From the Aging Research Center (ARC),
Department of Neurobiology, Care Sciences and Society,
Karolinska Institutet, Stockholm, Sweden

# COGNITIVE IMPAIRMENT IN THE NONDEMENTED ELDERLY

## Occurrence, risk factors, progression

Barbara Caracciolo


Karolinska Institutet

Stockholm 2011

Published by Karolinska Institutet. Printed by Larserics Digital Print AB, Stockholm.


ISBN 978-91-7457-335-0

*A mia madre e mio padre*

## ABSTRACT ENGLISH

This doctoral thesis investigated different issues related to cognitive impairment (CI) in the nondemented elderly, including occurrence of CI, risk factors leading to CI development, and progression of CI to dementia. Data were derived from the Kungsholmen Project, a community-based study of 75+ years old (*Studies II* and *IV*), and from the HARMONY Study (*Studies I and III*), a nation-wide, population-based study of twins in Sweden. The major findings are summarized below.

**Study I.** The prevalence of subjective cognitive impairment (SCI) and cognitive impairment no dementia (CIND) was estimated among nondemented elderly twins. Prevalence rates of SCI and CIND were 39 (38 to 39) and 25 (24 to 25) per cent. SCI was more prevalent among married people with higher education and socioeconomic status. A reverse pattern was observed in CIND. Both SCI and CIND were more prevalent among older compared to younger old. Probandwise concordance and tetrachoric correlations for SCI and CIND did not differ between monozygotic and dizygotic same-sex twins.

**Study II.** The incidence of amnestic mild cognitive impairment (aMCI), other cognitive impairment no dementia (oCIND), and dementia was estimated using 9-year follow-up data. Incidence rates per 1,000 person-years of aMCI, oCIND and dementia were 11.4 (8.6 to 15.1), 33.8 (28.7 to 39.8), and 70.4 (64.0 to 77.4). Both aMCI and oCIND incidence increased with advancing age in a nonlinear fashion. When correcting for attrition due to death, the increase with age appeared more linear and was similar to that observed for dementia.

**Study III.** The association of common chronic diseases with SCI and CIND was investigated, taking into account familial factors. In fully adjusted models, mental, musculoskeletal, respiratory, and urological diseases were associated with increased odds of both SCI and CIND. Gastrointestinal disorders were related to SCI, while endocrine diseases were associated with CIND. Multimorbidity was associated with 100% and 50% increased odds of SCI and CIND, respectively. In co-twin control analyses, the chronic diseases-SCI association remained significant, but the association with CIND was largely attenuated.

**Study IV.** Low mood was investigated in relation to aMCI and oCIND and their progression to dementia. People with low mood at baseline had a 2.7-fold (95% CI 1.9 to 3.7) increased risk of developing MCI at follow-up. The association was stronger for aMCI (HR 5.8; 95% CI 3.1 to 10.9) compared with oCIND (HR 2.2; 95% CI 1.5 to 3.3). Low mood at baseline was associated with a 5.3-fold (95% CI 1.2 to 23.3) increased risk of progression to dementia in aMCI.

**Conclusions.** Cognitive impairment is highly frequent in the elderly population. Rates increase with age, especially when detected longitudinally and corrected for attrition. Other sociodemographic factors can also affect the distribution of CI among the nondemented. Co-morbid chronic diseases and multimorbidity are associated to increased odds of subjective and objective CI, while low mood is a strong predictor of CI development and progression in the cognitively healthy elderly. Familial factors contribute to non-dementia CI in a complex fashion.



**Key words:** Attrition, chronic diseases, cognitive impairment no dementia, concordance, dementia, depressive symptoms, familial factors, incidence, low mood, mild cognitive impairment, multimorbidity, population-based, prevalence, prospective, sociodemographic factors, subjective cognitive impairment, twin study

# SAMMANFATTNING SVENSKA

Det övergripande syftet med denna avhandling var att studera faktorer som är relaterade till kognitiv nedsättning (CI) bland äldre personer utan demenssjukdom, samt att studera förekomst av CI, riskfaktorer för CI, samt riskfaktorer för demens hos personer med CI. Samtliga delstudier baseras på data från Kungsholmsprojektet, en befolkningsstudie med inriktning på personer 75 år och äldre *(Studie II och IV),* samt från HARMONY projektet *(Studie I och III),* en rikstäckande, populationsbaserad studie med svenska tvillingar.

**Studie I.** I denna studie studerades prevalens av subjektiv kognitiv nedsättning (SCI) och kognitiv svikt utan demenssjukdom (CIND) bland icke-dementa tvillingpar. Prevalensen för SCI och CIND var 39 respektive 25 procent. SCI förekom oftare bland gifta personer med hög utbildning och hög socioekonomisk status. Det omvända mönstret observerades för CIND. Prevalensen för både SCI och CIND var högst bland de allra äldsta. Överenstämmelsen bland probandernas SCI och förekomsten av CIND skiljde sigej mellan monozygota och dizygota samkönade tvillingpar.

**Studie II.** Incidens för amnestisk mild kognitiv nedsättning (aMCI), övriga kognitiva nedsättningar utan demenssjukdom (oCIND) och demens skattades med hjälp av en databas med 9 års uppföljning. Incidens per 1000 personer per år av aMCI, oCIND och demens var 11.4 (8.6-15.1), 33.8 (28.7-39.8), och 70.4 (64.0-77.4). Incidensen för både aMCI och oCIND ökade med åldern på ett ickelinjärt sätt. Vid korrigering för bortfall på grund av dödsfall uppfattades ökningen av incidens som mer linjär och mer lik den som observeras vid demenssjukdom.

**Studie III.** Sambandet mellan vanliga kroniska sjukdomar och SCI och CIND undersöktes efter att ha kontrollerat för ärftliga faktorer. I justerade modeller var mentala, muskulära, respiratoriska och urologiska sjukdomar associerade med högre förekomst av SCI och CIND. Sjukdomar i mag- och tarmkanalen var i stor utsträckning relaterade till SCI medan endokrina sjukdomar var relaterade till CIND. Multimorbiditet var förknippad med fördubbladrisk för SCI samt 0.5 gånger ökad risk för CIND. I kontrollanalysen i tvillingstudien var associationen mellan kroniska sjukdomar och SCI fortfarande signifikant, men associationen till CIND var dock försvagad.

**Studie IV.** Nedstämdhet undersöktes i relation till aMCI och oCIND samt deras progression till demens. Individer som led av nedstämdhet vid baslinjen hade 2.7 gånger (95% CI 1.9-3.7) större risk att utveckla MCI vid uppföljning. Sambandet var starkare för aMCI (HR 5.8; 95% CI 3.1-10.9) än för oCIND (HR 2.2; 95 CI 1.5-3.3). Nedstämdhet vid baslinjen var associerat med en 5.3 gånger (95% CI 1.2-23.3) ökad risk för progression till demens i aMCI.

**Slutsats.** Kognitiv svikt förekommer ofta i den äldre populationen. Antalet drabbade ökar med åldern, särskilt när prevalensen uppmäts i longitudinella studier med korrigeringar för bortfall. Andra sociodemografiska faktorer kan också påverka fördelningen av kognitiv svikt bland äldre icke-dementa personer. Komorbida kroniska sjukdomar och multimorbiditet är associerade med ökad risk för subjektiv och objektiv kognitiv svikt, medan nedstämdhet predicerar utveckling av CI hos kognitivt friska äldre personer.

**Sökord:** Attrition, befolkningsbaserad, demenssjukdom, depressiva symptom, familjära faktorer, incidens, kognitiv svikt, konkordans, kronisk sjukdom, mild kognitiv störning, multimorbiditet, nedstämdhet prevalens, prospektiv, sociodemografiska faktorer, subjektiv kognitiv störning, tvillingstudie

# SOMMARIO ITALIANO

Questa tesi di dottorato ha investigato diversi aspetti associati al deterioramento cognitivo negli anziani non dementi, inclusi occorrenza del deterioramento cognitivo, l'esame dei suoi fattori di rischio e la progressione verso la demenza. I dati sono stati derivati dal Kungsholmen Project, uno studio sulla popolazione di 75 anni o più d'età (Studi II e IV) e dall'HARMONY Study (Studi I e III), uno studio in gemelli anziani su base nazionale. Di seguito i risultati principali:

**Studio I.** La prevalenza del deterioramento cognitivo soggettivo (SCI) e del deterioramento cognitivo senza demenza (CIND) è stata calcolata su una popolazione di gemelli anziani. Si è rilevata una prevalenza del 39% (38-39%) e 25% (24-25%) per lo SCI ed il CIND. Contrariamente al CIND, lo SCI era più prevalente in persone sposate, di elevata educazione e condizione sociale. Sia SCI che CIND erano maggiormente prevalenti tra i più anziani. Tassi di concordanza e correlazioni tetracoriche non differivano tra gemelli monozigoti e dizigoti delllo stesso sesso.

**Studio II.** L'incidenza del deterioramento cognitivo amnestico (aMCI), del deterioramento cognitivo di altro tipo (oCIND), e della demenza è stata calcolata sulla base di 9 anni di osservazione longitudinale. I tassi d'incidenza per 1,000 persone-anno di aMCI, oCIND e demenza erano 11.4 (8.6-15.1), 33.8 (28.7-39.8), e 70.4 (64.0-77.4). L'incidenza sia dell'aMCI che dell'oCIND aumentava con l'avanzare dell'età in modo non lineare. Quando i tassi erano corretti per l'effetto della perdita di soggetti deceduti, l'aumento legato all'età appariva più lineare e maggiormente simile a quello osservato nella demenza.

**Studio III.** L'associazione delle malattie croniche comuni con SCI e CIND è stata investigata, prendendo in considerazione l'effetto di fattori familiari. In modelli completamente aggiustati, malattie mentali, muscolo-scheletriche, respiratorie e urologiche erano associate con un'aumentata probabilità sia di SCI che di CIND. I disordini gastrointestinali erano associati allo SCI, mentre le malattie endocrine erano associate al CIND. La polimorbidità era associata ad un aumento del 100% e 50% nella probabilita' di SCI e CIND, rispettivamente. Nelle analisi con gemello di controllo, l'associazione tra malattie croniche e SCI rimaneva significativa, mentre l'associazione con il CIND era attenuata.

**Studio IV.** L'umore depresso è stato studiato in relazione all'aMCI e all'oCIND e alla loro progressione verso la demenza. Persone con umore depresso alla valutazione di base avevano un rischio 2.7 volte maggiore di sviluppare MCI alla visita di controllo. L'associazione era più forte per gli aMCI (HR 5.8; 95% CI 3.1-10.9) che per gli oCIND (HR 2.2; 95% CI 1.5-3.3). Negli aMCI, un umore depresso alla valutazione di base era associato ad un rischio 5.3 volte maggiore (95% CI 1.2-23.3) di progressione verso la demenza.

**Conclusioni.** Il deterioramento cognitivo è molto frequente nella popolazione anziana senza demenza. I tassi aumentano con l'età, specialmente quando sono calcolati longitudinalmente, correggendo per l'effetto della perdita dei soggetti deceduti. Anche altri fattori sociodemografici possono influire sulla distribuzione del deterioramento cognitivo. La co-morbidità e la polimorbidità mediche sono associate a probabilità maggiori di deterioramento cognitivo soggettivo e oggettivo, mentre un umore depresso può predire sia lo sviluppo che la progressione a demenza del deterioramento cognitivo.

**Parole chiave:** concordanza, demenza, deterioramento cognitivo, deterioramento cognitivo soggettivo, fattori familiari, fattori sociodemografici, incidenza, longitudinale, malattie croniche, polimorbidità, prevalenza, sintomi depressivi, studio di coorte, studio di popolazione, studio su gemelli, umore depresso

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's Disease |
| All-CI | All Cognitive Impairment |
| ANOVA | Analysis of Variance |
| aMCI | Amnestic Mild Cognitive Impairment |
| APOE | Apolipoprotein E gene |
| ATC | Anatomical Therapeutic Chemical (classification system) |
| Aβ | Amyloid-β |
| BDRS | Blessed Dementia Rating Scale |
| CAMDEX | Cambridge Mental Disorders of the Elderly Examination |
| CERAD | Consortium to Establish a Registry for Alzheimer's Disease |
| CI | Cognitive Impairment |
| 95% CI | 95% Confidence Interval |
| CIND | Cognitive Impairment No Dementia |
| CSF | Cerebrospinal Fluid |
| DSM-III-R (DSM-IV) | Diagnostic and Statistical Manual of Mental Disorder, Revised Third Edition (Fourth Edition) |
| DZ | Dizygosity |
| GEE | Generalized Estimating Equation |
| HARMONY | Swedish words for "health" (Hälsa), "genes" (ARv), "environment" (Miljö), "and" (Och), and "new" (NY) |
| HR | Hazard Ratio |
| ICD-7 (ICD-8, ICD-9) | International Classification of Diseases and Related Health Problems, Eighth Revision (Eight Revision, Ninth Revision) |
| IR | Incidence Rate |
| LM | Low Mood |
| MCI | Mild Cognitive Impairment |
| MMSE | Mini-Mental State Examination |
| MZ | Monozygosity |
| naMCI | Non Amnestic Mild Cognitive Impairment |
| NPV | Negative Predictive Value |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Disorders and Stroke-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 |
| oCIND | Other Cognitive Impairment No Dementia |
| OR | Odds Ratio |
| PPV | Positive Predictive Value |
| RR | Relative Risk |
| SD | Standard Deviation |
| SES | Socioeconomic Status |
| VaD | Vascular Dementia |

# LIST OF PUBLICATIONS

This doctoral thesis is based on the following original papers, referred to in the text by their Roman numerals:

I. Caracciolo B, Gatz M, Xu W, Pedersen NL, Fratiglioni L. Subjective and objective cognitive impairment in Swedish twins: a population-based study. *Manuscript.*

II. Caracciolo B, Palmer K, Monastero R, Bäckman L, Winblad B, Fratiglioni L. Occurrence of cognitive impairment and dementia in the community: A 9-year long prospective study.
*Neurology* 2008; 70; 1778-1785.

III. Caracciolo B, Gatz M, Xu W, Marengoni A, Pedersen NL, Fratiglioni L. Chronic diseases in subjective cognitive impairment and cognitive impairment no dementia.
*Manuscript.*

IV. Caracciolo B, Bäckman L, Monastero R, Winblad B, Fratiglioni L. The symptom of low mood in the prodromal stage of mild cognitive impairment and dementia: a cohort study of a community dwelling elderly population. *Journal of Neurosurgery, Neurology, and Psychiatry*; ePub 6th January 2011.

# CONTENTS

# 1 INTRODUCTION

## 1.1 THE CHALLENGE OF GLOBAL AGING

We are living longer. This represents one of the achievements of the last century but also a significant challenge. Indeed, a longer life expectancy requires careful planning from society, including clearly defined public health policies. In 2005 almost 500 million people were age 65 and over, accounting for 8 percent of the world's population. These figures are expected to increase to nearly 1 billion people aged 65 and over by 2030, representing 12% of the world's population.[1, 2] While today's proportions of elderly people are typically highest in more developed countries, the most rapid increases in older populations are occurring in the less developed world. Between 2006 and 2030, the number of older people in less developed countries is projected to increase by 140 percent as compared to an increase of 51 percent in more developed countries.[1] These global changes are induced by the transition from a regime of high mortality and high fertility to a regime of low mortality and low fertility.[3] The so called "demographic transition" has been described as a reduction of mortality leading to increased survival, particularly of children.

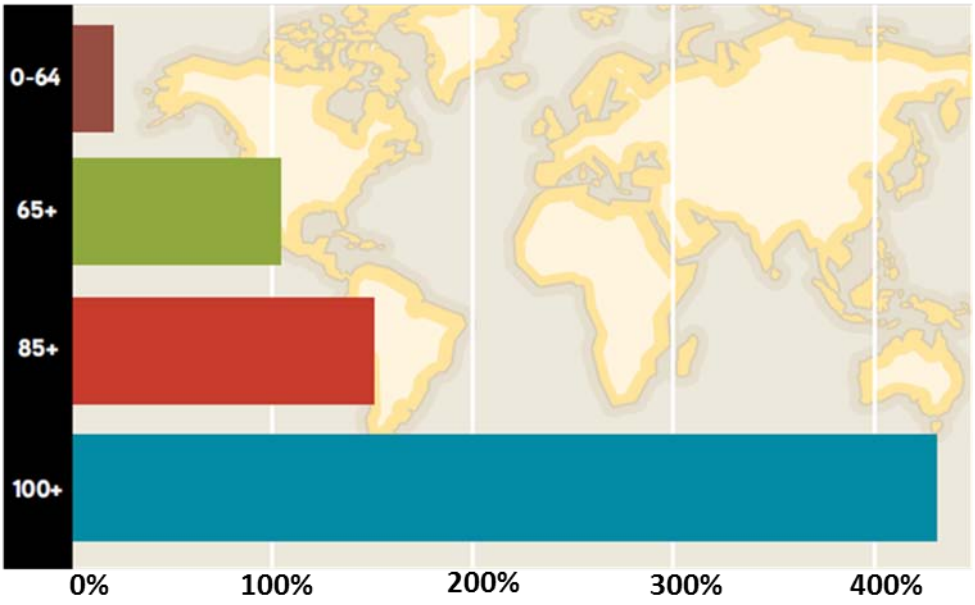


**Figure 1.** Projected increase in global population between 2005 and 2030, by age (World Population Prospects, United Nations, 2005).

The reduced child mortality will in time lead to reduced fertility, because parents realize that a limited number of offspring can ensure the transferral of the genetic pool to the next generation. Sustained reduction of fertility slows down population growth and produces reduction of births.[3] At the same time, lower mortality rates also promote a longer survival of the grown-up offspring, way beyond reaching adulthood. These two related mechanisms result in the disproportionally faster growth of older compared to younger population segments and result in an overall aging of the population. With time, these phenomena will lead to the progressive aging of the older population itself, with an increased proportion of older people living to increasingly advanced ages (Figure 1).[1, 3]

## 1.2 ALZHEIMERS DISEASE AND THE DEMENTIAS

A longer life is not necessarily a healthier life. Indeed, both at the individual and societal level, age-related diseases and disability represent the main challenges related to global aging. The Global Burden of Disease, a study conducted by the World Health Organization and the World Bank, predicted a very large increase in disability caused by age-related chronic disease in all regions of the world. As a consequence, chronic diseases, rather than infectious or childhood diseases and accidents, are becoming the major cause of loss of health and life worldwide.[1]

Alzheimer's disease (AD) represents one of the most common and invalidating chronic diseases of older age.[4, 5] From a clinical and behavioral perspective, AD manifests itself as a series of symptoms and signs that are currently known as dementia. This syndrome is characterized by progressive deteriorations in multiple cognitive domains that are severe enough to interfere with daily functioning.[6, 7] AD is the most common cause of dementia in the elderly, accounting for 60-70% of all demented cases.[8, 9] AD is strictly related to a neuropathological diagnosis determined by the presence of neurofibrillary tangles and senile plaques in the brain of a patient with dementia.[9] Vascular dementia (VaD) is the second most common cause of dementia in the elderly after AD. VaD is defined as loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology.[10] The combination of AD and

VaD pathological changes in the brain of older people is extremely common, making mixed dementia probably the most common type of dementia.[11]

### 1.2.1 Epidemiology

Both prevalence and incidence of dementia rise with increasing age and dementia occurrence is relatively constant across different countries.[12, 13] Several meta-analyses have resulted in similar estimates of dementia prevalence, notwithstanding differences in study designs and diagnostic criteria.[14] The age-specific prevalence of dementia almost doubles every five years, from approximately 1.5% in persons aged 60-69 years to 40% in nonagenarians. The global dementia prevalence in people aged over 60 is 3.9%, with the regional prevalence varying from 1.6% in Africa, 3.9% in Eastern Europe, 4.0% in China, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America. There is a similar pattern in the distribution of dementia subtypes across the world, with the two most common forms of dementia, AD and VaD, accounting for 60-79% and 15-25% of all dementia cases, respectively.[4] In Europe, the age-adjusted prevalence is 6.4% for dementia in general, 4.4% for AD, and 1.6% for VaD among people 65 years and older.[15, 16]

Even dementia incidence does not show great geographical variation in the world. The global annual incidence of dementia is around 7.5 per 1,000 population. The incidence rate of dementia increases exponentially with age, from approximately one per 1,000 person-years in people aged 60-64 years to more than 70 per 1,000 person-years in 90+ year-olds. The incidence rates of dementia across regions are quite similar in the younger-old (<75 years), but greater variations are seen among the older ages.[4] Slightly lower rates have been detected in the USA in comparison with Europe and Asia, and this is possibly due to differences in the study designs and the case ascertainment procedures.

It has been estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year. The number of dementia cases will double every 20 years to 81.1 million by 2040.[17] The highest number of people with dementia are in China (6 million), followed by the European Union (5 million), USA (2.9 million), and India (1.5 million). The rates of increase in the number of dementia cases are not uniform across the world; numbers in developed countries are expected to increase by

100% between 2001 and 2040, but by more than 300% in India, China, and other south Asian and western Pacific countries.[17]

### 1.2.2 Disease progression

Once the diagnosis of dementia has been made, progression can be fast. It has been estimated that more than 50% of the dementia cases reach the severe stage within three years. A study form the Kungsholmen Project reported an increase in the proportion of severe dementia among prevalent cases from 19% at baseline to 48% after three years, and to 78% after seven years.[18] This progression is due to both cognitive and functional decline.

Dementia is strongly associated with disability and was the major determinant of functional dependence and decline over a three-year period. For approximately half of the persons who developed functional dependence over three years disability was attributable to dementia.[19] In industrialised countries, mental disease and cognitive impairment are the most prevalent disorders among older adults living in nursing homes or other institutions. However, institutionalisation of dementia patients varies depending on age structure, urban or rural residence, and other cultural aspects.

Dementia triples the risk of death.[20] In a 75+ year old population, 70% of incident dementia cases die during the five years following the diagnosis, accounting for a mortality rate specific to dementia of 2.4 per 100 person-years.

The demands of healthcare and social service of the huge and rapidly growing numbers of dementia patients have a major economic impact at societal levels.[21] The worldwide direct costs of dementia in 2003 are estimated at 156 billion USD in the main scenario of a worldwide prevalence of 27.7 million demented persons. Due to these costs and the expected increase in the number of elderly people in developing countries, dementing conditions will present a great challenge.[22]

## 1.3 THE GREY AREA: COGNITIVE IMPAIRMENT WITHOUT DEMENTIA

In recent years the focus of research in the field of aging and dementia has gradually shifted from dementia to syndromes of cognitive impairment (CI) in people without overt dementia. This shift was initially driven by the prospect of implementing pharmacological interventions at an early stage of AD, in order to postpone or prevent the onset of the disease.[23] After the less than satisfying results of pharmacological trials on preclinical AD,[23] the interest is moving toward even earlier stages of neurodegeneration, when the CI is not yet manifest and there is still room for preventative strategies.[24, 25] The growing clinical and scientific work on early cognitive disorders has also made more and more apparent that the dementias are only the "tip of the iceberg" and that cognitive problems can represent, per se, an important target of prevention and possible therapeutic interventions.[26, 27] Indeed, even mild cognitive deficits can have a strong impact on people's lives and have important consequences at both a societal and public health level.[28-31]

### 1.3.1 How to define it?

Common to medical and epidemiological research is the definitional issue. In other words, once we have recognized the importance of a clinical and public health target we need to face the problem of reaching an agreement regarding a valid definition of the outcome of interest. This is extremely relevant in order to allow scientific findings to "sum up" and translate in recommendations and guidelines for the individuals concerned, the specialists working in the field and, last but not least, to determine public health policies.

During the last 20 years, many definitions of cognitive impairment have been suggested. Among others, "Age-Associated Memory Impairment" (AAMI), "Ageing-Associated Cognitive Decline" (AACD), "Age-Related Cognitive Decline" (ARCD), and "Mild Cognitive Disorder" (MCD), Mild Cognitive Impairment (MCI), and Cognitive Impairment No Dementia (CIND) have been put forward.[32] All these definitions share the common aim of classifying non demented elderly into one of two possible categories, cognitively impaired or cognitively unimpaired. Notwithstanding the common purpose, these definitions differ in the set of behavioral signs used to identify non-dementia CI. Important differences can in fact be observed when

considering the definitional criteria of the two most widely-known labels, MCI and CIND.

**MCI**. MCI's original construct referred to a cluster of clinical symptoms that included: a) not being demented; b) reporting a memory complaint, preferably corroborated by an informant; c) having preserved general cognitive functioning; d) having preserved functioning in daily life activities; and e) showing objective memory impairment. In this first definition of MCI, the focus was on memory problems. Deficits in cognitive domains other than memory were allowed, but isolated deficits in non-memory domains were not included. Moreover, the criterion of "preserved general functioning" was often operationalized like scoring above a specific cut-off at a measure of global cognitive functioning, such as the Mini Mental State Examination (MMSE),[33] which may have also excluded a proportion of people with deficits extended to other cognitive areas. The subsequent revision of MCI[34] led to dismissal of the criterion of "preserved general functioning" and to define objective cognitive impairment as a deficit in any cognitive domain. In an attempt to differentiate different forms of MCI, the Mayo Clinic group proposed MCI sub-types that included two broader categories of 1) aMCI, and 2) non amnestic MCI (naMCI). Within aMCI and naMCI main categories, subjects can be further classified as: i) aMCI single, when deficits are limited to the memory domain; ii) aMCI multiple, when the deficits are extended to other cognitive domains; iii) naMCI single, when the deficits are limited to one non-memory domain; and iv) naMCI multiple, when the deficits are extended to multiple non-memory domains.

**CIND.** CIND's refers to any type of CI in nondemented persons. More specifically, CIND requires: 1) objective impairment as defined by cognitive tests; and 2) absence of dementia. Early definitions of CIND also required a "clinical judgement" of cognitive impairment.[35-37] However, subsequent studies of CIND tended to omit this criterion, possibly due to the problematic issues of operationalization and reproducibility.[38-41] Although CIND subtypes are not widely used, attempts to create subcategories based on CIND severity[38] and on the number of impaired domains[41] have been made.

**The operationalization issue.** Besides variations between different definitions of CI, there have also been differences in the operationalization of the same definition (Table 1).[42] First, as both MCI and CIND are dichotomous outcomes, one problem is where to set the boundary between normal and impaired cognitive functioning, i.e. the choice of

the cut-off. In medicine, statistical cut-offs are widely used to discriminate between biological values within the "norm" and "abnormal" values. In cognitive testing, the same type of reasoning is used to determine how far below the average a performance at a specific cognitive task has to fall to be considered impaired. Commonly used cut-offs for both MCI and CIND are -1, -1.5, -2 SD from the mean, although percentiles-based cut-offs have also been adopted (Table 1). Besides having an impact on the frequency of a disease, the choice of a specific cut-off can determine the severity of the cases included. An important aspect related to this issue is the choice of the normative population. It has recently been reported that using external versus local norms for cognitive tests can strongly influence the classification of cognitive impairment.[43]

Secondly, another step in the operationalization of CI is to decide whether to consider differences in age and education when adjudicating cognitive scores. Indeed, these factors can affect cognitive test performance and lead to the (mis)classification of subjects who are "normal" -according to their age and educational level- in the cognitively impaired group. On the other hand, adjustment of cognitive scores by age and education evens out the effect of these important variables on cognitive impairment.

Thirdly, regarding CIND operationalization, a set of different tests measuring specific cognitive functions can be used rather than a single measure of global cognitive functioning, such as the Mini Mental State Examination (MMSE).[33] While the use of a test on global cognition may be handy, especially in large population-based studies, this type of measurement may (mis)classify as unimpaired milder cases of CI.

Decisions taken at any of these levels will result in different frequencies and distributions of MCI and CIND and will strongly influence all epidemiological and clinical findings.

### 1.3.2 Epidemiology

The vast majority of epidemiological investigations on CI syndromes have used MCI and CIND definitions. The epidemiology of alternative definitions has been well summarized by Panza et al, 2005.[32]

### *1.3.2.1 Prevalence*

**MCI**. The prevalence of MCI ranges between 1 and 11.1 per cent (Figure 2), when considering estimates coming from population-based studies using the original or revised Mayo Clinic criteria for aMCI.[44, 45] As shown in Figure 2, notwithstanding the relatively large interval, the majority (67%) of point estimates tend to fall between 2% and 6%, presenting similarities even in the face of differences in the operationalization criteria (Table 1). On the other hand, age-specific prevalence estimates of MCI are affected by high variability, especially in the older age groups. As described in Figure 3, some studies detected an exponential increase with increasing age, but other studies reported no substantial increase.

**CIND.** The prevalence of CIND ranges between 5.1% and 30% (Figure 4). An important source of variation is the use of both global and domain-specific cognitive measures of CIND (Table 1). Indeed, the highest prevalence of CIND has been reported by studies defining CIND as impairment on any cognitive task,[37, 46] while intermediate prevalence estimates have been reported when using CIND definitions based on a global measure of cognitive functioning, such as the MMSE, and a non-conservative cut-off of minus one standard deviation from the mean (Table 1).[38, 47-49] Notably, the lowest prevalence estimate of CIND comes from a study using a definition of CIND based on a measure of global cognitive functioning and a conservative cut-off of minus two standard deviations from the population mean (Figure 4, Table 1).[39] Age-specific prevalence estimates of CIND are also characterized by high variability (Figure 5). In fact, out of eight studies, only five reported prevalence rates that increased with age and the increase was not always linear (Figure 5).

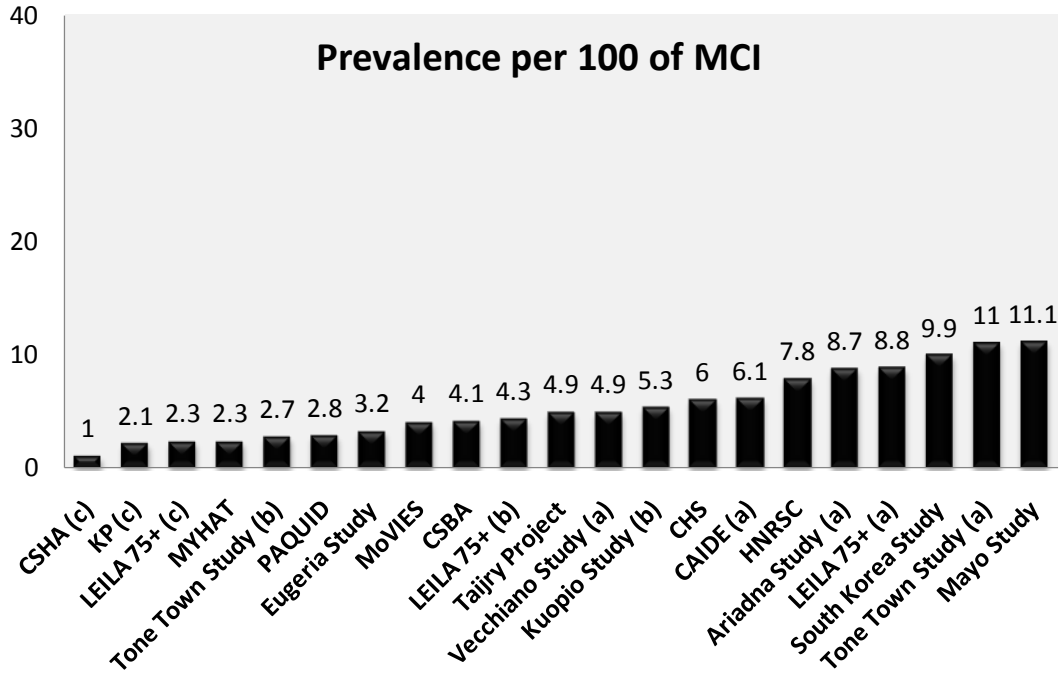


**Figure 2.** Prevalence per 100 of mild cognitive impairment (MCI) from major population-based studies using original or revised Mayo Clinic criteria for amnestic MCI.[45] Studies are described in Table 1.

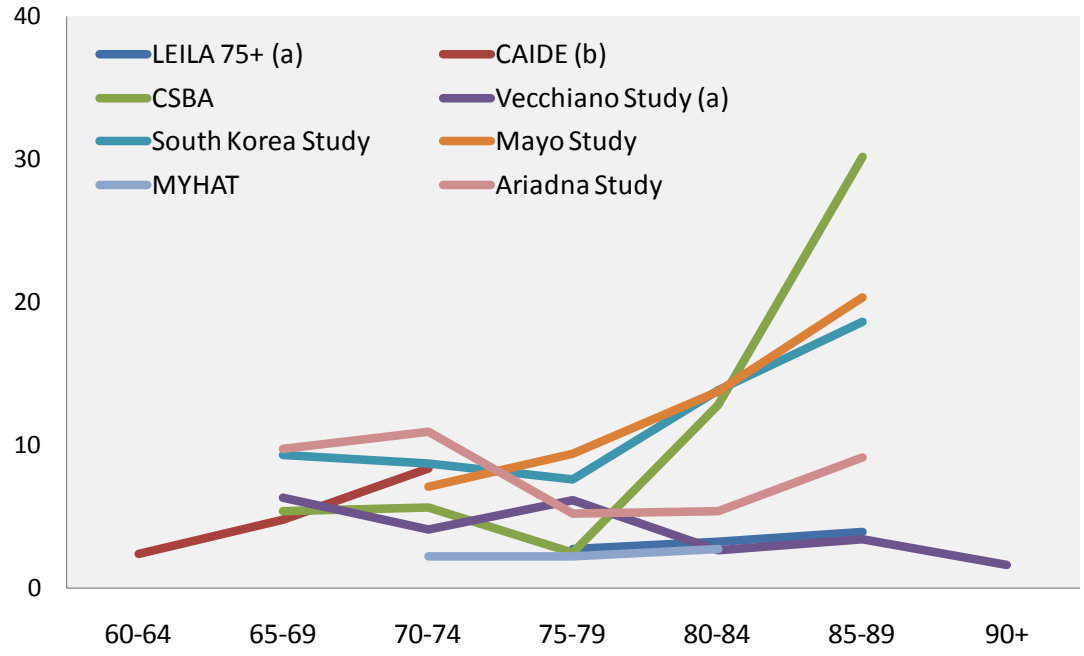


**Figure 3.** Age-specific prevalence per 100 of mild cognitive impairment (MCI) from major population-based studies using original or revised Mayo Clinic criteria for amnestic MCI.[45] Studies described in Table 1.

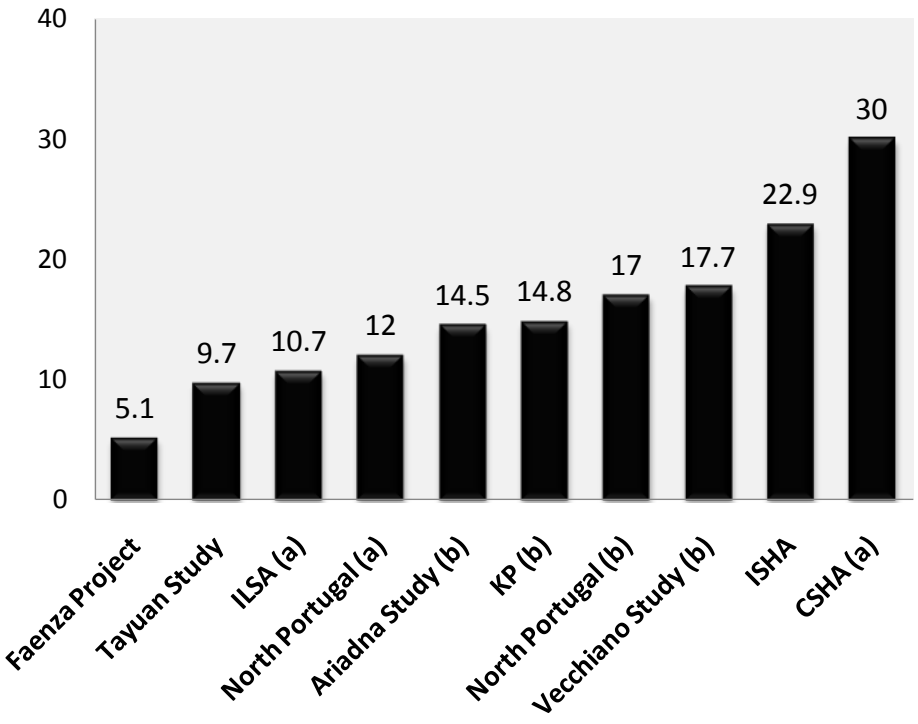


**Figure 4.** Prevalence per 100 of cognitive impairment no dementia (CIND) from major population-based studies. Studies are described in Table 1.

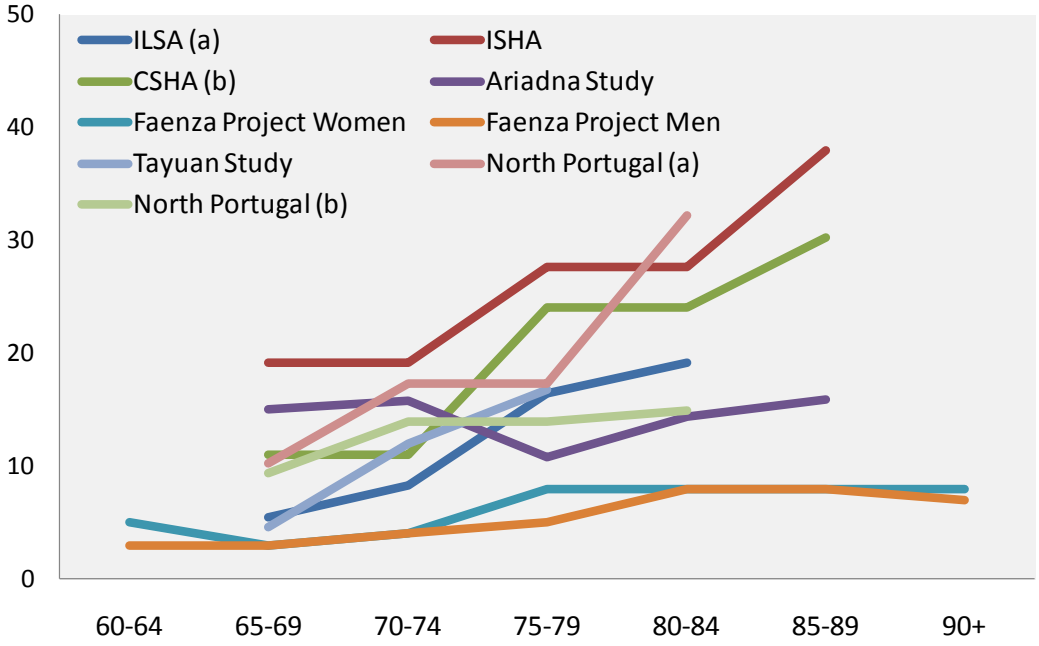


**Figure 5.** Age-specific prevalence per 100 of cognitive impairment no dementia (CIND). Estimates from major population-based studies are shown. Studies are described in Table 1.

### *1.3.2.2 Incidence*

**MCI.** The incidence of MCI ranges between 8.5 and 25.9 per 1000 person-years (Figure 6), when considering estimates coming from population-based studies using the original or revised Mayo Clinic criteria for aMCI.[44, 45] Although the variability appears high, it is reduced when excluding the two upper outliers, represented by estimates coming from studies with more inclusive criteria for MCI (Table 1). Indeed, in the ILSA study,[50] memory impairment was defined as scoring within the lowest 10$^{th}$ centile of the population distribution, while in CAIDE[51] the definition of "preserved general cognitive functioning" was less conservative (MMSE scores ≥20) as compared to other investigations. Age-specific incidence rates have been reported by a limited number of studies and are characterized by high variability (Figure 7). In fact, out of four studies, half reported an exponential increase in incidence rates with increasing age, half reported no increase at all.

**CIND.** There have been no population-based reports on the incidence of CIND.

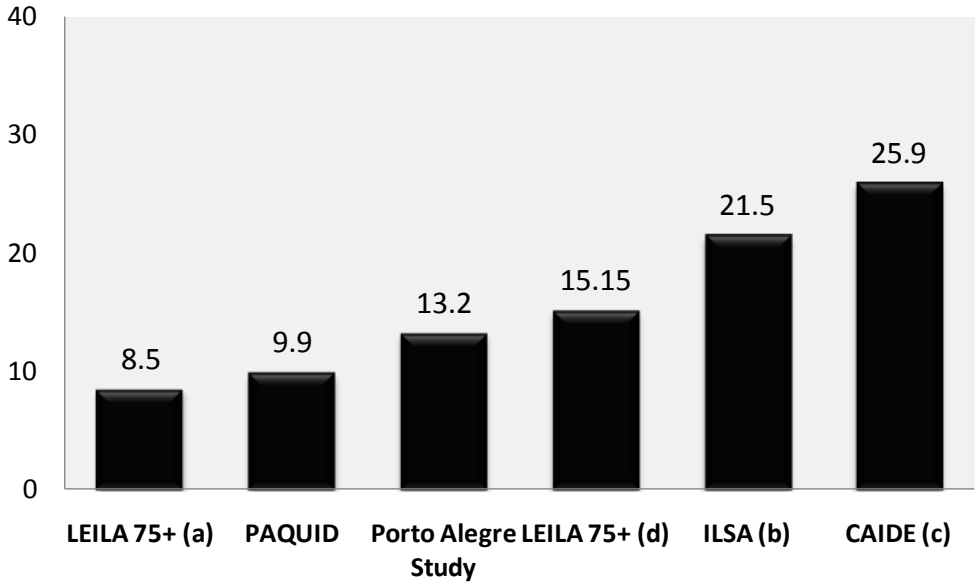


**Figure 6.** Incidence per 1000 person-years of mild cognitive impairment (MCI). Estimates from major population-based studies using original or revised Mayo Clinic criteria for amnestic MCI[45] are shown. Studies are described in Table 1.

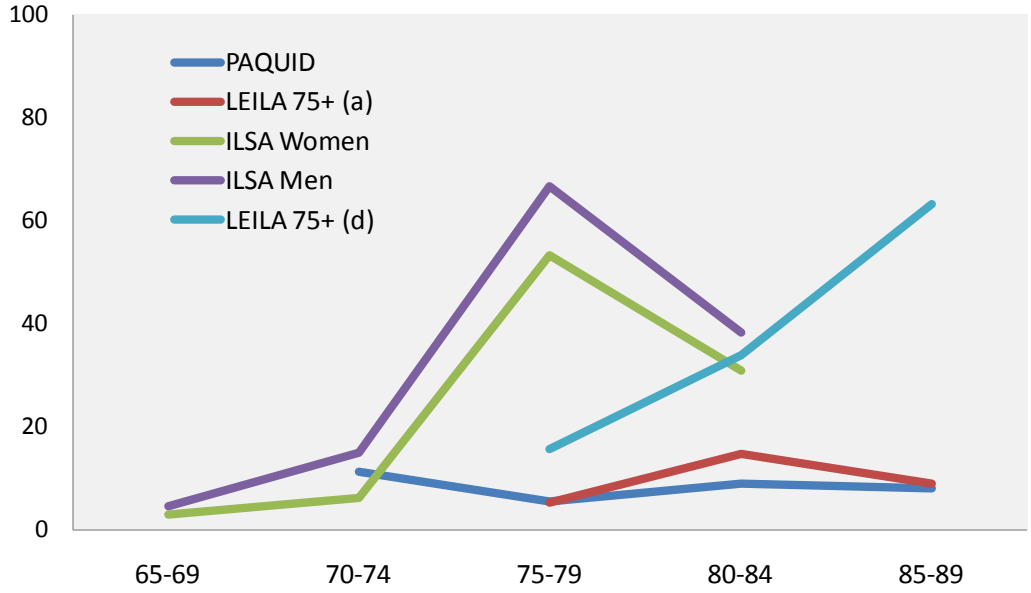


**Figure 7.** Age-specific incidence per 1000 person-years of mild cognitive impairment from major population-based studies using original Mayo Clinic criteria for amnestic MCI.[45] Studies are described in Table 1.

### 1.3.3 Correlates and risk factors

Our current knowledge on correlates and risk factors for MCI and CIND derives mostly from population-based studies carried out in the last 10 years. Interest to this topic initially originated from a will to verify whether CI syndromes share the same risk factors as dementia. A positive answer to this question would support the idea that MCI/CIND is on the same continuum with dementia and that its prevention would result in effective dementia prevention. So far, we had only partial answers to this focal question. Current evidence shows a certain degree of overlap between MCI/CIND and dementia regarding correlates and risk factors. However, differences in risk profiles between dementia and MCI/CIND suggest that CI without dementia may be a distinct entity, susceptible to specific factors. So far, alike the dementias and even more so, the etiology of MCI/CIND appear to be multifactorial. Nonetheless, several possible candidate risk factors have been poorly investigated and available reports are often contradictory.

#### *1.3.3.1 Sociodemographic factors*

**Age**. The majority of population-based studies of MCI and CIND found a positive association with age, with an estimated excess risk between 4 and 800 per cent of

older compared to younger people (Table 2, Part A). Lower point estimates come from studies that considered age as a continuous rather than a dichotomous variable.[50, 52] Notably, several studies did not find an association with age (Table 2, Part A). This may be due to the usual praxis of adjusting cognitive scores by age when defining MCI/CIND (see paragraph 1.3.1), which can attenuate the effect of age.

**Gender**. The majority of studies found no effect of gender on MCI/CIND. Studies on CIND reported either increased odds in women or no effect of gender (Table 2, Part A). Findings on MCI are more difficult to interpret. Indeed, out of four studies that detected an association, half found men to be more at risk of MCI and the other half reported women to be the high risk gender (Table 2, Part A). It is possible that gender differences may play a less important role in MCI/CIND compared to dementia syndromes, where association with female gender has been consistently observed, at least after age 85.[4]

**Education**. Studies on CIND reported either increased odds of CIND in less educated people or no effect of education (Table 2, Part A). Findings on MCI are less homogeneous, with some studies reporting higher odds of MCI in people with higher education. However, out of 21 studies investigating education in relation to MCI/CIND, 18 reported an association (Table 2, Part A). This suggests that, as previously observed for dementia,[53] education is relevant also in MCI/CIND. Effects may be stronger than those reported, as cognitive tests are usually adjusted for education.

**Other sociodemographic factors.** Only a few population-based studies of MCI/CIND investigated the association with socio-demographic factors other than age, gender, and education. The few available reports on *marital status* observed increased odds of CIND in unmarried persons,[54-56] while studies of MCI found no effect at all.[52, 54] Regarding *socio-economic status (SES)*, available evidence suggests increased odds of both MCI and CIND in economically disadvantaged people.[47, 55, 57] Based on these limited data, marital status and SES appear to be relevant factors for SCI and CIND development and should be more thoroughly investigated.

#### *1.3.3.2 Genetic factors*

APOE genotype is the only genetic factor that has been extensively studied in relation to MCI and CIND, although several other candidate susceptibility genes for dementia and AD could also be explored.

**APOE**. The allelic ε4 variation of this genotype is a well-known risk factor for AD,[58] which is why research into MCI/CIND has focused on this gene. Almost all studies reported an association between APOE-ε4 and MCI (Table 2, Part B).[51, 59-61] Findings using CIND as an outcome have been sparse (Table 2, Part B). In synthesis, APOE-ε4 is relevant to the development of MCI and more research on this gene using the definition of CIND is warranted.

#### *1.3.3.3 Somatic diseases*

Current evidence on MCI/CIND and somatic conditions is based essentially on the role of vascular diseases, which have been investigated extensively, while other somatic disorders have received limited attention in relation to CI syndromes.

**Vascular Diseases**. *Stroke* had no effect in studies using the MCI definition, although a differential role of this disease in men and women may be suspected (Table 2, Part B).[62] In contrast, most studies on CIND reported an association with stroke,[35, 55, 63] but more evidence coming from longitudinal studies is warranted (Table 2, Part B). *Hypertension* has been poorly investigated in relation to CIND and available evidence show no effect (Table 2, Part B).[51, 55, 64] Out of seven large population-based studies on MCI and hypertension, only three reported a positive association,[65, 66] while the rest found no effect (Table 2, Part B). Most studies investigating *heart disease* in relation to MCI/CIND found no effect. The only positive findings regard CIND (one out of three)[35] and naMCI (Table 2, Part B).[67] Finally, *diabetes* was associated to MCI/CIND in most investigations, although in two out of four studies reporting positive findings the association was present only in sub-groups, namely men and severe cases of diabetes (Table 2, Part B).[62, 68] Overall, available evidence on vascular diseases and MCI/CIND has been contradictory, with more than half of the studies reporting no effect and with positive findings often limited to sub-groups.

**Other somatic diseases**. Most evidence on the association between somatic diseases other than vascular come from investigations focused on specific cognitive functions

or on cognitive decline, rather than on cognitive impairment. Available findings suggest an association with several somatic diseases, such as hip fracture,[64] asthma and COPD,[69, 70] chronic kidney disease,[71, 72] liver disease,[73] thyroid dysfunction,[74] and cancer.[75, 76] Further investigations are warranted to confirm and expand these preliminary findings.

#### *1.3.3.4 Neuropsychiatric symptoms*

Neuropsychiatric symptoms are highly prevalent in MCI/CIND and have been the focus of several reviews[77, 78] and investigations (Table 2, Part C). Depressive symptoms, anxiety and apathy have been the most widely studied symptoms.

**Depressive symptoms.** Depressive symptoms have been extensively studied in relation to CI syndromes and have been consistently found associated to increased odds of both MCI and CIND. Indeed, out of six population-based cross-sectional investigations only one failed to find an association.[79] Similarly, out of eight, population-based, longitudinal studies of depressive symptoms, six found a positive association with MCI/CIND (Table 2, Part C).[60, 64, 80-82] Therefore, current evidence supports the view that depressive symptomatology often accompanies syndromes of CI and that cognitively healthy people with depressive symptoms are at increased risk of developing MCI/CIND.

**Anxiety.** After depressive symptoms, anxiety has been the most studied neuropsychiatric symptom in CI syndromes. Nonetheless, evidence from population-based investigations does not support the idea of increased levels of anxiety in MCI/CIND. In fact, only one[83] out of six large studies reported increased odds of MCI in people with anxiety symptoms (Table 2, Part C). The lack of longitudinal investigations does not allow conclusions to be drawn on the role of anxiety in the development of MCI/CIND.

**Apathy.** All three population-based studies reporting data on apathy found increased odds of both MCI and CIND in people with this symptom (Table 2, Part C).[79, 83, 84] However, similarly to anxiety, there are no longitudinal data on the progression to MCI/CIND in cognitively healthy people with apathy, therefore, its role as a possible risk factor for non-dementia CI is still unclear.

### *1.3.3.5 Environmental factors*

Environmental factors have been mostly studied in relation to specific cognitive domains or to cognitive decline rather than focusing on syndromes of CI.[85-89] Also when cognitive impairment has been the chosen outcome, most investigations used ad hoc definitions, rather than common criteria for non-dementia CI, making results difficult to summarize. Available findings on MCI/CIND are often inconsistent and more research from population-based studies using current definitions is warranted.

**Smoking**. One cross-sectional study reported decreased odds of CIND in relation to current cigarette smoking.[35] A follow-up of the same cohort reported instead increased risk of MCI in frequent smokers compared to infrequent/non-smokers (Table 2, Part D).[50] Other studies, both cross-sectional and longitudinal, found no effect of current or past cigarette smoking (Table 2, Part D).

**Diet**. There is some evidence linking dietary habits with syndromes of CI. Increased risk of MCI were found in people reporting higher levels of saturated fat intake,[90] while higher levels of vegetables and polyunsaturated fat consumption were associated to reduced odds of MCI in cross-sectional investigations,[91, 92] though not in longitudinal studies (Table 2, Part D).[93, 94] The duration of the follow-up may be crucial to understand the effect of dietary factors on non-dementia CI. Indeed, the only longitudinal study reporting an association had a follow-up of 21 years (Table 2, Part D).[90]

**Alcohol**. Out of five population-based studies, only one reported evidence of a protective effect of moderate alcohol drinking on rates of MCI.[95] The same study reported increased odds of MCI in relation to past hazardous drinking, and this result was replicated by a cross-sectional study on CIND (Table 2, Part D).[55] Overall, there is insufficient evidence to draw conclusions about the effect of moderate alcohol drinking on MCI/CIND.

**Exercise**. Only a few studies have reported data on the relationship between physical exercise and non-dementia CI. Available longitudinal evidence suggests a protective effect of physical exercise on MCI/CIND development (Table 2, Part D).[96-98]

**Leisure Activities**. Only two population-based longitudinal studies investigated leisure activities in relation to MCI/CIND. The study that reported a protective effect of leisure activities on MCI/CIND[99] had a longer follow-up compared to the one that

found no effect (Table 2, Part D).[64]

**Social Isolation**. This factor was associated to increased odds of MCI only in women,[62] while no effect was found by a longitudinal study of CIND with a relatively short follow-up (Table 2, Part D).[64] Longitudinal investigations with longer follow-up are warranted.

### 1.3.4 Progression to dementia

A potential area of investigation within dementia research has initially focused on the predictivity of MCI/CIND definitions for AD and dementia. Only recently some studies have focused on the identification of factors accelerating or promoting the progression of CI syndromes to dementia. As a consequence, the level of evidence for any of these factors is generally low.

#### *1.3.4.1 Progression rates and predictivity*

Cognitive impairment in nondemented elderly is one of the strongest risk factors for dementia. It has been estimated that over three years about one third of people with CIND will progress to dementia.[38] A recent meta-analysis estimated that in people with MCI the combined relative risks of annual progression to AD and dementia are 8.9 (95% CI 4.2-19.1) and 13.8 (95% CI 8.4-22.6).[100] Averaging several large population-based studies, the annual conversion rates of MCI to AD and dementia were 6.8% (95% CI 1.9-14.5%) and 4.9% (95% CI 1.6-9.9%), respectively.[100] These figures clearly show that only a proportion of people with MCI/CIND will progress to more advanced stages of CI, while others will remain stable or even improve.[38] This phenomenon has led to several attempts to increase the predictivity of MCI/CIND for AD and dementia. In a study from the Kungsholmen Project, a three-step procedure resulted in a sensitivity of 48-50% and a specificity of 89-92% for people with both subjective memory complaints and impairment on episodic memory or verbal fluency tasks. However, only 18% of future dementia cases were identified by this diagnostic procedure.[101] A recent study on primary care patients reported a sensitivity of 79.6% and a specificity of 66.4%, a positive predictive value (PPV) of 14.7% and a negative predictive value (NPV) of 97.8% by combining MMSE, episodic memory, and verbal fluency scores with other indicators such as subjective cognitive impairment, age, and

performance on instrumental activities of daily living (IADL).[102] Different biological markers have also been tested as possible predictors of dementia in MCI/CIND[103]. In the last few years cerebrospinal fluid (CSF) concentrations of CSF-tau and Aβ-42 have been studied extensively in relation to MCI[104]. However, it has been estimated that adding cerebrospinal fluid (CSF) biomarkers to bedside cognitive tests can reduce the misclassification rate in MCI from 38% to 30-24%, resulting in a relative improvement of merely 20-36% in accuracy.[105] Thus, the relatively little improvement in the prognostic value of MCI does not support the routine use of these expensive and not always widely available diagnostic techniques. The use of imaging markers appears more promising,[103] although studies have been characterized by high variability[106] and it is still under debate which technique may be the most predictive and suitable in CI syndromes.[107, 108]

#### *1.3.4.2 Risk factors for progression to dementia*

The fact that MCI/CIND definitions do not have a high PPV has negative consequences on our capacity to identify those subjects that will develop dementia. However, low PPV also implies that there are factors that can promote or prevent progression to AD and dementia in people manifesting syndromes of CI. The positive aspects are that some of these factors may be modifiable and that non-modifiable risk factors can help in identifying MCI/CIND people at higher risk of progressing toward AD and dementia.[109] The majority of available evidence on risk factors for progression to dementia in nondemented people with CI comes from relatively small clinic-based studies using the definition of MCI.

**Sociodemographic factors.** Age strongly influences dementia risk in MCI[62, 110-112] and is included in risk indexes for the progression of MCI to dementia.[109, 113] In a clinic-based study evaluating the 10-year risk of dementia of people with MCI age strongly influenced progression risk, which ranged from 0-0.06, in subjects aged 40 to 54 years, to 0.77-1.0, in subjects aged 70 to 85 years. Lower education has also been found to be associated to accelerated progression from MCI to dementia.[62, 111] There is insufficient evidence regarding an effect of gender on MCI progression rates, however, men and women with MCI were found to have different risk profiles for dementia.[62]

**Genetic factors.** *APOE* gene has been studied quite extensively in relation to the

progression of MCI to dementia, with inconsistent findings. Indeed, while the majority of longitudinal studies that examined the role of APOE-ε4 on MCI progression reported no effect,[111, 114-117] some investigations found a positive association.[62, 118, 119] Other genes possibly involved in the evolution of MCI are *CHRNA7*, *ACT*, and *MAPT*.[117, 118]

**Vascular Diseases**. *Stroke* was the only vascular factor associated to the progression of MCI to dementia in a population-based prospective study.[50] The relevance of stroke in MCI progression is only partly confirmed,[62, 120] as several other investigations did not find an association.[110, 114, 121] *Atrial fibrillation* was associated to an almost 5-fold increased risk of progression to dementia in a clinic-based study on MCI.[122] However, this result has not yet been replicated. *Diabetes* was not associated to accelerated progression of MCI to dementia in two out of three population-based studies.[50, 62, 123] In synthesis, evidence of the role of vascular diseases in MCI/CIND progression to dementia is contradictory. On the other hand, there is consistent evidence on the association of vascular cerebral lesions, such as periventricular and white matter hyperintensities, and increased risk of dementia in MCI. However, this association has been observed for vascular and mixed dementia but not for AD,[124-126] with the exception of findings from a case-crossover study on white matter lesions.[127]

**Other somatic diseases**. Non vascular somatic diseases have been investigated sparsely in relation to the progression of MCI/CIND to dementia.

**Neuropsychiatric symptoms.** *Depressive symptoms* have been extensively studied as possible risk factors for dementia in people with MCI/CIND, but results are contradictory. Out of 10 longitudinal studies, three found that depressive symptoms increased the risk of progressing to dementia;[128-130] two reported an association only in women or for isolated symptoms;[62, 131] three found no association;[132-134] and two recent studies reported that the presence of depressive symptoms decreased the risk of developing dementia.[135, 136] Therefore, it is not currently possible to draw conclusions as to the role of depressive symptoms on the progression of MCI/CIND to dementia. *Anxiety.* There is limited evidence on the role of anxiety symptoms in the progression of CI syndromes. One population-based study reported increased risk of AD in MCI with anxiety symptoms at baseline.[133] *Apathy.* A clinic-based study showed increased

baseline prevalence of apathy symptoms in MCI that later progressed to AD.[137] To support this finding, two other studies, one hospital-based[136] and one population-based, reported increased risk of AD and dementia in MCI with symptoms of apathy.[138] These preliminary findings, yet to be confirmed, suggest a possible role of apathy in the progression of MCI/CIND to dementia and AD.

**Environmental factors.** Environmental factors have been studied very sparsely in relation to the progression of MCI/CIND to dementia. Available evidence suggest moderate alcohol consumption[139] and adherence to a Mediterranean diet[94] as possible protective factors. The promising results on the protective effect of physical exercise on rates of cognitive decline[87] should be replicated in studies focusing on the evolution of CI syndromes.

## 1.4 FROM PRE-DEMENTIA TO PRE-COGNITIVE IMPAIRMENT

It is currently recognized that AD and dementia can be preceded by a long pre-clinical stage when functional impairment is not yet manifest and even cognitive deficits may not be detectable.[24, 140-142]

### 1.4.1 Subjective cognitive impairment

In their model of cognitive aging, Reisberg et al. (2008)[140] hypothesize a stage of pre-MCI, of an approximate duration of 15 years, characterized by subjective cognitive impairment (SCI) in the absence of objective cognitive deficits. Longitudinal studies support the idea that a proportion of people that will later develop dementia pass through a stage when cognitive deterioration is not yet evident but there is the subjective perception of a worsening in cognitive functioning.[143, 144] This model of cognitive decline is promising. However, reality may be more complex. Indeed, as previously observed for MCI/CIND, not all people with SCI progress to dementia and some persons SCI will not even evolve into a non-dementia CI syndrome.[143-145] Notwithstanding the variability in the possible outcomes of SCI, its impact at the individual and societal level may be important. It has been reported that people with subjective cognitive complaints have a worse scores on quality of life measures[146] and that these effects can persist over time.[147] People with cognitive complaints are also likely to seek for help for their problems through the health care system, with a reported

60% increase in health care utilization over a three-year period,[148] and/or using self-prescribed medications, including vitamins and nutraceuticals.[149]

#### *1.4.1.1 Epidemiology, risk factors, progression*

The great majority of information on SCI comes from cross-sectional studies that did not exclude cognitive impairment, or even dementia, from SCI definition.[141] This makes it difficult to generalize available findings to the current concept of SCI, which does not include objective cognitive deficits.

**Epidemiology**. Estimated prevalence of cognitive complaints is between 25 and 57 per cent.[145, 150-153] No population-based study has reported data on the prevalence of SCI without cognitive impairment. Also, no study reported data on the incidence of SCI with or without CI.

**Correlates and risk factors**. Studies on subjective cognitive complaints repeatedly showed association with older *age*.[145, 150-155] The majority of reports also found association with female *gender* [151-153, 156] and low *education*.[151, 153, 155, 157, 158] These results may not be generalizable to SCI without objective deficits. Indeed, the few studies that excluded cognitive impairment from the definition of SCI reported association with male gender[159] and high education.[160] Specific *personality traits* have been related to cognitive complaints.[161-164] The important contribution of *affective symptoms*, such as depressed mood and anxiety, is generally acknowledged.[140, 145, 159, 164, 165] APOE-ε4 allele has also been associated to cognitive complaints.[166-168] Other factors that have been associated to cognitive complaints are *poor physical health* and *pain*.[153, 161, 169-171]

**Progression to objective cognitive impairment and dementia**. Only recently SCI without CI has started to be studied longitudinally, with the aim to evaluate the progression to syndromes of objective CI and dementia.[143, 144, 172] In particular, in a large study on primary care patients, subjects with SCI at baseline and MCI at the 1 and ½ year follow-up had an almost 9-fold increased risk of dementia at the 3-year follow-up, compared to a two-fold increased risk of dementia in people with SCI that progressed to dementia without a detectable MCI stage, and to a 4-fold increased risk of dementia in people without SCI at baseline but with MCI at the 1 and ½ year visit.[143] A study on healthy volunteers with a follow-up of almost seven years reported a 4.5

increased risk of MCI or dementia in people with SCI at baseline.[144] The only longitudinal population-based study on SCI without objective CI (follow-up time: 9 years) found a 2-fold and a 1.5-fold increased risk of AD in people with higher and lower education and SCI at baseline.[172] This latter evidence suggests that SCI may be an important first sign of imminent AD, especially in persons with a high level of education who still perform well on formal cognitive tests.[172] Evidences from studies investigating cognitive complaints regardless of the presence/absence of objective cognitive impairment have been contradictory.[145, 164, 173] More community-based studies are warranted to further explore the natural history of SCI in cognitively healthy persons.

**Table 1.** Operationalization criteria for MCI and CIND in the studies described in Figures 2 to 7.

| Study | | Author, year | Age (yrs) | Study Pop. | Def | Operationalization | Reference | Cut-off MI | Cut-off CI |
|---|---|---|---|---|---|---|---|---|---|
| CSHA | (a) | Ebly et al,1995[174] | 65+ | 2,914 | CIND | Impairment at any test | External | NA | Not specified |
| | (b) | Graham et al, 1997[36] | 65+ | 2,914 | CIND | As above | As above | NA | As above |
| | (c) | Fisk et al, 2003[175] | 65+ | 1,790 | MCI | Original Mayo criteria[45] | As above | Not specified | NA |
| KP | (a) | Palmer et al, 2002[38] | 75+ | 1,435 | CIND | Global CI | Local | NA | -1 SD |
| | (b) | Palmer et al, 2008[176] | 75+ | 379 | MCI | MCI amnestic[44, 45] | Local | -1.5 SD | -1 SD |
| LEILA 75+ | (a) | Busse et al, 2003[177] | 75+ | 1,045 | MCI | Original Mayo criteria[45] | Local | -1 SD | SIDAM < 1 SD |
| | (b) | As above | 75+ | 1,045 | MCI | As above | As above | -1.5 SD | As above |
| | (c) | As above | 75+ | 1,045 | MCI | As above | As above | -2 SD | As above |
| | (d) | Luck et al, 2010[178] | 75+ | 1,692 | MCI | MCI amnestic[44, 45] | Local | -1 SD | NA |
| MYHAT | | Ganguli et al, 2010[179] | 65+ | 1,982 | MCI | MCI amnestic[44, 45] | External | Not specified | Not specified |
| Tone Town Study | (a) | Sasaki et al, 2009[59] | 65+ | 1,433 | MCI | MCI amnestic[44, 45] | Local | -1 SD | NA |
| | (b) | As above | 65+ | 1,433 | MCI | As above | | -1.5 SD | As above |
| PAQUID | | Larrieu et al, 2002[180] | 65+ | 1,265 | MCI | Original Mayo criteria[45] | Local | -1.5 SD | -1 SD |
| Eugeria Study | | Ritchie et al, 2001[181] | 60+ | 833 | MCI | Original Mayo criteria[45] | External | Not specified | Not specified |
| MoVIES | | Ganguli et al, 2004[110] | 65+ | 1,248 | MCI | Original Mayo criteria[45] | Local | -1.5 SD | MMSE < 24 |
| CSBA | | Ravaglia et al, 2008[182] | 65+ | 1,016 | MCI | MCI amnestic[44, 45] | Local | -1.5 SD | NA |
| Taijry Project | | Meguro et al, 2004[183] | 65+ | 1,654 | MCI | Original Mayo criteria[45] | Local | -1.5 SD | Not specified |

**Table 1** (continued).

| Study | | Author, year | Age (yrs) | Study Pop. | Def. | Operationalization | Reference | Cut-off MI | Cut-off CI |
|---|---|---|---|---|---|---|---|---|---|
| Vecchiano Study | (a) | Tognoni et al, 2005[184] | 65+ | 1,600 | MCI | Original Mayo criteria[45] | External | Not specified | Not specified |
| | (b) | Marengoni et al, 2011[36] | 60-98 | 1,012 | CIND | Global cognitive impairment | Local | NA | -1 SD |
| CAIDE | (a) | Kivipelto et al, 2001[185] | 65-79 | 1,449 | MCI | Original Mayo criteria[45] | Local | -1.5 SD | MMSE < 20 |
| | (b) | Hanninen et al, 2002[163] | 60-76 | 806 | MCI | As above | As above | As above | As above |
| | (c) | Tervo et al, 2004[51] | 60-76 | 747 | MCI | As above | As above | As above | As above |
| HNRSC | | Dlugaj et al, 2010[186] | 50-80 | 4,145 | MCI | MCI amnestic[44, 45] | Local | -1 SD | NA |
| Ariadna Study | (a) | Gavrila et al, 2009[48] | 65-96 | 1,074 | MCI | MCI amnestic[44, 45] | Local | -1.5 SD | NA |
| | (b) | As above | 65-76 | 1,074 | CIND | Global cognitive impairment | Local | NA. | -1 SD |
| South Korea Study | | Kim et al, 2011[57] | 65+ | 1,673 | MCI | MCI amnestic[44, 45] | Local | -1.5 SD | NA |
| Mayo Study | | Petersen et al, 2010[52] | 70-89 | 1,969 | MCI | MCI amnestic[44, 45] | Local | -1 SD | NA |
| Faenza Project | | De Ronchi et al, 2005[39] | 60+ | 7,930 | CIND | Global cognitive impairment | Local | NA | -2 SD |
| Tayuan Study | | Fei et al, 2009[54] | 65+ | 6,192 | CIND | Impairment at any test | External | NA | Not specified |
| ILSA | (a) | Di Carlo et al, 2000[35] | 65-84 | 3,425 | CIND | Impairment at any test | External | NA | Not specified |
| | (b) | Solfrizzi et al, 2004[50] | 65-84 | 2,963 | MCI | Original Mayo criteria[45] | Local | Lower 10$^{th}$ centile | MMSE<1.5 |
| North Portugal *Arouca* | (a) | Nunes et al, 2009[49] | 55-79 | 713 | CIND | Global cognitive impairment | Local | NA | -1 SD |
| *Sao João da Madeira* | (b) | As above | 55-79 | 433 | CIND | As above | As above | As above | As above |
| ISHA | | Unverzagt et al, 2001[37] | 65+ | 2,212 | CIND | Impairment at any test | Local | NA | Lower 7$^{th}$ centile |
| Porto Alegre Study | | Chaves et al, 2009[187] | 60+ | 345 | MCI | MCI amnestic[44, 45] | Local | -1.5 SD | NA |

**Table 2, Part A.** Major population-based studies concerning sociodemographic factors in relation to cognitive impairment no dementia (CIND) and mild cognitive impairment (MCI): Odds ratios (OR) or relative risk (RR) with 95% confidence intervals (CIs) are shown.

| Factors | Author, year | Study, Country | Age (yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Definition | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Age** | Graham, 1997[36] | CSHA, Canada | 65+ | 2,914 | Prevalent | NA | CIND | Positive |
| | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Positive; 1.09, 1.06-1.12 |
| | Frisoni, 2000[63] | KP, Sweden | 75+ | 1,435 | Prevalent | NA | CIND | No effect |
| | Unverzagt, 2001[37] | ISHA, USA | 65+ | 2,212 | Prevalent | NA | CIND | No effect |
| | De Ronchi, 2005[39] | Faenza Project, Italy | 60+ | 7,930 | Prevalent | NA | CIND | No effect |
| | Fei, 2009[54] | Taiyuan Study, China | 65+ | 6,192 | Prevalent | NA | CIND | Positive |
| | Gavrila, 2009[48] | Ariadna Study, Spain | 65-96 | 1,074 | Prevalent | NA | CIND | No effect |
| | Hanninen, 2002[163] | CAIDE, Finland | 60-76 | 806 | Prevalent | NA | MCI | Positive |
| | Busse, 2003[188] | LEILA 75+, Germany | 75+ | 1,045 | Prevalent | NA | MCI | No effect |
| | Ganguli, 2004[110] | MoVIES, USA | 65+ | 1,248 | Prevalent | NA | MCI | Positive; 1.04, 1.01-1.08 |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Prevalent | NA | MCI | Positive; 5.93, 3.17-11.10 |
| | Meguro, 2004[183] | Tajiri Project, Japan | 65+ | 1,501 | Prevalent | NA | MCI | No effect |
| | Tognoni, 2005[184] | Vecchiano Study, Italy | 65+ | 1,600 | Prevalent | NA | MCI | Negative; 0.44, 0.28-0.69 |
| | Artero, 2008[62] | 3-C Study, France | 65+ | 6,892 | Prevalent | NA | MCI | Positive in men: 1.02, 1.01-1.04 |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 1,016 | Prevalent | NA | MCI | Positive |
| | Nie, 2010[189] | Meta-analysis, China | 60+ | 43,430 | Prevalent | NA | MCI | Positive |
| | Petersen, 2010[52] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive; 2.31, 1.79-2.99 |
| | Larrieu, 2002[180] | PAQUID, France | 65+ | 2,084 | Incident | 5 | MCI | No effect |
| | Busse, 2003[177] | LEILA 75+, Germany | 75+ | 1,045 | Incident | 2.6 | MCI | No effect |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | Positive; 8.16 4.02–15.61 |
| | Tervo, 2004[51] | CAIDE, Finland | 60-76 | 747 | Incident | 3 | MCI | Positive; 1.08, 1.01-1.15 |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 1,016 | Incident | 4 | MCI | No effect |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | Positive; 1.06, 1.02-1.14 |
| | Unverzagt, 2011[80] | ISHA, USA | 65+ | 1,668 | Incident | 5 | MCI | Positive |

**Table 2, Part A (continued).**

| Factors | Author, year | Study, Country | Age (yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Gender, woman** | Graham, 1997[36] | CSHA, Canada | 65+ | 2,914 | Prevalent | NA | CIND | No effect |
| | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Positive |
| | Frisoni, 2000[63] | KP, Sweden | 75+ | 1,435 | Prevalent | NA | CIND | No effect |
| | Unverzagt, 2001[37] | ISHA, USA | 65+ | 2,212 | Prevalent | NA | CIND | Positive |
| | De Ronchi, 2005[39] | Faenza Project, Italy | 60+ | 7,930 | Prevalent | NA | CIND | No effect |
| | Fei, 2009[54] | Taiyuan Study, China | 65+ | 6,192 | Prevalent | NA | CIND | Positive |
| | Gavrila, 2009[48] | Ariadna Study, Spain | 65-96 | 1,074 | Prevalent | NA | CIND | Positive; 1.53, 1.06–2.22 |
| | Hanninen, 2002[163] | Kuopio Study, Finland | 60-76 | 806 | Prevalent | NA | MCI | No effect |
| | Busse, 2003[188] | LEILA 75+, Germany | 75+ | 1,045 | Prevalent | NA | MCI | No effect |
| | Ganguli, 2004[110] | MoVIES, USA | 65+ | 1,248 | Prevalent | NA | MCI | Negative, Men; 1.9, 1.3-2.8 |
| | Tognoni, 2005[184] | Vecchiano Study, Italy | 65+ | 1,600 | Prevalent | NA | MCI | No effect |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 1,016 | Prevalent | NA | MCI | No effect |
| | Nie, 2010[189] | Meta-analysis, China | 60+ | 43,430 | Prevalent | NA | MCI | Positive |
| | Petersen, 2010[52] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Negative, Men; 2.31, 1.79–2.99 |
| | Larrieu, 2002[180] | PAQUID, France | 65+ | 2,084 | Incident | 5 | MCI | Positive |
| | Busse, 2003[188] | LEILA 75+, Germany | 75+ | 1,045 | Incident | 2.6 | MCI | No effect |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Tervo, 2004[51] | CAIDE, Finland | 60-76 | 747 | Incident | 3 | MCI | Positive; 1.16, 0.63-2.16 |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 1,016 | Incident | 4 | MCI | No effect |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| | Unverzagt, 2011[80] | ISHA, USA | 65+ | 1,668 | Incident | 5 | MCI | No effect |

**Table 2, Part A (continued).**

| Factors | Author, year | Study, Country | Age (yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Education, low** | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Positive, High education; 0.61, 0.56-0.65 |
| | Frisoni, 2000[63] | KP, Sweden | 75+ | 1,435 | Prevalent | NA | CIND | No effect |
| | Unverzagt, 2001[37] | ISHA, USA | 65+ | 2,212 | Prevalent | NA | CIND | Positive |
| | De Ronchi, 2005[39] | Faenza Project, Italy | 60+ | 7,930 | Prevalent | NA | CIND | Positive, Illiteracy; 10.9, 7.0–16.7 |
| | Fei, 2009[54] | Taiyuan Study, China | 65+ | 6,192 | Prevalent | NA | CIND | Positive |
| | Gavrila, 2009[48] | Ariadna Study, Spain | 65-96 | 1,074 | Prevalent | NA | CIND | No effect |
| | Hanninen, 2002[163] | CAIDE, Finland | 60-76 | 806 | Prevalent | NA | MCI | Positive |
| | Ganguli, 2004[110] | MoVIES, USA | 65+ | 1,248 | Prevalent | NA | MCI | Positive; 1.8, 1.2-2.7 |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Prevalent | NA | MCI | Negative; 0.04, 0.02-0.07 |
| | Meguro, 2004[183] | Tajiri Project, Japan | 65+ | 1,501 | Prevalent | NA | MCI | Positive |
| | Tognoni, 2005[184] | Vecchiano Study, Italy | 65+ | 1,600 | Prevalent | NA | MCI | Positive; High education: 0.66, 0.51-0.85 |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 595 | Prevalent | NA | MCI | Positive |
| | Nie, 2010[189] | Meta-analysis, China | 60+ | 43,430 | Prevalent | NA | MCI | Positive |
| | Petersen, 2010[52] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive; 2.87, 1.78-4.63 |
| | Larrieu, 2002[180] | PAQUID, France | 65+ | 2,084 | Incident | 5 | MCI | Negative |
| | Lopez, 2003[60] | CHS, USA | 65+ | 3,608 | Incident | 5.8 | MCI | Positive; High education: 0.8, 0.61-0.99 |
| | Busse, 2003[177] | LEILA 75+, Germany | 75+ | 1,045 | Incident | 2.6 | MCI | No effect |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | Negative; 0.05, 0.03–0.06 |
| | Tervo, 2004[51] | CAIDE, Finland | 60-76 | 747 | Incident | 3 | MCI | Positive, High education: 0.80, 0.71-0.90 |
| | Ravaglia, 2008[182] | CSBA, Italy | 65+ | 1,016 | Incident | 4 | MCI | Positive |
| | Unverzagt, 2011[80] | ISHA, USA | 65+ | 1,668 | Incident | 5 | MCI | Positive; High education: 0.91, 0.85-0.97 |

**Table 2, Part B.** Major population-based studies concerning genetic factors and vascular diseases in relation to cognitive impairment no dementia (CIND) and mild cognitive impairment (MCI): Odds ratios (OR) or relative risk (RR) with 95% confidence intervals (CIs) are shown.

| Factors | Author, year | Study, Country | Age (yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **APOE-ε4** | Sasaki, 2009[59] | Tone Study, Japan | 65+ | 1,433 | Prevalent | NA | MCI | Positive |
| | Lopez, 2003[60] | CHS, USA | 65+ | 3,608 | Incident | 5.8 | MCI | Positive; 1.9, 1.14-3.31 |
| | Tervo, 2004[51] | CAIDE, Finland | 60-76 | 747 | Incident | 3 | MCI | Positive; 2.04, 1.15-3.64 |
| | Monastero, 2007[51] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| | Boyle, 2010[61] | RMAP, USA | 55+ | 600 | Incident | 10.2 | MCI | Positive; 1.36, 1.04-1.78 |
| **Stroke** | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Positive; 2.05, 1.26-3.35 |
| | Frisoni, 2000[63] | KP, Sweden | 75+ | 1,435 | Prevalent | NA | CIND | Positive |
| | Artero, 2008[62] | 3-C Study, France | 65+ | 6,892 | Prevalent | NA | MCI | Positive in men |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | Positive; 1.91 1.41-2.40 |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| **Hypertension** | Kivipelto, 2001[185] | CAIDE, Finland | 65-79 | 1,449 | Prevalent | NA | MCI | No effect |
| | Yaffe, 2009[190] | Osteoporotic Women, Int. | 55+ | 4,895 | Prevalent | NA | MCI | No effect |
| | Israeli-Korn, 2010[65] | Wadi Ara Study, Israel | 65+ | 767 | Prevalent | NA | MCI | Positive; 2.08, 1.18-3.65 |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | No effect |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Tervo, 2004[51] | CAIDE, Finland | 60-76 | 747 | Incident | 3 | MCI | Positive; 1.86, 1.05-3.29 |
| | Reitz, 2007[66] | MS, USA | 65+ | 918 | Incident | 4.7 | MCI | Positive; 1.40, 1.06-1.77 |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| **Heart Disease** | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Positive; 1.73, 1.11-2.68 |
| | Roberts, 2010[67] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive in na-MCI: 1.93; 1.22-3.06 |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | No effect |

**Table 2, Part B (continued).**

| Factors | Author, year | Study, Country | Age (yrs) | Study Pop. | Case finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Heart Disease** | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| **Diabetes** | Artero, 2008[62] | 3-C Study, France | 65+ | 6,892 | Prevalent | NA | MCI | Positive in men: 1.45, 1.09-1.94 |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Luchsinger, 2007[191] | MS, USA | 65+ | 918 | Incident | 6.1 | MCI | Positive; 1.4, 1.1-1.8 |
| | Roberts, 2008[68] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive in severe cases |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | Positive; 1.53, 1.13-2.08 |
| | Xu, 2010[123] | KP, Sweden | 75+ | 963 | Incident | 9 | MCI/CIND | No effect |

**Table 2, Part C.** Major population-based studies concerning neuropsychiatric symptoms in relation to cognitive impairment no dementia (CIND) and mild cognitive impairment (MCI): Odds ratios (OR) or relative risk (RR) with 95% confidence intervals (CIs) are shown.

| Factors | Author, year | Study, Country | Age (Yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Depression** | Kumar, 2006[192] | Path 60+, Australia | 60-64 | 2,551 | Prevalent | NA | MCI | Positive; 1.21, 1.01-1.44 |
| | Geda, 2008[83] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive; 2.78, 2.06-3.76 |
| | Artero, 2008[62] | 3-C Study, France | 65+ | 6,892 | Prevalent | NA | MCI | Positive; Men: 1.69, 1.27-2.25 |
| | | | | | | | | Positive; Women: 1.26, 1.0-1.6 |
| | Ravaglia, 2008[193] | CSBA, Italy | 65+ | 595 | Prevalent | NA | MCI | Positive; 2.1, 1.2-3.9 |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | Positive; 1.75, 1.28-2.39 |
| | Chan, 2010[79] | HK Study, China | 55+ | 788 | Prevalent | NA | MCI | No effect |
| | Lopez, 2003[60] | CHS, USA | 65+ | 3,608 | Incident | 5.8 | MCI | Positive; 1.5, 1.21-1.98 |
| | Barnes, 2006[82] | CHS, USA | 65+ | 2,220 | Incident | 6 | MCI | Positive, 1.38, 1.03-1.85 |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | Positive; 1.9, 1.1-3.1 |
| | Panza, 2008[134] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | No effect |
| | Stepaniuk, 2008[130] | CSHA, Canada | 65+ | 626 | Incident | 5 | MCI | Positive |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect |
| | Goveas, 2011[81] | WHIMS, USA | 65-79 | 6,376 | Incident | 8 | MCI | Positive; 1.98, 1.33-2.94 |
| | Unverzagt, 2011[80] | ISHA, USA | 65+ | 1,668 | Incident | 5 | MCI | Positive; 2.22, 1.16-4.25 |
| **Anxiety** | Forsell, 2003[194] | KP, Sweden | 75+ | 442 | Prevalent | NA | CIND | No effect |
| | Kumar, 2006[192] | Path 60+, Australia | 60-64 | 2,551 | Prevalent | NA | MCI | No effect |
| | Geda, 2008[83] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive; 3.00, 2.01-4.48 |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | No effect |
| | van d. Linde, 2010[84] | MRCCFA Study, GB | 65+ | 1,781 | Prevalent | NA | MCI/CIND | No effect |
| | Chan, 2010[79] | HK Study, China | 55+ | 788 | Prevalent | NA | MCI | No effect |
| **Apathy** | Geda, 2008[83] | Mayo Study, USA | 70-89 | 1,969 | Prevalent | NA | MCI | Positive; 4.53, 3.11-6.69 |
| | van d. Linde, 2010[84] | MRCCFA Study, GB | 65+ | 1,781 | Prevalent | NA | MCI/CIND | Positive |
| | Chan, 2010[79] | HK Study, China | 55+ | 788 | Prevalent | NA | MCI | Positive; 2.06, 1.28-3.30 |

**Table 2, Part D.** Major population-based studies concerning environmental factors in relation to cognitive impairment no dementia (CIND) and mild cognitive impairment (MCI): Odds ratios (OR) or relative risk (RR) with 95% confidence intervals (CIs) are shown.

| Factors | Author, year | Study, Country | Age (Yrs) | Study Pop. | Case-finding | F-up (yrs) | CI Def. | Association; RR/OR |
|---|---|---|---|---|---|---|---|---|
| **Exercise** | Geda, 2010[96] | Mayo Study, USA | 70-89 | 1,324 | Prevalent | NA | MCI | Negative; mid-life moderate: 0.68, 0.49-0.93 |
| | Laurin, 2001[97] | CSHA, Canada | 65+ | 4,615 | Incident | 5 | CIND | Negative; 0.58, 0.41-0.83 |
| | Middleton, 2008[98] | CSHA, Canada | 65+ | 4,683 | Incident | 5 | CIND | Negative in women; 0.62, 0.47-0.84 |
| **Leisure Activities** | Verghese, 2006[99] | BAS, USA | 75-85 | 437 | Incident | 5.6 | MCI | Negative; cognitive: 0.46, 0.24-0.91 |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| **Social Isolation** | Artero, 2008[62] | 3-C Study, France | 65+ | 6,892 | Prevalent | NA | MCI | Positive in women: 1.21, 1.04-1.42 |
| | Monastero, 2007[64] | KP, Sweden | 75+ | 718 | Incident | 3.4 | CIND | No effect |
| **Smoking** | Di Carlo, 2000[35] | ILSA, Italy | 65-84 | 3,425 | Prevalent | NA | CIND | Negative; current: 0.72, 0.54-0.98 |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | No effect; current and past |
| | Solfrizzi, 2004[50] | ILSA, Italy | 65-84 | 2,963 | Incident | 3.5 | MCI | Positive; frequent vs. infrequent/no smoking |
| | Luck, 2010[178] | LEILA 75+ | 75+ | 1,692 | Incident | 8 | MCI | No effect; lifetime exposure |
| **Diet** | Roberts, 2010[92] | Mayo Study, USA | 70-89 | 1,233 | Prevalent | NA | MCI | Negative; PUFA: 0.44, 0.29-0.66 |
| | Roberts, 2010[91] | Mayo Study, USA | 70-89 | 1,233 | Prevalent | NA | MCI | Negative; vegetables: 0.66, 0.44-0.99 |
| | Solfrizzi, 2006[93] | ILSA, Italy | 65-84 | 464 | Incident | 2.6 | MCI | No effect; PUFA |
| | Eskelinen, 2008[90] | CAIDE, Finland | 65-80 | 1,449 | Incident | 21 | MCI | Positive; fat at midlife: 2.36, 1.17-4.74 |
| | Scarmeas, 2009[94] | MS, USA | 65+ | 1,875 | Incident | 4.5 | MCI | No effect; MeDi Diet |
| **Alcohol** | Anttila, 2004[95] | CAIDE, Finland | 65-79 | 1,464 | Prevalent | 23 | MCI | Negative; no drinking: 2.08, 1.05-4.13 |
| | | | | | | | | Positive; past hazardous: 2.34,1.15-4.77 |
| | Espeland, 2005[195] | WHIMS, USA | 65-79 | 4,461 | Incident | 4.2 | MCI | No effect; baseline moderate |
| | Atti, 2010[55] | Faenza Project, Italy | 60+ | 7,389 | Prevalent | NA | CIND | Positive; past hazardous: 2.91, 1.05-8.04 |
| | | | | | | | | No effect; current moderate |
| | Roberts, 2010[91] | Mayo Study, USA | 70-89 | 1,233 | Prevalent | NA | MCI | No effect; current moderate |
| | Luck, 2010[178] | LEILA 75+, Germany | 75+ | 1,692 | Incident | 8 | MCI | No effect; baseline moderate |

In **Table 1, 2 and Figures 1-7**:

YRS = Years

F-up = Follow-up

MI = Memory Impairment

CI = Cognitive Impairment

Def. = Definition

OR = Odds Ratio

RR = Relative Risk

SD = Standard Deviation;

Reference = Source of the reference population

External = An external reference population is used

Local = The reference is the study population

NA = Not applicable

AD = Alzheimer's Disease

APOE = Apolipoprotein E gene

CSHA. Canadian Study of Health and Aging

KP. Kungsholmen Project

LEILA 75+. Leipzig Longitudinal Study of the Aged

MYHAT. Monongahela-Youghiogheny Healthy Aging Team (MYHAT) Project

Tone Town Study. Study of the town of Tone

PAQUID. Personnes Agées QUID

MoVIES. Monongahela Valley Independent Elders Survey

CSBA. Conselice Study of Brain Ageing

CAIDE. . The Cardiovascular Risk Factors, Aging and Dementia study

CHS. Cardiovascular Health Study Cognition Study

HNRSC. Heinz Nixdorf Recall Study Cohort study

Mayo Study. The Mayo Clinic Study of Aging

ILSA. Italian Longitudinal Study on Aging

ISHA. Indianapolis Study of Health and Aging

MS. Manhattan Study.

WHIMS. Women Health Initiative Memory Study

RMAP. Rush Memory and Aging Project

3-C Study. Three Cities Study

Osteoporotic Women Int. International study on postmenopausal women with osteoporosis.

HK. Hong Kong Study

MRCCFA. The Medical research Council Cognitive Function and Ageing Study

BAS. Bronx Aging Study

# 2 AIMS

## 2.1 GENERAL AIMS

The general aims of this thesis are to improve our knowledge of the *occurrence*, *correlates and risk factors*, and *progression* of cognitive impairment without dementia in the elderly population.

## 2.2 SPECIFIC AIMS

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

1. To determine the prevalence of subjective cognitive impairment and objective cognitive impairment in the nondemented elderly population and to explore the contribution of genetic background and early life environment to subjective and objective cognitive impairment (*Study I*).

2. To determine the incidence of cognitive impairment without dementia in the elderly population, to examine the impact of attrition due to death on observed incidence estimates, and to compare the observed and corrected estimates of the incidence of cognitive impairment with incidence rates of dementia (*Study II).*

3. To assess the association of common chronic diseases and multimorbidity with objective and subjective cognitive impairment without dementia, taking into account the contribution of genetic background and early-life environment (*Study III).*

4. To investigate the symptom of low mood as a predictor of cognitive impairment and its progression to dementia, taking into account cognitive impairment severity, time of assessment of low mood symptom, and interaction with other candidate risk factors *(Study IV).*

# 3 METHODS

The data used in this thesis are derived from two projects: The Kungsholmen Project and The HARMONY Study.

## 3.1 THE KUNGSHOLMEN PROJECT (*Studies II, and IV*)

### 3.1.1 Study population

The Kungsholmen Project is a community-based cohort study on aging and dementia. All registered inhabitants (n=2,368) who were living in the Kungsholmen district of Stockholm, Sweden, and were 75 years of age and older on October 1st 1987 were initially invited to be part of the project, and 1,810 (76.4%) agreed to participate in the baseline survey.[196, 197]

**Baseline survey.** At baseline (1987-1989), a two-phase survey consisting of a screening phase and a clinical phase was carried out. The screening phase included a health interview and the administration of the MMSE[33] for all 1,810 participants. In the clinical phase, all subjects who screened positive (MMSE≤23) and an age - and sex-stratified random sample of subjects who screened negative (MMSE >23) were invited to undertake a comprehensive physical, neurological, and psychiatric assessment, similar to the examination usually performed in clinical practice. During the clinical phase, 110 subjects refused to participate and 225 persons were diagnosed as having dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria (DSM-III-R).[6] Thus, 1,475 of 1,810 baseline participants were identified as being free of dementia. Of them, 40 subjects had missing data on education or MMSE < 20 and were excluded, leaving 1,435 subjects remaining for analysis. In Study II, 23 subjects were excluded because of missing data on cognitive tests. These values were imputed in Study IV. In addition to this, 342 prevalent cases of CI were detected at baseline, in Study II. In Study IV, changes in the way of adjudicating years of education led to slight changes in CI classification, which identified 337 prevalent cases (5 fewer than in Study II). Therefore, the baseline study population comprised 1070 subjects in Study II and then 1098 subjects in Study IV (Figure 8).

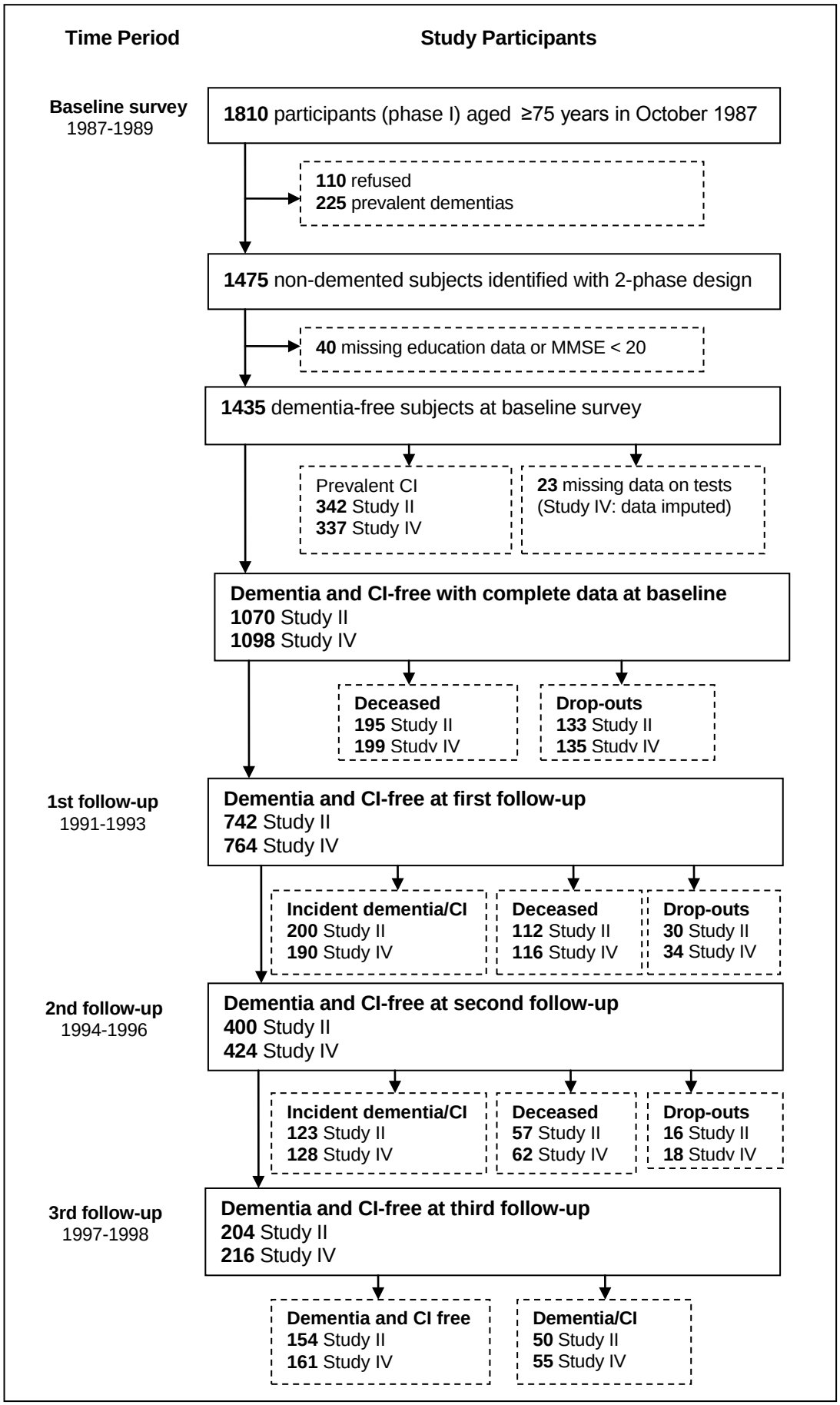


**Figure 8.** Flowchart of Kungsholmen Project study populations. CI=cognitive impairment.

**Follow-up examinations**. After the baseline survey, study participants underwent four waves of follow-up examinations, each with an average three-year interval.[198] In both Study 2 and Study 4, the first three waves of follow-up examinations were used (Figure 8). At each follow-up, all surviving subjects were assessed by way of a structured interview carried out by nurses and a clinical examination performed by physicians, which included basic cognitive testing. When possible, additional neuropsychological tests were performed by psychologists. If the subject was not able to answer, an informant, usually a next-of-kin, was interviewed. For those subjects who had died before the follow-up examination, information regarding their health status was obtained from the computerized inpatient register system, which is a register of discharge diagnoses from all Stockholm hospitals since 1969. The individual hospital records, discharge diagnoses, and death certificates were examined.

### 3.1.2 Data collection

During the screening phase of the baseline survey, a health interview was carried out to collect data on demographics, medical history, and cognitive functioning. The clinical phase of the baseline survey consisted of a dementia work-up including a structured interview, a comprehensive clinical examination, and psychological tests implemented following the standardized protocols.[196-198]

#### *3.1.2.1 Demographics*

Data on demographic variables (e.g., age, sex, and education) were collected from the subjects at the baseline interview. Years of education were derived by summing up the duration in years of the different levels of formal schooling (according to the Swedish system). The variable was dichotomized into low (<8 years) vs. high ( ≥8 years) according to a previous study within the Kungsholmen Project.[53] When adjudicating years of formal education, professional training was first counted as formal schooling but was later reclassified as non formal, extra curriculum, education.

#### *3.1.2.2 Medical history*

Data on medical history or comorbidities at baseline and during the entire follow-up period were obtained from the computerized inpatient register system, which recorded up to six different diagnosed disorders during each hospital admission. The

International Classification of Disease, Eight Revision (ICD-8) was used by the register system until 1986. Since 1987 the ICD Ninth Revision (ICD-9) has been employed.

#### *3.1.2.3 Medical drug use*

Data on medical drug use for the two weeks prior to the baseline interview were collected from the subjects and verified by inspecting drug prescriptions and containers. Medical drugs were coded in accordance with the *Anatomical Therapeutic and Chemical* (ATC) classification system.[199] Antidiabetic drugs were considered as medications used to control blood glucose levels (hypoglycemic medications or insulin injection, ATC code A10). Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ATC codes C02, C03, and C07).

#### *3.1.2.4 Clinical and genetic information*

Weight and height were measured using a standard scale in light clothing and no shoes.[200] BMI was calculated as weight in kilograms divided by squared height in meters. Arterial blood pressure (i.e., systolic Korotkoff phase I and diastolic phase V) was measured by nurses with the subjects seated after at least a five minute rest. Blood samples were taken at baseline and at each follow-up examination. Blood glucose level was measured using a glucose oxidase procedure.[201] Data on blood glucose were available for 95.9% (n=1,248) of the dementia-free subjects at baseline. Genomic DNA was prepared from peripheral blood samples that were taken at baseline, and *APOE* allelic status was determined following a standard procedure.[202]

#### *3.1.2.5 Psychiatric evaluation*

At baseline, nurses assessed mental health as part of a *general health status interview* consisting of questions with yes/no answers. The questionnaire investigated different health-related symptoms and included items on depressive symptoms, such as low mood, anxiety, feelings of loneliness, sleeping disturbances, reduced appetite, and tiredness. All of these symptoms aside from loss of appetite loaded on the same factor, as shown by a factor analysis with varimax rotation performed at baseline. Low mood had the highest loadings on this depression factor (0.81), followed by feelings of loneliness (0.70) and anxiety (0.64). At follow-ups, all patients underwent a structured psychiatric interview performed by physicians and based on the *Comprehensive*

*Psychopathological Rating Scale (CPRS).*[203] The interview covered several psychopathological areas, comprising symptoms of depression and anxiety. Mood-related symptoms included: low mood, suicidal ideation/thoughts of death, feelings of guilt and appetite disturbances. For each symptom, scores were graded in degrees of severity on a scale from 0 (the absence of a symptom) to 6 (extreme severity of the symptom). Scores were dichotomized into yes, for all scores exceeding 0, versus no, for a score equal to 0 (Study IV).

#### *3.1.2.6 Cognitive assessment*

**Nurse interview**. At baseline and follow-ups nurses collected *subjective memory complaints* by asking whether the participants had experienced troublesome memory problems recently. Functioning in daily life was investigated with the *Katz Index of Activities of Daily Living* (Katz' ADL).[204] All subjects were also evaluated with the *Mini Mental State Examination* (MMSE),[33] a measure of global cognitive functioning which encompasses basic cognitive functions, such as orientation, language, attention, episodic memory, and visuospatial abilities. The MMSE's score ranges from a minimum of 0 (worse performance) to a maximum of 30 (best performance). The MMSE is the most extensively studied screening tool for dementia. A meta-analysis of 34 studies separated into high and low prevalence settings reported optimal psychometric properties for the MMSE.[205] In memory clinic settings the MMSE had a pooled sensitivity (Se) of 79.8%, a specificity (Sp) of 81.3%, a positive predictive value (PPV) of 86.3% and a negative predictive value (NPV) of 73.0%. In mixed specialist hospital settings the Se, Sp, PPV and NPV were 71.1%, 95.6%, 94.2% and 76.4%, respectively. In non-clinical community settings the MMSE had a pooled Se of 85.1%, a Sp of 85.5%, a PPV of 34.5% and an NPV of 98.5%. In those studies conducted purely in primary care the Se, Sp, PPV and NPV were 78.4%, 87.8%, 53.6% and 95.7%, respectively. Thus the case-finding ability of the MMSE was best when confirming a suspected diagnosis in specialist settings with correct identification made in 27/30 positive results. It was modestly effective at ruling-out dementia in specialist settings. Conversely, in non-specialist settings, the MMSE was best at ruling out dementia, achieving about 29/30 correct classifications with less than three false negatives out of every 100 screens. Recently, the MMSE has also been found to be a promising screening tool for non-dementia CI.[206] A MMSE score of < or =28 showed a

sensitivity of 85.5% and a specificity of 66.7% for MCI compared with a definition based on a 60-min battery of validated tests evaluating different cognitive domains.[206]

In all cases suspected of CI, an *interview with a next-of-kin* was also conducted by nurses, to evaluate if there had been any significant change in cognitive abilities and whether the cognitive impairment was interfering with daily life activities. The interview was based on the Section H of the CAMDEX.[138]

**Physician interview**. At baseline and follow-ups physicians performed a cognitive examination covering: i) *autobiographic and semantic memory*, investigated by asking facts of general knowledge and past personal information; ii) *language*, investigated by object naming and speech comprehension; iii) *abstract thinking*, investigated with problem solving simulation and proverbs; and iv) *visuospatial abilities* and *praxis*, investigated by repeating simple motor activities and by copying figures.[196] From the first follow-up onwards, *episodic memory*, measured with the word recall task[207] described below, and *attention/working memory*, measured with the digit span forward and backwards,[208] were also included in the standard dementia workup. The *word recall task* consists of reading aloud a set of 12 commonly used words to the subject who is asked to remember as many words as possible. After the words presentation, to be carried out at a pace of 2 seconds per word, the subject says all the words she can recall, aloud and in a random order. The score, which ranges from a minimum of 0 (worst performance) to a maximum of 12 (best performance), represents the total number of correct hits. The test has been validated within the Kungsholmen Project.[207]

**Additional neuropsychological tests**. A sub-sample of participants received further neuropsychological assessment performed by psychologists. The evaluation included tests covering different cognitive domains. *Attention and executive functions* were tapped by the Trail Making test;[209] *episodic memory* was examined with tests of free and organized recall of random words plus a recognition task,[207] and with a test of face recognition;[207] *visuospatial abilities* were tapped with the block design task from the WAIS,[208] and the clock reading test;[210] *verbal abilities* were examined with letter and category fluency tasks.[211]

### 3.1.3 Diagnosis of dementia

The clinical diagnosis was based on 1) the next-of-kin interview performed by nurses, as described above;[138] and 2) a clinical examination performed by two physicians. The clinical examination was similar to a comprehensive geriatric examination usually performed in a clinical practice, but structured and defined with scoring criteria. It included a medical history, a physical and neurological examination, a cognitive examination (as described above), and assessment of depression (mood-related section of the CPRS).[203] DSM-III-R diagnostic criteria[6] were used for the clinical diagnosis of dementia and different types of dementia. Moreover, when only one item in the diagnostic criteria was not fulfilled, the subject was classified as affected by questionable dementia. The diagnostic procedure, which has been validated, comprised three steps.[196-198] In step one, a preliminary diagnosis was made after a common discussion among the physicians who examined the patient and the nurses who performed the next-of-kin interview. In step two, an external physician blind to the preliminary diagnosis made a second diagnosis based on collected data. In step three, in cases of discrepancy between the two diagnoses, a senior physician was consulted to make the final diagnosis.

The differential diagnosis of AD required gradual onset, progressive deterioration, and the lack of any other specific causes of dementia. The diagnosis of VaD required abrupt onset, stepwise deterioration, history of stroke, or focal deficits. Hachinski's ischemic scale[212] was used to support the differential diagnosis between AD and VaD. The diagnostic criteria used for AD and VaD were equivalent to "probable AD" according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[213] and to "possible VaD" according to the NINDS-AIREN criteria,[212] respectively.

For subjects who died in between follow-up examinations, two physicians made a diagnosis of dementia or subtypes by thoroughly reviewing medical records and death certificates.[198]

### 3.1.4 Definition of cognitive impairment

In people that were dementia-free according to the clinical examination, syndromes of cognitive impairment were defined using both MCI and CIND criteria.

### *3.1.4.1 MCI*

MCI was defined according to the original Mayo Clinic criteria for aMCI and was operationalized as follows: 1) *Memory complaint* was defined as a report by the subject, the next-of-kin, or both; 2) *Normal general cognitive function* was defined as scoring above a previously defined cutoff for cognitive impairment of 1 SD below age and education-specific means on the MMSE; 3) *Absence of dementia* was determined by physicians as described above; 4) *Normal activities of daily living* was defined as the absence of functional impairment on Katz' ADL scale, or slight functional impairment which was judged by the examining physician not to be attributable to cognitive impairment; 5) *Objective memory impairment* was defined as scoring at least 1.5 SD below age- and education-specific means on the word recall task described above. The means were based on age quartiles of the population at first follow-up, stratified by level of education (high vs. low). At baseline, prevalent cases of aMCI were defined as scoring 1.5 SD below the mean performance of the dementia-free population on the episodic memory section of the MMSE, corresponding to complete failure in recalling the three items. The cut-off of 1.5 SD, chosen both at baseline and follow-ups, has been shown to have increased stability over time compared to less stringent cut-offs, and minimizes the "back-to-normal" effect often observed in MCI when using a single test of episodic memory.[214]

### *3.1.4.2 CIND*

CIND was defined as global cognitive impairment and operationalized as follows: 1) *Absence of dementia* was determined by physicians as described above; 2) *Objective global cognitive impairment* was defined as scoring at least 1 SD below age- and education-specific means on the MMSE. The means were based on seven age strata of the dementia-free population at baseline stratified by education (high vs. low). The cutoff of 1 SD was chosen in order to include cases with even slight global cognitive impairment. The term oCIND, previously used in the PAQUID study with a similar meaning,[180] was preferred to the term CIND in order to avoid confusion with the different definition adopted by the Canadian and Indianapolis studies[36, 37, 46] as well as emphasizing the inclusion of non-dementia cognitive impairment cases other than aMCI.

Because of the adopted criteria, aMCI and oCIND were mutually exclusive. This allowed the definition of a larger group of cognitively impaired subjects without dementia, which included both aMCI and oCIND cases.

### 3.1.5 Covariates

*Education* was dichotomized into less than 8 years (low education) and more than 7 years (high education).

*Age* was categorized into four groups: 75-79, 80-84, 85-89, 90+ (*Study II*) and dichotomized based on the median of the population at each wave (*Study IV*).

*Depressive symptoms* (*Study II*) included reported perceived sadness and feelings of loneliness, from the general health interview performed by nurses at baseline. For the variable *low mood*, which was the main exposure in *Study IV*, information on perceived sadness from the baseline general health status interview and from the CPRS performed at follow-ups was merged.

*Dissatisfaction with own health* was coded based on responding with a "no" to the question "Do you feel healthy?", which was part of the general health interview at baseline (*Study II*).

Several diagnoses derived from the Inpatient Register were used in both *Study II* and *IV*: *hip fracture* in the last year (ICD-8 and ICD-9 codes 820, 821), history of *cerebrovascular disease* (ICD-8 and ICD-9 codes 430-438), history of *heart failure and arrhythmia* (ICD-8 and ICD-9 codes 427-429), history of *psychosis* (ICD-8 and ICD-9 codes 291-298).

For *diabetes*, information from the Inpatient Register (ICD-8 and ICD-9 code 250) was integrated with information from two additional sources: using blood glucose-lowering medications (ATC code A10), or having blood glucose (nonfasting) level higher than 11 mmol/L. *Multimorbidity* was defined as having two or more chronic diseases, based on diagnoses from the Inpatient Register (*Study IV*).

In *Study II*, further variables derived from the Inpatient Register were: *operation* within the last six months (any surgical intervention during a hospital admission in the previous six months), *hospitalization* within the last six months (any hospital

admission or discharge in the previous six months), *malignancy and unspecified tumors* in the last year (ICD-8 and ICD-9 codes 140-209, 230-239).

Variables regarding the use of medications were: *polypharmacy*, the absolute number of drugs used, as collected by a nurse and coded as a three-level ordinal variable: no drug use, one-to-four drugs, or five or more drugs; *antihypertensive drugs use* (ATC codes C02, C03, C07, C08 and C09) (*Study II*). In *Study IV*, psychoactive drugs were coded as follows: *neuroleptics* (ATC code: N05A), *anxiolytics* (ATC code: N05B), *hypnotics and sedatives* (ATC code: N05C), and *antidepressants* (ATC code: N06A). *High blood pressure* was defined as ≥ 180 arterial blood pressure (i.e., systolic Korotkoff phase I and diastolic phase V) (*Study IV*).

*Social network* was used as an indicator of social integration and coded as a four-level ordinal variable (extensive/moderate/limited/poor social network, based on information collected by nurses). *ApoE-ε4* allele was the only genetic factor considered, and was dichotomized into being a carrier of one or two ε4 alleles versus carrying no ε4 allele.

## 3.2 THE HARMONY STUDY (*Studies I and III*)

### 3.2.1 Study population

Participants were members of the population-based Swedish Twin Registry that was established in the 1960s, when all the twins in Sweden were identified.[215] In 1998-2001, all living twins in the registry, both same- and unlike-sex, who were born in 1935 and earlier (aged ≥65 years) were invited to participate in a study concerning dementia known as HARMONY, which is taken from the Swedish words for "health" (Hälsa), "genes" (ARv), "environment" (Miljö), "and" (Och), and "new" (NY).[216] Of the 20,269 eligible twin individuals, 5,771 could not be contacted by phone and 712 were contacted but were unable to partake in the interview and there was no available informant. For a further 93 subjects the information was incomplete or missing. Of the remaining 13,693 twin individuals, 1,138 were not available for interview because of sickness or severe cognitive impairment but there was an interviewable next of kin.

A total of 1,939 individuals were invited to participate in the clinical phase, including: 1) all twins who were screened positive; 2) those who were not able to be screened by telephone if the informant gave an indication that the reason was dementia; 3) twin partners to those who were diagnosed with dementia; and 4) normal controls. Clinical diagnoses were available for 1,357 individuals.

Finally, out of the 12,555 participants with cognitive screening data we excluded people with: clinical diagnosis of dementia (n=144), questionable dementia (n=125), cognitive impairment but missing clinical workup (n=358), and mental retardation (n=1). The final cohort consisted of 11,927 dementia-free twin individuals available for analysis in *Study I* (Figure 9). Out of this sample, 548 subjects were further excluded because of missing data on covariates, leaving 11,379 twin individuals available for *Study III* (Figure 9).

The participation rates were 71.4% for the screening phase, and 70.0 % for the clinical phase. The prevalence of dementia in this Swedish twin cohort was comparable with several major epidemiological studies of dementia prevalence in Europe and the USA.[216]

### 3.2.2 Data collection

The screening phase of HARMONY was performed telephonically and consisted of two parts. A *general health interview*, which focused on sociodemographic aspects and zygosity, health status, affective symptoms, and common diseases. During the general health interview subjects were asked if they agreed to participate in a *cognitive evaluation*, executed over the telephone, and covering different aspects related to subjective and objective cognitive functioning and activities of daily living.

Further information on medical diseases was derived from the inpatient registry system. The ICD-8 was used by the register system until 1986. The 9$^{th}$ revision (ICD-9) was used since 1987 onwards.

### 3.2.3 Cognitive evaluation

The cognitive evaluation consisted of the previously validated telephonic interview (TELE).[217, 218] Performance on the TELE is summarized in a total score that ranges

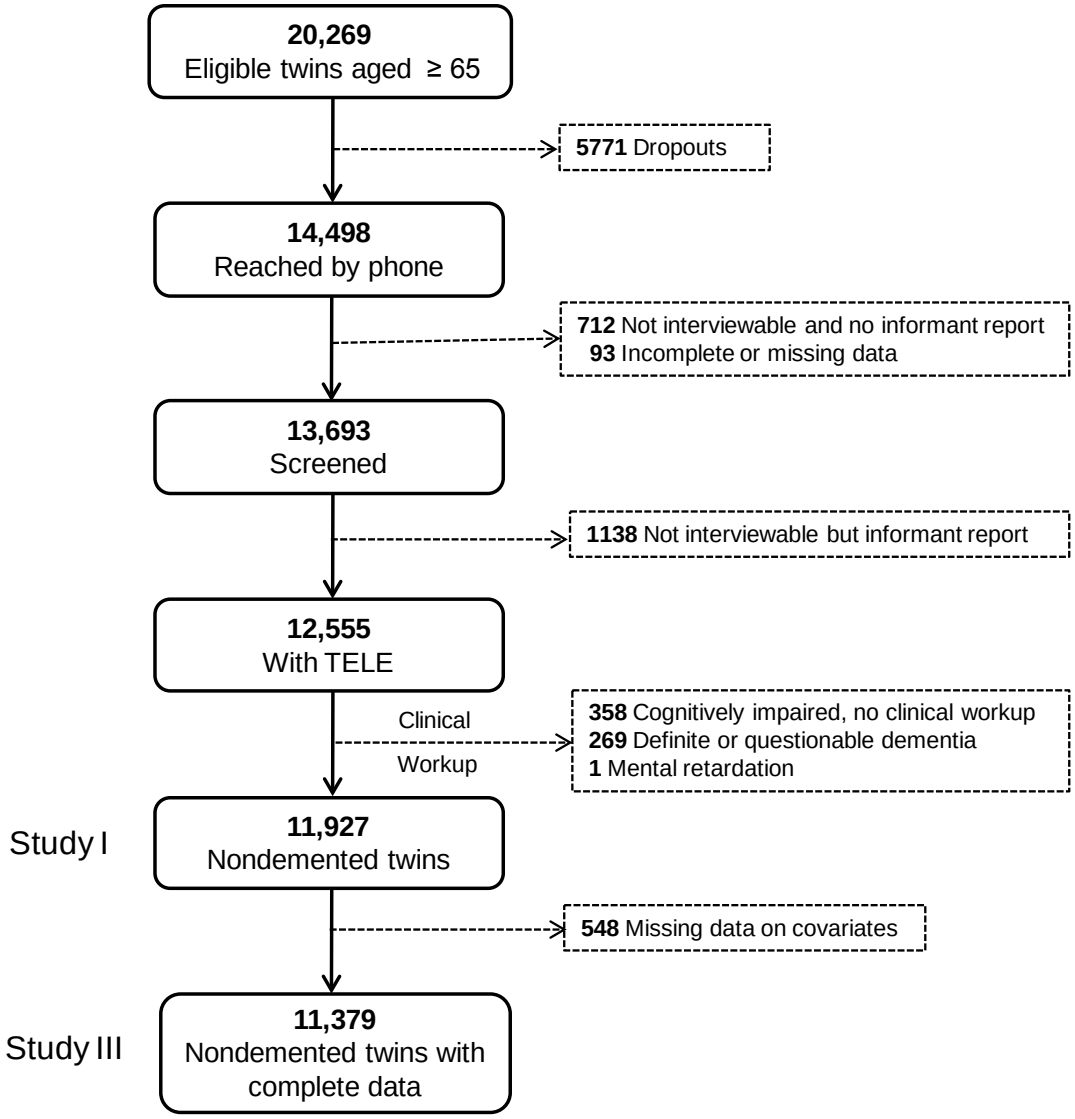


**Figure 9**. Flowchart of HARMONY study populations.

from 0 (worst performance) to 19 (best performance). TELE examines the following four cognitive areas: 1) orientation, assessed by 10 items of the mental status questionnaire (MSQ);[219] 2) attention, measured by counting backwards in threes;[220] 3) reasoning, tapped with questions about similarities and differences between pairs of nouns;[221] and 4) episodic memory, evaluated using a three-item free recall task.[33] In case of failure to recall all the items in the free recall condition, the subjects were administered a recognition task, in which they were required to identify the correct word or words within a list of distractors. TELE includes also a section investigating cognitive complaints, with a general question ascertaining subjective cognitive change "Have you noticed any change in your memory during the last three years?", followed

by more specific questions focusing on different cognitive problems such as forgetting errands, forgetting people's names, forgetting appointments, forgetting known places, and forgetting words. Further questions addressed whether respondents were living independently, their employment status, their recent visits for medical care, their eyesight and hearing, assistance with practical tasks in daily life, and their mood.

When people did not perform optimally or could not perform TELE, an informant was interviewed with questions regarding the subject's health, functional status, activities of daily living, and employment status. If cognitive problems were indicated, follow-up questions were used to obtain a history of the impairment and the pattern of decline, as well as a description of any contacts with the healthcare system concerning health problems. The eleven items of the Blessed Dementia Rating Scale (BDRS) were also included in the informant interview to assess cognitive functioning in everyday activities. The BDRS ranges from 0 to 17, with higher score indicating greater frequency of problems.[222]

Finally, people who were suspected of cognitive dysfunction according to TELE and BDRS combined underwent a comprehensive dementia workup. The dementia workup included a physical and neurological examination, a review of medical history, an informant interview, and a neuropsychological assessment as described in the protocol of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).

### 3.2.4 Diagnosis of dementia

Clinical diagnoses of dementia followed *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria.[7] Preliminary diagnoses made by the interviewing team were reviewed by a diagnostic board consisting of a neurologist and a psychologist. When DSM-IV criteria were completely fulfilled, subjects were diagnosed as having "dementia" in contrast with a category of "questionable dementia", which was used for individuals who did not fulfill one of the first three DSM-IV diagnostic criteria but did exhibit either cognitive impairment or functional disability.[223]

### 3.2.5 Definition of subjective and objective cognitive impairment

#### *3.2.5.1 SCI*

SCI was defined as any perceived cognitive change in the last three years in otherwise cognitively intact people. The operationalization criteria of SCI included: 1) presence of subjective cognitive complaints defined as self-reported memory change within the last three years when the subject was questioned as part of TELE; 2) absence of objective cognitive impairment defined as CIND, as described below; 3) absence of dementia defined on the basis of the clinical diagnosis, as described above.

#### *3.2.5.2 CIND*

CIND was defined as any cognitive impairment in the absence of dementia,[36, 37, 46] using the following operationalization criteria: 1) presence of cognitive impairment defined as a performance at least two standard deviations below the age and education specific mean in any of the four cognitive TELE tasks; and 2) absence of dementia defined on the basis of a clinical diagnosis following the DSM-IV criteria, as described above. The age-and education-specific means of TELE's cognitive tasks were based on the average performance of the dementia-free population classified into eight age- and education-specific groups. A conservative cut-off of 2 SD below the mean was chosen to improve specificity in the face of relatively simple cognitive tests.

Due to the operational definition adopted in this study, SCI and CIND were mutually exclusive.

### 3.2.6 Covariates

#### *3.2.6.1 Sociodemographics and zygosity*

Information on age and sex was obtained from the Swedish Twin Registry. Information on education and zygosity was gathered during the subject's telephonic interview and verified by an informant when the subject was unable to be interviewed or did not perform well on the TELE. The validity of ascertainment of zygosity based on a telephonic interview has been tested against blood markers and found valid in 99% of the cases.[224]

*Age* in years was categorized into four groups of five years each, plus a fifth group of people over 85 years of age.

*Education* was categorized into three groups based on the years of attained formal education, ranging from low (0 to 7 years), to average (8 to 10 years) and high (more than 10 years) education.

Information on *marital status* was dichotomized into married versus non married, including in the married category couples who were cohabiting without being married.

*Occupation* was defined on the basis of an open question about the subject's main occupation in life. These were assigned occupational codes by Statistics Sweden and those codes were categorized as either high occupational SES, including all "white collars" when the main occupation was non-manual, or low occupational SES, including all "blue collars" when the main occupation in life was manual.[225]

There were four possible categories of the variable *zygosity*: monozygotic, in the case of identical twins; same-sex dizygotic; unlike-sex dizygotic; and undetermined. This latter category included twin individuals for whom zygosity could not be ascertained.

#### *3.2.6.2 Chronic diseases*

Medical history was ascertained based on information coming from two sources: a) the Inpatient Register system, and b) self- and informant reports. The inpatient register encompasses all hospital's admissions in Sweden from 1969 onwards. The International Classification of Disease, 8th revision (ICD-8) was used in the register system until 1986; from 1987 onwards the International Classification of Disease, 9th revision (ICD-9) was used.

Diagnoses regarding common chronic diseases[226] were grouped according to the International Classification of Disease, 9th revision (ICD-9) as described in Table 3. More specifically, *psychosis* (dementia excluded) and *affective disorders* included ICD-8, 9 codes: 291-299. *Ischemic heart disease* included ICD-8, 9 codes: 410-414. *Cardiac dysrhythmia, heart failure or other myocardial insufficiency* included ICD-8, 9 codes: 427 and 428. *Hypertension* included ICD-8 codes: 400-404; and ICD-9 codes: 401-405. *Stroke* included ICD-8, 9 codes: 430-438. *Articular diseases* included ICD-8 codes: 712-718; and ICD-9 codes: 710-719. *Osteoporosis* included ICD-8 code: 723; and ICD-9 code: 733. *Hip fracture* included ICD-8 code: N820; and ICD-9 code: 821.

**Table 3.** Chronic diseases clusters according to ICD-9 (WHO).

| Disease groups | Diseases in the group |
|---|---|
| *Mental* | Psychosis and affective disorders |
| *Circulatory* | Ischemic heart disease, cardiac dysrhythmia, heart failure or other myocardial insufficiency, hypertension, stroke |
| *Musculoskeletal* | Articular diseases, osteoporosis, hip fracture |
| *Respiratory* | Chronic obstructive pulmonary disease, emphysema, asthma |
| *Endocrine* | Diabetes, thyroid dysfunction |
| *Gastrointestinal* | Intestinal diverticula, ulcerous colitis, Chron's disease, liver cirrhosis, cholelithiasis |
| *Urological* | Renal failure, renal calculosis, prostate hypertrophy, recurrent cystitis |
| *Malignancy* | Malignant tumors |

*Chronic obstructive pulmonary disease* (COPD) included ICD-8, 9 code: 491. *Emphysema* included ICD-8, 9 code: 492. *Asthma* included ICD-8, 9 code: 493. Diabetes included ICD-8, 9 code: 250. *Thyroid dysfunction* included ICD-8, 9 codes: 240-246. *Intestinal diverticula* included ICD-8, 9 code: 562. *Ulcerous colitis* included ICD-8 code: 563, and ICD-9 code: 556. *Crohn's disease* included ICD-8 code: 563; and ICD-9 code 555. *Liver cirrhosis* included ICD-8, 9 code: 571. *Cholelithiasis* included ICD-8, 9 code: 574. *Renal failure* included ICD-8 code: 582; and ICD-9 code 585. *Renal calculosis* included ICD-8, 9 code: 592. *Prostate hypertrophy* included ICD-8, 9 code: 600. *Recurrent cystitis* included ICD-8, 9 code: 595. *Malignant tumors* included ICD-8 codes 140-209; and ICD-9 codes: 140-208.

According to previous research, *multimorbidity* was defined as having at least two chronic diseases co-occurring in the same individual.[226]

#### *3.2.6.3 Current affective symptoms*

*Depressive symptoms* were assessed during the telephone screening using the short form of the Center for Epidemiologic Studies Depression Scale (CES-D).[227, 228] The short CES-D consists of 11 items scored on a 0 to 4 scale and related to the frequency

of symptoms (from 0=rarely/none to 4=Most/All of the time). Two items referring to feeling happy and enjoying life are reverse scored. The other nine items refer to poor appetite, feeling depressed, feeling like everything is an effort, restless sleep, feeling lonely, feeling that people are unfriendly, feeling sad, feeling disliked, and the feeling of not being able to "get going". CES-D total score was dichotomized using a cut-off of 9.[229]

*Anxiety symptoms* were assessed during the telephone screening by using the Composite International Diagnostic Interview – Short Form (CIDI-SF).[230] People were classified as having current anxiety symptoms if they reported any episode of worry or anxiety and answered positively to the question "are you still anxious?".

## 3.3 ANALYTICAL AND STATISTICAL STRATEGIES

The main aims of this thesis were achieved by carrying out a set of different analytic strategies, which implied the use of a wide range of statistical techniques. A summary of the analytical and statistical strategies used in each study is shown in Table 4.

### 3.3.1 General analytical strategies

1. **Occurrence of CI**. The occurrence of non-dementia CI was estimated both cross-sectionally (*Study I*) and longitudinally (*Study II*). Incidence rates were estimated using 9-year follow-up data and were corrected for the possible bias caused by attrition due to death.

2. **Correlates and risk factors for CI**. Different correlates and risk factors for non-dementia CI were investigated. The effect of age and gender on CI frequencies was evaluated both cross-sectionally (*Study I*) and longitudinally (*Study II*). Other sociodemographic characteristics such as education, marital status, and occupational SES were evaluated on prevalent CI cases (*Study I*). The contribution of familial factors, such as genetic background and early life environment, to CI syndromes was evaluated using prevalent cases (*Study I*). Association with history of chronic diseases and multimorbidity was evaluated on prevalent cases of non-dementia CI, taking into account the role of familial factors (*Study III*). Finally, low mood was investigated as a possible risk factor

for non-dementia CI, using 6-year follow-up data to estimate a 3-year risk and taking into account also other candidate risk factors for CI (*Study IV*).

3. **Progression to dementia**. Low mood was the only factor studied in relation to the progression of CI to dementia (*Study IV*) and was studied using 6-year follow-up data to estimate a 3-year progression risk.

### 3.3.2 General statistical procedures

Throughout the four studies a range of statistical tests was employed. However, the following techniques were used in all studies.

1) Chi-square test and Student's t-test or analysis of variance were performed to assess the statistical differences of proportions and means between groups. The Mann-Whitney test was used to test for differences in the medians between groups for continuous variables with non-normal distribution.

2) Missing information was estimated using Multiple Imputation, which assigns a value of 0 or 1 to the missing values. The procedure consists of three steps: firstly, all the variables that are considered related to the variable of interest are used as predictors to generated multiple plausible estimates of the missing values, which are stored in different datasets; secondly, independent data analyses are carried out on each complete dataset; finally, the different estimates are pooled together according to Rubin's formula.[231]

3) The combined effect of two factors was assessed by creating dummy variables based on the joint exposures to both factors. The statistical interactions were examined by incorporating the independent variables and cross-product terms in the same models.

All data analyses were carried out using SPSS statistical package (versions 14.0-18.0 of PASW for Windows, SPSS Inc., Chicago, IL, USA) and Stata (versions 9.0-10.0 for Windows, Stata-Corp, College Station, Texas).

### 3.3.3 Specific statistical procedures

#### *3.3.3.1 Study I*

1) Prevalence rates (cases per 100 subjects) were calculated in five different age groups according to sex and education. Ninety-five percent confidence intervals (95% CI) were calculated based on the binomial distribution.
2) Probandwise Concordance was calculated according to the formula of 2C/(2C+D), in which C is the number of twin pairs concordant for the studied outcome and D is the number of discordant twin pairs.[232]
3) Tetrachoric Correlations with 95% confidence intervals were run to further investigate the conditional probability of a twin to be affected by the outcome of interest, given that the co-twin was affected. Tetrachoric correlations represent the correlation of liability between relatives and are analogous to intra-class correlation based on continuous data.[232]

Both probandwise concordance and tetrachoric correlations were performed for monozygotic, dizygotic same-sex and dizygotic unlike-sex twin pairs independently.

#### *3.3.3.2 Study II*

1) Incidence rates were calculated as the number of new events divided by the time at risk (person-years), with 95% confidence intervals (CI) calculated according to the Poisson distribution. Subjects were considered at risk of developing dementia until they either 1) received a diagnosis of dementia; 2) dropped out from the study due to refusal or moving; or 3) died. Subjects were considered at risk of developing non-dementia CI until they either 1) received a diagnosis of dementia; 2) were classified for the first time as affected by a CI syndrome; 3) dropped out of the study due to refusal or moving; or 4) died.
2) Poisson Regression was used to evaluate the relative risk (RR) of having cognitive impairment associated with sociodemographic factors.

#### *3.3.3.3 Studies I and III*

Association of subjective and objective cognitive impairment with the covariates of interest was carried out following two strategies:

1) Unmatched generalized estimating equations (GEE) models on the whole cohort, which are conceptually equivalent to logistic regression but controls for the clustering of twins within a pair;
2) Conditional Logistic Regression on the twin pairs discordant for cognitive status, which allows matching for unmeasured familial factors, such as genetic background and early life environment.

If the association found with GEE models becomes attenuated in Conditional Logistic Regression models, familial factors are likely to play a role in the association. In contrast, if the association remains significant, the influence of genetic background and early environmental factors are likely to be marginal.[224]

#### *3.3.3.4 Study IV*

1) Multiple Cox Proportional-Hazards models were used to estimate the relative risk and 95% CI of syndromes of CI and dementia associated with baseline low mood, taking into account several potential confounders. For cases detected at the first wave of examinations, the baseline for low mood exposure was set at the study baseline. For cases detected at second wave of examinations, the baseline for low mood exposure was set at the second wave (first follow-up). The relative risks of CI in relation to baseline low mood were comparable between the two waves, therefore Cox regression analysis was performed using data from both waves. In order to preserve the three-year follow-up exposure for CI, baseline LM and all other variables varying with time were entered as time-dependent variables.
2) The same strategy was used in people with incident non-dementia CI to estimate the relative risk of progressing to dementia in relation to baseline low mood.
3) To test for additive interaction, the attributable proportion (AP) due to interaction was calculated together with the 95% CI.[233]

**Table 4.** Summary of the analytical and statistical strategies used in each study.

| Study | Aims | Main Covariates | Outcomes | Other Covariates | Main statistical procedures |
|---|---|---|---|---|---|
| *Study I* | Prevalence; age-, gender-, and education-specific prevalence; association with sociodemographic factors; effect of familial factors | Age; gender; education; familial factors | SCI and CIND | Marital status; occupational SES | Prevalence proportions; Generalized Estimating Equations; Conditional Logistic Regression; Concordance rates; Tetrachoric correlations |
| *Study II* | Incidence; age- and gender-specific incidence; association with sociodemographic factors; correction for attrition | Age and gender | aMCI and oCIND | Education; dissatisfaction with own health; hip fracture; operation; hospitalization; malignancy; number of drugs; stroke; heart disease; antihypertensive drugs use; diabetes; psychosis; depressive symptoms; social network; Apoe-ε4 | Incidence density; Poisson Regression; Multiple Imputation |
| *Study III* | Association with chronic diseases; association with multimorbidity; effect of familial factors | Chronic diseases; multimorbidity; familial factors | SCI and CIND | Age; gender; education; affective symptoms | Generalized Estimating Equations; Conditional Logistic Regression |
| *Study IV* | Association with low mood (CI development and progression) | Low mood | aMCI and oCIND | Age; gender; education; history of psychosis; psychotropic drug use; ApoE-ε4 allele; history of cerebrovascular disease; heart disease; diabetes; high blood pressure; hip fracture; multimorbidity; polypharmacy; social network | Cox Proportional Hazards Regression; Attributable Proportion |

SCI: subjective cognitive impairment; CIND: cognitive impairment no dementia; aMCI: amnestic mild cognitive impairment; oCIND other cognitive impairment no dementia; CI: cognitive impairment.

# 4 ETHICAL CONSIDERATIONS

## 4.1 THE KUNGSHOLMEN PROJECT

All people living in the Kungsholmen district aged ≥75 years and eligible for the study at baseline were sent a personal letter explaining the nature of the project and the importance of the subject's participation, yet emphasizing that this was voluntary. Thereafter, all participants were contacted by phone to check their availabilities, and to book a date for their first visit. At the screening evaluation, informed consents were obtained directly from the subject, after explaining the aims of the project and clarifying that all information would be kept strictly confidential. If there was any indication that 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 was to 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 proxy. All phases of the Kungsholmen Project received approval from the Ethics Committee at the Karolinska Institutet, Stockholm, Sweden.

- Phases I & II (baseline survey): Dnr. 87:148; Dnr. 87:234
- Phase III (the first follow-up examination): Dnr. 90:251
- Phase IV (the second follow-up evaluation): Dnr. 94:122
- Phase V (the third follow-up examination): Dnr: 99:308
- Death certificate and Inpatient register data: Dnr. 99:025; Dnr. 01:020

## 4.2 THE HARMONY STUDY

Informed consent was required from each participant during the telephone interview and again during the clinical phase. The data collection procedures were reviewed and approved by the Swedish Data Inspection Board, Stockholm, Sweden, the Regional Ethics Committee at Karolinska Institutet, Stockholm, and the Institutional Review Board of the University of Southern California. For the HARMONY survey, the approval from the Ethics Committee of the Karolinska Institutet was obtained (Dnr: 97: 051).

# 5 RESULTS

## 5.1 OCCURRENCE OF CI

### 5.1.1 Prevalence

In *Study I*, 4,602 persons with SCI without objective cognitive impairment and 2,927 cases of CIND were detected. The majority of people with SCI (58%) reported more than two complaints, with the most common complaint being "forgetting people's names" (85%), followed by "forgetting words" (49%). On the other hand, most CIND cases were mild (78%), having only one cognitive domain impaired.

Still in *Study I*, the overall prevalence of SCI was 39% (95% CI 38-39%) and that of CIND was 25% (95% CI 24-25%). As shown by the non-overlapping confidence intervals, the prevalence of SCI was significantly higher than that of CIND. The prevalence of SCI was higher among men compared to women (41 vs. 40 per cent) and in people with high compared to low/average educational level (42 vs. 40 per cent), high compared to low occupational SES (43 vs. 39 per cent) and in married compared to unmarried persons (41 vs. 40 per cent). SCI was also more prevalent in all older age groups compared to the youngest, although there was not a linear increase with increasing age (prevalence per cent: 65-69 yrs: 37, 70-74 yrs: 43, 75-79 yrs: 45, 80-84 yrs: 44, 85+ yrs: 40). Prevalence rates of CIND were higher among women compared to men (25 vs. 24 per cent) and in people with low/average compared to high educational level (27 vs. 15 per cent), low compared to high occupational SES (29 vs. 19 per cent) and in unmarried compared to married people (27 vs. 23 per cent). Similarly to what was observed in SCI, there was not a linear increase in the prevalence of CIND with increasing age, CIND was however more frequent in the oldest age group compared to the youngest (prevalence per cent: 65-69 yrs: 23, 70-74 yrs: 25, 75-79 yrs: 24, 80-84 yrs: 25, 85+ yrs: 33).

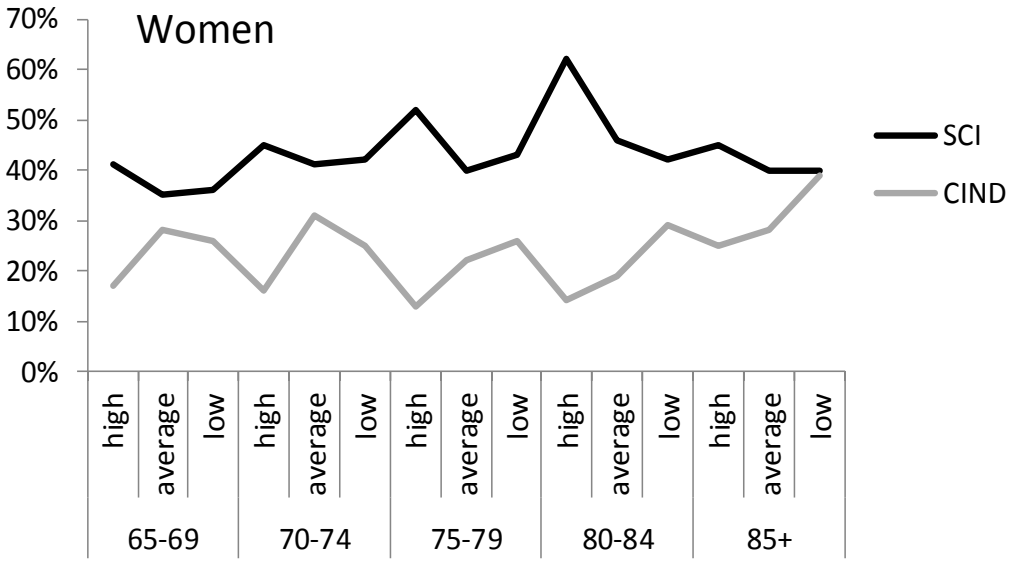


**Figure 10.** Age- and education-specific prevalence per 100 among women.

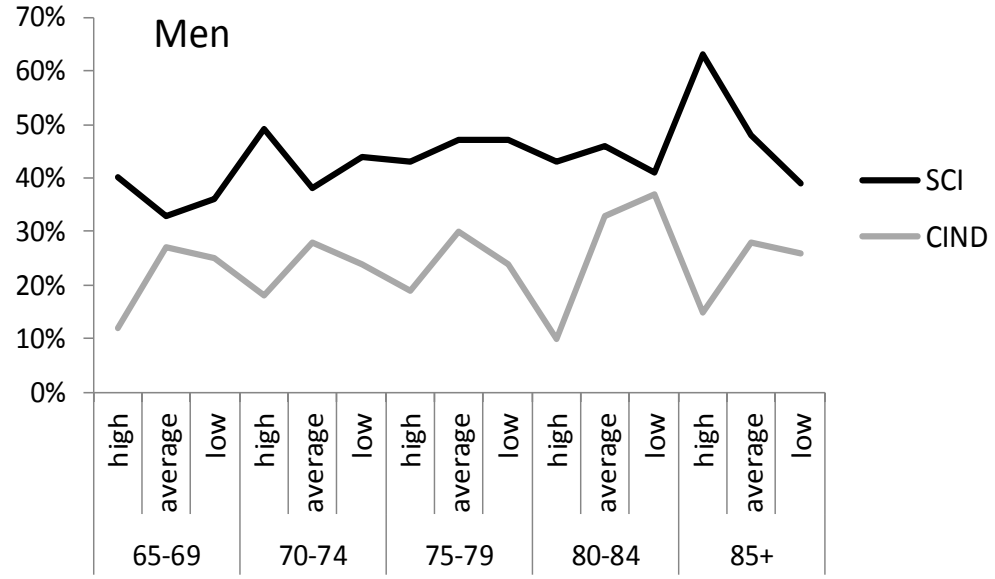


**Figure 11.** Age- and education-specific prevalence per 100 among men.

In age- and education-specific figures by gender, SCI was more prevalent in higher educated women regardless of the age group (Figures 10 and 11). Among men, the trend with education was less linear and showed variation between the different age groups. On the other hand, CIND was consistently more prevalent among people with low/average education compared with people with high education, regardless of both age and gender.

### 5.1.2 Incidence

In *Study II*, during the nine-year follow-up period (4,292 person-years of follow-up) 49 incident aMCI cases and 145 incident oCIND cases were detected. Overall incidence rates were 11.4 (95% CI: 8.6 to 15.1) for aMCI and 33.8 (95% CI: 28.7 to 39.8) for oCIND per 1000 person-years. Gender distributions were similar for aMCI (men: 12.5 [7.2 to 21.5]; women: 11.1 [8.0 to 15.4]) and oCIND (men: 38.4 [28.2 to 52.3]; women: 32.3 [26.7 to 39.1]). For both men and women, age-specific incidence rates of oCIND were higher than those of aMCI. Incidence rates of aMCI and oCIND increased with advancing age, for men more than for women, and in oCIND more than in aMCI (Figures 12 and 13).

After correcting for mortality during follow-up, 64 incident aMCI and 196 oCIND cases were detected during 4,655 person-years of follow-up. Overall incidence rates of aMCI and oCIND increased to 13.7 (10.3 to 18.2) and 42.1 (36.5 to 48.6) per 1000 person-years. As indicated by age- and gender-specific estimates, corrected and observed incidence rates were similar in the younger age groups, but differed among people aged 85+ (Figures 12 and 13).

In Figure 14, aMCI and oCIND groups were merged, and age-specific dementia rates were graphed. Compared to observed rates, corrected rates of non-dementia CI showed a more linear increase with age and the slope representing CI's trend with age resembled the slope with age of dementia.

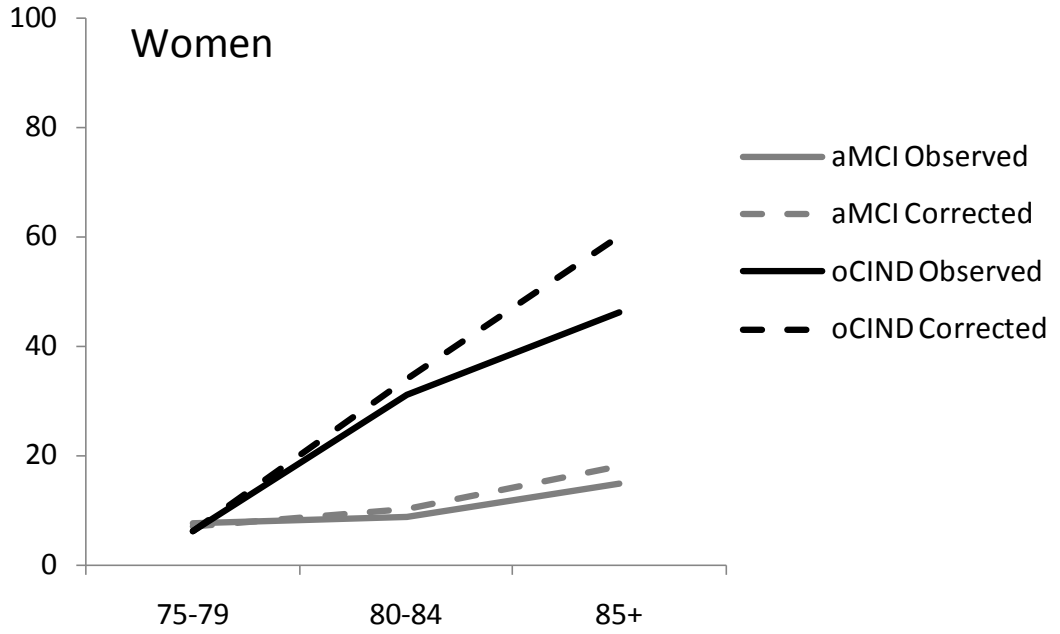


**Figure 12.** Age-specific incidence per 1000 person-years of aMCI and oCIND among women. Both observed and corrected rates are shown.

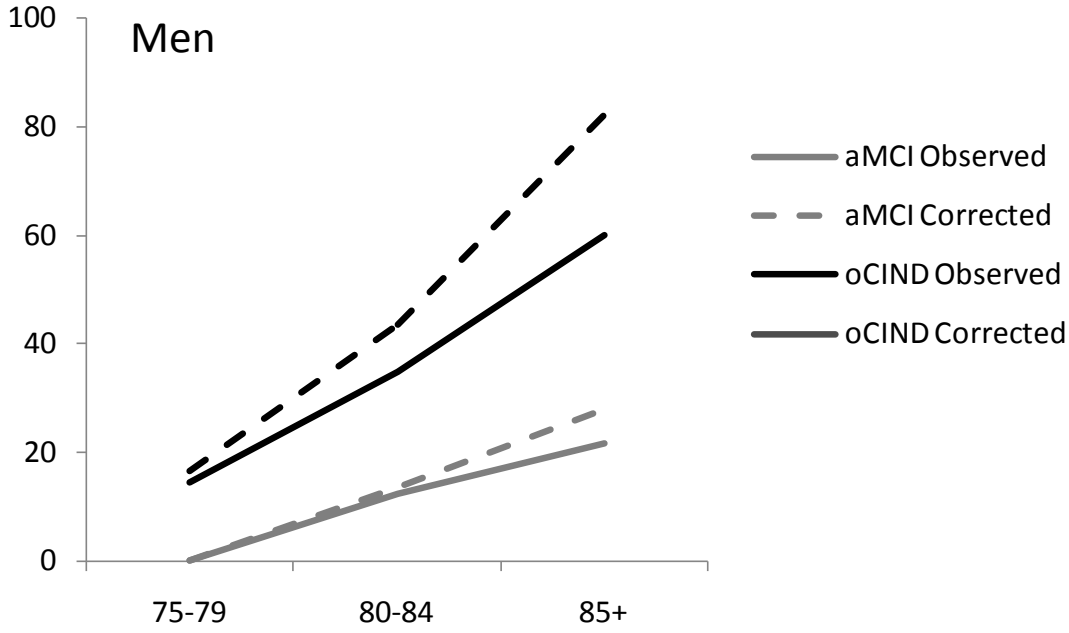


**Figure 13.** Age-specific incidence per 1000 person-years of aMCI and oCIND among men. Both observed and corrected rates are shown.

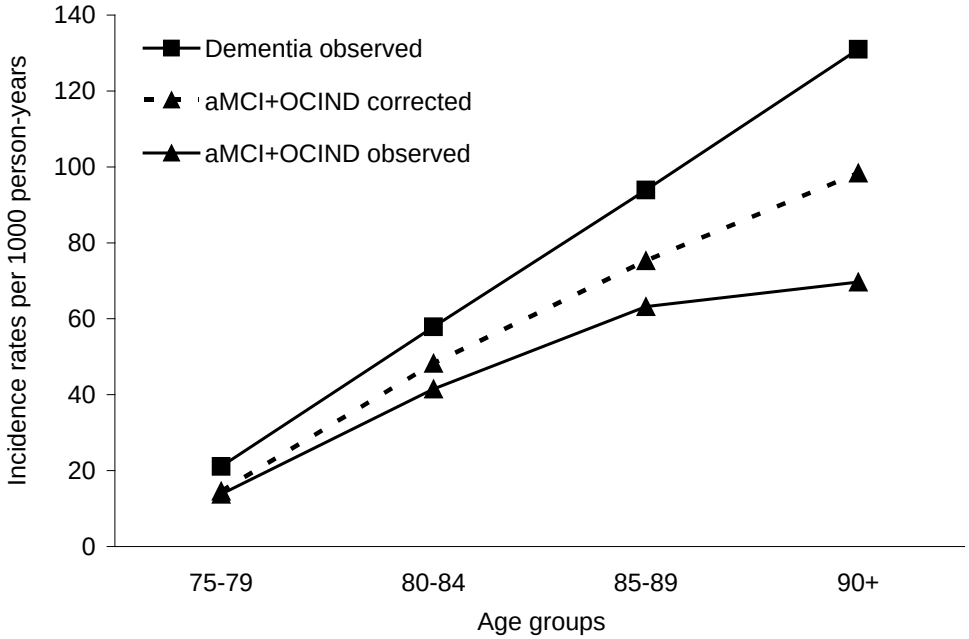


**Figure 14.** Observed and corrected age-specific incidence per 1000 person-years of aMCI+oCIND compared to age-specific incidence rates of dementia. Reprinted with permission from Caracciolo et al, Neurology, 2008[40].

## 5.2 CORRELATES AND RISK FACTORS FOR CI

### 5.2.1 Sociodemographic factors

In *Study I*, the results of the GEE models performed on the whole cohort confirmed the positive association of SCI with higher education and married status and the negative association of these same factors with CIND. In addition, increased odds of SCI were observed in all older age groups compared to the youngest old (65-69 years old) while in CIND only the oldest old (85+ years old) had increased odds compared to the youngest old (Table 5). In models including SES, this factor was associated to increased odds of SCI and to decreased odds of CIND, while the association of education with SCI was no longer significant (Table 5). A multiplicative positive interaction between SES and education was observed for CIND (education*SES: $B=0.440$, $p<0.05$) but not for SCI. Supplementary analyses (*Study I*) showed that when comparing people with cognitive complaints with and without objective CI, CIND with cognitive complaints were significantly older, but similar on the remaining sociodemographic characteristics.

**Table 5**. Association of cognitive impairment (CI) syndromes with sociodemographic variables. Odds Ratios or Relative Risks with 95% confidence intervals from Generalized Estimating Equations (GEE) models and Poisson Regression.

| | **Prevalent Cases** | | | | **Incident Cases** | | | |
|---|---|---|---|---|---|---|---|---|
| | **SCI** | | **CIND** | | **aMCI** | | **oCIND** | |
| | *Model 1* | *Model 2* | *Model 1* | *Model 2* | *Observed* | *Corrected* | *Observed* | *Corrected* |
| **Age groups** | | | | | | | | |
| 65-68 | 1.0 | 1.0 | 1.0 | 1.0 | - | - | - | - |
| 70-74 | 1.3 (1.2-1.4) | 1.3 (1.2-1.4) | 1.0 (0.9-1.2) | 1.1 (0.9-1.2) | - | - | - | - |
| 75-79 | 1.4 (1.3.1.6) | 1.5 (1.3.1.7) | 1.0 (0.8-1.1) | 0.9 (0.8-1.1) | 1.0 | 1.0 | 1.0 | 1.0 |
| 80-84 | 1.4 (1.2-1.6) | 1.5 (1.3-1.7) | 1.0 (0.9-1.2) | 1.0 (0.9-1.2) | 1.8 (0.7-5.0) | 2.1 (0.8-5.5) | 3.8 (1.8-7.9) | 4.0 (2.0-8.1) |
| 85+ | 1.2 (1.0-1.5) | 1.3 (1.0-1.6) | 1.4 (1.1-1.7) | 1.4 (1.1-1.8) | 3.1 (1.2-8.2) | 3.8 (1.4-10.6) | 5.9 (2.9-12.0) | 7.2 (3.6-14.3) |
| **Gender** | | | | | | | | |
| Man | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Woman | 1.0 (0.9-1.0) | 1.0 (0.9-1.0) | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) | 1.2 (0.6-2.3) | 1.3 (0.7-2.5) | 1.3 (0.9-1.8) | 1.4 (1.0-2.0) |
| **Education** | | | | | | | | |
| Low | 1.0 | 1.0 | 1.0 | 1.0 | - | - | - | - |
| Average | 0.9 (0.9-1.0) | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) | - | - | - | - |
| High | 1.2 (1.1-1.3) | 1.1 (1.0-1.3) | 0.5 (0.44-0.58) | 0.7 (0.6-0.8) | - | - | - | - |
| **Married** | | | | | | | | |
| No | 1.0 | 1.0 | 1.0 | 1.0 | - | - | - | - |
| Yes | 1.1 (1.0-1.2) | 1.1 (1.0-1.2) | 0.9 (0.8-0.9) | 0.8 (0.7-0.9) | - | - | - | - |
| **SES** | | | | | | | | |
| Low | - | 1.0 | - | 1.0 | - | - | - | - |
| High | - | 1.2 (1.1-1.3) | - | 0.7 (0.6-0.7) | - | - | - | - |

SCI=subjective cognitive impairment; CIND=cognitive impairment no dementia; aMCI=amnestic mild cognitive impairment; oCIND=other cognitive impairment no dementia; Model 1=adjusted for age, gender, education, marital status, zygosity; Model 2= adjusted for age, gender, education, marital status, zygosity, and SES; Observed=observed estimates; Corrected: estimates corrected for attrition due to death.

Still in *Study I*, co-twin control Conditional Logistic Regression models on SCI- or CIND-discordant twin pairs (n=2,870 and n=2,222) showed confounding by familial factors in the association of SCI with education and SES, and in the association of CIND with marital status (SCI/high education: OR 1.1, 95% CI 0.9-1.2; SCI/high SES: OR 1.1, 95% CI 0.9-1.4; CIND/Married: OR 0.9, 95% CI 0.8-1.1). In contrast, the association of CIND with education and SES and that of SCI with marital status were still significant (CIND/high education: OR 0.8, 95% CI 0.7-0.9; CIND/high SES: OR: 0.8, 95% CI 0.7-0.9; SCI/married: OR 1.2, 95% CI 1.0-1.4).

In *Study II*, Poisson Regression models confirmed the age and gender trends (Table 5). More specifically, we detected a 1.8 (95% CI 1.2-2.7) increased risk of aMCI and a 2.0 (95% CI 1.6-2.5) increased risk of oCIND for a five-year increment in age. Men had a 20% higher risk of aMCI and a 30% higher risk of oCIND compared to women, but the association was not significant (Table 5). In models corrected for attrition the strength of the association with age was enhanced and men were significantly more at risk of oCIND compared to women (Table 5).

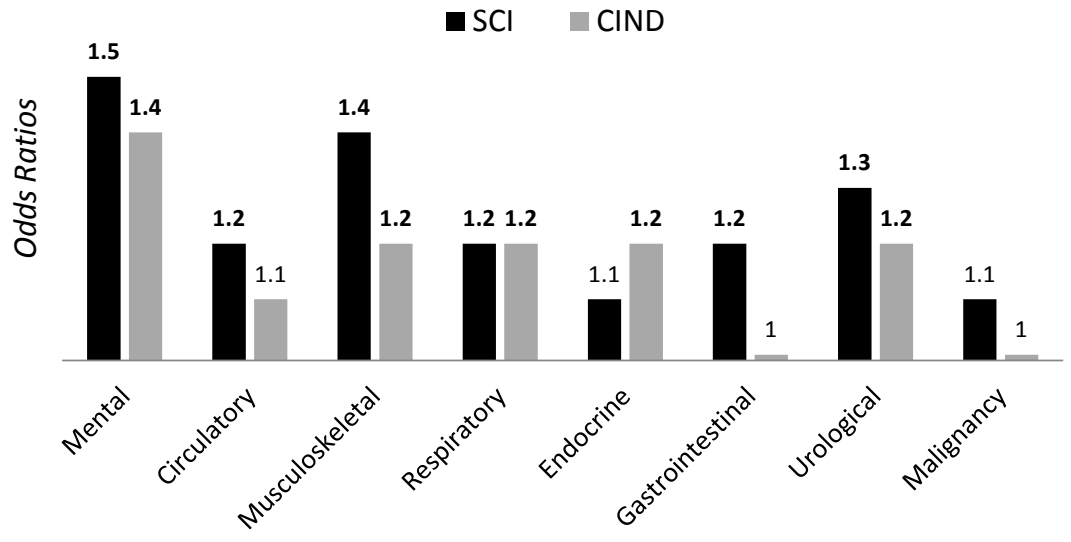


**Figure 15**. Association of common chronic diseases with subjective cognitive impairment (SCI) and cognitive impairment no dementia (CIND). Results from fully adjusted models controlling for sociodemographisc, zygosity, chronic diseases, and current affective symptoms. Numbers bolded refers to associations with p<0.05.

### 5.2.2 Chronic diseases and multimorbidity

In *Study III*, GEE models (adjusted for sociodemographics and zygosity) were performed in the whole cohort and showed positive associations of circulatory, musculoskeletal, respiratory, endocrine, gastrointestinal, urological diseases and malignancy with SCI. Similarly, circulatory, musculoskeletal, respiratory, endocrine and urological diseases were significantly associated with increased odds of CIND. In fully adjusted models further controlling for other diseases and current affective symptoms, the associations of endocrine diseases and cancer with SCI and that of circulatory disease with CIND were no longer significant (Figure 15).

There was also a significant dose-dependent relationship between number of chronic diseases and odds of SCI, while in CIND this effect was less evident. Multimorbidity, defined as the co-occurrence of two or more chronic diseases in the same individual, was present among 61% (n=2,817) of people with SCI, compared to 58% (n=1,616) of CIND and 49% (1,895) of NCI people. In GEE models, multimorbidity was associated with SCI and CIND after basic (SCI: OR 2.0, 95% CI 1.8-2.3; CIND: OR 1.5, 95% CI 1.3-1.8) and full adjustment for potential confounders (SCI: OR 1.9, 95% CI 1.7-2.2; CIND: OR 1.4, 95% CI 1.3-1.7).

Still in *Study III*, in co-twin control Conditional Logistic Regression models on SCI- or CIND-discordant twin pairs (n=1,720 and n=926), the associations of chronic diseases with CIND were no longer significant, with the exception of cancer (OR 1.7, 95% CI: 1.0-2.7). In contrast, the associations of SCI with most chronic diseases, including circulatory (OR 1.3, 95% CI: 1.1-1.7), musculoskeletal (OR 1.5; 95% CI: 1.2-1.8), respiratory (OR 1.5, 95% CI: 1.1-2.2), gastrointestinal (OR 1.8, 95% CI: 1.4-2.8) and urological (OR 1.4, 95% CI: 1.1-1.7) diseases were unchanged. The dose-dependent association with the number of chronic diseases could still be observed for SCI but not for CIND. Similarly, multimorbidity was still associated with SCI (OR 1.9, 95% CI 1.4-2.6) but no longer with CIND (OR 1.3, 95% CI 0.9-2.0).

### 5.2.3 Familial factors

In *Study I,* concordance rates for SCI and CIND were similar in monozygotic and same-sex dizygotic twins and were lower in unlike-sex dizygotic twins (Table 6). These patterns were confirmed by tetrachoric correlation coefficients, which did not

significantly differ between monozygotic and same-sex dizygotic twins. In unlike-sex dizygotic twins the correlation coefficients were lower compared to both monozygotic and same-sex dizygotic twins.

**Table 6**. Probandwise concordance rates and tetrachoric correlations for monozygotic, dizygotic same-sex, and dizygotic unlike-sex twins in subjective cognitive impairment (SCI) and cognitive impairment no dementia (CIND).

| | Monozygotic | | Dizygotic | | Unlike sex | |
|---|---|---|---|---|---|---|
| | Probandwise Concordance Rates | Tetrachoric Correlations (95% CI) | Probandwise Concordance Rates | Tetrachoric Correlations (95% CI) | Probandwise Concordance Rates | Tetrachoric Correlations (95% CI) |
| **SCI** | 52 | 0.24 (0.18-0.30) | 51 | 0.22 (0.17-0.27) | 43 | 0.04 (0-0.10) |
| **CIND** | 31 | 0.23 (0.16-0.28) | 29 | 0.17 (0.12-0.22) | 26 | 0.09 (0.04-0.14) |

### 5.2.4 Low mood

In *Study IV*, during the 3,711.5 person-years (minimum 1.2; maximum 8.2) of follow-up, 160 persons developed MCI. Of these, 40 were classified as aMCI and 120 as oCIND. Fifty-three percent (n=21) of aMCI and 31 percent (n=37) of oCIND occurred in people with baseline low mood (LM). When considering aMCI and oCIND together, the incidence of MCI in people with baseline LM was about 2.5 times higher than that detected among persons without baseline LM. This ratio was constant across both waves of examinations. Cox regression analysis performed using data from both waves and adjusted for sociodemographic characteristics confirmed the increased risk of all outcomes in relation to the presence of baseline LM, although the association was stronger for aMCI. Adjustment for other covariates, including follow-up LM, history of psychosis, psychotropic drug use, ApoE-ε4 allele, history of cerebrovascular disease, heart disease, diabetes, high blood pressure, hip fracture, multimorbidity, and polypharmacy, did not substantially change the results. Stratified analyses showed that the increased risk of aMCI and oCIND associated with baseline LM was neither substantially modified by follow-up LM nor by the other factors (as listed above). However, an additive interaction was found between baseline LM and ApoE-ε4 allele for the risk of developing aMCI (Attributable Proportion: 0.5, 95% CI: 0.1-0.96), but

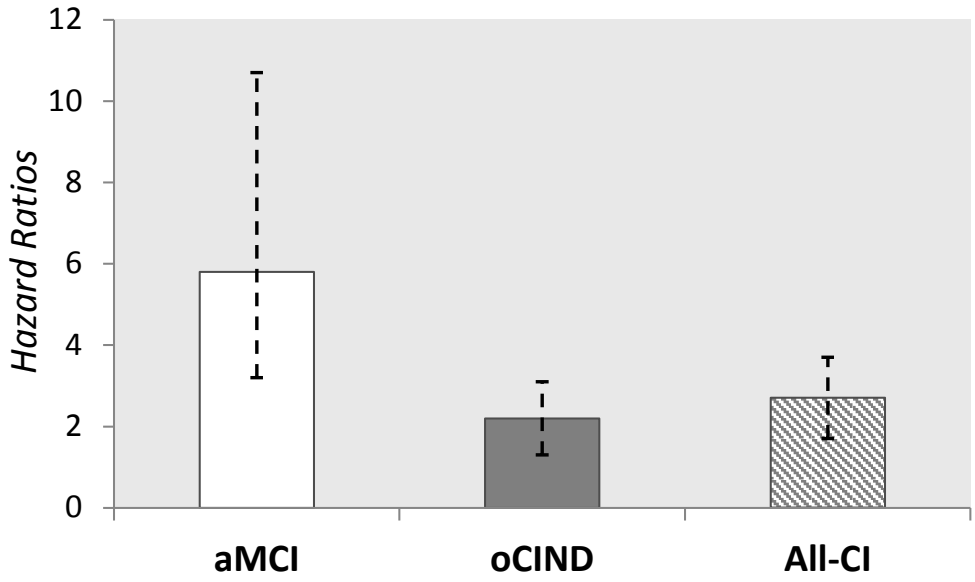


**Figure 16**. Hazard ratios with 95% confidence intervals of baseline low mood in relation to the development of amnestic mild cognitive impairment (aMCI), other cognitive impairment (oCIND) and all cognitive impairment (All-CI). Models are adjusted for age, gender, and education.

not for the risk of developing oCIND. No other interactions were observed.

During the follow-up, 158 cognitively healthy persons developed dementia bypassing MCI. In these people, the HR of low mood was 1.6 (95% CI 1.1-2.3) after adjustment for age, sex, and, education. Further adjustment for other covariates did not affect the relationship of dementia with baseline LM. However, the association was no longer significant after adjustment for follow-up LM (HR 1.4, 95% CI 0.9-2.0).

## 5.3 PROGRESSION TO DEMENTIA

### 5.3.1 Low mood

In *Study IV*, during the 1,354.8 person-years (minimum 0.7; maximum 4.5) of follow-up, 50 people with MCI progressed to dementia. Eleven cases of dementia occurred in people with aMCI and 39 cases of dementia occurred in people with oCIND. Among the aMCI persons who progressed to dementia, eight (70%) had baseline LM, detected before the development of aMCI, and three (27%) had follow-up LM, which was detected at the time of aMCI classification. Among the oCIND that progressed to

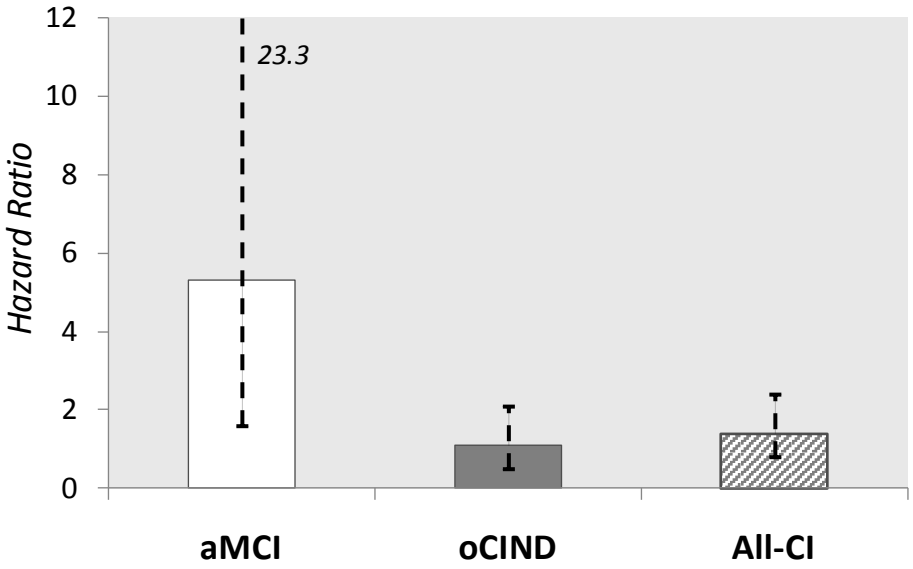


**Figure 17**. Hazard ratios with 95% confidence intervals of baseline low mood in relation to the progression to dementia of amnestic mild cognitive impairment (aMCI), other cognitive impairment (oCIND) and all cognitive impairment (All-CI). Models are adjusted for age, gender, and education.

people with aMCI and 39 cases of dementia occurred in people with oCIND. Among the aMCI persons who progressed to dementia, eight (70%) had baseline LM, detected before the development of aMCI, and three (27%) had follow-up LM, which was detected at the time of aMCI classification. Among the oCIND that progressed to dementia, 14 (33%) had baseline LM and six (15%) had follow-up LM. Cox regression analysis confirmed the association of baseline LM with an increased risk of progression to dementia in people with aMCI, but not in those with oCIND (Figure 17). Only for aMCI, the association was strengthened after further adjustment for ApoE-ε4 allele. Adjustment for other factors did not substantially change the association. On the other hand, follow-up LM was not associated with an increased risk of progression to dementia in people with aMCI or in people with oCIND.

# 6 DISCUSSION

## 6.1 SUMMARY AND INTERPRETATIONS OF THE FINDINGS

### 6.1.1 Occurrence of CI

In *Study I*, the overall prevalence of SCI and CIND was 39% and 25%, respectively. These figures are within the 25-57% and 5-32% ranges previously reported for cognitive complaints[145, 150-153] and CIND.[35, 37-39, 47-49, 54, 174] Notably, our estimates of CIND were similar to those reported by the Canadian Study of Health and Aging,[174] which used operational criteria close to those adopted in the present study. SCI was significantly more common than CIND in the nondemented elderly population. Although the cross-sectional study design does not allow clear inferences concerning SCI progression, the higher frequency of SCI compared with CIND may imply that not all people with SCI will develop objective cognitive impairment.

In *Study II*, the overall incidence rates of aMCI and oCIND were 11.4 and 33.8 per 1000 person-years. The observed aMCI incidence rates were similar to those reported by the MoVIES,[110] LEILA75+[177] and PAQUID[180] studies. The higher figures reported in the ILSA[50] and CAIDE[51] studies may be due to differences in the operationalization criteria. For oCIND, comparison with other studies is not possible as no incidence estimate of CIND/oCIND has been previously reported. After correction for attrition due to death, incidence rates of both aMCI and oCIND increased to 13.7 and 42.1 per 1000 person-years, respectively. This finding shows that disregarding the effect of mortality during follow-up when estimating the incidence of non-dementia CI leads to an underestimation of approximately 20%.

The prevalence of SCI unlike that of CIND increased with increasing age, although both SCI and CIND were more prevalent among the oldest old (*Study I*). Our observation of a lack of a clear trend with age in prevalent estimates of CIND is in line with some population-based studies,[39, 48] while differs from others.[36, 37, 54] The discrepancies can be explained by differences in the operationalization of CIND. More specifically, the lack of a trend with age could be due to the use of internal rather than external reference populations[43] when correcting CIND scores by age. Indeed, age is going to be leveled out when the reference is the same population

measured at the same time point as the ongoing study. This is confirmed by the observation that the majority of studies reporting an increase in the prevalence of CIND with age used an external reference population to define normative cut-offs for different tests.[35, 36, 54] Another possible mechanism at work can be selective survival. If older people with CIND are more likely to die, a snapshot of the population such as that carried out in prevalence estimates would not detect an increase with age. The estimates resulting from the longitudinal observation of people without CI at baseline are more reliable. Indeed, a clear age-related increase in the prevalence of both aMCI and oCIND was detected using incident cases (*Study II*). The trend with age for incident non-dementia CI was more evident after correction for attrition due to death. This may also be attributable to the effect of selective survival, which can level out the incidence curve in old ages.

### 6.1.2 Correlates and risk factors for CI

#### *6.1.2.1 Sociodemographic factors*

In *Study I*, older age groups had 20 to 30 per cent increased odds of SCI compared to the youngest old (age 65-79) while a 40% increase in the odds of CIND was observed only among the oldest compared to the youngest old. These findings are in agreement with the most of previous studies on cognitive complaints, which reported an association with older age.[145, 150-155] As discussed above, population-based studies using prevalent cases of CIND reported contradictory findings regarding an association with age.[35-37, 39, 48, 54, 63] In *Study II*, a two-fold increased risk of incident CIND for a 5-year increase in age was detected. Comparison with other studies is difficult, as no previous report has investigated the effect of age on CIND longitudinally. Older age was also associated to an 80 per cent increased risk of incident aMCI (*Study II*). This is in line with most incidence studies on aMCI, which reported a positive effect of age.[50, 51, 80, 178]

No clear effect of gender was observed on prevalent or incident estimates of non-dementia CI (*Studies I and II*). However, a significant 40 per cent increased risk of oCIND was detected after correction of incidence estimates for attrition due to death (*Study II*). It is possible that non-dementia CI might be more common in men that in women.[52, 110] The lack of association or association with female gender reported by most prevalence[35-37, 39, 48, 54, 63, 163, 182, 184, 188, 189] and incidence[50, 51, 80, 177, 178, 180, 182

studies may, once again, be explained by selective survival. Indeed, men generally have higher mortality rates compared to those in women, especially in older ages. Sex-specific mechanisms can underlie the higher occurrence of non-dementia CI in men compared to women. It is well documented that women are at increased risk of dementia compared to men, especially after age 85.[4] This effect can be due to a faster progression of women with neurodegenerative brain pathology from normal cognitive functioning to overt dementia syndromes.[234] On the other hand, men may be more exposed than women to other risk factors, which could be related to a slower progression from normal cognitive functioning to dementia.[52] Therefore, men, as opposed to women, could experience a longer transitional period in an intermediate stage of non-dementia CI.

In *Study I,* education was the most relevant sociodemographic factor in relation to prevalent CIND. After adjustment for age, gender, and marital status, higher education was associated to a 50% decrease in the odds of CIND. When occupational SES was also taken into account, the effect was attenuated to a 30% decrease in the odds of CIND. This finding is in line with the majority of studies on CIND, which found a negative association of higher education with CIND.[35, 37, 39]

Decreased odds of CIND were observed in people who were married and had higher occupational SES. Also these findings are in line with previous reports.[47, 54-56] A reverse pattern was observed for SCI, with increased odds associated to higher education, married status, and higher occupational SES. Most previous studies on cognitive complaints regardless of objective CI are in contrast with our current findings on education and SCI.[151, 153, 155, 157, 158] On the other hand, in a study which did not include objective CI, SCI was more prevalent among highly educated people.[160] The discrepancies between studies on cognitive complaints, as well as the reverse pattern observed for SCI and CIND in *Study I,* can be explained with the cognitive and brain reserve hypothesis.[235] Indeed, older people with higher education and SES, and who are married may be protected against overt cognitive impairment even in the face of initial loss of brain integrity because of improved use of cognitive strategies (high vs. lower education), improved lifestyle (high vs. lower SES) and richer social network (married vs. unmarried). In people with high cognitive and brain reserve, cognitive complaints, rather than objective CI, may be among the first signs of underlying neurodegeneration.[236-238] An alternative hypothesis might be that people with higher

education, higher SES, and who are married may take a greater interest in their health and be more aware of even minimal cognitive changes. This is in agreement with findings showing that people with richer social networks have higher odds of SCI[150] and that people with higher education had a lower chance of anosognosia of their cognitive deficits.[239] However, additional analyses stratified by CIND showed no difference in education, SES, or marital status when directly comparing subjects with or without cognitive complaints, suggesting that the pattern of associations observed for SCI are essentially driven by the comparison with CIND (*Study I*).

Still in *Study I*, co-twin control analysis showed confounding by familial factors in the association of SCI with education and SES and in that of CIND with marital status. On the other hand, the association of CIND with education and SES and that of SCI with marital status were unchanged. These results suggest that genetic background and early life environment may play a role in the association of sociodemographic factors with SCI, rather than with CIND. Indeed, people with SCI had higher education and occupational SES. This implies that people with SCI, as opposed to people with CIND of the same age and education, were more likely to come from families with higher SES and to have higher baseline intelligence, a characteristic strongly influenced by genetic background.[240] The relationship between adult life academic and occupational attainment with intelligence and parental SES is confirmed by a meta-analysis conducted on 83 longitudinal studies.[241] On the other hand, in the case of CIND, familial factors explained the positive association with unmarried status. This may suggest that some other characteristics, also strongly influenced by familial factors, can determine both marital status and CIND in late life. One possible candidate is personality traits.[242] Indeed, neuroticism has been linked to both accelerated cognitive decline[243] and higher rates of divorce.[244]

#### *6.1.2.2 Chronic diseases and multimorbidity*

In *Study III*, most common chronic diseases were associated with increased odds of subjective and objective CI. More in detail, both SCI and CIND were related to mental, musculoskeletal, respiratory, and urological diseases. Although clusters of diseases have been investigated sparsely in relation to subjective or objective cognitive impairment, available data support our findings. Notably, mental diseases have been associated to both SCI and CIND and there is agreement as to the complex relationship

between psychiatric conditions and subjective and objective cognitive functioning.[64, 77, 140, 145] Regarding musculoskeletal diseases, the relationship between osteoporosis, hip fracture and cognitive decline is well known albeit not yet well understood,[64, 245] whereas articular diseases are associated with chronic pain, which has been related to cognitive complaints[153] and slower cognitive processing speed.[246] Our findings of an association of SCI and CIND with respiratory and urological diseases are in agreement with previous reports linking asthma and COPD to cognitive impairment[69, 70] and with the growing evidence of an association between chronic kidney disease and reduced cognitive performance.[71, 72]

SCI, but not CIND, was associated with circulatory and gastrointestinal diseases. With regard to circulatory diseases and SCI, our results are at odds with a study which failed to find an association between SCI and any specific circulatory diseases,[159] but are in agreement with a report on improved subjective cognitive functioning after successful coronary bypass surgery.[247] The present findings of a lack of association of circulatory diseases with CIND is in line with some[55, 64] but in disagreement with other sets of evidence.[49, 55, 248] The discrepancies can be explained by alternative operationalizations of CIND, different severity and types of circulatory disease, as well as heterogeneity in study populations. On the other hand, gastrointestinal diseases have generally been neglected in their relation to cognition. One exception is the known association of impaired cognition with severe liver disease and, according to recent research, also with mild biliary cirrhosis.[73] Our findings of an association with SCI can imply that gastrointestinal diseases have an impact on sub-clinical forms of cognitive impairment.

CIND, but not SCI, was associated with endocrine diseases. This is in agreement with previous studies, which reported a positive association between diabetes and thyroid dysfunction with cognitive impairment.[55, 74] The lack of association of endocrine diseases with SCI may be explained by the severity of the cognitive deficits linked to this type of somatic conditions, which may make it more probable for subjects with endocrine diseases to be in the CIND rather than the SCI category.

Finally, no association with malignancy was found in either SCI or CIND when considering unmatched analysis conducted on the whole cohort. This is in line with some reports[76] but at odds with other investigations that focused on the relationship

between specific cognitive functions and types of cancer,[76] aspects not investigated in *Study III*.

A dose-dependent effect in the relationship of chronic diseases with SCI and CIND was observed. This relation was linear in SCI but not in CIND. In particular, multimorbidity defined as having at least two chronic diseases, was associated with 100% increased odds of SCI and to 50% increased odds of CIND, after adjustment for potential confounders including current affective symptoms. These findings are in agreement with previous studies which reported a positive association between cognitive complaints and CIND with poor health and multimorbidity.[56, 61, 64, 161, 249]

After controlling for familial factors, the association of CIND with malignancy was strengthened and reached significance. This suggests that the effect of cancer on cognition may be mediated by environmental factors related to adult life and also confirms the results of a previous study on a smaller sample of Swedish twins, which reported an association between cancer and cognitive dysfunction when familiar factors were taken into account.[75] On the other hand, control for familiar factors attenuated the association of CIND with all other disease clusters, including mental, musculoskeletal, respiratory, endocrine, gastrointestinal and urological diseases. This indicates a role of genetic background and early life environment in determining the relationship of CIND with most chronic diseases. Conversely, the association of SCI with circulatory, musculoskeletal, respiratory, gastrointestinal and urological diseases was not influenced by familial factors. This implies that, at least at the level of SCI, adult life environments play the major role in determining an association with chronic diseases.

Both general and specific mechanisms may lie behind the association of SCI and CIND with chronic diseases observed in *Study III*. Examples of specific mechanisms are low oxygen levels in chronic respiratory diseases, insulin resistance in diabetes, and thyroid hormones deficiency or excess in thyroid dysfunction, all conditions which can directly affect the brain. On a more general level, both physical and mental co-morbidities can generate tiredness and lack of concentration, possibly resulting in the subjective feeling of “not being as sharp as before” and in eventual impaired cognitive performance. Another mechanism that may be involved is the reduction in functional independence associated with several chronic diseases and the consequent reduction in leisure and

social activities, known protective factors for cognitive decline.[250] Moreover, several chronic conditions can reduce the amount or the quality of sleep, with known reduced cognitive efficiency[251] and long-term increased risk of cognitive impairment.[252] In addition, chronic stress may accompany chronic diseases and impact on the brain through the imbalance of the adrenocortico axis.[253] It has also been suggested that both circulatory and kidney diseases might impact on the brain through microvascular damage,[76] while a possible cytokine activated immune system dysregulation in the brain may be a common response to inflammation or injury in any organ system in the body.[76]

#### *6.1.2.3 Familial factors*

In *Study I*, probandwise concordance for SCI was higher than that of CIND, indicating a more prominent role of familial factors in subjective rather than objective cognitive impairment. However, tetrachoric correlation coefficients were similar between SCI and CIND and were all below 0.25, indicating a poor association of familiar factors with both SCI and CIND. In particular, both probandwise concordance rates and tetrachoric correlation coefficients did not differ between monozygotic and same-sex dizygotic twins, suggesting a limited contribution of genetic background to both SCI and CIND. This is in line with previous findings on cognitive dysfunction.[254] Both concordance rates and tetrachoric correlation coefficients for SCI and CIND were lower in unlike-sex dizygotic twins compared to monozygotic and same-sex dizygotic twins, pointing to a possible gender effect.

#### *6.1.2.4 Low mood*

In *Study IV*, low mood reported three years before MCI detection substantially increased the risk of developing MCI. In particular, low mood was associated with a 5.8-fold increased risk of aMCI, a 2.2-fold increased risk of oCIND, and a 2.7-fold increased risk of All-MCI (aMCI+oCIND), after adjustment for sociodemographic factors. These findings are in line with previous evidence from other longitudinal studies.[60, 82, 130, 255, 256] The excess risk of aMCI associated with low mood was almost triple that for oCIND (HR 5.8 versus 2.2), suggesting the presence of a gradient in the relationship between low mood and cognitive impairment severity. Indeed, in our study the definition of amnestic MCI excluded people with global cognitive impairment

(MMSE mean=26). On the other hand, oCIND included more severely impaired cases with global cognitive impairment (MMSE mean=21), who did not fulfill criteria for dementia. In addition, we also observed a group of people who rapidly progressed to dementia, bypassing MCI (MMSE mean=8), for whom the excess risk associated with low mood was 60%, lower than that observed in both aMCI and oCIND.

Also in *Study IV*, a synergistic interaction of low mood and ApoE-ε4 was observed, with increased risk of aMCI in people with both baseline low mood and at least one ApoE-ε4 allele. This is in line with results from a study on primary care patients[256] and supports the hypothesis that low mood may be related to AD-type neuropathology.[257, 258] Conversely, none of the other factors under investigation interacted with low mood. In particular, no modification of the relationship of baseline low mood with MCI was observed when taking into account history of psychosis, psychotropic drug use, and vascular factors. Indeed, low mood in prodromal MCI can be independent from history of depression.[256] It has also been reported that depressive symptoms in MCI are particularly resistant to treatment.[106, 259] On the other hand, the lack of interaction of low mood with vascular factors confirms previous findings from the Cardiovascular Health Study and does not support the "vascular depression hypothesis".[82, 260]

### 6.1.3 Progression to dementia

Low mood was associated with a 5.3-fold increased risk of progression to dementia in people with aMCI (*Study IV*). This finding is in line with some studies on the progression of MCI[62, 128-130] and is at odds with others.[132, 133, 135, 136, 261] Indeed, most of the studies that found no or inverse association focused on depressive symptoms measured at the same time as MCI detection.[133, 135, 136, 261] The current findings showed that only low mood measured at baseline, three years before the detection of MCI, predicted subsequent progression of MCI to dementia. Conversely, low mood that co-occurred with MCI did not predict further progression to dementia. These results support the hypothesis that the symptom of low mood may be relevant in the prodromal stage of MCI, losing its importance at more advanced stages, when the cognitive deficits are already manifested. Our results do not confirm previous evidence from a report based on the Religious Order Study,[132] which found no increase in depressive symptoms in the prodromal stage of dementia. Indeed, the generalizability of those

results has been questioned, as religious order people might have higher resilience to depressive symptoms.[262]

The observed effects of low mood on the development and progression of non-dementia CI can have different explanations. One possibility would be that low mood is a risk factor for cognitive impairment and particularly memory functioning, which would likely be mediated by the interplay between psychosocial stress and the activity of the adreno-cortico-axis, whose imbalance has known effects on neurogenesis and hippocampal physiology.[263] An alternative explanation would be that low mood and MCI share a common neuropathogenic substrate. In this case the narrow time frame that we observed for the relationship between low mood and cognitive decline could be explained by the stage of the underlying neurodegenerative process. In earlier stages, when cognitive deterioration is not yet manifest, low mood could be one behavioral sign of neurodegeneration, as in the concept of "amyloid-associated depression".[258] In more advanced stages, when the neurodegeneration has become more pervasive, MCI could represent a later manifestation of the process leading to dementia.

Low mood is not the only risk factor that has been investigated by our group in relation to the progression of CI syndromes to dementia. Table 7 lists the latest reports on this topic from the Kungsholmen Project and collaborative studies.

**Table 7**. Latest reports from the Kungsholmen Project and collaborative studies on risk factors for progression of CI syndromes to dementia.

| Authors | Study | Factors |
|---|---|---|
| Caracciolo et al[264] | Kungsholmen Project | Feelings of loneliness versus social isolation |
| Caracciolo et al[265] | Kungsholmen Project | Multimorbidity |
| Xu et al[123] | Kungsholmen Project | Diabetes and prediabetes |
| Xu et al[266] | Kungsholmen Project | APOE-ε4 |
| Clerici et al[267] | Milan Clinical Study | Vascular risk factors and white matter lesions |

## 6.2 METHODOLOGICAL CONSIDERATIONS

### 6.2.1 Generalizability

The Kungsholmen population consisted of individuals aged ≥75 years that were living in a geographically defined central area of Stockholm. This population had comparable age and sex compositions as well as access to a similar health care system in Stockholm. However, the Kungsholmen population did differ from the rest of the urban area of Sweden in terms of the proportion of pensioners, women, highly educated persons, and marital status. Caution is needed when generalizing the findings from the Kungsholmen population to a younger population or to rural areas. The major findings from this population may be generalized to the urban population aged over 75 in Western society.

The HARMONY population included twins aged ≥65 years derived from the Swedish Twin Registry that covers the whole of Sweden. If twins are different from the general population (non-twins) in terms of the outcome of interest, the results will not be applicable to the general population. However, the prevalence of CIND in this population was similar to that reported in the CSHA, which was based on the general elderly population. Moreover, it has been previously reported that the prevalence of dementia detected in HARMONY was similar to that reported in the Kungsholmen population.[216] It has also been shown that twins surviving into later life are similar to a representative sample of non-twins of the same age in terms of health status and behavioral functioning.[268] Nevertheless, the comparison of the results from the cohort as a whole with the matched pairs provides important information about the potential role of genetic and familial influences. The major findings from this population may also be generalizable to a population aged 65 years and older in Western society.

### 6.2.2 Internal validity

Besides generalizability issues, internal validity is another aspect that can strongly impact on the quality of epidemiological investigations. Indeed, in both the Kungsholmen Project and the HARMONY Study, the possibility of a partial misclassification of both the outcomes and the exposures cannot be ruled out. Moreover, residual confounding from factors which have not been taken into account is unavoidable in observational research.

#### *6.2.2.1 Outcomes*

In the Kungsholmen Project (*Studies II* and *III*) non-dementia CI was defined as aMCI and oCIND. Both definitions rely on current criteria for CI. Specifically, aMCI focuses on memory deficits in persons with otherwise preserved general cognitive and daily life functioning,[45] whereas oCIND matches up with a global characterization of CIND, based on a cognitive screening measure such as the MMSE.[33, 38] Although widely used, these definitions of cognitive impairment are mere approximations of the true phenomenon. Indeed, aMCI was operationalized based on one single measure of episodic memory and a cut-off of minus 1.5 SD, which showed low sensitivity for pre-clinical dementia.[269] Furthermore, such criteria can guarantee extremely high specificity[269] and almost zero probability of "going back to normal".[214] In other words, while we are almost certain that our aMCI cases were truly cognitively impaired, by using only the aMCI definition we would have classified a considerable proportion of people with CI as unimpaired. That was the rationale behind the choice of using an ancillary definition of CI, oCIND. The term oCIND was adopted to emphasize the fact that this category included people with global CI who were excluded by definition from the aMCI category. The choice of a cut-off of minus 1 SD for oCIND aimed at increasing the sensitivity of the definition and additionally to capture people with slight global cognitive impairment. Moreover, oCIND was based on the MMSE, which has recently shown good sensitivity and specificity for non-dementia CI.[206] Nonetheless, it is probable that even after combining the two definitions of aMCI and oCIND some cases of CI were left undetected. Specifically, aMCI and oCIND did not include isolated non-memory CI. However, the validity and predictivity of this type of cognitive deficits is still undergoing debate. In a follow-up of people with MCI sub-types defined according to the revised Mayo criteria, naMCI-single was the most unstable group and had an extremely high probability of reverting to normal cognitive functioning after a one and a half years.[214]

Another aspect that may have reduced the validity of our estimates is the relatively long 3-year time interval in between follow-ups. During this time a variable proportion of subjects may develop CI and progress to dementia. These persons, who were classified as unimpaired at the previous evaluation, will be diagnosed as demented at follow-up, apparently "bypassing" the non-dementia CI stage. A closely related phenomenon is the possible death of people who developed CI during the follow-up intervals. Again,

non-dementia CI will not be detectable at follow-up examinations and this would further bias incidence estimates. In *Study II*, we corrected for attrition due to death by imputing the cognitive status of subjects who died without a dementia diagnosis and who were not previously classified as non-dementia CI. However, this did not correct for the possible bias associated to the rapid transition to dementia in people who were cognitively intact at baseline. The possible consequences are in the direction of an underestimation of both the occurrence of non-dementia CI (*Study II*) and related estimates (*Study IV*).

In the HARMONY Study (*Studies I and III*), non-dementia CI was defined as SCI and CIND. Although the definition of CIND was based on current criteria for CIND,[36, 37, 46] there is currently no agreement as to the definition of SCI.[270] Specifically, different assessment questions have been used in different studies to detect subjective cognitive complaints and validation studies have been sparse.[270] A few standardized questionnaires on cognitive complaints have been devised, none of which is widely adopted or highly validated.[270] In comparison with other investigations, the question on subjective cognitive complaints adopted in the HARMONY study may be particularly promising, although this possibility is yet to be tested. Indeed, the question included an enquiry about a change in memory (not just a "memory problem"), referred to a specific time-frame ("have you noticed any change in your memory in the last three years?"). This type of formulation may have captured the initial deterioration in cognitive abilities experienced both in normal and accelerated cognitive aging. One limitation regards the generalizability of a question about memory to any cognitive problem. It has to be considered that elderly people do not generally have informed knowledge on cognitive processes and that, in their naïve jargon, the term "memory" is often used as a passe-partout for any cognitive impasse. This is supported by the frequencies of specific "memory" problems reported in HARMONY by subjects with SCI. Indeed, the most common complaints ("forgetting names", "forgetting words") regarded the language, rather than memory, domain.

CIND definition in HARMONY was based on impairment on any test of a telephone cognitive screening (TELE). The validity of this telephonic evaluation has been previously evaluated, showing satisfactory psychometric properties when used to identify possible dementia cases.[218] Although the sensitivity and specificity of TELE for non-dementia CI is yet to be tested, our estimates of the prevalence of CIND based

on the cognitive tasks included in TELE are identical to those reported by the CSHA, which employed a full neuropsychological battery coupled with clinical in-person evaluation of the cases.[174] To define impairment on the single tasks of TELE, a cut-off of minus 2 SD was used. Indeed, the short format of the cognitive tests included in TELE tended to generate a ceiling effect in subjects' performances. While a conservative cut-off may have caused the exclusion of very mild cases of CIND, this choice is justified by the necessity of balancing false negatives and false positives. Nonetheless the relatively high prevalence of CIND reported in *Study I* suggests that the false negatives, although undoubtedly present, may not have been over-represented using the current operationalization.

#### *6.2.2.2 Exposures*

The accuracy and validity of the measures used to define the exposures under study are also a possible source of bias and can strongly influence the internal validity of a scientific investigation. Across all studies (*Studies I-IV*) classification accuracy of sociodemographic variables was guaranteed by the careful work of the respective research teams for the Kungsholmen Project and the HARMONY Study. In particular, in both projects, the variable education underwent through several revisions. In the HARMONY Study (*Studies I and III*), the latest revision of the variable education was used. In the Kungsholmen Project, an earlier categorization of the variable was adopted in *Study II*, while a revised categorization was used in *Study IV*. Changes originated from a conceptual discussion within the research team, which led to the reclassification as low educated of people with professional education. This change slightly affected CIND and MCI categories, with subsequent minor changes in the classification of the study populations between *Study II* and *Study IV*.

In both the HARMONY Study and the Kungsholmen Project, multiple indicators of medical morbidity were used. This was done to limit misclassification, which is often the case when using a single source of information. In particular, all chronic diseases investigated in *Study III* were derived from a combination of information coming from national inpatient registers and self- and informant-reports. Possible limitations are that neither disease severity nor disease duration was taken into account. Moreover, the ascertainment of the cases was cross-sectional. As a consequence, our current estimates

on the association of chronic diseases and multimorbidity with non-dementia CI have to be interpreted as rough approximations of the true phenomenona.

In *Study IV*, the main exposure was a single depressive symptom, low mood, evaluated using a single question and gathered from different questionnaires at KP baseline and follow-ups. However, the baseline question had the highest loadings on a depression factor extrapolated from the general health interview it belonged to, whereas, at follow-ups, low mood item was part of a standardized and validated psychiatric battery. The comparability of the two instruments in measuring the same symptom is supported by the similar incidence rates of low mood at first and second follow-ups. In addition, although no severity grading of the symptom of low mood was performed at the KP baseline evaluation, this information was available at follow-ups. Although these elements support the validity of the current assessment of low mood, a measure based on answers to multiple similar questions on low mood would increase reliability of the estimates.

#### *6.2.2.3 Confounders*

Several confounders have been taken into account in the four studies of this thesis. In *Studies I* and *III*, special attention has been devoted to the careful control of the role of genetic background and early environment on estimates of non-dementia CI and additionally on its association with other factors, namely sociodemographic variables and chronic diseases.

Other major confounders taken into account were somatic and psychiatric co-morbidity, social integration, and APOE-ε4 in *Studies II* and *IV*, as well as affective disorders in *Study III*.

There are, however, several other possible confounders that could not be taken into consideration. Specifically, the possible effects of personality traits and premorbid intelligence were not evaluated. Information on baseline intelligence is relevant when cross-sectionally evaluating the presence of objective CI and can help discriminate between individual differences in intellectual abilities and CI as a result of cognitive decline.[269] On the other hand, personality traits have been repeatedly associated to subjective CI and some evidence suggested their possible role as moderators of the effect of depression on cognitive impairment.[161-164, 271] Other confounders, particularly

relevant to *Study IV*, are recent life events and a history of depression. The first factor can be related to late-life depressive symptoms and the second can indicate a longer exposure and proneness to depressive symptoms. While stressful life events were not taken into account in the present thesis, we adjusted for history of depression. Nonetheless, as our diagnoses were registry-based, an underestimation of the effect of history of depression on the association of low mood with non-dementia CI cannot be ruled out.

# 7 CONCLUSIONS

## 7.1 GENERAL CONCLUSIONS

Cognitive impairment is highly frequent in the elderly population. The prevalence of CI increases with age, especially when the rates are detected longitudinally and corrected for attrition. Other sociodemographic factors may also affect the distribution of CI among nondemented people. Co-morbid chronic diseases and multimorbidity are associated to increased odds of subjective and objective CI, while low mood is a strong predictor of CI development and progression to dementia in the cognitively healthy elderly. Familial factors may contribute to non-dementia CI in a complex fashion.

## 7.2 SPECIFIC CONCLUSIONS

1. Subjective and objective cognitive impairment are both highly prevalent among the nondemented elderly yet have distinct sociodemographic profiles. Familiar factors play a relatively limited role in determining SCI and CIND but can partly explain the association of SCI and CIND with sociodemographic factors.
2. The incidence of cognitive impairment is high among the nondemented elderly, and increases with age. Estimates are higher when corrected for attrition due to death, especially in the oldest old and in men. Comparison with estimates of dementia showed a similar trend with age only after correction.
3. Several chronic diseases are associated with both subjective and objective CI and the association is stronger when chronic diseases co-occur. Genetic and early-life environmental factors may partially explain the association of CIND, but not that of SCI, with chronic diseases and multimorbidity.
4. Low mood is more strongly associated with amnestic than with global CI. Progression toward dementia is predicted by low mood manifest in the prodromal stage of non-dementia CI but not by low mood co-occuring with CI. These findings indicate that low mood is particularly prominent in the very early stages of cognitive decline.

# 8 RELEVANCE AND IMPLICATIONS

We showed that non-dementia CI is highly frequent among the nondemented elderly, especially after correction for attrition due to death and when taking into account also subjective CI. The relatively low contribution of familial factors to SCI and CIND suggests a role of adult life environments in the development of CI.

We found that a multiplicity of factors, including biological aspects (such as age and gender), socioeconomic factors (such as education and SES), and somatic and mental syndromes and symptoms (such as chronic diseases and low mood) are associated with the occurrence of non-dementia CI. A heterogeneous development of CI is suggested. Some of the factors are modifiable and may be prevented or treated, while non-modifiable correlates and risk factors for CI can help to improve prognosis by identifying subjects at risk of accelerated cognitive decline.

Improvements in the accuracy of estimates of non-dementia CI as well as advancements in the understanding of its etiology are of extreme importance both at societal and individual levels. Indeed, accurate estimates of CI occurrence can help planning of both health care policies and expenditures. On the other hand, a more thorough knowledge of the mechanisms underlying MCI development and evolution could result in better preventative strategies and prognostic procedures. Whereas preventative strategies can reduce the occurrence of CI in the nondementated elderly, with important economic consequences, more precise prognostic procedures can improve the management of affected people and reduce the psychological burden associated to both subjective and objective CI.

# 9 FUTURE DIRECTIONS

Our estimates of the occurrence of non-dementia CI should be replicated using similar criteria across different populations. To reduce the variability of prevalence and incidence estimates of CI, steps should also be made towards an increased homogeneity in the defining and operationalization criteria of CI syndromes. This aim could be primarily achieved by a) devising longitudinal community-based studies focusing on the comparative validity, stability, and predictivity of alternative constructs of non-dementia CI and of different operationalization criteria within the same construct; and b) evaluating accumulated evidence in the framework of expert-based consensus panels.

To disentangle the relative contribution of biological, socioeconomic, somatic, environmental, and psychosocial aspects to the development and progression of non-dementia CI, more evidence from longitudinal, community-based, studies is warranted. These prospective investigations should allow the comparison of multiple factors, which can be achieved by the inclusion of repeated and detailed multi-dimensional evaluations including medical, clinical, and genetic information coupled with in-depth interviews on environmental and psychosocial exposures. Special attention should be devoted to the timing of the different factors that can contribute to the complex etiology and variable evolution of non-dementia cognitive impairment.

# 10 ACKNOWLEDGEMENTS

This doctoral thesis has been conducted at the *Aging Research Center (ARC), Department of Neurobiology, Care Sciences and Society, Karolinska Institutet* and *Stockholm Gerontology Research Center.* I would like to express my sincere thanks and gratitude to everyone who has encouraged me and provided me with invaluable help for the completion of this thesis, especially to:

Professor **Laura Fratiglioni**, my main supervisor, who provided me with the great opportunity of working with her. Without you I could not have made the necessary progress both as a person and a researcher. Over the years, you have been a teacher, a coach, and a role model. You have taught me not only by sharing your wide epidemiological and neurological knowledge and encouraging me to always better my skills, but also by teaching me the pragmatics of life. I will always be grateful for all the lessons I have learned from you, especially for those I did not want to learn.

Professor **Bengt Winblad**, the initiator of the Kungsholmen Project and my co-supervisor, who supported me from the very beginning and gave me shelter. Your reassuring presence during the years of my PhD has given me strength and I thank you for your constant encouragement and scientific guidance.

Professor **Margaret Gatz** and Professor **Nancy L. Pedersen,** who ideated and directed the HARMONY STUDY. I greatly appreciated the chance of learning new methods and intriguing scientific problems. Margy, I have no words to express how much I valued our methodological chats and how much your deep knowledge has stimulated me. Nancy, thank you for your kindness and your promptness to offer scientific advice, life-saving material, and knowledgeable comments.

Professor **Lars Bäckman**, responsible for the cognitive aspects of the Kungsholmen Project and valuable coauthor. You always have an original approach to scientific problems and I greatly appreciate your constant encouragement.

I would like to express a special thank you to my colleague, close friend, and coauthor **Weili Xu**. You taught me many things, above all that you do not need to come from the same family, let alone from the same country, to feel related. Thank you for sharing both your deep wisdom and your warm heart with me.

My sincere thanks go to my colleagues and friends: **Stephanie Paillard-Borg,** whose radiant personality brightened up even the greyest days; **Huixin Wang** and **Anita Karp**, for enlightening discussion on life and science; **Roberto Monastero**, **Alessandra Marengoni**, and **Katie Palmer** for being valuable coauthors; **Debora Rizzuto**, **Giola Santoni**, and **Nicola Orsini** for their help in statistics; **Sofia Österman, Mia Kivipelto**, and **Ingmar "Pingo" Kareholt**, for making the first years of my PhD studies unforgettable and for constant friendship. Also, a big thank you goes to my dear friends and colleagues **Alina Solomon**, **Sara Hjulström**, and **Erika Johnson-Laukka** for intellectually stimulating discussion and for having been "there" for me over the years.

Special thanks to the past and present coordinators of the course on cognitive processes at Karolinska Institutet, **Håkan Fisher** and **Sari Karlsson** for practical help, guidance, and support during my teaching experience as a PhD student.

My thanks go also to my colleagues at the ARC and the *Stiftelsen Stockholm Läns Äldrecentrum*. Especially to: Professor **Marti Parker** for being a staple of intelligence and practicality for all of us; **Maria Wahlberg** for careful and prompt assistance in data management and statistical software; **Cecilia Annerholm** for being a life saver over the years; **Helene von Strauss**, for having being invaluably helpful in these last few months; **Maria Youhang** for practical help; **Sven Erik Wånell**, **Britt-Marie Gulbrandsen**, **Zoltan Pethö**, and **Christian Lynghaug,** for help in my work; and **Inger Raune**, for her kindness and our stimulating conversations. Special thanks go to **Almira Osmanovic Thunström**, for help with this thesis, and to **Grégoria Kalpouzos**, my roommate, for sharing interesting scientific input and chocolate.

I am also grateful to **Melissa End**, a friend and the careful reviser of the English in this thesis.

I appreciate all participants of the "*Kungsholmen Project*" and the "*HARMONY Study*" for providing invaluable information as the basis of this thesis. Also, thanks to all those involved in the planning, data collection, and management of the studies.

I would like to thank my former teachers and supervisors: Professor **Pierluigi Zoccolotti**, the tutor of my master thesis in psychology at La Sapienza University in Rome; Professor **Salvatore Giaquinto,** the supervisor of my clinical and research activities at the IRCCS San Raffaele Pisana in Rome; and Professor **Francesco Forastiere**, the main tutor of my master in epidemiology at La Cattolica del Sacro Cuore University in Rome. Thank you all for having believed so strongly in my research capabilities and having helped me to find my way.

Finally, I would like to express my thanks to my family. To my mother, **Maria Antonietta,** for having supported me through the years, both spiritually and practically. With your courage, strength, and energy you have always inspired me. To my father, **Rino**, for having passed to me his love for knowledge and rational thinking. I will never forget our early intellectual arguments, your eloquence, enthusiasm and wit. To my brothers, **Massimo** and **Giancarlo** for their constant support, encouragement, and sincere friendship. To my wonderful daughter, **Adina**, for having brought joy into my life and for teaching me new things every day. To my "bonus" children, **Channa** and **Noah**, for being amazing persons to have around, and to my acquired family in USA, for their warm encouragement. Finally, I would like to thank my husband **Larry**, for his companionship, patience, and support. You have always believed in me and I am grateful to you for that and so much more.

The research included in this thesis was financially supported by grants from the *Forskningsrådet för Arbetsliv och Socialvetenskap*, the *Swedish Brain Power*, the *Gamla Tjänarinnor Foundation*, and the *Gun and Bertil Stohnes Foundation*.

# 11 REFERENCES


1. Department of Economic and Social Affairs, Population Division: *World Population Ageing 2009.* New York: United Nations, 2010.
2. Centers for Disease Control and Prevention. Public health and aging: trends in aging--United States and worldwide. *JAMA* 2003;289:1371-1373.
3. Department of Economic and Social Affairs, Population Division: *World Population Ageing: 1950-2050.* New York: United Nations, 2007.
4. Qiu C, De Ronchi D, Fratiglioni L. The epidemiology of the dementias: an update. *Curr Opin Psychiatry* 2007;20:380-385.
5. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci* 2009;11:111-128.
6. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R).* Washington, DC: American Psychiatric Association, 1987.
7. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).* Washington, DC: American Psychiatric Association, 1994.
8. Fratiglioni L, Winblad B, von Strauss E. Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. *Physiol Behav* 2007;92:98-104.
9. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006;368:387-403.
10. Roman GC. Vascular dementia: distinguishing characteristics, treatment, and prevention. *J Am Geriatr Soc* 2003;51:S296-304.
11. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. *JAMA* 2004;292:2901-2908.
12. Fratiglioni L, De Ronchi D, Aguero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging* 1999;15:365-375.
13. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;54:S10-15.
14. Fratiglioni L, von Strauss E, Qiu C. *Epidemiology of the dementias of old age.* In: Jacoby R DT, Thomas A and Oppenheimer C, eds, ed. London, England: Oxford University Press, 2008.
15. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4-9.
16. McVeigh C, Passmore P. Vascular dementia: prevention and treatment. *Clin Interv Aging* 2006;1:229-235.
17. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112-2117.
18. Aguero-Torres H, Qiu C, Winblad B, Fratiglioni L. Dementing disorders in the elderly: evolution of disease severity over 7 years. *Alzheimer Dis Assoc Disord* 2002;16:221-227.
19. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von Strauss E, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. *Am J Public Health* 1998;88:1452-1456.

20. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. *J Clin Epidemiol* 1999;52:737-743.
21. Cotter VT. The burden of dementia. *Am J Manag Care* 2007;13 Suppl 8:S193-197.
22. Wimo A, Jonsson L, Winblad B. An estimate of the worldwide prevalence and direct costs of dementia in 2003. *Dement Geriatr Cogn Disord* 2006;21:175-181.
23. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol* 2010;9:702-716.
24. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9:119-128.
25. Duara R, Loewenstein DA, Greig MT, et al. Pre-MCI and MCI: Neuropsychological, Clinical, and Imaging Features and Progression Rates. *Am J Geriatr Psychiatry* 2011.
26. Massoud F, Belleville S, Bergman H, et al. Mild cognitive impairment and cognitive impairment, no dementia: Part B, therapy. *Alzheimers Dement* 2007;3:283-291.
27. Chertkow H, Massoud F, Nasreddine Z, et al. Diagnosis and treatment of dementia: 3. Mild cognitive impairment and cognitive impairment without dementia. *CMAJ* 2008;178:1273-1285.
28. Luppa M, Heinrich S, Matschinger H, et al. Direct costs associated with mild cognitive impairment in primary care. *Int J Geriatr Psychiatry* 2008;23:963-971.
29. Frank L, Lloyd A, Flynn JA, et al. Impact of cognitive impairment on mild dementia patients and mild cognitive impairment patients and their informants. *Int Psychogeriatr* 2006;18:151-162.
30. Peres K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Restriction in complex activities of daily living in MCI: impact on outcome. *Neurology* 2006;67:461-466.
31. Widera E, Steenpass V, Marson D, Sudore R. Finances in the older patient with cognitive impairment: "He didn't want me to take over". *JAMA* 2011;305:698-706.
32. Panza F, D'Introno A, Colacicco AM, et al. Current epidemiology of mild cognitive impairment and other predementia syndromes. *Am J Geriatr Psychiatry* 2005;13:633-644.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
34. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256:240-246.
35. Di Carlo A, Baldereschi M, Amaducci L, et al. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *J Am Geriatr Soc* 2000;48:775-782.
36. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* 1997;349:1793-1796.
37. Unverzagt FW, Gao S, Baiyewu O, et al. Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. *Neurology* 2001;57:1655-1662.
38. Palmer K, Wang HX, Backman L, Winblad B, Fratiglioni L. Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. *Am J Psychiatry* 2002;159:436-442.

39. De Ronchi D, Berardi D, Menchetti M, et al. Occurrence of cognitive impairment and dementia after the age of 60: a population-based study from Northern Italy. *Dement Geriatr Cogn Disord* 2005;19:97-105.
40. Caracciolo B, Palmer K, Monastero R, Winblad B, Backman L, Fratiglioni L. Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. *Neurology* 2008;70:1778-1785.
41. Narasimhalu K, Ang S, De Silva DA, et al. Severity of CIND and MCI predict incidence of dementia in an ischemic stroke cohort. *Neurology* 2009;73:1866-1872.
42. Fratiglioni L, Caracciolo B, Palmer K. [Variability of epidemiological measures in mild cognitive impairment and dementia]. *Ann Ist Super Sanita* 2005;41:81-86.
43. Arsenault-Lapierre G, Whitehead V, Belleville S, Massoud F, Bergman H, Chertkow H. Mild cognitive impairment subcategories depend on the source of norms. *J Clin Exp Neuropsychol* 2011:1-8.
44. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005;62:1160-1163; discussion 1167.
45. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303-308.
46. Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. *Neurology* 1994;44:1593-1600.
47. Marengoni A, Fratiglioni L, Bandinelli S, Ferrucci L. Socioeconomic Status During Lifetime and Cognitive Impairment No-Dementia in Late Life: The Population-Based Aging in the Chianti Area (InCHIANTI) Study. *J Alzheimers Dis* 2011.
48. Gavrila D, Antunez C, Tormo MJ, et al. Prevalence of dementia and cognitive impairment in Southeastern Spain: the Ariadna study. *Acta Neurol Scand* 2009;120:300-307.
49. Nunes B, Silva RD, Cruz VT, Roriz JM, Pais J, Silva MC. Prevalence and pattern of cognitive impairment in rural and urban populations from Northern Portugal. *BMC Neurol* 2010;10:42.
50. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* 2004;63:1882-1891.
51. Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord* 2004;17:196-203.
52. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology* 2010;75:889-897.
53. Qiu C, Backman L, Winblad B, Aguero-Torres H, Fratiglioni L. The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen Project. *Arch Neurol* 2001;58:2034-2039.
54. Fei M, Qu YC, Wang T, Yin J, Bai JX, Ding QH. Prevalence and distribution of cognitive impairment no dementia (CIND) among the aged population and the analysis of socio-demographic characteristics: the community-based cross-sectional study. *Alzheimer Dis Assoc Disord* 2009;23:130-138.
55. Atti AR, Forlani C, De Ronchi D, et al. Cognitive Impairment after Age 60: Clinical and Social Correlates in the "Faenza Project". *J Alzheimers Dis* 2010.
56. Lyketsos CG, Toone L, Tschanz J, et al. Population-based study of medical comorbidity in early dementia and "cognitive impairment, no dementia (CIND)":

association with functional and cognitive impairment: The Cache County Study. *Am J Geriatr Psychiatry* 2005;13:656-664.
57. Kim KW, Park JH, Kim MH, et al. A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea. *J Alzheimers Dis* 2011;23:281-291.
58. Qiu C, Kivipelto M, Aguero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry* 2004;75:828-833.
59. Sasaki M, Kodama C, Hidaka S, et al. Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community. *Int J Geriatr Psychiatry* 2009;24:1119-1126.
60. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003;60:1394-1399.
61. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc* 2010;58:248-255.
62. Artero S, Ancelin ML, Portet F, et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry* 2008;79:979-984.
63. Frisoni GB, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. Mild cognitive impairment in the population and physical health: data on 1,435 individuals aged 75 to 95. *J Gerontol A Biol Sci Med Sci* 2000;55:M322-328.
64. Monastero R, Palmer K, Qiu C, Winblad B, Fratiglioni L. Heterogeneity in risk factors for cognitive impairment, no dementia: population-based longitudinal study from the Kungsholmen Project. *Am J Geriatr Psychiatry* 2007;15:60-69.
65. Israeli-Korn SD, Masarwa M, Schechtman E, et al. Hypertension increases the probability of Alzheimer's disease and of mild cognitive impairment in an Arab community in northern Israel. *Neuroepidemiology* 2010;34:99-105.
66. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 2007;64:1734-1740.
67. Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnestic mild cognitive impairment. *Neurobiol Aging* 2010;31:1894-1902.
68. Roberts RO, Geda YE, Knopman DS, et al. Association of duration and severity of diabetes mellitus with mild cognitive impairment. *Arch Neurol* 2008;65:1066-1073.
69. Moss M, Franks M, Briggs P, Kennedy D, Scholey A. Compromised arterial oxygen saturation in elderly asthma sufferers results in selective cognitive impairment. *J Clin Exp Neuropsychol* 2005;27:139-150.
70. Antonelli-Incalzi R, Corsonello A, Trojano L, et al. Correlation between cognitive impairment and dependence in hypoxemic COPD. *J Clin Exp Neuropsychol* 2008;30:141-150.
71. Tsai CF, Wang SJ, Fuh JL. Moderate chronic kidney disease is associated with reduced cognitive performance in midlife women. *Kidney Int* 2010;78:605-610.
72. Thornton WL, Shapiro RJ, Deria S, Gelb S, Hill A. Differential impact of age on verbal memory and executive functioning in chronic kidney disease. *J Int Neuropsychol Soc* 2007;13:344-353.

73. Newton JL, Hollingsworth KG, Taylor R, et al. Cognitive impairment in primary biliary cirrhosis: symptom impact and potential etiology. *Hepatology* 2008;48:541-549.
74. Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology* 2008;33:1013-1022.
75. Heflin LH, Meyerowitz BE, Hall P, et al. Cancer as a risk factor for long-term cognitive deficits and dementia. *J Natl Cancer Inst* 2005;97:854-856.
76. Gasquoine PG. Cognitive impairment in common, noncentral nervous system medical conditions of adults and the elderly. *J Clin Exp Neuropsychol* 2011:1-11.
77. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. *J Alzheimers Dis* 2009;18:11-30.
78. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dement Geriatr Cogn Disord* 2008;25:115-126.
79. Chan WC, Lam LC, Tam CW, et al. Prevalence of neuropsychiatric symptoms in chinese older persons with mild cognitive impairment-a population-based study. *Am J Geriatr Psychiatry* 2010;18:948-954.
80. Unverzagt FW, Ogunniyi A, Taler V, et al. Incidence and risk factors for cognitive impairment no dementia and mild cognitive impairment in African Americans. *Alzheimer Dis Assoc Disord* 2011;25:4-10.
81. Goveas JS, Espeland MA, Hogan P, et al. Depressive symptoms, brain volumes and subclinical cerebrovascular disease in postmenopausal women: The Women's Health Initiative MRI Study. *J Affect Disord* 2011.
82. Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Arch Gen Psychiatry* 2006;63:273-279.
83. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry* 2008;65:1193-1198.
84. van der Linde R, Stephan BC, Matthews FE, Brayne C, Savva GM. Behavioural and psychological symptoms in the older population without dementia--relationship with socio-demographics, health and cognition. *BMC Geriatr* 2010;10:87.
85. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry* 2009;17:542-555.
86. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing* 2008;37:505-512.
87. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2011;269:107-117.
88. Leung GT, Fung AW, Tam CW, et al. Examining the association between participation in late-life leisure activities and cognitive function in community-dwelling elderly Chinese in Hong Kong. *Int Psychogeriatr* 2010;22:2-13.
89. Plassman BL, Williams JW, Jr., Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med* 2010;153:182-193.
90. Eskelinen MH, Ngandu T, Helkala EL, et al. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. *Int J Geriatr Psychiatry* 2008;23:741-747.

91. Roberts RO, Geda YE, Cerhan JR, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dement Geriatr Cogn Disord* 2010;29:413-423.
92. Roberts RO, Cerhan JR, Geda YE, et al. Polyunsaturated fatty acids and reduced odds of MCI: the Mayo Clinic Study of Aging. *J Alzheimers Dis* 2010;21:853-865.
93. Solfrizzi V, Colacicco AM, D'Introno A, et al. Dietary fatty acids intakes and rate of mild cognitive impairment. The Italian Longitudinal Study on Aging. *Exp Gerontol* 2006;41:619-627.
94. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol* 2009;66:216-225.
95. Anttila T, Helkala EL, Viitanen M, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ* 2004;329:539.
96. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol* 2010;67:80-86.
97. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;58:498-504.
98. Middleton L, Kirkland S, Rockwood K. Prevention of CIND by physical activity: different impact on VCI-ND compared with MCI. *J Neurol Sci* 2008;269:80-84.
99. Verghese J, LeValley A, Derby C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology* 2006;66:821-827.
100. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;119:252-265.
101. Palmer K, Backman L, Winblad B, Fratiglioni L. Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. *BMJ* 2003;326:245.
102. Jessen F, Wiese B, Bickel H, et al. Prediction of Dementia in Primary Care Patients. *PLoS One* 2011;6:e16852.
103. Chertkow H, Nasreddine Z, Joanette Y, et al. Mild cognitive impairment and cognitive impairment, no dementia: Part A, concept and diagnosis. *Alzheimers Dement* 2007;3:266-282.
104. van Rossum IA, Vos S, Handels R, Visser PJ. Biomarkers as predictors for conversion from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. *J Alzheimers Dis* 2010;20:881-891.
105. Mitchell AJ, Monge-Argiles JA, Sanchez-Paya J. Do CSF biomarkers help clinicians predict the progression of mild cognitive impairment to dementia? *Pract Neurol* 2010;10:202-207.
106. Modrego PJ. Predictors of conversion to dementia of probable Alzheimer type in patients with mild cognitive impairment. *Curr Alzheimer Res* 2006;3:161-170.
107. Vemuri P, Wiste HJ, Weigand SD, et al. Serial MRI and CSF biomarkers in normal aging, MCI, and AD. *Neurology* 2010;75:143-151.
108. Karow DS, McEvoy LK, Fennema-Notestine C, et al. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease. *Radiology* 2010;256:932-942.
109. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology* 2009;73:173-179.

110. Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology* 2004;63:115-121.
111. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology* 2006;66:828-832.
112. Hsiung GY, Donald A, Grand J, et al. Outcomes of cognitively impaired not demented at 2 years in the Canadian Cohort Study of Cognitive Impairment and Related Dementias. *Dement Geriatr Cogn Disord* 2006;22:413-420.
113. Ito K, Corrigan B, Zhao Q, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. *Alzheimers Dement* 2011;7:151-160.
114. DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology* 2004;63:220-227.
115. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol* 2005;62:975-980.
116. Wang PN, Lirng JF, Lin KN, Chang FC, Liu HC. Prediction of Alzheimer's disease in mild cognitive impairment: a prospective study in Taiwan. *Neurobiol Aging* 2006;27:1797-1806.
117. Barabash A, Marcos A, Ancin I, et al. APOE, ACT and CHRNA7 genes in the conversion from amnestic mild cognitive impairment to Alzheimer's disease. *Neurobiol Aging* 2009;30:1254-1264.
118. Samaranch L, Cervantes S, Barabash A, et al. The effect of MAPT H1 and APOE epsilon4 on transition from mild cognitive impairment to dementia. *J Alzheimers Dis* 2010;22:1065-1071.
119. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *Jama* 1995;273:1274-1278.
120. Gamaldo A, Moghekar A, Kilada S, Resnick SM, Zonderman AB, O'Brien R. Effect of a clinical stroke on the risk of dementia in a prospective cohort. *Neurology* 2006;67:1363-1369.
121. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Carmelli D. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. *Arch Neurol* 2001;58:643-647.
122. Ravaglia G, Forti P, Maioli F, et al. Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. *Dement Geriatr Cogn Disord* 2006;21:51-58.
123. Xu W, Caracciolo B, Wang HX, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes* 2010;59:2928-2935.
124. Bombois S, Debette S, Bruandet A, et al. Vascular subcortical hyperintensities predict conversion to vascular and mixed dementia in MCI patients. *Stroke* 2008;39:2046-2051.
125. Staekenborg SS, Koedam EL, Henneman WJ, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* 2009;40:1269-1274.
126. Marra C, Ferraccioli M, Vita MG, Quaranta D, Gainotti G. Patterns of Cognitive Decline and Rates of Conversion to Dementia in Patients with Degenerative and Vascular Forms of MCI. *Curr Alzheimer Res* 2011;8:24-31.

127. Wolf H, Ecke GM, Bettin S, Dietrich J, Gertz HJ. Do white matter changes contribute to the subsequent development of dementia in patients with mild cognitive impairment? A longitudinal study. *Int J Geriatr Psychiatry* 2000;15:803-812.
128. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol* 2004;61:1290-1293.
129. Gabryelewicz T, Styczynska M, Luczywek E, et al. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *Int J Geriatr Psychiatry* 2007;22:563-567.
130. Stepaniuk J, Ritchie LJ, Tuokko H. Neuropsychiatric impairments as predictors of mild cognitive impairment, dementia, and Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2008;23:326-333.
131. Houde M, Bergman H, Whitehead V, Chertkow H. A predictive depression pattern in mild cognitive impairment. *Int J Geriatr Psychiatry* 2008;23:1028-1033.
132. Wilson RS, Arnold SE, Beck TL, Bienias JL, Bennett DA. Change in depressive symptoms during the prodromal phase of Alzheimer disease. *Arch Gen Psychiatry* 2008;65:439-445.
133. Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* 2007;68:1596-1602.
134. Panza F, D'Introno A, Colacicco AM, et al. Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. *Dement Geriatr Cogn Disord* 2008;25:336-346.
135. Ramakers IH, Visser PJ, Aalten P, Kester A, Jolles J, Verhey FR. Affective symptoms as predictors of Alzheimer's disease in subjects with mild cognitive impairment: a 10-year follow-up study. *Psychol Med* 2010;40:1193-1201.
136. Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* 2009;27:390-398.
137. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24:253-259.
138. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* 1986;149:698-709.
139. Solfrizzi V, D'Introno A, Colacicco AM, et al. Alcohol consumption, mild cognitive impairment, and progression to dementia. *Neurology* 2007;68:1790-1799.
140. Reisberg B, Prichep L, Mosconi L, et al. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. *Alzheimers Dement* 2008;4:S98-S108.
141. Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *Int Psychogeriatr* 2008;20:1-16.
142. Thorvaldsson V, Macdonald SW, Fratiglioni L, et al. Onset and rate of cognitive change before dementia diagnosis: findings from two Swedish population-based longitudinal studies. *J Int Neuropsychol Soc* 2011;17:154-162.

143. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry* 2010;67:414-422.
144. Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement* 2010;6:11-24.
145. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry* 2000;15:983-991.
146. Mol M, Carpay M, Ramakers I, Rozendaal N, Verhey F, Jolles J. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. *Int J Geriatr Psychiatry* 2007;22:393-400.
147. Mol ME, van Boxtel MP, Willems D, Verhey FR, Jolles J. Subjective forgetfulness is associated with lower quality of life in middle-aged and young-old individuals: a 9-year follow-up in older participants from the Maastricht Aging Study. *Aging Ment Health* 2009;13:699-705.
148. Waldorff FB, Siersma V, Waldemar G. Association between subjective memory complaints and health care utilisation: a three-year follow up. *BMC Geriatr* 2009;9:43.
149. Reisberg B, Shulman MB. Commentary on "a roadmap for the prevention of dementia II: Leon Thal Symposium 2008." Subjective cognitive impairment as an antecedent of Alzheimer's dementia: policy import. *Alzheimers Dement* 2009;5:154-156.
150. Trouton A, Stewart R, Prince M. Does social activity influence the accuracy of subjective memory deficit? Findings from a British community survey. *J Am Geriatr Soc* 2006;54:1108-1113.
151. Montejo P, Montenegro M, Fernandez MA, Maestu F. Subjective memory complaints in the elderly: Prevalence and influence of temporal orientation, depression and quality of life in a population-based study in the city of Madrid. *Aging Ment Health* 2011;15:85-96.
152. Park MH, Min JY, Min HY, Lee HJ, Lee DH, Song MS. Subjective memory complaints and clinical characteristics in elderly Koreans: a questionnaire survey. *Int J Nurs Stud* 2007;44:1400-1405.
153. Westoby CJ, Mallen CD, Thomas E. Cognitive complaints in a general population of older adults: prevalence, association with pain and the influence of concurrent affective disorders. *Eur J Pain* 2009;13:970-976.
154. Tobiansky R, Blizard R, Livingston G, Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychol Med* 1995;25:779-786.
155. Gagnon M, Dartigues JF, Mazaux JM, et al. Self-reported memory complaints and memory performance in elderly French community residents: results of the PAQUID Research Program. *Neuroepidemiology* 1994;13:145-154.
156. Blazer DG, Hays JC, Fillenbaum GG, Gold DT. Memory complaint as a predictor of cognitive decline: a comparison of African American and White elders. *J Aging Health* 1997;9:171-184.
157. Bassett SS, Folstein MF. Memory complaint, memory performance, and psychiatric diagnosis: a community study. *J Geriatr Psychiatry Neurol* 1993;6:105-111.
158. Schofield PW, Jacobs D, Marder K, Sano M, Stern Y. The validity of new memory complaints in the elderly. *Arch Neurol* 1997;54:756-759.

159. Benito-Leon J, Mitchell AJ, Vega S, Bermejo-Pareja F. A population-based study of cognitive function in older people with subjective memory complaints. *J Alzheimers Dis* 2010;22:159-170.
160. Geerlings MI, Jonker C, Bouter LM, Ader HJ, Schmand B. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am J Psychiatry* 1999;156:531-537.
161. Comijs HC, Deeg DJ, Dik MG, Twisk JW, Jonker C. Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics. A 6-year follow-up study. *J Affect Disord* 2002;72:157-165.
162. Ponds RW, Jolles J. Memory complaints in elderly people: the role of memory abilities, metamemory, depression, and personality. *Educational Gerontology* 1996:341–357.
163. Hanninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. *Acta Neurol Scand* 2002;106:148-154.
164. Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord* 2006;22:471-485.
165. Elfgren C, Gustafson L, Vestberg S, Passant U. Subjective memory complaints, neuropsychological performance and psychiatric variables in memory clinic attendees: a 3-year follow-up study. *Arch Gerontol Geriatr* 2010;51:e110-114.
166. Small GW, Chen ST, Komo S, et al. Memory self-appraisal in middle-aged and older adults with the apolipoprotein E-4 allele. *Am J Psychiatry* 1999;156:1035-1038.
167. Dik MG, Jonker C, Comijs HC, et al. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* 2001;57:2217-2222.
168. van der Flier WM, Pijnenburg YA, Schoonenboom SN, Dik MG, Blankenstein MA, Scheltens P. Distribution of APOE genotypes in a memory clinic cohort. *Dement Geriatr Cogn Disord* 2008;25:433-438.
169. Ponds RW, Commissaris KJ, Jolles J. Prevalence and covariates of subjective forgetfulness in a normal population in The Netherlands. *Int J Aging Hum Dev* 1997;45:207-221.
170. Jorm AF, Masaki KH, Davis DG, et al. Memory complaints in nondemented men predict future pathologic diagnosis of Alzheimer disease. *Neurology* 2004;63:1960-1961.
171. Stewart R, Russ C, Richards M, Brayne C, Lovestone S, Mann A. Depression, APOE genotype and subjective memory impairment: a cross-sectional study in an African-Caribbean population. *Psychol Med* 2001;31:431-440.
172. van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MM. Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimers Dement* 2007;3:92-97.
173. Glodzik-Sobanska L, Reisberg B, De Santi S, et al. Subjective memory complaints: presence, severity and future outcome in normal older subjects. *Dement Geriatr Cogn Disord* 2007;24:177-184.
174. Ebly EM, Hogan DB, Parhad IM. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. *Arch Neurol* 1995;52:612-619.
175. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology 2003;61:1179-1184.

176. Palmer K, Backman L, Winblad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry* 2008;16:603-611.
177. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Br J Psychiatry* 2003;182:449-454.
178. Luck T, Luppa M, Briel S, et al. Mild cognitive impairment: incidence and risk factors: results of the leipzig longitudinal study of the aged. *J Am Geriatr Soc* 2010;58:1903-1910.
179. Ganguli M, Chang CC, Snitz BE, Saxton JA, Vanderbilt J, Lee CW. Prevalence of Mild Cognitive Impairment by Multiple Classifications: The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) Project. *Am J Geriatr Psychiatry* 2010;18:674-683.
180. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology* 2002;59:1594-1599.
181. K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology* 2001;56:37-42.
182. Ravaglia G, Forti P, Montesi F, et al. Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population. *J Am Geriatr Soc* 2008;56:51-58.
183. Meguro K, Ishii H, Yamaguchi S, et al. Prevalence and cognitive performances of clinical dementia rating 0.5 and mild cognitive impairment in Japan. The Tajiri project. *Alzheimer Dis Assoc Disord* 2004;18:3-10.
184. Tognoni G, Ceravolo R, Nucciarone B, et al. From mild cognitive impairment to dementia: a prevalence study in a district of Tuscany, Italy. *Acta Neurol Scand* 2005;112:65-71.
185. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. *Neurology* 2001;56:1683-1689.
186. Dlugaj M, Weimar C, Wege N, et al. Prevalence of mild cognitive impairment and its subtypes in the Heinz Nixdorf Recall study cohort. *Dement Geriatr Cogn Disord* 2010;30:362-373.
187. Chaves ML, Camozzato AL, Godinho C, Piazenski I, Kaye J. Incidence of mild cognitive impairment and Alzheimer disease in Southern Brazil. *J Geriatr Psychiatry Neurol* 2009;22:181-187.
188. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Subclassifications for mild cognitive impairment: prevalence and predictive validity. *Psychol Med* 2003;33:1029-1038.
189. Nie H, Xu Y, Liu B, et al. The prevalence of mild cognitive impairment about elderly population in China: a meta-analysis. *Int J Geriatr Psychiatry* 2010.
190. Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 2009;66:324-328.
191. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol* 2007;64:570-575.
192. Kumar R, Jorm AF, Parslow RA, Sachdev PS. Depression in mild cognitive impairment in a community sample of individuals 60-64 years old. *Int Psychogeriatr* 2006;18:471-480.

193. Ravaglia G, Forti P, Lucicesare A, et al. Prevalent depressive symptoms as a risk factor for conversion to mild cognitive impairment in an elderly Italian cohort. *Am J Geriatr Psychiatry* 2008;16:834-843.
194. Forsell Y, Palmer K, Fratiglioni L. Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. *Acta Neurol Scand Suppl* 2003;179:25-28.
195. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. *Am J Epidemiol* 2005;161:228-238.
196. Fratiglioni L, Grut M, Forsell Y, et al. Prevalence of Alzheimer's disease and other dementias in an elderly urban population: relationship with age, sex, and education. *Neurology* 1991;41:1886-1892.
197. Fratiglioni L, Viitanen M, Backman L, Sandman PO, Winblad B. Occurrence of dementia in advanced age: the study design of the Kungsholmen Project. *Neuroepidemiology* 1992;11 Suppl 1:29-36.
198. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology* 1997;48:132-138.
199. Nordic Council on Medicines: *Guidelines for ATC classification.* Uppsala, Sweden: Nordic Council on Medicines, (NLN Publication No.16), 1985.
200. 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.
201. Nilsson E, Fastbom J, Wahlin A. Cognitive functioning in a population-based sample of very old non-demented and non-depressed persons: the impact of diabetes. *Arch Gerontol Geriatr* 2002;35:95-105.
202. Qiu C, Kivipelto M, Aguero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry* 2004;75:828-833.
203. Åsberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica* (suppl) 1978;271:132-138.
204. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* 1983;31:721-727.
205. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009;43:411-431.
206. De Marchis GM, Foderaro G, Jemora J, et al. Mild cognitive impairment in medical inpatients: the Mini-Mental State Examination is a promising screening tool. *Dement Geriatr Cogn Disord* 2010;29:259-264.
207. Backman L, Forsell Y. Episodic memory functioning in a community-based sample of old adults with major depression: utilization of cognitive support. *J Abnorm Psychol* 1994;103:361-370.
208. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale-Revised.* New York: The Psychological Corporation, 1981.
209. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press, 1985.
210. Christensen A-L. *Luria's neuropsychological investigation.* Copenhagen, Denmark: Munksgaard, 1984.

211. Lezak MD. *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press, 1995.
212. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.
213. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
214. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry* 2009;17:368-375.
215. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med* 2002;252:184-205.
216. Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. *Neurobiol Aging* 2005;26:439-447.
217. Gatz M, Reynolds C, Nikolic J, Lowe B, Karel M, Pedersen N. An empirical test of telephone screening to identify potential dementia cases. *Int Psychogeriatr* 1995;7:429-438.
218. Gatz M, Reynolds CA, John R, Johansson B, Mortimer JA, Pedersen NL. Telephone screening to identify potential dementia cases in a population-based sample of older adults. *Int Psychogeriatr* 2002;14:273-289.
219. Kahn RL, Goldfarb AI, Pollack M, Peck A. Brief objective measures for the determination of mental status in the aged. *Am J Psychiatry* 1960;117:326-328.
220. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;23:433-441.
221. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566-572.
222. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797-811.
223. Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. *Neurobiol Aging* 2005;26:439-447.
224. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med* 2002;252:184-205.
225. Andel R, Crowe M, Pedersen NL, et al. Complexity of work and risk of Alzheimer's disease: a population-based study of Swedish twins. *J Gerontol B Psychol Sci Soc Sci* 2005;60:P251-258.
226. Marengoni A, Winblad B, Karp A, Fratiglioni L. Prevalence of chronic diseases and multimorbidity among the elderly population in Sweden. *Am J Public Health* 2008;98:1198-1200.
227. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
228. Carpenter JS, Andrykowski MA, Wilson J, et al. Psychometrics for two short forms of the Center for Epidemiologic Studies-Depression Scale. *Issues Ment Health Nurs* 1998;19:481-494.

229. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health* 1993;5:179-193.
230. Kessler RC, Ustun TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004;13:93-121.
231. Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* New York: Wiley, 1987.
232. Gatz M, Pedersen NL, Berg S, et al. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *J Gerontol A Biol Sci Med Sci* 1997;52:M117-125.
233. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004;50:3085-3092.
234. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* 2005;62:685-691.
235. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. *J Alzheimers Dis* 2007;12:11-22.
236. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol* 2009;8:619-627.
237. van Norden AG, Fick WF, de Laat KF, et al. Subjective cognitive failures and hippocampal volume in elderly with white matter lesions. *Neurology* 2008;71:1152-1159.
238. Barnes LL, Schneider JA, Boyle PA, Bienias JL, Bennett DA. Memory complaints are related to Alzheimer disease pathology in older persons. *Neurology* 2006;67:1581-1585.
239. Spitznagel MB, Tremont G. Cognitive reserve and anosognosia in questionable and mild dementia. *Arch Clin Neuropsychol* 2005;20:505-515.
240. Deary IJ, Johnson W, Houlihan LM. Genetic foundations of human intelligence. *Hum Genet* 2009;126:215-232.
241. Strenze T. Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence* 2007;35:401-426.
242. Jang KL, Livesley WJ, Vernon PA. Heritability of the big five personality dimensions and their facets: a twin study. *J Pers* 1996;64:577-591.
243. Wang HX, Karp A, Herlitz A, et al. Personality and lifestyle in relation to dementia incidence. *Neurology* 2009;72:253-259.
244. Cramer D. Personality and marital dissolution. *Personality and Individual Differences* 1993;14:605-607.
245. Rolland Y, Abellan van Kan G, Benetos A, et al. Frailty, osteoporosis and hip fracture: causes, consequences and therapeutic perspectives. *J Nutr Health Aging* 2008;12:335-346.
246. Lee DM, Pendleton N, Tajar A, et al. Chronic widespread pain is associated with slower cognitive processing speed in middle-aged and older European men. *Pain* 2010;151:30-36.
247. Sandau KE, Lindquist RA, Treat-Jacobson D, Savik K. Health-related quality of life and subjective neurocognitive function three months after coronary artery bypass graft surgery. *Heart Lung* 2008;37:161-172.

248. Panza F, Frisardi V, Capurso C, et al. Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. *J Alzheimers Dis* 2010;21:691-724.
249. Aarts S, van den Akker M, Hajema KJ, et al. Multimorbidity and its relation to subjective memory complaints in a large general population of older adults. *Int Psychogeriatr* 2011;23:616-624.
250. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;3:343-353.
251. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2005;25:117-129.
252. Malhotra RK, Desai AK. Healthy brain aging: what has sleep got to do with it? *Clin Geriatr Med* 2010;26:45-56.
253. Peavy GM, Salmon DP, Jacobson MW, et al. Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry* 2009;166:1384-1391.
254. Reynolds CA, Fiske A, Fratiglioni L, Pedersen NL, Gatz M. Heritability of an age-dependent categorical phenotype: cognitive dysfunction. *Twin Res Hum Genet* 2006;9:17-23.
255. Rosenberg PB, Mielke MM, Xue QL, Carlson MC. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *Am J Geriatr Psychiatry* 2010;18:204-211.
256. Geda YE, Knopman DS, Mrazek DA, et al. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Arch Neurol* 2006;63:435-440.
257. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron* 2009;63:287-303.
258. Sun X, Steffens DC, Au R, et al. Amyloid-associated depression: a prodromal depression of Alzheimer disease? *Arch Gen Psychiatry* 2008;65:542-550.
259. Bhalla RK, Butters MA, Becker JT, et al. Patterns of mild cognitive impairment after treatment of depression in the elderly. *Am J Geriatr Psychiatry* 2009;17:308-316.
260. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997;54:915-922.
261. Panza F, Capurso C, D'Introno A, et al. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. *Int J Geriatr Psychiatry* 2008;23:726-734.
262. Modrego PJ. Depression in the prodromal phase of Alzheimer disease and the reverse causal hypothesis. *Arch Gen Psychiatry* 2009;66:107.
263. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* 2004;161:1957-1966.
*264.* Caracciolo B, Wang H, Bäckman L, Winblad B, Fratiglioni L. Feelings of loneliness and social isolation as risks factors for mild cognitive impairment and its progression to dementia. A 12-year long community-based study. *Under Submission.*
*265.* Caracciolo B, Baars L, Marengoni A, Bäckman L, Winblad B, Fratiglioni L. Multimorbidity as a risk factor for MCI and its progression to dementia. A 12-year long community-based study. *Under Submission.*
266. Xu W, Wang Y, Caracciolo B, et al. Enhanced risk of mild cognitive impairment and its progression to dementia among APOE ε4 carriers. *Under Submission.*

267. Clerici F, Caracciolo B, Imperatori SF, et al. The combined effect of vascular risk factors and white matter lesions on the progression of MCI to dementia. *Under Submission.*
268. Simmons SF, Johansson B, Zarit SH, Ljungquist B, Plomin R, McClearn GE. Selection bias in samples of older twins? A comparison between octogenarian twins and singletons in Sweden. *J Aging Health* 1997;9:553-567.
269. Duff K. Predicting premorbid memory functioning in older adults. *Appl Neuropsychol* 2010;17:278-282.
270. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Eur Psychiatry* 2008;23:321-330.
271. van den Heuvel N, Smits CH, Deeg DJ, Beekman AT. Personality: a moderator of the relation between cognitive functioning and depression in adults aged 55-85? *J Affect Disord* 1996;41:229-240.

# 12 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2008

**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)

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

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

**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.

**2009**

**Atti Anna-Rita**. The effect of somatic disorders on brain aging and dementia: Findings from population- based studies.

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

**Paillard-Borg Stephanie**. Leisure activities at old age and their influence on dementia development.

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

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

**2010**

**Fors Stephan.** Blood on the tracks. Life-course perspectives on health inequalities in later life.

**Keller Lina.** Genetics in dementia. Impact of sequence variations for families and populations.

**2011**

**Schön Per**. Gender matters. Differences and change in disability and health among our oldest women and men. 2011.