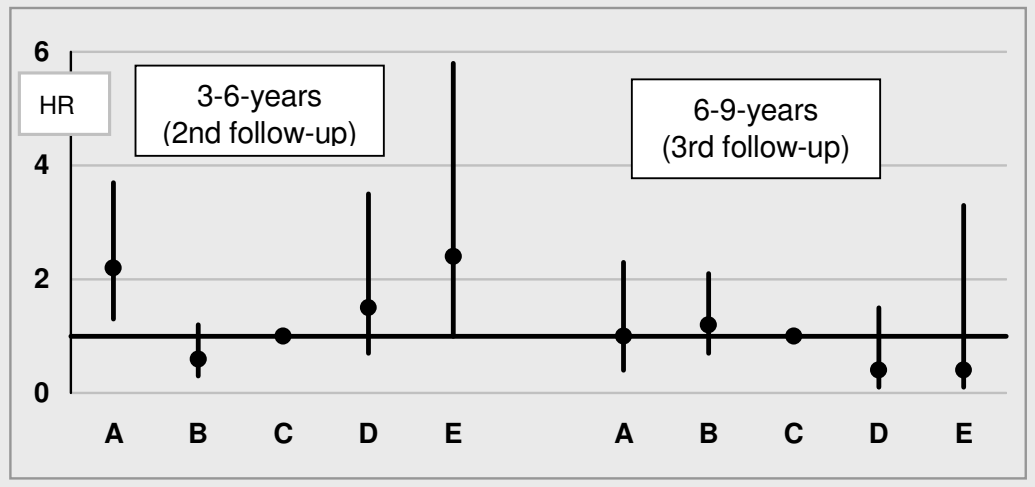


I=<21.2;
II=21.2-23.5;
III=23.4-25.6,
IV>25.6

4.3 WEIGHT LOSS AND INCIDENT DEMENTIA (STUDY II)

In order to verify whether persons with weight changes occurred between baseline and three-year follow-up had a diverse probability of developing dementia, a further analysis was implemented considering persons with no or minimal BMI changes (within 5% of baseline BMI) as reference category. Figure 11 shows the HR for developing dementia during the second and the third follow-up. An unintentional weight loss greater than 10% of baseline BMI was associated with a two-fold higher risk of dementia in the subsequent three years. No associations were detectable when only the last three years were of follow-up were considered.

Figure 11. Risk of developing dementia according to BMI changes between baseline and three-year follow-up: Hazard ratios (HR) and 95% confidence intervals.



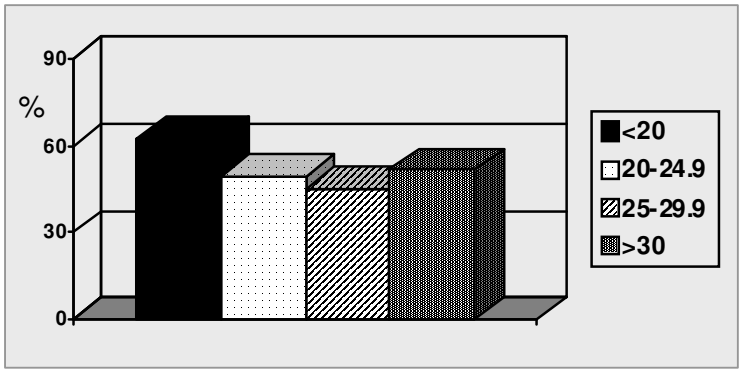
A=weight decrease >10% between baseline and three years follow-up
B=weight decrease 5-10%
C=weight stable within 5% (Reference)
D=weight increase 5-10%
E=weight increase >10%

4.4 MORTALITY AND MISSING DATA IN STUDIES I AND II

Given the tight relationship between dementia, anemia, and body weight with mortality, we briefly report some data that might be useful for the understanding of the results. Between baseline and three years of follow-up, a significantly higher proportion of anemic subjects died compared to non-anemic persons (37.1% versus 20.7%, p<0.001). The sex-, age-, education-adjusted HR of dying for anemic subjects was 1.16, 95% CI: 1.14-2.23.

The association between BMI and mortality observed in the dementia-free cohort of the Kungsholmen Project was U-shaped. The highest probability of dying was observed among underweight and obese subjects (62.4% and 51.6% respectively; Figure 12).

Figure 12. Mortality in relation to baseline BMI.



Hemoglobin data were missing for 58 people (4.8%); they had similar socio-demographic characteristics as compared to subjects with available hemoglobin concentration. Conversely, cumulative mortality was higher in person with missing information (42% versus 22.2%, p=0.03) who, on average, had also a slightly lower MMSE scores (mean 26.4±2.0 versus 26.9±1.9, p=0.051). Missing information was due to either refusal to provide blood samples or technical reasons. When all persons with missing data were considered as being anemic, the sex-, age- and education-adjusted HR for dementia was 1.51, 95% CI: 1.05-2.17. Similar results were observed when all subjects with missing data were regarded as not anemic: HR was equal to 1.48, 95% CI: 0.96-2.26.

Out of 1,435 individuals, 174 (12.1%) persons had missing information concerning weight or height, making it impossible to calculate BMI. Persons with missing data were twice as likely to be women (p<0.001), on average they were four years older (p<0.001), had a lower mean MMSE score (p<0.001) and higher nine-year dementia incidence and mortality (p<0.001). A sensitivity analysis was then implemented to evaluate possible biases introduced by the missing information (Table 9).

Table 9. Sensitivity analysis using different imputations to evaluate the possible effect of missing information on BMI: Hazard ratios (95% confidence intervals) for dementia according to different BMI levels.

	BMI		
	<20	***20-24.9***	***≥25***
Imputation 1: *All subjects with missing BMI information have BMI<20*	1.29 (1.02-1.63)	1	0.80 (0.63-1.01)
Imputation 2: *All subjects with missing BMI information have BMI=20-24.9*	0.94 (0.69-1.27)	1	0.73 (0.58-0.92)
Imputation 3: *All subjects with missing BMI information have BMI≥25*	1.02 (0.75-1.40)	1	0.99 (0.81-1.21)

4.5 SOCIAL FACTORS, MEDICAL CONDITIONS AND CIND (STUDY III)

In the Faenza Project, 402 (5.4%) CIND cases were detected. CIND people were older, less educated, more frequently unmarried, and were more likely to have a low SES. Among the medical conditions, stroke, diabetes, and depressive symptoms were associated with CIND. The associations between social factors and medical conditions with CIND were independent (Table 10). Noticeably, the point estimate of the association between hypertension* and CIND was below one, suggesting a negative association with the outcome.

Table 10. Medical conditions and social factors associated with CIND.

MEDICAL CONDITIONS	SOCIAL FACTORS
History of stroke	Age
Depressive symptoms	Education
Diabetes	Unmarried status
Hypertension*	Low SES

The effect of having more than one condition/factor was investigated using a 0-3 grade medical- and social-score. The adjusted ORs for CIND related to each score are reported in Table 11. ORs were increased for increasing numbers of factors (chi square for trend, $p < 0.001$). When the two scores were included simultaneously in the model, results were confirmed, suggesting an independent effect of the two scores.

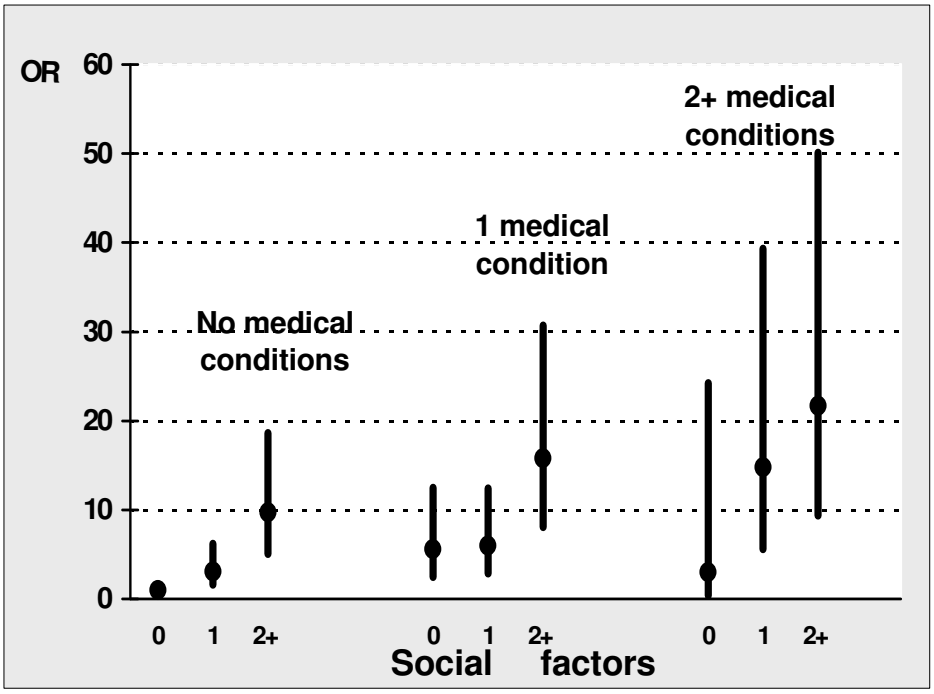
Table 11. Odds ratios (OR) and 95% confidence intervals (95% CI) for CIND according to an increasing number of medical conditions and social factors.

	MEDICAL CONDITIONS	SOCIAL FACTORS
	OR (95% CI)	*OR (95% CI)*
None	1 (ref.)	1 (ref.)
One	1.9 (1.5-2.3)	2 (1.3-3.1)
Two	2.7 (1.7-4.3)	5.4 (3.6-8.2)
Three	4.9 (1.2-19.1)	9.1 (5.0-16.3)

The combined effect of medical conditions and social factors is reported in Figure 13. The co-occurrence of one medical condition and one social factor was strongly associated with CIND (OR: 6.0, 95% CI: 2.9-12.4). In the presence of social factors,

having one or 2+ comorbidities was associated with an increased probability of CIND (OR: 15.8, 95% CI: 8.1-30.7; OR: 21.7, 95% CI: 9.4-50.1, respectively).

Figure 13. Combined effect of medical conditions and social factors: Odds ratios (OR) and 95% confidence intervals (95% CI) for CIND.



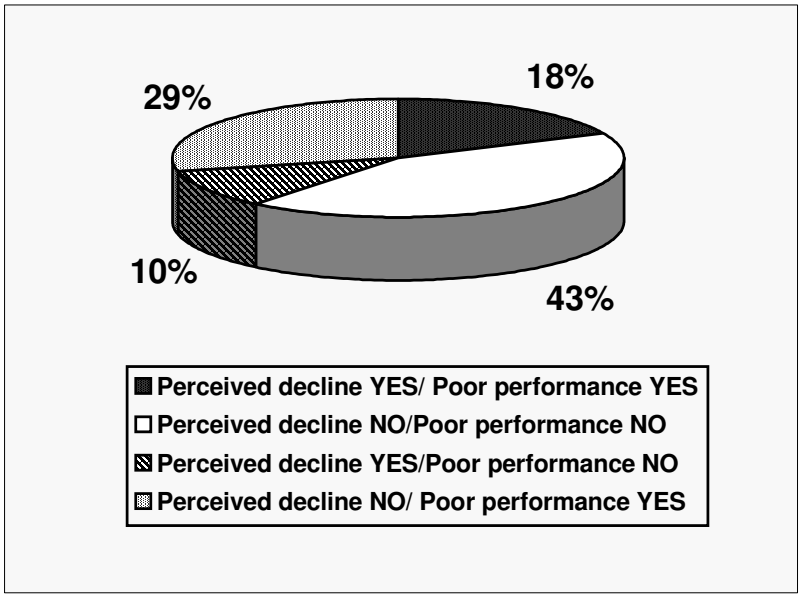
When the study population was stratified by age (<75 years and ≥75 years), results from the fully adjusted logistic regression models showed some relevant differences. Marital status and diabetes were significantly associated with CIND only in the younger elderly people (OR: 2.6, 95% CI: 1.5-4.3 and 2.1, 95% CI: 1.3-3.5 respectively). Further, in this younger age stratum a marginally significant association emerged also between cardiovascular disease and CIND (OR: 1.6, 95% CI: 1.0-2.6; p=0.065). Conversely, age remained significantly associated with CIND only among the 75+ years old persons (OR: 1.1, 95% CI : 1.0-1.1).

The gender stratified analysis showed similar results to those detected for the whole population, although low SES (OR: 2.0, 95% CI: 1.2-3.5) and unmarried status (OR: 2.4, 95% CI : 1.3-4.3), was associated with CIND only in men, whereas diabetes was associated with CIND only in women (OR: 1.7, 95% CI: 1.2-2.5).

4.6 PERCEIVED COGNITIVE DECLINE (STUDY IV)

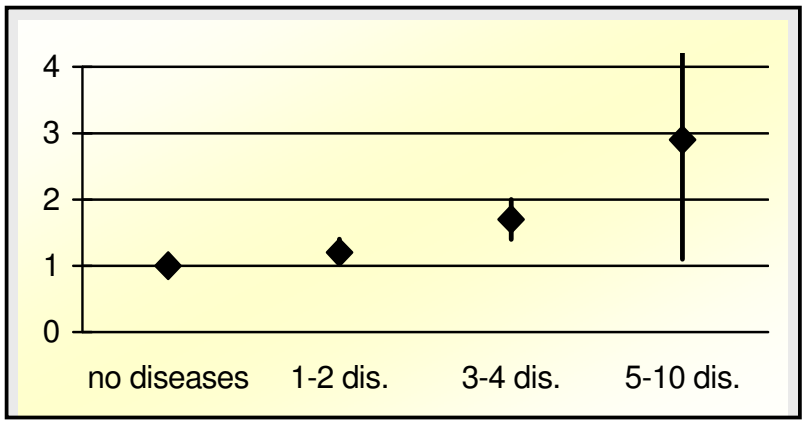
In cognitively intact elderly, 20.1 % and 8.3% of participants reported very mild and mild cognitive decline, respectively. On the basis of the combination between perceived decline and MMSE performance (< 25th percentile or ≥ 25 percentile) four groups were created. The proportions of participants with an agreement between perceived decline and poor cognitive performance (both present or both absent) or a disagreement (either perceived decline but good cognitive performance, or no perceived decline but poor cognitive performance), are reported in Figure 14.

Figure 14. Distribution of the study population-based on participant's perception of cognitive decline and performance on MMSE.



Compared to persons with no decline, subjects reporting a cognitive decline were older, more likely to be women, and had a lower education and low SES. An increasing number of diseases was associated with a higher probability of cognitive decline with a dose-dependent association (Figure 15).

Figure 15. Association between multimorbidity and perceived "Very mild cognitive decline" compared to "No decline" on the Global Deterioration Scale (GDS). Odds ratios and 95% confidence intervals.



Among others, the diseases related to a very mild GDS decline were stroke, diabetes, depressive symptoms, and anxiety, whereas mild GDS decline was significantly related to stroke, malignancy, diabetes, cardiovascular disease, depressive symptoms, and anxiety. Hypertension was negatively associated with GDS decline.

With regard to scoring below the 25th percentile on MMSE, multimorbidity was not associated with an increased probability of poor MMSE performance. When specific diseases were considered, only stroke and depressive symptoms were associated with a lower MMSE score independently of socio-demographics covariates (Table 12).

Table 13 reports OR and 95% CI concerning the combination of perceived decline on GDS and performance on MMSE. Subjects with perceived cognitive decline but higher MMSE scores had more severe multimorbidity, being more likely to be affected by respiratory disease, cardiovascular disease, depressive symptoms, and anxiety.

Neither multimorbidity nor specific diseases were associated to no perceived cognitive decline and low MMSE score.

Table 12. Medical conditions associated with perceived "Very mild cognitive decline" and "Mild cognitive decline" compared to "No decline", and associated with poor cognitive performance on MMSE (< 25 pct).

VERY MILD DECLINE	MILD DECLINE	POOR COGNITIVE PERFORMANCE
Stroke	Stroke	Stroke
Depressive symptoms	Depressive symptoms	Depressive symptoms
Anxiety symptoms	Anxiety symptoms	
Diabetes	Diabetes	
	Cardiovascular dis.	
	Malignancy	

Table 13. Association between perceived cognitive decline (GDS score=2/3 versus 1) and cognitive performances on the MMSE (< 25 pct). Odds ratios (OR) and 95% confidence intervals (95% CI).

	Perceived decline YES / Poor performance NO			
Multimorbidity	*OR*	*(95%CI)*		
No diseases	1	(ref.)		**Respiratory & Cardiovascular disease**
1-2 dis.	1.5	(1.2-1.9)		
3-4 dis.	1.7	(1.3-2.4)		**Depressive & Anxiety symptoms**
5-10 dis.	6.9	(2.0-24.3)		

5 DISCUSSION

This doctoral thesis deals with the role of mental and somatic morbidity on cognitive functioning in the general population. Data are provided by two different population-based projects. Outcomes include dementia, CIND, and perceived cognitive decline.

5.1 SUMMARY OF FINDINGS

The main findings from this thesis are summarized below:

- Anemia -defined by WHO criteria- increases the risk of developing dementia and AD in the next three years. When a cut-off above the WHO threshold is adopted, still anemic persons are at higher risk of developing dementia. The association is confirmed by using different cut-offs and the findings are consistent with a dose-response effect: the lower the hemoglobin, the higher the risk of dementia (*Study I*).
- Being overweight in late-life is not associated with an increased dementia risk over nine-years of follow-up rather a protective effect for higher BMI value is suggested. Weight-loss is a good predictor of incipient dementia and AD (*Study II*).
- Diabetes, stroke, and depressive symptoms as well as low education, low SES, and unmarried status are associated with a higher probability of having CIND. The combination of medical conditions and social factors further strengthens the association, suggesting a joint effect (*Study III*).
- Among older adults with no detectable cognitive impairment, self-perceived cognitive decline is associated with female gender, advanced age, low education, low SES, and multimorbidity. The higher the number of diseases, the higher is the probability of perceived cognitive decline. Respiratory and cardiovascular diseases together with depressive and anxiety symptoms may account for the discrepancy between perceived cognitive decline and performance on cognitive tests (*Study IV*).

5.2 METHODOLOGICAL ISSUES

All the four studies included in this thesis have a population-based design, and include also institutionalized persons. In addition, the Kungsholmen Project (*Studies I and II*) is a prospective study; follow-ups are regularly carried out every third year and medical records and death certificate are reviewed for people who die in between the follow-ups. This study design guaranties a correct temporal relation between the exposure and the outcome, and a good ascertainment of the incident cases.

The major strength of the Faenza Project is the large sample size, almost eight thousand persons, recruited in a well-defined area with a very low migratory rate at the time at which data were collected. However, the Faenza Project has a cross-sectional design. This allows the estimation of prevalence figures, but the observed associations need to be interpreted with caution as exposures and outcomes are assessed at the same time. Furthermore, since prevalence reflects both incidence and disease duration, the use of prevalent cases may have introduced some bias due to differential survival among affected and non-affected individuals. For example, the co-occurrence of diabetes (or stroke, or depression) and CIND might have had a synergistic effect on mortality already before entering the study. If this is the case, the putative association between exposure and outcome would have been biased toward the null hypothesis.

5.2.1 Internal validity

Internal validity includes issues of random and systematic errors. Random error is the inherent imprecision of a given process of measurement, which remains even after systematic error is eliminated[194]. The simplest way to reduce random error is to increase sample-size. Both the Kungsholmen Project and Faenza Project are large cohort studies. Furthermore, the high prevalence of all exposures considered allowed meaningful estimates. In Study II, however, the statistical power was limited by the small number of incident dementia cases when only the last three years of follow-up were examined.

Systematic errors are all processes that lead to deviation of results from the truth, such as confounding[194]. Confounding is the distortion of the estimated effect of an exposure on an outcome caused by the presence of a an extraneous factor associated with both

the exposure and the outcome. In all analyses, the major confounders were carefully chosen on the basis of the available literature, of the pathophysiological knowledge of researchers planning the study, and on the results of univariate analyses. Further, confounding effects were controlled for by using proper statistical approaches (i.e., developing multiple models or performing stratified analyses) in all the four studies. Nevertheless, residual confounding cannot be completely ruled out.

Systematic errors include also biases other than confounding, such as selection and classification biases. Selection bias occurs when the procedures adopted by researchers to select participants among eligible subjects, or the participation rate itself, are influenced by some kind of distortions. If this occurs, the relation between exposure and outcome among participants might be different than among eligible persons. Errors in the measurements of either the exposure or the outcome lead to misclassification. If misclassification occurs equally among cases and non-cases (non-differential misclassification), the effect of such bias on the estimate is less relevant than in the case of differential misclassification bias[194].

The Kungsholmen Project

Selection bias. Dropouts are the first potential source of selection bias. In the screening phase the dropout rate was 23.6%[195]. Non-participants were similar to participants concerning sociodemographic characteristics except for dropouts due to death since they were older and more frequently men than the screened population[196]. Furthermore, in longitudinal studies, it is also important to consider response rate at follow-up. In the Kungsholmen Project, the participation rate at all follow-ups was high, ranging between 85% and 94%.

***Misclassification of the cognitive outcomes*.** The detection of prevalent dementia cases at baseline was carried out with a two-phase design (see Figure 5 for details). A screening phase was conducted on all persons who agreed to participate, and a clinical phase was done for all subjects who screened positive together with a random sample of those who screened negative. Therefore, it is possible that some milder cases of dementia at baseline screened negative and were then regarded as non-demented. Neuroimaging is not mandatory for dementia diagnosis, although it can be helpful

especially to differentiate between AD and VaD cases. The lack of neuroimaging in the Kungsholmen Project is more likely to have introduced an imprecision in the identification of dementia subtypes rather than in the detection of overall dementias. In addition, given the frequent co-occurrence of vascular lesions and neurodegenerative pathology both contributing to the clinical expression of dementia among elderly[197] even if neuroimaging would be available, pure AD and pure VaD cases would be rare and difficult to define.

Misclassification of the exposures. The exposure in Studies I and II are anemia and BMI. Anemia was ascertained through direct measure of hemoglobin concentration, which decreases the possibility of misclassification bias. If any, the misclassification is likely to be non-differential. BMI was based on body weight and height that were directly measured at baseline and at follow-ups. Out of 1435 subjects, 174 had missing information concerning either weight or height. Persons with missing information were more likely to be women, older, and to have a low MMSE score and a higher three-year mortality rate. It is plausible that persons with missing BMI data were actually bed-ridden/chair-bound persons for whom measurement was unfeasible. This might have introduced a differential misclassification bias. Results from a sensitivity analysis confirmed the inverse association between being overweight and dementia development, and showed a statistically significant association between being underweight and incident dementia.

The Faenza Project

Selection bias. In the Faenza Project the dropouts were 31.4% of the screened population[175]. Persons who refused to participate were more frequently men, had lower education, and were younger. Thus, it is possible that younger men with low education have been under-represented in our study. Medical conditions frequently occurring in young-old men such as hypertension, diabetes, or respiratory disease may be under-represented as well. However, if occurred, this bias would have introduced a dilution of the effect and led to an underestimation of the association of morbidity with cognitive functioning rather than an overestimation.

Misclassification of the cognitive outcomes. In the screening phase of the Faenza Project, we tried to minimize the proportion of false negatives, as highly educated persons may score >28 on MMSE even in the presence of cognitive disturbances. First, we added to the MMSE a more functionally oriented screening test such as the GDS. Furthermore, in both tests we used very high cut-off points to ensure high sensitivity, as recommended (7). In the clinical phase, in order to minimize the possibility of a misclassification of the cognitive outcomes, a double diagnostic procedure was implemented to make the clinical diagnosis of dementia. Although CIND, and not dementia, is the outcome of Study III, dementia diagnoses are relevant as they were used as exclusion criteria to identify CIND cases among the non-demented persons.

The use of a global measure of cognitive performance to define CIND may be questioned. However, the MMSE is recommended in the guidelines for the Report of the Quality Standards Subcommittee of the American Academy of Neurology[199]. In addition, the overall performance of MMSE has good concurrent validity with other comprehensive neuropsychological assessment instruments[200] (9), and MMSE score is found to be reliable predictor of AD (10). In order to be as conservative as possible, CIND was operationally defined on the basis of the MMSE using a cut-off of 2 standard deviations (SD) below the mean rather than 1.5 or 1 SD. Furthermore, we adopted the age- and education-adjusted scores that are widely used for Italian elderly persons both in clinical practice and in cognitive research[193]. In our study, the adjustment for age and education led to a 31% decrease in the number of CIND cases (from 584 to 402). The use of unadjusted scores in our population with a relatively low educational attainment (10.8% of illiterate) would have led to a very high impact of different educational backgrounds on cognitive performance.

Misclassification of the exposures. Studies III and IV explore the effect of several determinants, including medical conditions, social factors, and perceived decline. Information gathered from medical conditions was derived from many sources: clinical judgment by the physician who carried out the clinical evaluation, review of the medical records when available, information from the participant or the informant in case of severely cognitively impaired people. Imprecision is implicit in the retrospective assessment of risk factors, especially when informants are interviewed. The closeness between the participant and the informant (mostly spouses), however,

might have reduced this possibility. Furthermore, imprecision is more relevant in the assessment of some conditions than others: for severe conditions such as diabetes, hypertension, and stroke it is unlikely that a large underestimation had occurred. If a misclassification had occurred, however, this should lead to a lower report from the cognitively impaired subjects. Thus, the detected associations might be underestimated. Laboratory and neuroimaging data were not available in the Faenza Project, which may also lead to imprecision in the diagnostic procedure. For example, the diagnosis of diabetes could not be supported by blood glucose tests, and only clinically evident stroke was included. This misclassification seems more likely to be non-differential. Furthermore, cognitive dysfunction after stroke often involves other domains than memory, such as attention and executive functions, which are very poorly captured by the MMSE[172]. This limitation needs to be taken into account when interpreting the findings from both Study III and Study IV. Finally, in the Faenza Project, no specific measures for SES were available, and we did not have access to information on social mobility. The description of SES in our study relies on the occupation held for the longest period during working life.

5.2.2 External validity

Findings from Study I -anemia is associated with an increased risk to develop dementia- are in line with a study carried out in the nineties, which had AD as main outcome[134], and with more recently published articles on anemia-related cognitive decline[132,133]. A recent meta-analysis on this issue[201] reported a significantly increased risk of incident dementia in anemic subjects. The pooled hazard ratio of 1.94, 95% CI: 1.32-2.87 supported the conclusions that anemia should be taken into account when evaluating risk of incident dementia. However, the authors suggested caution in drawing any causal relations since available studies were few and methodologically different. Further, robust research was recommended. Indeed, there is currently a renewed interest in anemia since observational studies have consistently documented independent, strong associations between anemia (even mild) with major adverse functional outcomes in older adults. In light of observational epidemiological evidence linking mild with decline in physical and cognitive functioning, frailty, and disability

in community-dwelling older adults, randomized clinical trials assessing the impact of successful anemia treatment on such outcomes are needed[202].

In *Study II,* we did not confirm the hypothesis that being overweight in late-life is a risk factor for dementia (and AD). This finding is consistent with the most of the reports concerning late-life body weight, although in disagreement with other studies. Many conflicting findings concerning the association between BMI and dementia risk can be explained by taking into account some major methodological issues:

1) Age at BMI assessment, together with different follow-up lengths (period at risk), might be crucial. Since the association between adiposity and dementia is suggested to be time-dependent[203], a life-course approach could help in clarifying apparent paradoxical findings.

2) In the clinical assessment of adiposity, besides BMI, a large variety of measures and indexes are currently used and different cut-offs and reference categories have been adopted. On one side, this is useful since BMI alone might not be totally representative of body composition especially at older ages, on the other side, the use of different indices might hamper comparison among studies. There is general agreement, however, that attention to changes instead of single adiposity measures could further contribute to a better understanding of this relationship.

3) The inclusion of different birth cohorts across studies introduces also the possibility of cohort effects. Early life events related to birth cohort may influence both adult adiposity and cognition throughout adult life.

4) Because of selective survival, also the relationship between BMI and mortality need to be considered when interpreting the association between BMI and dementia. The well known "U-shape" association between BMI and mortality[204] is not consistent over the whole lifespan as the obesity-related excess in mortality decreases with increasing age at all levels of obesity[205]. The association between BMI and mortality in the elderly, taking dementia diagnosis into account, has been recently explored. The presence of dementia did not explain the association between low BMI and higher mortality, but dementia may explain the association between weight loss and higher mortality [206]

Study III provides a picture of the principal characteristics of persons affected by CIND. Our findings are in agreement with previous reports concerning diabetes[207], depressive symptoms[208], and stroke[209] and may have relevant public health implications as all these medical conditions are suitable for preventive actions. In clinical settings, awareness of the medical comorbidity in CIND might be helpful in the early detection of cases and their treatment. Only one other cross-sectional study provided information on the pattern of comorbidity in elderly with CIND[210]. In the Cache County Study, CIND participants did not differ from cognitively intact persons nor from demented individuals concerning number of diseases. However, medical comorbidity was more serious in CIND persons. Seriousness of medical comorbidity was significantly associated with worse day-to-day, as well as cognitive, functioning.

Study IV demonstrates that physical and mental morbidity might be responsible for perceived cognitive decline in persons performing otherwise well in cognitive tests. Indeed, subjective memory complaints have been largely investigated in the literature in relation to cognitive functioning. However, although suggested by clinical experience, the hypothesis that several medical conditions might have an effect on brain aging has never been tested previously in studies including such a large number of diseases. Sparse reports of an effect of depression[211], anxiety[212], and chronic obstructive pulmonary disease[213] on subjective memory difficulties and cognitive tests are in line with our findings.

5.3 INTERPRETATION OF THE FINDINGS

Taken altogether the four studies included in this thesis consistently confirm the relevance of somatic conditions on cognitive functioning. Theoretically, somatic conditions might either be risk factors for dementia, or early predictors of an already ongoing disease, or correlates of a clinically undetected syndrome. In the case of dementia, which is known to have a long preclinical phase, long follow-ups are needed to distinguish between risk (or protective) factors and conditions linked to the outcome in a non-causal pathway. We had the opportunity to test BMI with a nine-year long follow-up. However, the interpretations of findings from *Study I* (three-year follow-up) and *Studies III* and *IV* (cross-sectional design) need to be taken cautiously.

5.4 BIOLOGICAL PLAUSABILITY

5.4.1 Dementia

Dementia is a multifactorial syndrome[214] and many different medical and psychosocial hypotheses have been suggested to explain its origin[215]. In light of our findings, we will concentrate our attention on the cerebral hypoperfusion and atherosclerotic hypotheses, which may explain our findings.

Hypoperfusion hypothesis.

Several epidemiological population-based studies on low blood pressure, as well as heart failure and renal dysfunction suggest that cerebral hypoperfusion might be potentially involved in dementia and cognitive disorders. Episodic hypotension can result in cerebral hypoperfusion, which may contribute to dementia[216] development through cortical watershed microinfarcts, which further aggravate the neurodegenerative process ongoing in AD[217]. Both cross-sectional and prospective population-based studies consistently reported an association of low blood pressure, as well as heart and renal failure, with dementia and AD. The relationship between blood pressure and dementia is age-dependent. A prospective investigation from the Rotterdam Study involving more than 6,000 subjects[218] suggested that low systolic and diastolic blood pressure at baseline were associated with a higher risk of dementia at follow-up in subjects under treatment for hypertension. The association was independent of the presence of diabetes, history of myocardial infarction, and baseline cognitive score. Data from the Kungsholmen Project demonstrated that persons with heart failure had an 80% increased risk of dementia and AD. Heart failure and low diastolic pressure (<70 mm Hg) together had an additive effect on the risk for dementia, which tripled[219]. Controversial results in the literature might be easily explained from a life-course perspective: hypotension may play a protective role in healthy middle-aged and younger-old people. Conversely, in elderly affected by multiple chronic diseases and altered compensatory mechanisms, low blood pressure may cause cerebral hypoperfusion and induce or accelerate cognitive decline. Furthermore, as already observed for anemia, also the definition of hypotension is arbitrary since the blood

pressure level that induces cerebral hypoperfusion is greatly variable in the elderly population, depending on the integrity of antiregulatory mechanisms of cerebral circulation and the presence of associated diseases[220].

In summary, the "hypoperfusion-hypoxigenation hypothesis" is supported by (1) evidence from epidemiological population-based studies showing that low blood pressure, heart and renal failure, and anemia link cerebral hypooxigenation to dementia and AD; (2) evidence that pharmacotherapy which increases or improves cerebral perfusion reduces AD symptoms; (3) evidence of preclinical detection of AD candidates using regional cerebral perfusion and glucose uptake studies; (4) evidence of parallel cerebrovascular and neurodegenerative pathological markers (including plaques and tangles) in both AD and VaD; (5) evidence that chronic brain hypoperfusion can trigger hypometabolic, cognitive, and neurodegenerative changes typical of AD[221].

Atherosclerotic hypothesis.

The atherosclerotic hypothesis suggests that vascular factors and disorders occurring over the lifespan are involved in the pathogenesis and clinical expression of dementia and AD[28]. Indeed, vascular risk factors often coexist in the elderly and may act in a synergistic way to increase the risk of dementia and poor cognitive functioning. Several studies have consistently shown that the risk of AD and dementia increases with increasing number of vascular risk factors[81]. Most vascular risk factors and related disorders are modifiable or treatable, and can serve as targets for the development of primary preventive strategies against dementia. The many potential clinical and public health implications of this hypothesis are intuitive and concern mainly changes in dietary habits and lifestyles.

The vascular hypothesis is suitable for both VaD and AD due to the following evidence: (1) AD and VaD share many risk factors; (2) clinical symptoms in AD and VaD are overlapping; (3) cerebral infarction increases AD incidence by 50%; (4) most autopsied AD brains contain cerebrovascular pathology; (5) mild cognitive impairment (a transition stage for AD) converts either to AD either to VaD[222-223].

5.4.2 Cognitive Impairment in non-demented persons

The association between chronic diseases and CIND or perceived cognitive decline can be explained by the frailty hypothesis[186].

Frailty hypothesis.

Frailty is the "results of a multi-systemic reduction in reserve capacity to the extent that a number of physiological systems are close to, or have just past, the threshold of symptomatic clinical failure"[224]. In other words, frailty is a state of vulnerability clinically disclosed as a non-specific syndrome, with several symptoms and signs, and is known to lead to various degrees of disabilities[225]. Frail persons have partially lost some functions and have failed in maintaining the homeostasis. As a consequence they are at increased risk of disability, morbidity, and death from minor external stresses[226]. Frailty has also been described as being on a continuum; from healthy to slightly, moderate, or very frail[225]. However, even if the concept has been well described, there is no single generally accepted clinical definition of frailty, and figures of prevalence and incidence are lacking. In the last decade, research on frailty has demonstrated that comorbidity is a risk factor for frailty, and disability is an outcome of frailty[224, 227]. Conversely, whether also cognitive functioning might be an outcome of frailty is a relatively newer issue. In the Rush Memory and Aging Project, physical frailty in old age was associated with incident AD and cognitive decline[228] and with AD pathology in both persons with and without dementia[229].

The findings from the present thesis are consistent with the frailty hypothesis since anemia, low body weight or weight-loss, multimorbidity, and chronic disease are common features in frail individuals. The frailty syndrome is a valid concept, easily recognizable by physicians in their daily practice, and a useful marker of risk for adverse health outcomes, which adds value to traditional medical assessments that focus on diagnoses[230].

6 CONCLUSIONS

The findings of the present thesis support the hypothesis that several somatic disorders have an effect on brain aging and dementia. This thesis suggests that late-life anemia is a risk factor for dementia; diabetes, stroke, and depressive symptoms are clinical correlates of CIND, and mental and somatic morbidity accounts for the discrepancy between perceived cognitive decline and cognitive performance. Finally, we do not confirm that being overweight in late-life is a risk factor for dementia, but we suggest that weight-loss is a good predictor of incipient dementia.

7 GENERALIZABILITY

The generalizability of a study, also known as external validity, is the validity of the inference that a study pertains also to people outside of the studied population[204]. Since no study population can be completely representative of all populations in the world, the consideration of the distinctive features of the studied population is crucial when interpreting research findings from population-based studies.

The Kungsholmen Projects includes elderly aged 74+ living in a geographically well-defined urban area of Stockholm, Sweden. We excluded the oldest-old persons (i.e., those age 95+) since we aimed to investigate the relationship between somatic disorders and dementia or brain aging in an homogeneous population. Conversely, individuals surviving up to this very old age might have had specific characteristic (genetics / selective survival) which might alter the patterns of associations found between somatic diseases and brain aging. The Kungsholmen cohort had comparable availability to access to care as all persons resident in other urban areas in Sweden, but they had a relatively higher educational level. Therefore, findings from *Study I* and *Study II*, both based on data from the Kungsholmen Project, are generalizable to elderly aged 75-95 years living in urban areas of high income countries.

The Faenza Project consists of persons aged 61+ living in a geographically defined area in a wealthy province of Northern Italy. This population had comparable gender and age composition to other inhabitants in Northern Italy, and similar access to healthcare systems to other areas in Northern Italy. However, the mean educational level of the Faenza Project was extremely low and this constitutes a limitation for the generalizability of our findings, if educational level is not taken into account.

8 RELEVANCE AND IMPLICATIONS

The lengthening of the lifespan in all populations worldwide has led to an increased prevalence of aging related disorders, including dementia and cognitive impairment. Dementia is a principle cause of mortality[231], disability, and institutionalization in older people[232]. Cognitive impairment is even more frequent than dementia among younger-old subjects[175]. Given the possibility that CIND might evolve to an overt dementia syndrome, the psychological distress related to this condition is possibly even more severe than dementia itself and has many potential repercussions both at the individual and societal level. Last, brain aging also imposes a heavy economic burden both on society and the affected families.

The present thesis deals with both dementia (*Study I and II*) and CIND (*Study III*) and takes into account also a more subjective perspective (*Study IV*). In spite of some methodological difficulties, all the findings of this thesis have their own relevance, especially as the exposures of interest concern conditions highly prevalent in the aged population, such as anemia, changes in body weight, diabetes, stroke, depressive symptoms, cardiovascular and respiratory disease[24]. In addition, all the clinical disorders investigated are related to many other adverse health outcomes.

From a scientific viewpoint, our findings contribute to a better understanding of the mechanisms leading to dementia and cognitive impairment, by providing further evidence for the hypoperfusion and atherosclerotic hypotheses, and are in favor of the frailty hypothesis. In other words, our research supports the notion that dementia and cognitive impairment are multifactorial disorders probably resulting from a cumulative exposure during the life-course.

Besides scientific relevance, the present findings also have many different clinical and epidemiological implications. Indeed, anemia, body weight, diabetes, stroke, depressive symptoms, cardiovascular and respiratory disease are potentially modifiable health determinants. Whether the prevention of chronic disease would be translated into a reduction of cognitive disorder occurrence, however, is under debate. In the United Kingdom, for example, a model taking into account differences in mortality and survival in different health states, predicted that much of the estimated assumed prevention of dementia through improvement of the risk factor profile would be attenuated by the increased survival of the population, with little change in overall dementia rate. Apart from epidemiological estimates, in terms of individual health, the control of risk factors is crucial to prevention of an adverse outcome (primary prevention) and the management of the adverse associated condition is essential to improve prognosis and quality of life of affected persons (secondary prevention).

9 FUTURE DIRECTIONS

All the topics addressed in the four studies of this thesis are suitable to be further explored. First, the detected associations between anemia and incident dementia need to be replicated. Further studies should have longer follow-ups and should be interpreted in a time perspective. It is possible that approaching the question of the hemoglobin-dementia association from a lifespan perspective would add useful information to the understanding of the brain aging processes, further supporting the hypoperfusion hypothesis. If confirmed, these findings could have many relevant clinical and epidemiological implications. Indeed, anemia is an easily modifiable risk factor, which is highly prevalent at older ages and, generally, highly prevalent in low income countries. The combined effect of anemia and adiposity indices on both prevalent and incident dementia would also be of interest especially in light of the possible relation with mortality or other adverse outcomes. Approaching dementia epidemiology according to a lifespan (or life-long) approach which takes into account also age at assessment, survival, and attrition, has recently opened a new scenario on the understanding of dementia risk factors.

The main limitation of the Faenza Project, the cross-sectional design, will be soon overcome by the inclusion of new longitudinal data. Indeed, a follow-up wave has been conducted in the past two years, including all CIND cases as well as a random sample of cognitively intact individuals (n=465). Both community-dwelling and institutionalized persons were asked to participate. The assessment included an interview and a clinical evaluation conducted by physicians together with the administration of the CAMDEX[233]. Out of 465 interviewed persons, 312 consented to give blood samples. The Faenza Project research team is now working on the diagnoses, and have a number of plans for future studies. The first objective is to verify the progression of CIND cases, not only in relation to incident dementia but also in relation to mortality and disability; the second aim is to prospectively investigate those persons with discrepancy between perceived cognitive decline and cognitive performance.

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11 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2009.

1991

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

1992

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

1993

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

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

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

1994

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

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

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

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

Forsell Yvonne: Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine: Autonomy in nursing home settings.

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

1996

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

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

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

1997

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

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

1998

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

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

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

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

1999

Almberg Britt: Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita: Cognitive functioning in late senescence. Influences of age and health.

Zhu Li: Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla: Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva: Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis: Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina: The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin: The impact of lifestyles on the occurrence of dementia.

2002

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

2003

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

2004

Berger Anna-Karin: Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease

Cornelius Christel: Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project

Qiu Chengxuan: The relation of blood pressure to dementia in the elderly: A community-based longitudinal study

Palmer Katie: Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina: According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna: Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana: Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina: Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari: Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita: Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan: Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga: Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik: Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia: Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Erika Jonsson Laukka: Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna: Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta: Drug use among the very old living in ordinary households- Aspects on well-being, cognitive and functional ability.

Rehnman Jenny: The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla: Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna: Medication management and patient compliance in old age.

2008

Gavazzeni Joachim: Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra: Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi: The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Weili Xu: Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina: Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda: Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran: Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra: The association between steroid hormones and cognitive performance in adulthood.

Rana AKM Massud: The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh

Stéphanie Paillard-Borg: Leisure activities at old age and their influence on dementia development.

Åsa Livner: Prospective and retrospective memory in normal and pathological aging.