# Bio-behavioral inquiries regarding cognitive aging and distance to death

The role of gender, APOE, grip strength and subjective memory

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Deparment of Psychology

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*Till Kajsa, Bella, Nora och Elliot*

# Abstract

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To better understand the nature of cognitive functioning later in life, it is important to gain further knowledge regarding factors that contribute to cognitive aging. Therefore, the overall aim of this thesis was to investigate cognitive change in relation to a select set of bio-behavioral markers (i.e. gender, APOE, grip strength and subjective memory) while taking time to death into account. The studies are all based on the OCTO-Twin study, a Swedish longitudinal population-based study on people aged 80 years and older, assessed every other year, at a maximum of five times.

The aim of **study I** was to examine gender differences in levels and rates of change in cognitive performance in the oldest old in the context of time to death. The study did not show any cognitive differences between men and women, with the exception that men showed a steeper rate of decline in semantic memory. This effect was driven by those who had developed dementia and therefore declined at a faster rate than women. The aim of **study II** was to explicate the assumed negative association between the apolipoprotein E (APOE) ε4 and levels and rates of cognitive change later in life. We found that there was a negative effect of the APOE ε4 allele prior to death also late in life, especially when it came to episodic memory performance. Notably, the influence of APOE on levels and rates of change was highly influenced by incident dementia. The aim of **Study III** was to examine potential associations regarding levels and change between cognitive performance and grip strength later in life. The results indicated consistent developmental associations across all cognitive domains in levels and rates of cognitive change and grip strength. In **study IV**, we investigated level and rate of change in subjective memory in relation to impending death, in addition to its associations with objective memory measurements. The results showed a subjective decline in memory in relation to impending death and that the level and within-person change in subjective memory and objective memory are related. In sum, this thesis shows that gender, APOE, grip strength and subjective memory are related to cognitive decline in relation to impending death.

Keywords: *Cognitive functioning, Oldest old, Time to death, Gender, APOE, Grip strength, Subjective memory*

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# Swedish summary

Medellivslängden i Sverige ökar. Denna trend kan även observeras i resten av världen; framförallt i länder med hög välfärd. Medellivslängden ökar av flera skäl, såsom ökade ekonomiska resurser, förbättrad sjukvård och mer kunskap om hur ohälsa kan förebyggas. Den ökade medellivslängden innebär en rad olika möjligheter och utmaningar. En utmaning är att allt fler individer drabbas av kognitiv svikt och demens.

Kognitiv funktion avser förmågan att bearbeta information, tillämpa kunskap och att minnas. Dessa förmågor kräver att vi är uppmärksamma, att vi kan producera och förstå språk, att vi minns, att vi kan lösa problem och att vi kan fatta beslut. Därför är en intakt kognitiv funktion en av de enskilt viktigaste bidragande orsakerna till livskvalitet och hälsa.

Tidigare trodde man att människans kognitiva förmåga ensidigt försämrades med stigande ålder. Sedan många år tillbaka vet man dock numera att det finns flera möjliga utfall för det kognitiva åldrandet. För vissa kan det handla om en nedgång, medan andra individer har en fortsatt utveckling och stabilitet långt uppe i åldrarna. Dessutom skiljer sig utfallen sig åt beroende på vilka kognitiva förmågor som studeras. Exempelvis skiljer sig så kallade kristalliserade förmågor åt i jämförelse med fluida förmågor i avseende att de inte kräver lika stor andel mentala resurser. Därför försämras de kristalliserade förmågorna inte lika mycket med stigande ålder som de fluida förmågorna. Emellertid vet vi att även om kristalliserade och fluida förmågor påverkas olika mycket av stigande ålder, kommer alla kognitiva förmågor förr eller senare att uppvisa en försämring. Studier visar att generellt sett påbörjas en försämring av våra kognitiva förmågor när vi uppnår en ålder av 40-50 år.

En metodologisk utmaning för forskare som studerar åldersrelaterade kognitiva förändringar i longitudinella studier (det vill säga studier där man följer upp individer genom upprepade mätningar) är den över tid ökande risken för bortfall från studien på grund av att deltagarna avlider. Det innebär att över tid kommer studien att bestå av en mer selekterad grupp individer som är friskare och överlever längre. Denna grupp tenderar att prestera bättre i kognitiva tester och även att försämras i en långsammare takt vad gäller dessa. Ju längre studien pågår, ju mer ökar då risken för denna bias i studien. Ett sätt att hantera denna metodologiska utmaning är att undersöka kognitiv förmåga i samband med avstånd till död istället för kronologisk ålder. Det gör man

genom att mäta hur lång tid individen har kvar att leva mellan varje mättillfälle och död. Detta är möjligt att göra i longitudinella studier där man undersöker hur individer som har avlidit presterade vid mättillfällena innan de avled. Det är numera vedertaget bland forskare inom forskningsfältet kognitivt åldrande att försämring i kognitiva funktioner accelererar före döden samt att individuella skillnader i kognitiv förändring senare i livet återspeglar underliggande processer i samband med avstånd till död snarare än ökad kronologisk ålder. Detta metodologiska paradigm är essentiellt för denna avhandling då studie I-IV undersöker kognitiv förändring i relation till avstånd till död.

Inom forskning om kognitivt åldrande talas det ofta om att mäta åldersrelaterade kognitiva förändringar. I longitudinella studier tar dessa åldersrelaterade kognitiva förändringar sig ofta i uttryck i form av genomsnittliga tillväxtkurvor som representerar dessa förändringar. Emellertid påverkas åldersrelaterad kognitiv förändring av flera olika faktorer, såsom biologiska, neurologiska och hälsorelaterade faktorer. En av utmaningarna för forskare inom kognitivt åldrande handlar om hur man fångar dessa underliggande mekanismer för åldersrelaterad kognitiv förändring. Därför är det av betydelse att undersöka kognitivt åldrande i relation till beteende och biologiska processer som medföljer och påverkar det kognitiva åldrandet.

Utifrån detta var det övergripande syftet med denna avhandling att undersöka kognitiv förändring senare i livet (80+) i förhållande till en utvald uppsättning av biologiska och beteendefaktorer som medföljer och påverkar kognitivt åldrande; det vill säga könsskillnader, genetik (APOE), en fysiologisk markör för åldrande (handstyrka) samt subjektivt minne. Som nämnts ovan tar avhandlingen dessutom hänsyn till individuella skillnader i överlevnad och utgår från ett svenskt populationsbaserat urval av individer som vid studiens början var över 80 år gamla.

Det finns könsskillnader i kognitiv funktion som anses vara vedertagna. Generellt presterar kvinnor bättre än män i test som mäter episodiskt minne, medan män presterar bättre i test som mäter spatial förmåga. Dessa könsskillnader har visat sig vara relativt små men stabila över livsloppet på så sätt att kvinnor och män verkar förändras i samma takt vad gäller dessa förmågor. På så sätt bibehålls dessa könsskillnader även långt upp i åldrandet. Det finns även andra könsskillnader som är uppenbara senare i livet. Bland annat lever kvinnor generellt sätt längre än män. Därav skulle man kunna se en kvinna som är 80 år som ”biologiskt yngre” än en man med samma ålder. Då vi vet att de kognitiva förmågorna är relaterade till skillnader i livslängd samt att kvinnorna lever längre än män, testades i **studie I** könsskillnader i kognitiv

förmåga när hänsyn togs till överlevnad. Resultaten visade inga könsskillnader i kognitiv förmåga med undantag av att män visade en brantare försämring i semantiskt minne. Denna könsskillnad var relaterad till demens då män som utvecklat demens under studieperioden visade en brantare försämring i semantiskt minne i jämförelse med de kvinnor som utvecklade demens. Bland de individer som inte utvecklade demens fanns det inte någon signifikant skillnad mellan kvinnor och män. Överlag var det små skillnader mellan kvinnor och män vad gäller både prestation och förändring, även när det togs hänsyn till könsskillnader i livslängd. Det visar att äldre män och kvinnor är mer kognitivt lika än olika, även när det tas hänsyn till att kvinnor är ”biologiskt yngre” än män som är lika gamla.

En annan viktig faktor för den kognitiva förmågan senare i livet är gener. Bland gener är apolipoprotein E (APOE) den som har funnits ha den största kända påverkan på den kognitiva förmågan. Det finns tre alleliska varianter av APOE: ε2, ε3 och ε4. Varje individ bär dessa i par, vilket ger sex möjliga genotyper: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4 och ε4ε4. Av dessa är ε4 allelen en riskfaktor för kognitiv svikt och för att utveckla demens. Då både avstånd till död och APOE är två viktiga faktorer för att förstå skillnader i åldersrelaterade kognitiva förändringar, var syftet med **studie II** att undersöka den negativa inverkan av APOE ε4 för kognitiv förändring i relation till avstånd till död. Resultaten visade att det fanns en negativ effekt av APOE ε4 allelen, särskilt för episodiskt minne. Det var överlag relativt stora effekter av ε4 allelen på kognitiv prestation i jämförelse med tidigare fynd. Detta indikerar att det är möjligt att den negativa effekten av ε4 allelen för den kognitiva förmågan är särskilt betydande senare i livet.

En annan betydande aspekt för att förstå kognitivt åldrande är hälsa. Handstyrka anses vara en känd fysiologisk markör för allmän hälsa. Det finns indikationer på att det finns åldersrelaterade samband mellan kognitiv förmåga och handstyrka senare i livet. Detta åldersrelaterade samband föreslås drivas av åldersrelaterade förändringar i hjärnan som påverkar både den kognitiva förmågan och handstyrkan. Dock har samband mellan kognitiv funktion och handstyrka i stort sett enbart kunnat påvisas i tvärsnittsstudier (det vill säga studier med ett mättillfälle). Det finns överlag få studier som har undersökt om och hur dessa två funktioner förändras tillsammans med ökad ålder i longitudinella studier. Med tanke på att en förestående död speglar ett underliggande globalt biologiskt åldrande, vilket påverkar både kognitiva och fysiologiska funktioner, är det även av betydelse att undersöka samband mellan förändringar i kognitiv funktion och handstyrka i relation till avstånd till död. **Studie III** syftade därför till att undersöka om kognitiv förmåga och hand-

styrka förändrades på ett liknande sätt i relation till avstånd till död. Resultaten visade samband mellan kognitiv förmåga och handstyrka både vad gäller nivå och förändring av prestation. Dessa samband var konsekventa över flera kognitiva domäner. Det var överlag relativt stora samband mellan kognitiva funktioner och handstyrka i jämförelse med vad som tidigare har påvisats. Detta indikerar att det är möjligt att samband mellan kognition och handstyrka är som tydligast senare i livet.

En annan aspekt som är av betydelse för forskning om kognitivt åldrande är om vi som individer kan värdera vår egna kognitiva förmåga och minne när vi blir äldre. Subjektivt minne innebär vår medvetenhet om vår egen minnesstatus; det vill säga om vi faktiskt kan notera och är medvetna om de förändringar i minnet som de facto äger rum. Därför betraktas ofta subjektivt minne som en tidig markör för kognitiv försämring och demens, varav undersökningar av subjektivt minne är väl etablerade i kliniska sammanhang av demens. På senare år har det utförts en ansenlig mängd studier angående subjektivt minne och dess relation till objektiva minnestest. Det har även utförts en del studier om hur subjektivt minne och objektivt minne förändras tillsammans. Vi vet dock fortfarande lite om förändringar i subjektivt minne i samband med förestående död samt om subjektivt minne och objektivt minne förändras på ett liknande sätt i relation till avstånd till död. Detta perspektiv är av teoretisk betydelse då både skillnader i överlevnad samt subjektivt minne har visat sig vara av betydelse för att förstå kognitivt åldrande. Syftet med **studie IV** var därför att undersöka om subjektivt minne förändrades samt om objektivt minne och subjektivt minne förändrades på ett liknande sätt i relation till avstånd till död. Resultaten visade att subjektivt minne visar en nedgång. Det fanns även samband mellan både nivå och förändring av objektivt och subjektivt minne i relation till avstånd till död.

Sammanfattningsvis visar resultaten i denna avhandling betydelsen av skillnader i överlevnad för kognitiv förmåga och förändring senare i livet (d.v.s. en terminal nedgång). Dessutom visar avhandlingen att kön, APOE, handstyrka och subjektivt minne kan relateras till kognitiv prestation och försämring på äldre dagar.

# Original papers

This thesis consists of a summary and the following four papers, which are referred to by their roman numerals:

I. Praetorius, M., Thorvaldsson, V., Johansson, B. & Hassing, L.B. (2014). Gender differences in cognitive performance in old age: Adjusting for longevity. *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry, 27*(3), 129-134.

II. Praetorius, M., Thorvaldsson, V., Hassing, L.B. & Johansson, B. (2013). Substantial effects of apolipoprotein E ε4 on memory decline in very old age: longitudinal findings from a population-based sample. *Neurobiology of Aging, 34*(12), 2734–2739.

III. Praetorius Björk, M., Johansson, B. & Hassing, L.B. (2016). I forgot when I lost my grip - strong associations between cognition and grip strength in level of performance and change across time in relation to impending death. *Neurobiology of Aging, 38*, 68-72.

IV. Praetorius Björk, M., Johansson, B & Hassing, L.B. (*Submitted*). Terminal decline in subjective memory in the oldest old and its links with objective memory - A longitudinal investigation in the oldest old.

# Contents

# Figures and Tables

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# Preface

An intact intellectual ability is essential for well-being and everyday functioning in old age. Further knowledge regarding factors that contribute to cognitive function later in life is fundamental to better understand the nature of cognitive aging. This thesis takes a broad perspective on cognitive change later in life by examining several bio-behavioral markers (i.e. gender, APOE, grip strength and subjective memory), while conducting an alternative time parameterization (i.e. time to death instead of time from birth) and also (i.e. study III and IV) investigating bivariate developmental time to death processes between cognitive performance and other bio-behavioral constructs (i.e. grip strength, and subjective memory). By using this analytic approach, the results in the present thesis may hopefully provide some further knowledge in the expanding research field of cognitive aging.

# Introduction

## Cognitive abilities and memory

Cognitive abilities are functional characteristics of the individual and refer to abilities such as processing information, applying knowledge and changing preferences. The abilities require attention, producing and understanding language, remembering, solving problems and making decisions. Memory refers specifically to our ability to store, retain and recall information and experiences.

The most common theoretic model of cognitive functioning used in cognitive aging research is the Gf-Gc theory (Catell, 1941). In this model, fluid abilities (Gf) and crystallized abilities (Gc) are factors of general intelligence. Fluid ability is the ability to solve problems, identify patterns and think logically, independent of acquired knowledge (Cattell, 1971). It is necessary for all logical problem solving; especially scientific, mathematical and technical problem solving. Crystallized intelligence is defined as the ability to use knowledge and experience that we obtain throughout life. It is an indication of the level someone's general knowledge and vocabulary, and it also involves the ability to reason using words and numbers (Cattell, 1971). Crystallized intelligence is culture-specific and depends on educational experiences. Because it is dependent on culture and environmental experiences, crystallized intelligence is prone to change positively throughout life. A new learned piece of knowledge or a new learned word adds a new component to the crystallized abilities. These abilities are automated and do not require as much mental resources as fluid intelligence. Therefore, crystallized abilities are not as affected by aging as fluid abilities.

Cognitive abilities are in this thesis represented as spatial ability, reasoning, perceptual speed, short-term memory, working memory, episodic memory and semantic memory. These are described briefly below.

Spatial ability is the capacity to understand and remember the spatial relations among objects. It is divided into several sub-categories, like spatial navigation, spatial visualization, etc. Reasoning ability broadly refers to problem solving ability. It is frequently divided into inductive, logical and abstract reasoning.

Perceptual speed reflects cognitive efficiency. It involves the ability to automatically and fluently perform relatively easy or over-learned cognitive tasks, especially when a high level of mental efficiency is required (Salthouse, 1996). It relates to the ability to process information automatically and therefore quickly, without intentionally thinking. Perceptual speed is a part of processing speed and separated from decision speed. Perceptual speed is assessed by the speed of responding with simple answers, where everyone would get perfect scores if there were no time limits.

Memory can be divided into several distinct subsystems (Tulving, 1985). In this thesis, I refer to memory as short-term memory, working memory, episodic and semantic memory.

Short-term memory (or active/primary memory – the definition of this aspect varies) is the capacity to hold a small amount of information for a short period of time. There is a distinct relationship between short-term memory and working memory. If short-term memory is a capacity for holding information, working-memory is more of a theoretical framework that refers to the structure and processes used for temporarily storing and manipulating information. Working memory consists of four basic storage processes: the phonological loop, the visuospatial sketchpad, the episodic buffer and the central executive (Baddeley, 2000). The phonological loop stores auditory information by silently rehearsing sounds or words in a continuous loop (for example, the repetition of your partner's personal identification number over and over again). The visuospatial sketchpad stores visual and spatial information. It is engaged when performing spatial tasks (like judging distances) or visual ones (like visualizing patterns). The episodic buffer is linking the information from verbal, visual and spatial units. The episodic buffer also has connections to long-term memory and semantic meaning. The central executive essentially acts as a supervisory system that channels information to the three component processes.

Long-term memory is a kind of memory where associations among items are stored. It is divided into *declarative memory (explicit memory)* and *procedural memory (implicit memory)* (Tulving & Schacter, 1990). This thesis focuses

on the declarative memory, which refers to memories that are consciously available, and is divided into two subcategories: episodic memory and semantic memory. Episodic memory is the kind of memory we use when we think about what we have done in the past (Tulving, 1983). It is divided into different sub-fields of memory: verbal and visuospatial memory. The sub-fields are then divided into sub-categories consisting of verbal recall and recognition and visuospatial recall and recognition (Herlitz & Rehnman, 2008). Semantic memory is a structured record of facts, concepts and skills that we have acquired. It is also defined as a part of crystallized abilities. Episodic and semantic memory was initially separated as two independent categories of memory, but there is strong evidence that they co-vary (Kahana & Howard, 2002).

# Aging and cognition

Research shows that the process of age-related cognitive decline varies between individuals and between cognitive domains. Furthermore, the interpretation and conclusion of cognitive aging also varies as a function of study design (e.g. cross-sectional design vs. longitudinal design) and how aging is measured (e.g. as increased chronological age or years of survival). However, eventually all individuals within all cognitive domains will show a decline in cognition when they reach an advanced age. This cognitive decline is a function of age-related changes in the brain, such as regional changes in the brain (see e.g. Burzynska et al., 2015; Cabeza & Nyberg, 2000; Kennedy et al., 2015; Raz et al., 2005, Resnick et al., 2000; Sowell et al., 2003) and neuroanatomical changes (see e.g. Boyle et al., 2013; Diniz, Pinto Jr. & Forlenza, 2008; Hedden, Oh, Younger & Patel, 2013, Yankner, Lu & Loerch, 2008). These age-related changes in the brain affect cognitive performance negatively, but the individual's ability to compensate for age-related changes in the brain is related to genes, lifestyle and socioeconomic factors.

Next, I address methodological factors that are related to study designs and how aging is modelled in cognitive aging research, which affects interpretations and conclusions regarding age-related cognitive decline.

## Cognitive aging in relation to distance from birth

Most research in cognitive aging measures age-related cognitive change in relation to increased chronological age, i.e. distance from birth. It is however debated in the literature in which age the age-related cognitive decline actually starts. Salthouse (2009) claims that the cognitive decline begins as early as

when adults are in their 20s and 30s. These findings were based on cross-sectional data while longitudinal designs suggest that cognitive decline begins in adults when they are in their 40s (Singh-Manoux, et al., 2012) to 60s (Nilsson, Sternäng, Rönnlund & Nyberg, 2009).

Regarding the debate of when and how age-related cognitive decline actually begins, Rönnlund, Nyberg, Bäckman and Nilsson, (2005), demonstrated that as a function of how we define and measure change, different conclusions can be drawn. Using data from the Betula study (Nilsson et al., 1997), the authors estimated episodic- and semantic memory change in a sample of 10 age cohorts (35–80 years old), using four different designs: a cross-sectional design, a longitudinal design (across two waves at a five year interval), a longitudinal design that adjusted for practice effects and cross-sectional design that adjusted for the effect of cohort differences in educational attainment. Interestingly, these four designs resulted in different interpretations of long-term memory change. For example, they showed that cross-sectional analyses indicated gradual age-related decrements in episodic memory performance while the longitudinal data revealed no episodic memory decline before age of 60 years.

Another aspect of cognitive change in aging relates to the variations in how the various cognitive abilities can be affected. Although the debate of when and how age-related cognitive decline begins, we know that cognitive abilities are not equally affected. The various cognitive domains differ in characteristics and demands of mental resources. The cognitive domains are also different from each other as they change differently as a function of aging. In terms of crystallized and fluid abilities, crystallized abilities do not require as much mental resources as fluid abilities or processing speed, and are therefore not as negatively affected of aging in comparison to the others. Moreover, the semantic memory performance is preserved and can actually develop in a positive direction in to relatively high ages. All cognitive domains do however eventually show a decline in higher ages as a function of an aging brain (Park & Reuter-Lorenz, 2009).

Not only does cognitive aging vary depending on cognitive domains, also individuals demonstrate a substantial variation in terms of initial level of performance and how they change. The variation between individuals is increased with aging, i.e. we are becoming even more cognitively different with increasing age (McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002). For example, some individuals show a steep decline while others do not change significantly over time. The variation between individuals that is ob-

served in later life is influenced of our genetic setup and the environment. Even if the genetic influence on cognitive functions is considered as large, also in later life (McClearn et al., 1997), the genetic influence is decreased in higher ages and the variation between individuals in later life relies more on other factors, e.g. among others, education (e.g. Stern, 2002), cognitive (Mitchell et al., 2012) - and physical activity (Lindwall et al., 2012) etc (which refers to the cognitive reserve hypothesis, p. 17).

## Cognitive aging in relation to distance to death

In longitudinal studies of aging, there will be mortality-related drop out. A methodological challenge in studies of later life cognitive functioning is how to handle the effect of this type of drop outs. The high level of drop out due to death will eventually result in a more select sample of healthy survivors who live longer, perform better and decline less on the cognitive tests. This is shown in several studies that demonstrate that non-survivors show a steeper cognitive decline in comparison to survivors (e.g. Ghisletta, McArdle & Lindenberger, 2006; Laukka, MacDonald & Bäckman, 2006; 2008; Riegel & Riegel, 1972; Small, Fratiglioni, von Strauss & Bäckman, 2003; Wilson Beck, Bienias & Bennett, 2007). Therefore, healthy individuals who live longer are more likely to score higher on cognitive tests, and the true variability in the general population will not be captured unless mortality-related selection is accounted for (Thorvaldsson, 2008). A way to handle the mortality-related selection is to model cognitive change in relation to proximity to death. This may be modelled in time to death models, where cognitive performance and change is conditioned on the remaining survival between each time of measuring and death. However, this modeling approach requires a sample of deceased individuals in which the time between each time of measuring and death within each individual can be calculated.

The time-to-death-based models better account for mortality-related selection in comparison to age-based models, this may be seen in studies that have compared models using a function of age and time to death (see e.g. Gerstorf, Ram, Lindenberger & Smith, 2013; Thorvaldsson, Hofer & Johansson, 2006). These studies suggest that modeling cognitive change as a conditional function of time to death better accounts for individual changes than age-based time structures. Overall, time to death models tend to show steeper average rates of change than age-based models. For this thesis, similar analyses of the OCTO-twin material were conducted where a model measuring change as time in the study was compared with a time to death model. In order to be able to compare similar models in the context of within-person change, the age-based model (i.e. time in the study) was based on the exact

time between the first time of measuring and the other measurements within each induvial. The time to death model showed a steeper decline and better model fit to the data across all cognitive domains, which also supports the same trend in the OCTO-twin study (see Table 3 in the Appendix). Thus, the time to death model shows a steeper decline in cognition and better accounts for individual changes in cogntive performance than the model based on time in study.

Attenuation in cognitive performance prior to death refers to the terminal decline hypothesis, which suggests that changes in cognitive performance are related to proximity to death (Kleemeier, 1962; Riegel & Riegel, 1972; Siegler, 1975). Support for the terminal decline hypothesis in terms of an attenuation in cognitive performance close to death has been found in several longitudinal studies of analyses of samples of deceased individuals showing an onset of accelerated cognitive decline closer to death (Batterham, Mackinnon & Christensen, 2011; Boyle et al., 2013; Dodge Wang, Chang & Ganguli, 2011; Macdonald, Hultsch & Dixon, 2011; Muniz-Terrera, van den Hout, Piccinin, Matthews & Hofer, 2013; Sliwinski et al., 2006; Thorvaldsson et al., 2008; Wilson, Beckett, Bienias, Evans & Bennett, 2003; Wilson, Bienias, Evans & Bennett 2007; Wilson et al., 2012). The onset of decline refers to a specific time, prior to death, when the individual shows a steeper cognitive decline closer to death.

Yet, the terminal decline hypothesis can be questioned in terms of when the onset of terminal decline actually begins. Table 4 (see appendix) reveals that the onset of terminal decline varies across studies. For example, when it comes to processing speed, the most frequently studied cognitive domain within this context ($n$ = 6 studies), the onset of steeper decline varies between 2.63 years (Wilson et al., 2012) and up to 14.8 years before death (Thorvaldsson et al., 2008) across studies. The second most studied cognitive domain in relation to impending death is episodic memory ($n$ = 5 studies). The onset of terminal decline in episodic memory varies from 2.62 years (Wilson et al., 2012) up to 8.4 years before death (Sliwinski et al., 2006) across studies. There are also differences in the onset of terminal decline across domains between studies. Thorvaldsson et al. (2008) suggest large differences when it comes to the onset of terminal decline across three cognitive domains with an onset of steeper decline 6.6 years before death in verbal ability up to an onset of 14.8 years before death in perceptual speed. In comparison, Wilson et al. (2012) suggest small differences when it comes to the onset of terminal decline across domains from an onset of 2.32 years in semantic memory and up to 2.63 years before death in perceptual speed. The findings of an onset of

terminal cognitive decline that varies within specific domains, between studies and between domains within studies indicates that the onset of terminal decline seems to be sensitive to specific sample characteristics and the kind of psychometric tests used in the studies.

Other interesting findings in recent years have to do with secular trends. According to the "Flynn effect", cohorts born later perform better on cognitive tests in comparison to cohorts born earlier (Lynn, 1982). This has been found across ages and countries (Flynn, 1987) and replicated in several studies (e.g. Karlsson, Thorvaldsson, Skoog, Gudmundsson, & Johansson, 2015; Sacuiu et al., 2010; Schaie, 2005). Yet, this trend has not been confirmed in studies that modelled cognitive performance conditioned on mortality. In contrast, when these studies compared two different birth cohorts, they found that the later born cohort performed better on the cognitive tasks, but also showed a steeper decline closer to death (Gerstorf, Ram, Hoppmann, Willis & Schaie, 2011; Hülür, Infurna, Ram, & Gerstorf, 2013). These results indicate that the cohort effects reported in cognitive performance are not necessarily detectable when distance to death is accounted for.

Cognitive performance and change in relation to proximity to death is essential for this thesis, as every study of cognitive change in the oldest old in studies I-IV are based on this methodological framework.

# Theoretical accounts on cognitive aging

In the previous sections, I have presented research showing how the interpretation and conclusion of cognitive aging varies as a function of study design and how aging is measured. Next, I will briefly discuss some of the theories and hypotheses that in the history of the research on cognitive aging have been presented trying to explain why and how aging affects cognitive abilities.

## The common cause hypothesis

The common cause hypothesis was initially presented by Lindenberger and Baltes (1994; 1997), and it argues that decline in a common factor drives decline in both cognitive and non-cognitive functions, such as sensory functions. This common factor has been hypothesized to be the integrity of the central nervous system (Lindenberger & Baltes, 1994). The common cause hypothesis was further explored when Christensen, Mackinnon, Korten and

Jorm (2001) found support for a common factor involved in both cognitive functioning and physical functioning.

The common cause hypothesis was developed based on cross-sectional data (Baltes & Lindenberger, 1997). However, studies based on longitudinal designs provide little evidence that age-related cognitive change is related to similar changes in sensory- (e.g. Anstey, Hofer & Luszcz, 2003; Lindenberger & Ghisletta, 2009; Sternäng, Jonsson, Wahlin, Nyberg & Nilsson, 2010) and physical functions (for a review, see Clouston et al., 2013). These weak longitudinal associations of similar age-related changes raise serious questions as to whether it is in fact probable that a common factor can produce the observed effects. Instead, it is more likely that there are unique effects behind these associations (Li & Lindenberger, 2002). For example, Hofer, Berg and Era (2003) find support for associations between cognition and vision, but no support for associations between cognition and hearing. Based on these findings, Hofer et al. (2003) argue that it is more likely that specific peripheral losses affect specific cognitive abilities rather than a general central sensory decline.

## The processing speed theory

Another theory on cognitive aging is the processing speed theory (Salthouse, 1996). This theory argues that an age-related slowing down of mental processing speed results in a general decline in other cognitive domains. According to this theoretical account, the amount of variation that is explained by a reduced processing speed is most pronounced for fluid abilities (e.g. spatial ability, reasoning, etc.) and less evident for crystallized abilities (e.g. verbal ability, general knowledge, etc.) (Verhaegen & Salthouse, 1997). The slowing down of processing speed is assumed to be an effect of an age-related slowing down in the central nervous system.

It has been argued that support for the processing speed theory mainly comes from studies using cross-sectional designs (e.g. Luszcz & Bryan, 1999; Sternäng, Wahlin & Nilsson, 2008). However, support for the processing speed theory is also confirmed in studies based on longitudinal designs (e.g. Finkel, Reynolds, McArdle & Pedersen, 2005; 2007; Finkel, Reynolds, McArdle, Hamagami & Pedersen, 2009). However, the overall findings in longitudinal designs only provide evidence of a small effect of processing speed on age-related cognitive change (e.g. Sliwinski & Buschke, 1999). Longitudinal associations have also been found to be generally weaker than cross-sectional associations (e.g. Lemke & Zimprich, 2005), which indicates

weak support for the notion that changes in processing speed account for observed age-related cognitive decline.

### Theories regarding how to maintain cognitive functions

Whereas the common cause hypothesis and the processing speed theory focus on explaining cognitive decline, there are other theories that reflect on how we may retain cognitive functions as we get older. Two major theories are the theory of successful aging (Rowe & Kahn, 1999) and the theory of selective optimization with compensation (Baltes & Baltes, 1990). Both of these theories focus on how cognitive functioning later in life may be retained by the individual utilizing his or her preserved functional abilities. However, in the past decade, much research on cognitive aging has focused specifically on how mental activity and mental exercises may counteract a decline in cognitive abilities based on the concept of "use it or lose it" (Swaab, 1991). The major theory in this particular field of research is the cognitive reserve hypothesis (Stern, 2002). This theory is based on research showing that intellectual enrichment may decrease the risk of developing dementia later in life through built-up mental resources that enable the individual to better cope with dementia pathology and thus delay the onset of the disease (Scarmeas & Stern, 2003). The cornerstone of this theory is that the brain is plastic, and there is some evidence that the aging brain may to some extent compensate for these structural and neuropathological age-related changes (Kuehn, 2015; Park & Reuter-Lorenz, 2009). Hence, "mental activity" builds up a larger neuronal capacity and recruits additional brain regions to compensate for age-related cognitive changes (Tucker & Stern, 2011). This is also supported by several other studies that show that lifestyle and socioeconomic factors, such as higher education and higher levels of cognitive, social and physical activity throughout the course of life, are positively related to the ability to compensate for age-related changes in the brain (see e.g. Lui & Yaffe, 2010; Middleton, Barnes & Lindenberger, 2014; Richards & Deary, 2005; Scarmeas & Stern, 2003; Stern, 2002; Wilson et al., 2013). Today, this is an important field of research in the study of cognitive aging in how to prevent age-related cognitive decline.

## Bio-behavioral aspects of cognitive aging

Cognitive developmental processes due to increasing age are influenced by several biological, neurological and health-related factors that contribute to the overall decline that is seen as aging effects. One of the challenges in research on cognitive aging is how to capture the underlying mechanisms of

age-related cognitive decline (Piccinin, Muniz, Sparks & Bontempo, 2011). The concept of bio-behavioral is here used broadly to refer to complex interactions between behavior and biological processes accompanying and influencing cognitive aging. In this thesis, cognitive aging is subsequently explored from multiple bio-behavioral perspectives. More specifically, the focus is on gender, genetics (the APOE allele), a physiological marker of aging (grip strength) and self-assessed cognition (subjective memory), which are all analyzed in relation to impending death. These bio-behavioral aspects are discussed in more detail in the next section, as they are also essential and in fact the basis of the four empirical studies of this thesis.

## Gender differences in cognitive abilities

Gender differences in cognitive performance are generally speaking considered to be few and relatively small (Hyde, 1981; 2014), i.e. men and women are overall more cognitively alike than unlike. However, the literature provides support for three conclusive differences. Women generally outperform men in episodic memory tasks (Herlitz & Rehnman, 2008; Maitland, Herlitz, Nyberg, Backman & Nilsson, 2004), especially in tasks of verbal episodic memory (Herltz, Nilsson & Bäckman, 1997; Lewin, Wolgers & Herlitz, 2001), and tasks of face recognition (Lewin & Herlitz, 2002; Lewin et al., 2001; Rehnman & Herlitz, 2007). Men in other hand tend to perform better than women in general knowledge (Lynn, Irwing & Cammock, 2002; Lynn & Irwing, 2002; Lynn, Ivanec & Zarevski, 2009) and in spatial ability tasks (Lewin et al., 2001; Voyer, Voyer & Bryden, 1995; Voyer, Postma, Brake & Imperato-McGinley, 2007), especially in tasks of spatial navigation (Astur, Tropp, Sava, Constable & Markus, 2004; Lövden et al., 2007).

Even if gender differences in cognitive performance are considered to be relatively few and small, they have been shown to be quite stable across ages, which means that men and women seem to decline virtually in parallel rather than in a divergent manner (Aartsen, Martin & Zimprich, 2004; de Frias, Nilsson & Herlitz, 2006; Finkel, Reynolds, McArdle, Gatz & Pedersen, 2003; Finkel, Reynolds, Berg & Pedersen, 2006; Gerstorf, Herlitz & Smith, 2006). Therefore, gender differences in cognitive performance are apparent also in very advanced ages (Read et al., 2006).

Not only are there gender differences in cognitive functioning later in life, women also tend to outlive men (see e.g. Austad, 2006; Eskes & Haanen, 2007; Oksuzyan, Juel, Vaupel & Christensen, 2008). A woman aged 80 with an average life expectancy could therefore be seen as "biologically younger" than a man aged 80 with an average life expectancy. In previous research on

gender differences in levels and rate of change in cognitive performance, adjustments are typically made for differences in age and education (see e.g. Aartsen et al., 2004; de Frias et al., 2006; Finkel et al., 2003; 2006; Gerstorf et al., 2006).

However, to our knowledge it has not been studied whether differences in distance to death may affect gender differences in cognition. It is possible that modeling cognitive change in relation to impending death, which accounts for mortality-related selection, could result in different interpretations regarding gender differences in cognitive functioning later in life, as compared to previous findings. Therefore, gender differences in levels and rate of change in cognitive performance in relation to impending death were studied in Study I.

## Cognitive performance and APOE

An important factor for individual differences in cognitive functioning later in life is the genetic setup. Among genes, the Apolipoprotein E (APOE) ε4 allele is known to have the greatest impact on cognition and is also an established risk factor for developing dementia, in particular Alzheimer's disease.

Apolipoprotein (APOE) is a plasma protein and there are three allelic variations of APOE: ε2, ε3 and ε4. The allele variations yield six possible genotypes of APOE: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4 and ε4ε4. The ε3 allele is the most frequent, with a gene frequency of ≈ 70-80% in the population. Approximately 5-10% and 10-15% carry the ε2 or the ε4 allele (Lahiri, 2004). Studies have shown a lower frequency of the ε4 allele and a higher frequency of ε2 allele in older populations (Lewis & Brunner, 2004).

The APOE ε2 allele is considered a protective factor for Alzheimer's disease and is associated with longevity (Corder et al., 1996). On the contrary, the association between the ε4 allele and an increased risk of developing Alzheimer's disease is the most replicated finding in genetic research (see e.g. Lahiri, 2004; Reynolds et al., 2010). Approximately 40-60% of all cases of Alzheimer's disease carry the ε4 allele (Parker et al., 2005; Ward et al., 2012) and APOE is found in amyloid plaques and neurofibrillary tangles, which are both markers of Alzheimer's disease.

Further, as being a risk factor for dementia, the ε4 allele is also associated with an increased risk of cognitive impairment in old age (Bretsky, Guralnik, Launer, Albert & Seeman, 2003; Packard et al., 2007; Schiepers et al., 2011), where the episodic memory is particularly vulnerable (Nilsson et al., 2006;

Wilson, Bienias, Berry-Kravis, Evans & Bennett, 2002; Wilson et al., 2002). However, the finding of an increased risk of cognitive impairment in ε4 carriers in old age is not entirely conclusive, as some studies have found no relationship (e.g. Jorm et al., 2007; Luciano et al., 2009). It is possible that the non-conclusive results is a result of a natural selection, which with increasing age lowers the frequency of ε4 carriers and reduces the negative effect of the ε4 genotype on cognitive functions late in life (i.e. it reduces the power from the effect of ε4 allele on cognitive performance). The negative effect of the APOE ε4 allele on Alzheimer's disease has also been found to become weaker in higher ages (Sando et al., 2008), which gives additional support for the assumption of natural selection effects.

Two meta-analyses that examined the effect of APOE ε4 on cognitive performance in old age have been published in recent years with, interestingly enough, inconclusive results (Small, Rosnick, Fratiglioni & Bäckman, 2004; Wisdom, Callahan & Hawkins, 2011). Small et al. (2004) found that the ε4 allele has a negative effect on cognitive performance in normal aging, but that the negative effect of the ε4 allele was reduced at more advanced ages. Wilson et al. (2011) found little impact of the ε4 on cognitive performance. However, and in contrast to previous findings, the results indicate larger differences with higher ages between APOE ε4 carriers in comparison to non-APOE ε4 carriers.

APOE ε4 is the gene that has the largest impact on cognition and has also been found to be a risk factor for many other conditions related to cardiovascular diseases (for reviews, see e.g. Eichner et al., 2002; Sudlow, González, Kim & Clark, 2006). Given that time to death and APOE ε4 are two important factors in understanding cognitive aging, Study II was designed to specifically study the association between the APOE ε4 allele and cognitive decline in relation to impending death.

## Cognitive performance and grip strength

Overall health constitutes a significant bio-behavioral aspect of cognitive aging. Grip strength is a known physiological marker of overall health (Cooper et al., 2011, Leong et al., 2015). Furthermore, it is suggested that there are age-related associations between cognitive performance and grip strength later in life, and that a shared common cause drives this relationship (Christensen, Mackinnon, Korten & Jorm, 2001).

A systematic review and meta-analysis on the relationship between cognition and physical functions found support only for a small cross-sectional rela-

tionship between cognition and grip strength (Clouston et al., 2013). The conclusion drawn from the review was that there are few longitudinal studies that have examined whether cognition and grip strength share a similar variability of change later in life. Two studies that measured change across occasions of measuring suggest that change in grip strength is related to change in cognition (Atkinson et al., 2010; Tabbarah, Crimmins & Seeman, 2002). However, only two studies have examined whether cognition and grip strength share a similar variability of intra-individual change in a multi-wave design (i.e. ≥ 3 waves) (Deary et al., 2011; Sternäng et al., 2015). These studies show mixed results. Deary et al. (2011) find no support for correlated slopes between fluid ability and grip strength, whereas Sternäng et al. (2015) find support for a change in grip strength predicting a change in cognition across four cognitive domains (i.e. verbal ability, spatial ability, processing speed and memory). This was an association that became more evident after the age of 65.

Age-related associations between cognitive functions and sensory/sensorimotor functions are suggested to be stronger in samples of older individuals (e.g. Baltes & Lindenberg, 1997; Anstey & Smith., 1999). Despite this, no previous studies have examined whether cognition and grip strength share a similar variability of change in samples 80 years and older in relation to impending death.

Given that impending death reflects underlying global biological aging, it is important to examine whether a change in cognition is related to a change in grip strength in proximity to death. This was therefore tested in Study III.

## Subjective and objective memory

Another bio-behavioral aspect that is of interest when it comes to cognitive aging is the ability to rate one's own cognition and memory.

Subjective memory refers to our awareness of own memory status; in other words, how we rate our own memory performance. Subjective memory is often considered a predictor of future cognitive impairment (Fritsch, McClendon, Wallendal, Hyde & Larsen, 2014; Steinberg et al., 2013) and future dementia (Jessen et al., 2010; Mitchell, 2008; St John & Montgomery, 2002), where examining subjective memory is well-established in clinical settings related to dementia (Abdulrab & Heun, 2008).

In cognitive aging research and in clinical settings, it is important to understand whether older individuals are able to evaluate their memory perfor-

mance correctly. It is suggested that individuals who are better at evaluating their memory performance are more likely to implement effective strategies, which may subsequently improve their memory performance (Lachman & Andreoletti & Pearman, 2006). In contrast, individuals who over- or underestimate their memory abilities may not make the required effort when it comes to the memory tasks, which may in turn result in poor performance (Crumley, Stetler & Horhota, 2014). Meta-memory awareness may also result in anxiety regarding memory, which may influence individual well-being negatively (Mol et al., 2007; Verhaeghen, Geraerts & Marcoen, 2000).

Studies have tried to identify predictors related to subjective memory later in life, beyond objective memory measurements. Several factors, like depression, anxiety, health, personality, self-efficacy and negative affect (see e.g. Comijs, Deeg, Dik, Twisk & Jonker, 2002; Levy-Cushman & Abeles, 1998), have been found to be related to subjective memory. One study that studied potential predictors of subjective memory in adult age (i.e. 45 to 94 years of age) found that personality measures such as conscientiousness, self-esteem and neuroticism explained about a third of the variance in subjective memory, whereas objective memory performance only explained 4% (Pearman & Storandt, 2004).

In general, it seems as if subjective memory is related to future upcoming changes in objective memory performance (Hohman, Beason-Held, Lamar & Resnick, 2011; Luszcz, Anstey & Ghisletta, 2015), and is being a reliable predictor of future subsequent dementia (see e.g. Jessen et al., 2010; Johansson, Allen-Burge & Zarit., 1997; Mitchell, 2008; Rönnlund, Sundström, Adolfssond & Nilsson, 2015; St John & Montgomery, 2002). Yet, there are overall weak associations between subjective memory and objective memory later in life when the two memory dimensions are compared at the same occasion. A meta-analysis examining the correlation between subjective and objective memory among 53 cross-sectional studies found a very small correlation of $r$ = .06, where the effect size ranged from -.29 to .41 across studies (Crumley et al., 2014). The results from this meta-analysis showed that subjective memory explained less than 1% of the variance in objective memory performance. There are many possible methodological concerns that may explain this small effect size, as well as the high variability of the results of the studies. One is due to sample characteristics. Crumley et al. (2014) shows that samples of higher ages – who were more educated, had a higher frequency of women and were less depressed – showed a more significant association between subjective and objective memory. Other factors that are related to the variability between the studies are most likely also related to how the

subjective and objective memory assessments have been operationalized. Regarding subjective memory, another review on the topic identified 34 self-report measures comprising 640 cognitive self-report items among studies that have examined subjective memory later in life (Rabin et al., 2015). Many of these studies used global questionnaires or just a single question of global subjective memory. These questions are designed to be general and are independent of task and situational characteristics that may influence performance. Research shows that older adults are, in comparison to younger adults, more accurate when making memory-specific task predictions (Hertzog, Dixon & Hultsch, 1990), as well as when they are asked to assess how well they have done on a previously completed task (Hertzog, Saylor, Fleece & Dixon, 1994). When these types of subjective evaluations are not available, other more detailed scales and protocols based on experiences of own memory strengths and failures are also to prefer when predicting actual memory functioning (e.g. Eckerström et al., 2013). However, in longitudinal ongoing population-based studies, it is sometimes the case that none of these operationalizations of subjective memory are available and that a global measurement of subjective memory is the only available information. In these cases, more sophisticated longitudinal analyses could be required to better understand the association between subjective and objective memory. In recent years, several studies have implemented such analyses and examined temporal associations or whether subjective and objective memory changes together over time (Hülür, Hertzog, Pearman, Ram & Gerstorf, 2014; Hülür, Hertzog, Pearman & Gerstorf, 2015; Snitz et al., 2015; Zimprich & Kurtz, 2015). Many of these studies suggest that there are longitudinal associations between changes in subjective and objective memory over time. It is also suggested that both cross-sectional (Crumley et al., 2014) and longitudinal associations (Hülür et al., 2014) between subjective and objective memory become stronger with increasing age. However, little is known regarding changes in subjective memory in relation to impending death, as well as links between subjective and objective memory in this context. Therefore, Study IV was designed to study developmental associations between subjective and objective memory in relation to impending death.

# Summary of the empirical studies

## Aims

The overall aim of the thesis is to study levels and rates of change in cognitive performance later in life in relation to gender, APOE, grip strength and subjective memory while taking impending death into account. To my knowledge, few or no previous studies have applied this perspective to formal tests in a population-based sample of oldest old individuals followed until death.

In Study I, the specific aim is to examine gender differences in levels and rates of change in cognitive performance in the oldest old while taking differences in remaining survival time between men and women into account.

In study II, the impact of the APOE ε4 allele is examined in levels and rates of cognitive change in old age in relation to impending death.

In Study III, the aim is to study whether cognition and grip strength changed together in relation to impending death.

In Study IV, the aim is to examine subjective memory change and a possible association of shared variability of change between subjective and objective memory in relation to impending death.

## Methods

### Sample for the studies – The OCTO-Twin study

This thesis is entirely based on data from the OCTO Twin Study (The origins of variance in the Oldest Old) (McClearn et al., 1997). The study included a population-based twin sample aged 80 and older who were born 1893-1913, where both twins were alive at inclusion (N = 702 individuals/351 pairs of twins). Participants were examined five times (T1-T5) at two year intervals.

The assessments at each occasion proceeded between 1991-1993 (T1), 1993-1995 (T2), 1995-1997 (T3), 1997-1999 (T4) and 1999-2002 (T5).

All examinations were conducted at the participant's home with a broad-based bio-behavioral test battery administered by experienced registered nurses specifically trained for the study and continuously supervised. A typical test session took about 3.5 to 4 hours, including rest periods. An assessment of cognitive impairment and dementia was performed. All suspected cases of dementia were brought up to a consensus conference with a physician, a nurse and a neuropsychologist.

The general aim of the OCTO-Twin study was to examine how the importance of genetic and environmental factors contribute to continued well-being, health and functional capacity. The study was administrated in collaboration with Karolinska Institutet, University of Stockholm; Institute for Gerontology, Jönköping University and Pennsylvania State University. The OCTO-Twin study was funded by the National Institute of Health (NIH).

## Participants

At study entry, the average OCTO-Twin participant was 83 years old with an average education of 7 years. See table 1.

Table 1. Background characteristics of the OCTO-Twin Sample across the study period

| | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|
| *N* | 702 | 624 | 438 | 315 | 222 |
| Drop out (due to death), *n* | - | 78 | 186 | 123 | 93 |
| Age, *M (SD)* | 83.58 (3.17) | 85.50 (3.09) | 87.26 (2.86) | 89.08 (2.81) | 90.82 (4.57) |
| Years to death, *M (SD)* | 6.52 (4.11) | 5.39 (3.71) | 4.70 (3.21) | 3.98 (2.77) | 3.17 (2.39) |
| Education, *M (SD)* | 7.14 (2.29) | 7.16 (2.29) | 7.16 (2.26) | 7.12 (2.15) | 7.11 (2.21) |
| Female, *n (%)* | 468 (66.7) | 416 (66.7) | 295 (67.4) | 225 (71.4) | 165 (74.3) |
| APOE ε4, *n (%)* | 177 (25.2) | 164 (26.3) | 126 (29.1) | 86 (27.3) | 54 (17.2) |
| Prevalent dementia, *n (%)* | 108 (15.4) | - | - | - | - |
| Pre-demented survivors, *n* | 108 | 86 | 47 | 20 | 9 |
| Incident dementia, *n (%)* | - | 42 (6.7) | 80 (18.3) | 100 (31.8) | 126 (56.8) |
| Dementia each wave, *n (%)* | 108 (15.4) | 128 (20.5) | 127 (29.0) | 120 (38.1) | 135 (60.8) |

## Cognitive measures

The cognitive test battery covers several domains across the dimension of crystallized and fluid abilities; namely spatial and reasoning ability (Block design and Figure Logic), short-term memory (Digit span forward), working memory (Digit span backward), semantic long-term memory (Information test and Synonyms), episodic long-term memory (Thurstone's picture memory task, Prose recall and Memory-in-reality test) and motor and perceptual speed (Symbol-Digit).

### Spatial and reasoning ability

The Kohs Block design test is a part of the Dureman-Sälde battery (also known as the DS Battery (Dureman, Kebbon & Österberg, 1971)), and was used to assess spatial ability. The participants were presented with different models in two colors (red and white). They were then asked to reconstruct replicas of the models with blocks. Everyone started with a model of four blocks and ended with a model of 16 blocks. The maximum score was 42 and the time limit was 20 minutes. The Figure logic task (also a part of the DS battery; Dureman et al., 1971) was used to measure reasoning ability. The participants had to identify one figure out of five that was different from the others. There were a total of 30 items and the possible scores were 0-30. The respondents had 8 minutes to complete the task.

### Motor and perceptual speed

Motor and perceptual speed was measured with a modified version of the speeded Symbol-Digit Substitution test from the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1991) which tests information processing speed, attention, visual scanning and tracking. The participants were given a record form with symbol-digit pairs followed by a series of digits. The participants were asked to provide a written (i.e. the motor function) response of the matching digit under each of the provided symbols as quickly as possible without skipping any numbers. Participants received one point for each correctly matched symbol. The score was the sum of the correct number of symbol–digit matches in two 45 second trials. The maximum score was 30.

### Short-term memory and working memory

The Digit Span test measures both short-term memory (Digit Span Forward) and working memory capacity (Digit Span Backward) and is part of the CVB (which is a Swedish version of WAIS) scales (Jonson & Molander, 1964).

The examiner reads a random sequence of digits at the rate of one digit per second. In Digit Span Forward, the participants were asked to repeat the numbers in the same order. In Digit Span Backward, the participants were asked to repeat the numbers in reverse order. When the participants repeated the numbers in the same order at one level of digits, the examiner reads the next level of digits until the participant fails. The maximum score for Digit Span Forward was 9 points and the possible score ranged from 0-9 points. For Digit Span Backward, the maximum score was 8 points and the possible score ranged from 0-8 points.

### Semantic long-term memory

The Information test was used to assess general knowledge. The test is a modified version of the Wechsler Adult Intelligence Scale (Wechsler, 1981) and consists of 44 questions regarding general knowledge. The possible scores ranged from 0-44 points. A higher score indicates a higher level of general knowledge. The Synonyms task is a part of the DS Battery (Dureman et al., 1971). The tasks, which tests knowledge of verbal meaning, require the participant to match a target word among five choices of potential synonyms, where one of them is the correct one. The test consisted of 30 items and the possible score ranged from 0-30. The test limit was 7 minutes. The words were presented in a magnified form for participants who had problems reading the words due to visual impairment.

### Episodic long-term memory

The Memory-in-reality test (Johansson, 1988/1989) measures the ability to recall and recognize objects placed in a model of an apartment. Only the recall part, a delayed (30-min) free recall test of 10 objects, was used for analyses in the present thesis. The Prose recall test (a Swedish version of the Logical Memory in the Wechsler Memory Scale) is a verbal memory test where participants are asked for immediate free recall of a brief story (100 words, maximum score is 16). Responses are coded for the amount of information recalled. The Thurstone's picture memory task (Thurstone & Thurstone, 1949) is a non-verbal memory test. Participants are shown 28 drawn pictures and are then asked to recognize these among other pictures. The maximum score for Thurstone's picture memory was 28 points.

## Bio-behavioral markers in the studies

### Gender

Gender was defined as men (0) and women (1).

### APOE

The two APOE markers (rs429358 and rs7412) were genotyped separately using Illumina GoldenGate assays (see Reynolds et al., 2013). The APOE haplotype was determined by PCR amplification of a 227-bp fragment of the APOE gene containing two polymorphic sites (rs7412 and rs429358) that account for the three alleles: ε2, ε3 and ε4. APOE was coded as non-ε4 carriers (0) and ε4 carriers (1).

### Grip strength

Grip strength was measured by having the participants squeeze a Martin vigorimeter (Elmed Inc., Addison, IL, USA; medium size bulb) three times for each hand, with the final score being the maximum force (in pounds per square inch) exerted in the 6 trials.

### Subjective memory

The participants were asked to rate their own overall memory with the question "do you consider yourself to have a good or a bad memory?" The subjective memory was measured using a 7-point scale ranging from 1 = very good to 7 = very bad.

## Other measures and covariates

### Age

Age was defined in years at first measurement occasion (T1).

### Education

Education was defined as total years of education. The educational level in the OCTO-Twin sample is low (see Table 1), but typical for a Swedish cohort born in the late 1800s and early 1900s.

### Dementia

Diagnoses of dementia were considered in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, third edition (American Psychiatric Association, 1987). Alzheimer's disease was identified according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders (McKhann et al., 1984) and vascular dementia according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (Roman

et al., 1993). All suspected cases of dementia were determined at a consensus conference with a physician, a nurse and a neuropsychologist.

### Cardiovascular Disease (CVD)

An expert diagnosis based on a number of factors was made by a physician based on a concurrent review of (i) medical records, including reported medical history; (ii) use of pharmaceuticals; and (iii) self-reported information about diseases (Nilsson, Johansson, Berg, Karlsson & McClearn, 2002) in accordance with the ICD-10 criteria (ICD-10: World Health Organization, 1992). An independent second opinion on classification was performed by another physician on a 20% subsample, which produced only marginal amendments.

The conditions of interest for subsequent analyses were hypertension (which was diagnosed in cases where either the records contained information of specific hypertension treatment, or in cases with more than one diastolic value of at least 95 mmHg or systolic value higher than 160 mmHg), type 2 diabetes mellitus (diagnosed using the 1980 WHO criteria when the diagnostic level for venous whole blood glucose was 6.7 mmol/l), congestive heart failure, myocardial infarction, angina pectoris and stroke. Cardiovascular disease (CVD) in Study 2 was defined as life-time prevalence of myocardial infarction, congestive heart failure or angina pectoris.

## Statistical analyses

Study I-IV analyzed individual differences in levels and rates of change in cognitive performance using hierarchical linear models that are used for hierarchical structured data (Field, 2009; Snijders & Bosker, 1999). The OCTO-twin data set provides three hierarchical structured levels of variation: repeated measure (i.e., time) nested within individuals nested within twin pair.

Study I and II estimated the effect of twinship by adding a third level of variance in the SPSS Mixed level modelling framework. In study III and IV, twinship was adjusted for by using the TYPE=COMPLEX with CLUSTER command in Mplus, which takes into account the non-independence of observations due to the cluster sampling of twin data (Muthén & Muthén, 1998-2010). All models used maximum likelihood for the estimation of model parameters, which is robust against a missing at random missing data assumption (Little & Rubin, 1987).

Study I and II examined cognitive change by using univariate models. Study III and IV examined bivariate developmental trends by using bivariate time to death growth curve models. The bivariate growth curve is a bivariate extension of the univariate growth curve (McArdle, 1988), which makes it possible to examine three bivariate relationships: (1) correlation among the intercepts, (2) correlation among the slopes and (3) correlation among the residuals. In other words, (1) is the level of performance in y related to the level of performance in x? (2) Is the amount of rate of change in y related to the amount of rate of change in x? (3) Are occasion-specific fluctuations in y related to occasion-specific fluctuations in x, after estimating for the rate of change in y and x?

### Time to death

The OCTO-twin study constitutes of individuals who are already deceased. The participants were followed until death in the terms of remaining survival. Information about the exact time of death was obtained from the Swedish Census Register. This made it possible to calculate a slope that consisted of the remaining survival between each time of measurement (T1-T5) and death. The time metrics are defined as $\lambda it$ = (age at death – $\lambda$age at T1) + (age at death – $\lambda$age at T2) + … (age at death – $\lambda$age at T5). To correspond with the traditional representations of number lines and time (i.e. that values are increasing to the right with the progression of time), the time metric was reversed and coded using negative values counting down to death: $\lambda it$ = [(age at death – $\lambda$age at T1) - (age at death – $\lambda$age at T1 x 2)] + [(age at death – $\lambda$age at T2) - (age at death – $\lambda$age at T2 x 2)] … + [(age at death – $\lambda$age at T5) - (age at death – $\lambda$age at T5 x 2)]. We specified the time factors as one-year linear effects of "time to death" and centered intercepts to two years prior to death. The reason why we did not center the time metric at the point of actual death is due to the impossibility of obtaining performance scores at the actual time of death. However, the choice of where to center the time metric before death is optional.

To exemplify, after the time metric was reversed and centered two years prior to death for a participant who was examined at 10, 8, 6, 4 and 2 years before death, the time metric was coded as -8, -6, -4, -2 and 0.

# Summary of study I

The aim was to investigate potential gender differences in levels and rates of change in cognitive performance while taking differences in life expectancy between men and women into account. The sample consisted of 574 individuals from the OCTO Twin Study, aged 80 years and older. Individuals with dementia at the first time of measurement were excluded ($n$ = 108), as were 20 individuals with unknown date of death.

Cognitive performance was tested at five occasions with an interval of two years using ten tests representing semantic memory, episodic memory, short-term memory, spatial ability as well as motor and perceptual speed. We constructed factor scores for these five domains using regression scores for each factor at each measurement. All cognitive domains were thereafter transformed into a $T$ distribution with $M$ = 50 and $SD$ = 10.

Age at first time of measurement, education and incident dementia were specified as level 2 covariates (i.e. fixed effects) and grand mean centered. For the purpose of investigating gender differences on levels and rates of change in cognitive performance, we also included gender into the models. The analyses reflected no significant gender differences in the level of cognitive performance. However, men showed an 82% steeper linear change in semantic memory than women ($\beta$ = 0.36, CI 95%: 0.07, 0.66). There were no significant gender differences in accelerated change.

To further explore the gender differences in the rate of semantic memory change, we included an interaction term of incident dementia and gender conditioned on the level of performance and on linear change. This resulted in two effects: the effect of gender on semantic memory change was reduced to non-significance ($\beta$ = 0.12, CI 95%: -0.18, 0.42) and there was a significant interaction effect between gender and incident dementia for the linear rate of change in semantic memory ($\beta$ = 0.94, CI 95%: 0.31, 1.57). This interaction effect reflected that men who developed dementia over the study period showed a steeper decline in comparison to the subsequent demented women, while there were no significant gender differences in semantic memory decline among individuals who remained non-demented over the study period.

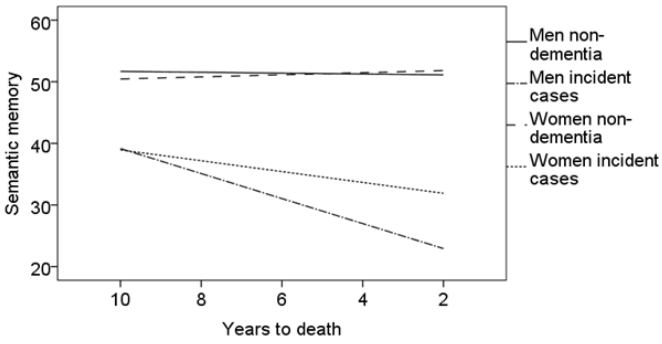


Figure 1. Gender differences in average linear change per year prior to death in semantic memory.

Our results support previous findings showing minor to non-existing gender differences in levels and rates of change in cognitive performance among non-demented individuals at very advanced ages. These findings suggest that even when taking gender differences in longevity into account, the oldest old men and women are overall more alike than unlike when it comes to cognitive functions.

# Summary of study II

The aim was investigate the negative association between the APOE ε4 and levels and rates of change in cognitive performance later in life using time to death as an alternative time metric. The sample consisted of 482 non-demented individuals. Ten cognitive tests were administered at five occasions with an interval of two years. The cognitive test scores were all standardized on a baseline distribution and then transformed to a *T* distribution with $M$ = 50 and $SD$ = 10. Individuals with dementia at baseline ($n$ = 108), missing information on APOE genotype ($n$ = 96) and individuals with unknown date of death ($n$ = 16) were excluded.

First, the effect of the APOE ε4 allele was conditioned on levels of performance and rates of linear change while accounting for sex, education, age, stroke, CVD, hypertension and diabetes. This model resulted in that the ε4 allele was significantly related to lower performance levels and steeper rates of decline in all three long-term episodic memory tests. The APOE ε4 allele was also significantly related to lower levels of performance on the Information test and there was a trend in the same direction regarding the Synonym test, while the ε4 allele was significantly related to a steeper decline in both semantic memory tests (i.e. Information and Synonyms). The ε4 allele was also significantly related to a lower average performance, but not de-

cline, on both short-term memory tests. Comparisons on other cognitive domains indicated non-significant trends that always favored non-carriers.

Thereafter, incident dementia was included into the models. This resulted in the negative effect of the ε4 allele being reduced to non-significance on both levels of performance and rates of change in all cognitive measures, except for the MIR Recall test, where the ε4 allele still had a significant negative effect. However, even when we accounted for the effect of incident dementia, the negative effect of the ε4 allele in the episodic memory tests was relatively large (i.e. 0.19 to 0.31 baseline *SD*) as compared with effect sizes reported in two meta-analyses: $d$ = -0.03 and $d$ = -0.14 respectively (see Small et al., 2004 and Wisdom et al., 2011).

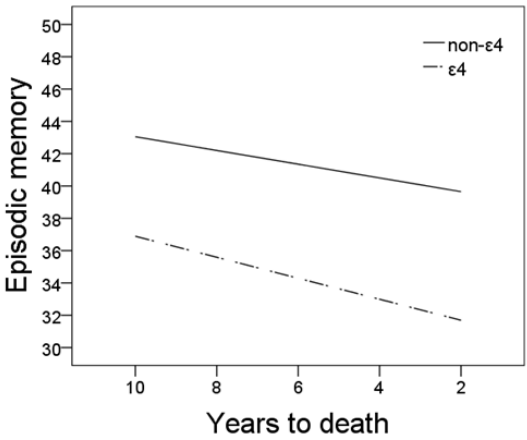


Figure 2. Estimated mean growth curve in episodic memory (Thurstone's Picture Memory) by differences in APOE genotype after adjusting for incident dementia.

These findings suggest that the APOE ε4 allele is indeed related to lower cognitive performance and a steeper rate of decline also at very advanced ages. This is especially clear for the memory domain, where the influence of the ε4 allele may be considered to be relatively large in comparison to previously reported findings.

# Summary of study III

The aim was to examine associations of levels and change between cognitive performance and grip strength in relation to impending death. The sample

consisted of 449 non-demented individuals drawn from the OCTO-twin study. Ten cognitive tests were used to construct factor scores for semantic memory, episodic memory, short-term memory, working memory, spatial ability as well as motor and perceptual speed. Individuals with dementia ($n$ = 233) and individuals with unknown date of death ($n$ = 20) were excluded.

Analyses of bivariate developmental associations of correlated intercepts and slopes between cognition and grip strength resulted in associations of level performances between cognition and grip strength in all cognitive outcomes ranging from $r$ = .19 in short-term memory to $r$ = .47 in fluid ability. Furthermore, there were significant associations between rates of change in cognition and in grip strength in four out of six cognitive domains: semantic memory, episodic memory, spatial ability and short-term memory, with effect sizes ranging from $r$ = .38 in short-term memory up to $r$ = .78 in spatial ability.

Table 2.Correlations of level of performance and change in cognition and grip strength prior to death

| | Grip strength | | |
|---|---|---|---|
| Cognitive performance | *r* | *SE* | *p* |
| Semantic memory | | | |
| Level of performance | .31 | 0.06 | <.001 |
| Rate of change | .49 | 0.18 | .005 |
| Episodic memory | | | |
| Level of performance | .33 | 0.07 | <.001 |
| Rate of change | .59 | 0.21 | .006 |
| Spatial ability | | | |
| Level of performance | .47 | 0.06 | <.001 |
| Rate of change | .78 | 0.25 | .002 |
| Motor and perceptual speed | | | |
| Level of performance | .41 | 0.08 | <.001 |
| Rate of change | .30 | 0.34 | .372 |
| Short-term memory | | | |
| Level of performance | .19 | 0.08 | .017 |
| Rate of change | .38 | 0.20 | .056 |
| Working memory | | | |
| Level of performance | .26 | 0.08 | .001 |
| Rate of change | -.30 | 0.43 | .480 |

These findings indicate that there is a high possibility of associations between level of performance and rate of change between cognition and grip strength later in life.

# Summary of study IV

The aim was to examine subjective memory change and potential bivariate associations between subjective memory and objective memory in relation to time to death. The sample consisted of 449 non-demented individuals drawn from the OCTO-twin study. All cases of dementia at baseline and during the study period ($n$ = 233), and individuals with unknown date of death ($n$ = 20), were excluded.

With the purpose of examining whether fluctuations of occasion-specific changes in subjective memory were related to fluctuations of occasion-specific changes in objective memory (i.e. a longitudinal within-person association), the same procedure used in study III was also used here. However, the bivariate time to death growth curve model was extended by a final mod-

el, where the residuals in the two memory dimensions were constrained to equality over the study period, and thereafter correlated between the two constructs.

Both memory domains demonstrated an accelerated decline. There were significant correlations of level of performance ($r$ = .29) and short-term fluctuations of occasion-specific change ($r$ = .10) between subjective memory and objective memory, while the slope correlation was not significant ($r$ = .04; $p$ = .88). The results show that both subjective memory and objective memory demonstrate a decline in proximity to death, and that subjective and objective memory show a shared variability of levels (i.e. correlated intercepts) and change. The association of shared variability of change occurred at within-person level (i.e. correlated residuals) but not a between-person level (i.e. correlated slopes).

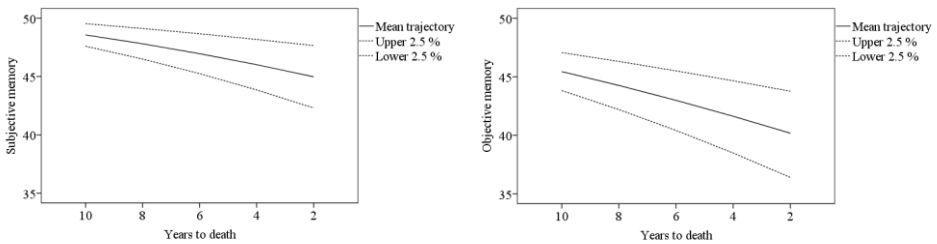


Figure 3. Mean trajectories and CI 95% for levels and accelerated change in subjective and objective memory prior to death.

Yet, the correlations were small, which suggests that level and change in subjective memory is not a valid marker of simultaneous performance and change in objective memory at very advanced ages.

# General discussion

The most important findings of this thesis and their contribution to the literature are briefly presented below (1-4).

1. Our results established that at a very advanced age, men and women are more cognitively alike than unlike, even when taking differences in longevity into account.

Previous studies have found that there are overall few and small differences between men and women. Our results demonstrate an overall lack of gender differences in levels and rates of cognitive performance even when taking gender differences in longevity into account.

2. Our results show that the APOE ε4 allele overall has large negative effects on cognitive performance even in very old age, especially when it comes to episodic memory performance.

In comparison to previous findings reported in two meta-analyses (Small et al., 2004 and Wisdom et al., 2011), our results demonstrate that even when we adjust for the effect of dementia for the association between cognition and APOE, there are still relatively large associations between cognitive performance and APOE.

3. Our results demonstrate consistent associations in levels and change between cognitive performance and grip strength across several cognitive domains.

Previous studies suggest associations between level of cognitive performance and level of grip strength, but it is unclear whether cognition and grip strength change conjointly (Clouston et al., 2013). Our results indicate the possibility that developmental associations between cognition and grip strength are apparent at very advanced ages.

4. Our results indicate that there are cross-sectional and longitudinal within-person associations between subjective and objective memory in the oldest old, but that these associations are to be considered as small.

Cross-sectional and longitudinal associations between subjective and objective memory have been suggested to increase over time (Crumley et al., 2015; Hülür et al., 2014). The results in the present study confirm that associations between subjective and objective memory are present also in the oldest old, but they do not provide support for stronger associations later in life.

In the next section, I further discuss these findings in relation to previous research, address limitations and methodological considerations and finally present some overall conclusions and directions for future research.

# Modelling time to death

Chronological age has conventionally been used as a predictor in research on cognitive aging. However, chronological age is not by itself the underlying causal mechanism for cognitive decline. Age-related decline in cognition is driven by several age-related factors related to structural and functional changes in neurological, biological, and health-related factors (e.g. Piccinin et al., 2011a). These factors contribute to the decline that is often seen as the age effect in cognitive aging. Attempts have been made to better model the effects of the underlying mechanisms of cognitive aging by, for instance, using alternative time-metric parameterizations. Proximity to death may be seen as a marker of overall health and vitality. Therefore, modeling cognitive change as time to death could contribute to a better understanding of cognitive aging. It has previously been shown that modeling cognitive change in relation to proximity to death better accounts for individual changes and that these models tend to show steeper average rates of change than when modeling cognitive change conditioned on increased chronological age (see Gerstorf et al., 2013; Thorvaldsson et al., 2006). The same trend is seen also in the OCTO-twin study. In the introduction, a time to death model was compared with a model where every individual got an individual slope based on his or her individual time between the measurements in the study. Comparisons between these models showed that the time to death model demonstrated a steeper decline and a better fit to the data in comparison to the other model. This was a trend that was consistent across all cognitive domains (see Table 3, Appendix). Furthermore, similar trends are also seen in outcomes other

than cognitive performance, such as vision, subjective health, emotional loneliness, perceived control (Gerstorf et al., 2013) and life satisfaction (Gerstorf, Ram, Röcke, Lindenberger & Smith, 2008). However, it is important to keep in mind that the age-based (or as the example in this thesis, time in study) and time-to-death-based models reflect different population processes and will result in different interpretations. If the process being studied is assumed to be driven by effects related to chronological age, then such a model is to be preferred. For example, Gerstorf et al. (2013) found that changes in cognitive, sensory and physical functions are better described by time to death models, whereas changes in self-reported data are more or less described equally well by models based on age or time to death. Nevertheless, these findings show that proximity to death may be an important factor to consider, when possible, when studying age-related changes, both in cognition but also in other health-related factors.

In study I-IV, we studied cognitive performance in relation to proximity to death. We explored cognitive performance and change in relation to gender and APOE (Study I and II) and found evidence of similar developmental processes when it comes to changes in cognition in relation to grip strength (Study III) and subjective memory (Study IV). These findings are discussed below.

# Gender differences in cognition

Overall, gender differences in cogntive performance are found to be few and small (Hyde, 1981; 2014). Yet, research has shown that there are gender differences in some domains. Women generally tend to outperform men in episodic memory (Herlitz et al., 1997; Herlitz & Rehnman, 2008), whereas men tend to perform better in spatial ability tasks (Lewin et al., 2001; Lövden et al., 2007). These differences between men and women have been found to be stable across the course of life (Aartsen et al., 2004; de Frias, et al., 2006; Gerstorf et al., 2006; Finkel, et al., 2006), and, subsequently, also apparent later in life (Read et al., 2006).

We also know that there are gender differences when it comes to longevity, as women tend to outlive men. Given the gender differences in cognitive performance and longevity, we simply asked the question: if we adjust for differences in longevity, does that influence the results concerning gender differences in cognitive performance at a very advanced age? If that is the case, will the differences favor men, given that even though they are the same

chronological age, men are closer to death? The main finding in Study I was that when taking differences in time to death into account, men and women perform more or less the same, and they also show similar patterns of cognitive decline. A conclusion that may be drawn from the results of study I, in combination with previous research findings, is that there are overall few and small gender differences in cognitive performance later in life. In other words, men and women perform more or less equally well and change in a similar manner at a very advanced age even when accounting for differences in survival.

# APOE and cognition

Two meta-analyses have evaluated the association between the APOE ε4 allele and cognition in old age (Small et al., 2004 and Wisdom et al., 2011). They both conclude that the ε4 allele is associated with cognitive impairment. However, both meta-analyses report overall small associations, with the largest effect sizes being with regard to the association between the ε4 allele and episodic memory. The average effect sizes for episodic memory reported by Small et al. (2004) and Wisdom et al. (2011) were $d = 0.03$ and $d = 0.14$ ($d = 0$ - 0.2 is considered a small effect size), respectively. The results from our study, in which time to death was accounted for, reflect that the ε4 carriers performed, on average, 0.40–0.57 baseline *SD* lower than the non-carriers in the episodic memory tests. After adjusting for the effect of incident dementia, the negative effect of the ε4 allele on episodic memory was reduced, and the ε4 allele carriers performed, on average, 0.19 and 0.31 baseline *SD* lower than the non-ε4 carriers. In other words, even when adjusting for the effect of incident dementia, the negative effect of the ε4 allele on episodic memory was substantially larger in our study as compared to the effect sizes reported in the two meta-analyses (Small et al., 2004; Wisdom et al., 2011). The episodic memory tests in the OCTO-twin study consist of three different subcategories of episodic memory: object recall (Mir recall), picture recognition (Thurstone's picture memory) and word recall (Prose recall). The negative effect of the ε4 allele on episodic memory performance was constant across all three tests, which strengthens the assumption that episodic memory is particularly affected by the ε4 allele. In relation to the different conclusions of the two meta-analyses, in which Small et al. (2004) find that the impact of the APOE ε4 allele tends to get smaller at a very advanced age, whereas Wilson et al. (2011) find that it gets larger, our findings are more in line with the conclusion of Wilson et al. (2011), given our relatively large effect sizes in

this sample of very old individuals. However, we did not test the effect of age directly.

## Grip strength and cognitive performance

A shared common link between cognition and grip strength is suggested by Christensen et al. (2001). The common link between cognition and sensory/sensorimotor functions (e.g. grip strength) is suggested to be stronger among older individuals (e.g. Baltes & Lindenberger, 1994; Anstey et al., 1999). However, scholars have found empirical evidence of a cross-sectional relationship (Clouston et al., 2013), whereas little is still known regarding age-related associations when it comes to changes between these two factors. In Study III, we investigated whether cognitive function and grip strength share similar variability of levels of performance and rates of change in the oldest old. There were significant intercept correlations across all cognitive domains and significant slope correlations in four out of six cognitive domains. For the association between level of performance in cognition and grip strength (i.e. correlated intercepts), the associations ranged from $r$ = .19 in short-term memory to $r$ = .47 in spatial ability. There associations between rates of change in cognitive performance and grip strength (i.e. correlated slopes) ranged from $r$ = .38 in short-term memory to $r$ = .78 in spatial ability. In a meta-analysis, Clouston et al. (2013) report effect sizes for the association of level of performance between cognitive performance and grip strength to be $\beta$ = .14 and $\beta$ = .05 in global cognition and in fluid ability, respectively. Our effect sizes for cross-sectional association between cognition and grip strength may be considered relatively large in comparison to the findings of Clouston et al. (2013). In the same meta-analysis, there was no support for the notion that cognition and grip strength share similar variability of intra-individual change (Clouston et al., 2013). However, our results demonstrate that cognition and grip strength share similar variability of change in proximity to death. In a recent study, Sternäng et al. (2015) suggest that changes in cognitive performance is derived by changes in grip strength. This association was particularly apparent after the age of 65. Our results further indicate that developmental associations between changes in cognitive performance and changes in grip strength may be even stronger at very advanced ages.

## Subjective and objective memory

Subjective memory is considered a reliable predictor for future upcoming decline in objective memory performance (Hohman, Beason-Held, Lamar & Resnick, 2011; Johansson et al., 1997; Luszcz et al., 2015) as well as for future subsequent dementia (Jessen et al., 2010; Johansson et al., 1997; Mitchell, 2008; Rönnlund et al., 2015; St John & Montgomery, 2002). Yet, there are weak associations between subjective memory and objective memory later in life when the two memory constructs are compared at the same time. It is, however, suggested that cross-sectional (Crumley et al., 2015) and longitudinal associations (Hülür et al., 2014) between subjective and objective memory become stronger with increasing age, but little is known regarding associations between subjective and objective memory in relation to impending death. In Study IV we therefore explored subjective memory further by studying the associations between subjective and objective memory from this perspective. We found that both subjective and objective memory showed an accelerated decline in relation to impending death. There were significant correlations between level of performance and occasion-specific change between the two memory dimensions. However, the cross-sectional ($r$ = .29) and longitudinal within-person ($r$ = .10) associations are considered relatively small and do not support the notion regarding stronger associations with increasing age. On the contrary, our results suggest that there are small associations between global measures of subjective and objective memory also in the oldest old. Even if subjective memory may predict future cognitive impairment (e.g. Fritsch, et al., 2014) and dementia up to ten years later (e.g. Rönnlund et al., 2015), short-term fluctuations and rate of change in global subjective memory ratings are not particularly sensitive to simultaneous changes in objective memory. This is possibly an effect of change in the two memory constructs being derived through different factors. Thus, whereas the variability in objective memory decline later in life is primarily influenced by dementia pathology (e.g. Piccinin et al., 2011b; Wilson et al., 2012), subjective memory is only partially influenced by cognitive impairment and dementia pathology (e.g. Wilson et al., 2015), but possibly to a larger extent affected by other factors, such as depression (Hülür et al., 2014; Pearman et al., 2014), mood (Yates, Clare & Woods, 2015) and personality traits like consciousness and neuroticism (Hülür et al., 2015; Pearman & Storandt, 2004).

To sum up, even if subjective memory ratings may predict the risk of a future development of dementia and cognitive decline, the results of Study IV demonstrate that changes in global subjective memory ratings are not particularly sensitive to simultaneous changes in objective memory in the oldest old.

# Limitations and methodological considerations

Even if the study design is considered strong in the context of studying cognitive change in the oldest old – based on the many follow-ups, the extensive cognitive test battery, the opportunity to study cognitive change in relation to impending death in a population-based sample, followed until death – the studies in this thesis still have limitations.

As the thesis primarily focuses on developmental processes in "normally aging" individuals, Study I-IV handles the impact of dementia in different ways. In Study III and IV, all individuals with prevalent dementia at baseline as well as all individuals who developed dementia (incident cases) over the study period were excluded from specific analyses, whereas only cases of prevalent dementia were excluded in Study I and II. There are advantages and disadvantages associated with both approaches for dealing with the effect of dementia. For example, the exclusion of all cases of dementia in Study III and IV effectively minimized the effect of dementia in comparison to treating dementia as a covariate, which was done in study I and II. However, handling data in this way led to a large reduction of the sample size, which decreases the statistical power. Therefore, this method may be used in population-based studies with overall large samples, but it is not recommended in studies using smaller samples.

In Study I and II, we chose to not exclude individuals who developed dementia over the study period (i.e. the incident cases). The advantage of this approach has to do with statistical power and also provides the opportunity to both adjust for the effect of dementia, but also to benefit from the information from the incident demented individuals by, for example, including dementia as an interaction effect with another covariate (as in Study I and II).

It is also important to note that neither of these two methods can fully handle the effect of dementia, as cognitive decline later in life to a large extent is related to dementia pathologies. Given that cognitive functioning is affected by dementia pathologies several years before being diagnosed with dementia, in combination with the very advanced age of the individuals in this sample (80+), an unknown proportion of the non-demented sub-sample was likely also to be at some extent affected by dementia pathology.

A reason for excluding demented individuals, instead of statistically controlling for dementia, is related to the low reliability of the test-scores of the demented individuals. This was especially important in Study III-IV. For exam-

ple, separate analyses of the incident demented sub-sample showed slope correlations between cognition and grip strength of $r > .90$ in some cognitive domains. The conclusions drawn from these findings were that these individuals did not have the ability to perform; not on the cognitive tasks or the grip strength assessment. Accordingly, the information provided from these individuals was not considered to be useful here with regard to the research question. In Study IV, the individuals who developed dementia (i.e. the incident cases) were excluded from the analyses for the reason that individuals without sufficiently intact cognitive ability are not able to make a valid judgment of their own memory status. The exclusion or statistical control of dementia cases complicates a generalization of our findings to a general population of Swedish individuals aged 80 and above (given that a large proportion of this age segment is suffering from dementia).

Another fact that also complicates a generalization of our findings to a general population of Swedish individuals aged 80 and above is that the original OCTO-twin material itself is comprised of a selected group of individuals. When entering the study, the average OCTO-twin individual had a life expectancy of around 90 years of age. It is a very long life expectancy, especially twenty years ago when the average life expectancy was 74.8 years for men and 80.5 years for women. In other words, the OCTO-twin study was comprised of a selected group of survivors already at the study entry.

Another limitation regarding the external validity of the findings is related to the Flynn effect. An increase in the level of performance in cognitive tasks across generations has been observed. These secular trends are often referred to as the Flynn effect (Flynn, 1984; Flynn, 1987; Lynn, 1982) and have been observed in several cognitive domains in samples of younger ages (Pietschnig, Voracek & Formann, 2010; Rodgers & Wänström, 2010; Rönnlund, Carlstedt, Blomstedt, Nilsson & Weinehall, 2013) and also in studies of individuals of higher ages, where later born cohorts perform at higher levels (Baxendale, 2010; Bowles, Grimm & McArdle, 2005; Christensen et al., 2013; Rönnlund & Nilsson, 2008, 2009; Sacuiu et al., 2010; Skirbekk, Stonawski, Bonsang & Staudinger, 2013) and show a less steep decline than earlier born cohorts (Schaie, 2005; Gerstorf et al., 2011).

The OCTO-twin study started in 1992, and given the Flynn effect and the fact that the study was conducted more than twenty years ago, it is questionable whether the sample is representative of a present-day individual aged 80 and above. Interestingly, these secular trends in levels and rates of change in cognitive performance are not found when studying change in models condi-

tioned on time to death, on the contrary, in these models, the later born cohorts tend to show a steeper decline prior to death (Gerstorf et al., 2011; Hülür et al., 2013). Given these findings, it is possible that the secular trends, observed in cognitive functioning, do not apply in models accounting for mortality-related selection. Given the non-existing cohort effects seen in time-to-death-based models, it can be argued that the individuals of the OCTO-twin study are cognitively representative of an average individual aged 80 and above even today, when the time to death modelling approach in Study I-IV is implemented in studies on cognitive aging.

# Conclusions and future directions

There are several methodological challenges in longitudinal research on cognitive aging. One is the high drop-out rate of the participants due to death. This fact will eventually result in a sample consisting of a rather selected group of healthy survivors, who live longer, perform at a higher level and decline less in cognitive functions. A way to deal with this methodological challenge is to examine cognitive performance and change in the context of proximity to death, rather than chronological age. In recent years, several studies have focused their attention on cognitive decline in relation to proximity to death. A conclusion drawn from studies that implement this analytic approach in longitudinal research on cognitive aging is that modeling cognitive performance conditional on proximity to death is to prefer (when possible) due to the fact that this modelling approach better accounts for age-related mortality selection in the data in comparison to age-based models (e.g. Thorvaldsson, 2008). In the future, more research could therefore benefit from using this approach.

Another methodological challenge in research on cognitive aging is related to how the information in longitudinal data is optimally analyzed. In all studies, the research design provides different types of interpretations and conclusions. This has been especially clear in research regarding aging effects on cognitive functions (see e.g. Sliwinski & Buschke, 1999; 2004), in which the core issue (i.e. the aging effect) can really only be captured within a longitudinal design. Cognitive functions later in life have frequently been examined using cross-sectional designs. Cross-sectional data only provide information regarding between-person differences. Subsequently, cross-sectional designs only permit comparisons between groups of people at different ages, and therefore do not allow for any conclusions concerning aging or developmental effects in cognition across time. While cross-sectional data only contain

between-person information, longitudinal data contain both within-person (how an individual changes over time relative to their previous values) and between-person (how an individual differs from others) information. In that sense, the advantage of using longitudinal designs in research on cognitive aging is the ability to distinguish the between-person and within-person relationships in cognition and other covariates (Sliwinski & Buschke, 1999).

Many central theories on cognitive aging focus on within-person processes (e.g. the common cause hypothesis, the terminal decline hypothesis, etc.); in other words, underlying processes that take place within a given individual. Despite the fact that the majority of cognitive aging theories posit within-person processes, the studies undertaken to empirically evaluate these theories often involve analyses of between-person data (Curran & Bauer, 2011). Therefore, when studying cognitive aging, it is necessary to use longitudinal designs that allow data to also be analyzed using a within-person approach that opens up for conclusions regarding developmental changes reflecting the aging effect.

Another approach to try to capture all the information given from longitudinal designs is to examine if and how changes in cognition are related to changes in other constructs. This analytic approach may be conducted by analyzing two or more constructs that are measured simultaneously in a multi-wave setting ($\geq$ 3 waves) (see e.g. Deary et al., 2011; Small, Dixon & McArdle, 2011). These types of analyses provide alterative interpretations of cognitive change in relation to univariate models (as used in Study I and II). While Study I and II examine how two time-invariant co-variates (i.e. APOE and gender) co-vary with within-person cognitive decline, the design of Study III and IV provides additional knowledge to the research field of cognitive aging in terms of whether the trajectories of cognitive change co-vary with the trajectories in another construct (e.g. study III) or whether within-person changes in cognitive performance co-vary with within-person changes in another construct (e.g. study IV). Among others, Hofer et al. (2009) argue that although much may be learned from between-person correlations of slopes from growth curve models, within-person associations can provide valuable information about developmental change between two or more variables that cannot be captured by correlated change alone.

Furthermore, one of the main goals in cognitive aging research is how to prevent or delay the onset of cognitive decline within individuals. For this purpose, better knowledge regarding the nature of cognitive aging is needed. There are therefore many reasons to further examine age-related cognitive

decline in multivariate analytic approaches while taking between-person and within-person associations into account in future research of cognitive aging. Such multivariate analytic approaches enable the possibility to investigate how changes in cognitive performance co-vary with other bio-behavioral and health-related factors. Such studies may result in better knowledge of cognitive aging processes, which could lead to the possibility of conducting more and better interventions to prevent or delay the onset of age-related cognitive decline within individuals in the future.

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# Appendix and paper I-IV

Table 3. Estimated level and rate of decline in cognition as a function of time in study (Tis) and time to death (Ttd)

| | Semantic memory | | Episodic memory | | Short-term memory | | Working memory | | Spatial ability | | Perceptual speed | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tis[a] | Ttd[b] | Tis | Ttd | Tis | Ttd | Tis | Ttd | Tis | Ttd | Tis | Ttd |
| | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) | β (SE) |
| Fixed effects | | | | | | | | | | | | |
| Intercept | 51.96 | 49.70 | 52.68 | 49.43 | 52.02 | 50.60 | 52.07 | 49.80 | 52.03 | 49.06 | 51.86 | 48.68 |
| | (0.46) | (0.51) | (0.38) | (0.50) | (0.34) | (0.38) | (0.39) | (0.41) | (0.45) | (0.47) | (0.47) | (0.46) |
| Slope | 0.04 | -0.79 | 0.07 | -0.96 | -0.19 | -0.51 | -0.32 | -0.66 | 0.15 | -1.22 | 0.05 | -0.98 |
| | (0.13) | (0.10) | (0.16) | (0.12) | (0.07) | (0.12) | (0.09) | (0.14) | (0.16) | (0.12) | (0.14) | (0.11) |
| Slope$^2$ | -0.06 | -0.05 | -0.08 | -0.05 | - | -0.03 | - | -0.03 | -0.09 | -0.08 | -0.08 | -0.05 |
| | (0.02) | (0.01) | (0.02) | (0.01) | | (0.01) | | (0.01) | (0.02) | (0.01) | (0.02) | (0.01) |
| Random effects | | | | | | | | | | | | |
| Intercept | 59.72 | 76.63 | 38.27 | 66.97 | 30.75 | 42.89 | 33.06 | 45.57 | 56.23 | 65.52 | 62.96 | 58.50 |
| | (4.48) | (4.60) | (4.07) | (4.38) | (3.70) | (6.00) | (4.99) | (4.66) | (4.76) | 4.45 | (5.08) | (4.41) |
| Slope | 1.63 | 1.46 | 2.31 | 1.93 | 0.91 | 2.25 | 0.72 | 2.25 | 2.22 | 1.65 | 2.25 | 0.87 |
| | (0.49) | (0.28) | (0.54) | (0.25) | (0.19) | (0.61) | (0.19) | (0.55) | (0.62) | (0.41) | (0.79) | (0.53) |
| Slope$^2$ | 0.01 | 0.01 | 0.01 | 0.01 | - | 0.01 | - | 0.01 | 0.03 | 0.01 | 0.03 | 0.01 |
| | (0.01) | (0.01) | (0.01) | (0.01) | | (0.01) | | (0.01) | (0.01) | (0.01) | (0.01) | (0.01) |
| Residuals | 5.86 | 6.56 | 7.37 | 8.27 | 26.97 | 26.78 | 44.23 | 42.72 | 11.75 | 12.93 | 12.34 | 14.25 |
| | (0.65) | (0.60) | (0.81) | (0.70) | (1.75) | (1.73) | (2.71) | (2.81) | (1.11) | (1.00) | (1.00) | (1.25) |
| AIC[c] | 8518.572 | 8053.378 | 7262.775 | 6828.515 | 12485.524 | 11940.907 | 13138.467 | 12546.674 | 9416.629 | 8841.327 | 9321.097 | 8804.558 |
| BIC[c] | 8560.536 | 8094.948 | 7303.643 | 6868.941 | 12511.650 | 11984.115 | 13164.593 | 12589.882 | 9458.775 | 8883.107 | 9362.959 | 8846.022 |

*Note:* [a]Tis = time in study; [b]Ttd = time to death; [c]Model-fit statistics; all models are conditioned on age at baseline (which was grand mean centered)

Table 4.Studies of terminal decline and terminal drop

| Study | *n* | Follow-up years | Cognitive domains | Change point | Pre-terminal decline | Terminal decline |
|---|---|---|---|---|---|---|
| Wilson et al., 2003 | 753 | 8 | Global cognition | 3.58 | -0.26 | -1.47 |
| | | | Episodic memory | 3.42 | -0.17 | -1.91 |
| | | | Semantic memory | 3.33 | -0.39 | -1.76 |
| | | | Working memory | 3.83 | -0.23 | -1.16 |
| | | | Perceptual speed | 2.75 | -0.74 | -2.22 |
| | | | Spatial ability | 6.00 | -0.08 | -0.88 |
| Sliwinski et al., 2006 | 445 | 25 | Episodic memory | 8.4 (7.1, 9.8) | -0.77 (-0.66, -0.99) | -1.42 (-1.29, -1.67) |
| Wilson et al., 2007 | 853 | 8 | Global cognition | 3.5 | 0.07 | -0.54 |
| Thorvaldsson et al., 2008 | 288 | 15 | Verbal ability | 6.6 (4.3, 11.7) | -0.04 (-0.13, 0.05) | -0.52 (-0.78, -0.25) |
| | | | Spatial ability | 7.8 (6.3, 10.6) | -0.31 (-0.42, -0.21) | -0.59 (-0.85, -0.33) |
| | | | Perceptual speed | 14.8 (10.8, 16.6) | -0.22 (-0.33, -0.10) | -0.44 (-0.60, -0.28) |
| Batterham et al., 2011 | 896 | 12 | MMSE | 7.1 | -0.38 | -1.06 |
| | | | Episodic memory | 6.6 | -0.16 | -0.60 |
| | | | Processing speed | 8.5 | -0.38 | -0.86 |
| Dodge et al., 2011 | 1230 | 14 | Learning | 5.25 (1.25, 8.25) | -0.11(-0.19, -0.04) | -0.21 (-0.39, -0.02) |
| | | | Memory | 5.08 (1.29, 7.98) | -0.14 (-0.20, -0.06) | -0.18 (-0.37, 0.01) |
| | | | Executive | 9.75 (1.25, 8.25) | -0.29 (-0.38, -0.21) | -0.33 (-0.44, -0.22) |
| | | | Language | 6.08 (2.91, 10.70) | -0.30 (-0.37, -0.22) | -0.37 (-0.53, -0.21) |
| | | | Psychomotor speed | 9.41 (5.75, 13.08) | -0.48 (-0.58, -0.41) | -0.38 (-0.54, -0.26) |

| | | | | | | |
|---|---|---|---|---|---|---|
| MacDonald et al., 2011 | 265 | 12 | Verbal speed | 9.5 | 20.42 | 99.54 |
| | | | Working memory | 3.5 | -0.06 | 0.06 |
| | | | Episodic memory | 6.8 | -0.27 | -0.04 |
| | | | Semantic memory | 8.2 | -0.43 | -0.11 |
| | | | Crystallized ability | 6.4 | -0.07 | -0.07 |
| Wilson et al., 2012 | 174 | 15 | Episodic memory | 2.62 | -0.31 | -5.35 |
| | | | Semantic memory | 2.32 | -0.32 | -4.89 |
| | | | Working memory | 2.35 | -0.23 | -4.10 |
| | | | Perceptual speed | 2.63 | -0.63 | -5.64 |
| Boyle et al., 2013 | 856 | 2-18 (*M* = 7.5) | Global cognition | 2.59 (2.87, 2.32) | -0.34 (-0.42, -0.25) | -2.99 (-3.42, -2.58) |
| Muniz-Terrera et al., 2013 | 2039 | 17 | MMSE | 5.66 (6.08, 5.24) | -0.13 (-0.19, -0.08) | -0.61 (-0.71, -0.51) |
| Muniz-Terrera et al., 2013 | 2078 | 21 | MMSE | 6.2 (6.6, 5.7) | -0.12 (-0.16, -0.08) | -0.91 (-1.0, -0.8) |