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GENETIC AND LIFESTYLE INFLUENCES ON MEMORY, BRAIN STRUCTURE, AND DEMENTIA

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Genetic and lifestyle influences on memory, brain structure and dementia
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To my mother

"Just keep swimming" – Dory

ABSTRACT

This doctoral thesis investigated genetic, inflammatory, and lifestyle influences on cognition, brain structure, and dementia. The influence of *TOMM40* polymorphisms (Study I), a *PICALM*, *BIN1* and *CLU* genetic risk score (GRS; Studies II, III), and inflammatory cytokines (Study IV) was assessed, as well as potential interactions with physical activity (Studies II-IV). All studies were based on the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), including a subsample that had participated in magnetic resonance imaging (MRI).

In **Study I**, the influence of *TOMM40* polymorphisms (rs11556505 and rs2075650) on episodic memory and hippocampal volume was investigated. There was no independent influence of *TOMM40* polymorphisms on episodic memory and hippocampal volume. However, carriers of an *APOE* ε4 allele who also harbored *TOMM40* risk alleles relied more heavily on hippocampal volume for episodic memory performance.

Study II confirmed our hypothesis that high genetic risk (GRS >4) based on Alzheimer's disease (AD) candidate genes (*PICALM* rs3851179, rs541458, *BIN1* rs744373, and *CLU* rs11136000) was associated with worse episodic memory performance in non-demented older adults. Interestingly, there was an interaction between physical activity and GRS. The combination of physical inactivity and high genetic risk was most detrimental to memory performance, whereas a high GRS could be compensated for by physical activity. In **Study III**, we investigated if the same GRS was associated with incident dementia, primarily AD. Despite the associations with memory performance in Study II, there was no effect of GRS on incident dementia during a follow-up period of 6 years. Nonetheless, we did replicate previous work showing that physical inactivity is associated with increased risk of dementia.

Study IV investigated the influence of inflammatory cytokines and physical activity on gray-matter volume and global cognitive decline. Although there was no relation between inflammatory cytokines and brain volume, high levels of IL-12p40 in individuals who were physically inactive were associated with smaller lateral prefrontal cortex and hippocampal volumes, as well as with global cognitive decline over 6 years. This suggests that levels of inflammation may be especially detrimental for brain and cognitive integrity in individuals who are physically inactive.

In summary, the studies in this thesis suggest that physical inactivity is associated with reduced episodic memory performance, compromised structural brain volume, and dementia risk. Moreover, physical inactivity in combination with a high GRS or systemic inflammation was especially detrimental to episodic memory as well as to frontal and hippocampal volumes, respectively.

SAMMANFATTNING

Den här avhandlingen undersökte betydelsen av gener, inflammation och livsstilsfaktorer för episodiskt minne, hjärnans struktur och risk för att utveckla demens. Rollen av *TOMM40* polymorfier (Studie I), *PICALM*, *BIN1* och *CLU* genetisk riskpoäng (Studier II, III), och inflammatoriska markörer (Studie IV) belystes, samt om det fanns någon interaktion mellan dessa faktorer och fysisk aktivitet. Studierna baserades på data från SNAC-K och inkluderade en undergrupp som genomgått magnetisk resonanstomografi.

I **Studie I** undersökte vi om *TOMM40* polymorfier (rs11556505, rs2075650) var associerade med episodiskt minne och hippocampusvolym. Det fanns ingen association mellan *TOMM40*, episodiskt minne och hippocampus volym men de som var *APOE* ε4-bärare och dessutom bärare av en *TOMM40* riskallel var mer beroende av hippocampus för episodiskt minne.

Resultaten från **Studie II** bekräftade vår hypotes att en hög genetisk riskpoäng baserad på *PICALM* (rs3851179, rs541458), *BIN1* (rs744373) och *CLU* (rs11136000) riskalleler var associerade med sämre episodiskt minne. Kombinationen av fysisk inaktivitet och hög genetisk risk var mest skadligt för episodiskt minne, medan en hög genetisk risk kunde kompenseras av fysisk aktivitet. Detta tyder på att individer med genetisk sårbarhet kan ha störst nytta av fysisk aktivitet. I **Studie III** undersökte vi om samma riskpoäng, baserad på riskgener för Alzheimers sjukdom var associerad med risk för demens, speciellt AD. Trots associationerna med episodiskt minne i Studie II fann vi ingen effekt av hög genetisk risk poäng på incidensen av nyinsjuknande i demens över 6 år. Dock replikerade vi tidigare studier genom att visa att fysisk inaktivitet är associerad med ökad risk för demens.

Studie IV undersökte relationen mellan inflammatoriska cytokiner, fysisk aktivitet och hjärnvolym liksom kognitiv förmåga. Trots att det inte fanns en relation mellan inflammatoriska cytokiner på hjärnvolym var höga IL-12p40 värden hos fysiskt inaktiva individer associerade med mindre volym i lateral prefrontal cortex och hippocampus. Detta tyder på att höga värden av inflammation kan vara särskilt skadligt för hjärnvolym hos individer som är fysiskt inaktiva.

Sammanfattningsvis visar studierna i denna avhandling att fysisk inaktivitet är kopplad till sämre minnesprestation, mindre hjärnvolym, och ökad risk för demens. Dessutom är fysisk inaktivitet i kombination med hög genetisk risk eller systemisk inflammation speciellt skadligt för episodiskt minne respektive frontal och hippocampusvolym.

LIST OF SCIENTIFIC PAPERS

I. **Ferencz, B.,** Laukka, E. J., Lövdén M., Kalpouzos, G., Keller, L., Graff, C., Wahlund, L. O., Fratiglioni, L., & Bäckman, L. (2013). The influence of *APOE* and *TOMM40* polymorphisms on hippocampal volume and episodic memory in old age. *Frontiers in Human Neuroscience, 22*(7), 198.

II. **Ferencz, B.,** Laukka, E. J., Welmer, A. K., Kalpouzos, G., Angleman, S., Keller, L., Graff, C., Lövdén, M., & Bäckman, L. (2014). The benefits of staying active in old age: physical activity counteracts the negative influence of *PICALM*, *BIN1* and *CLU* risk alleles on episodic memory functioning. *Psychology and Aging, 29*(2), 440-449.

III. **Ferencz, B.,** Bäckman, L., Fratiglioni, L., & Laukka, E. J. Effects of a genetic risk score and physical inactivity on dementia incidence: A 6-year follow-up. *Manuscript.*

IV. Papenberg, G., **Ferencz, B.,** Mangialasche, F, Mecocci, P., Cecchetti, R., Kalpouzos, G., Fratiglioni, L., & Bäckman, L. (2016). Physical activity and inflammation: effects on gray-matter volume and cognitive decline in aging. *Human Brain Mapping, 37*(10), 3462-3473.

ADDITIONAL PUBLICATIONS

I. Papenberg, G., Becker, N., **Ferencz, B.,** Naveh-Benjamin, M., Laukka, E. J., Bäckman, L., & Brehmer, Y. (2016). Dopamine receptor genes modulate associative memory in old age. *Journal of Cognitive Neuroscience, 29*, 245-253.

II. **Ferencz, B.,** & Gerritsen, L. (2015). Genetics and underlying pathology of dementia. *Neuropsychology Review, 25*(1), 113-124.

III. Okun, M. S., & **Ferencz, B**. (2013). *Parkinson's treatment: 10 secrets to a happier life: Swedish Edition.* Stockholm, Sweden: Books on Demand.

IV. Laukka, E. J., Lövdén, M., Herlitz, A., Karlsson, S., **Ferencz, B.,** Pantzar, A., Keller, L., Graff, C., Fratiglioni, L., & Bäckman, L. (2013). Genetic effects on old-age cognitive functioning: a population-based study. *Psychology and Aging, 28*(1), 262-274.

V. **Ferencz, B.,** Karlsson, S., & Kalpouzos G. (2012). Promising genetic biomarkers of preclinical Alzheimer's Disease: the influence of *APOE* and *TOMM40* on brain integrity. *International Journal of Alzheimer's Disease, 2012*: 15p, ID 421452.

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid beta
AD	Alzheimer's disease
ADL/IADL	Activities of daily living/Instrumental activities of daily living
APOE	Apolipoprotein E
APP	Amyloid beta precursor protein
BIN1	Bridging integrator 1
BBB	Blood-brain barrier
BMI	Body Mass Index
CD	Caudate
CLU	Clusterin
CNS	Central nervous system
CRP	C-reactive protein
DSM	Diagnostic Statistical Manual of Mental Disorders
EOAD	Early onset Alzheimer's disease
G-CSF	Granulocyte-colony stimulating factor
GRS	Genetic risk score
GWAS	Genome-wide association study
HC	Hippocampus
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-12p40	Interleukin-12p40
IL-12p70	Interleukin-12p70
ICV	Intracranial volume
IPL	Inferior parietal lobule
ITC	Inferior temporal cortex
LD	Linkage disequilibrium
LPFC	Lateral prefrontal cortex
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging

MTL	Medial temporal lobe
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PICALM	Phosphatidylinositol binding clathrin assembly protein
PSEN1, 2	Presenilin 1, 2
PT	Putamen
SNAC-K	Swedish National study on Aging and Care – Kungsholmen
SNP	Single nucleotide polymorphism
TOMM40	Translocase of outer mitochondrial membrane 40
TNF-α	Tumor necrosis factor-alpha
VBM	Voxel-based morphometry
VC	Visual cortex
WHO	World health organization

1 INTRODUCTION

"A fundamental characteristic of development across the lifespan – at multiple levels of analysis, and from birth to death – is that the human organism changes. It becomes different in form, nature, characteristics, and many other respects. The transformations that occur across the lifespan are changes that involve periods and varieties of gains, losses, and maintenance." – Roger A. Dixon (2000)

Inherent to this quote is the idea that change is not necessarily negative in nature. Already in 1809, Darwin stated that *"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."* In terms of cognition, is it possible that some individuals are more resilient to changes and losses? Could some benefit more than others from environmental support? This thesis will discuss some of these fundamental questions concerning variability in cognitive performance in old age with a focus on genetic and lifestyle influences in aging and dementia.

Although there is a mean negative age trend, not all cognitive domains decline in aging. In addition, there is a high degree of interindividual variability in old-age cognitive performance (Figure 1).

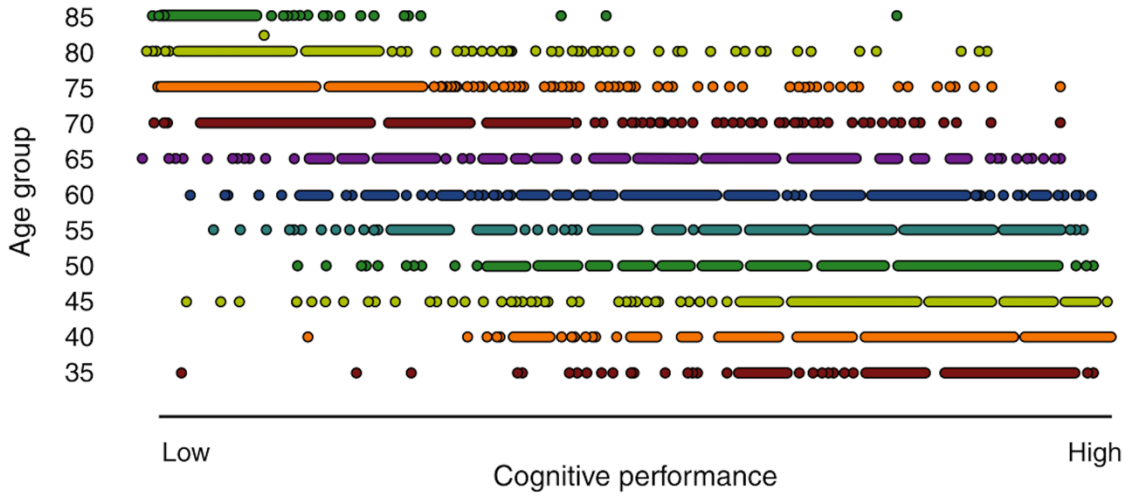

Figure 1. Variability in cognitive performance at different ages. Reproduced with permission (Bäckman, 2008; Habib, Nyberg, & Nilsson, 2007).

Nyberg and colleagues (2012) proposed the concept of brain-maintenance to encompass the variability seen in individual performance as we age. Offered as a complement to the concept of cognitive reserve, brain-maintenance focuses on aspects that preserve and maintain structural, chemical, and functional brain integrity as we age. Brain reserve implies a passive threshold suggesting that some individuals will withstand pathology, and maintain cognitive performance, depending on the individual's initial brain resources. Only when this threshold

is passed will pathology influence performance negatively. Cognitive reserve is considered more active, and implies that an individual can maintain performance in old age by compensating for potential losses. Brain-maintenance focuses on factors that maintain brain integrity in old age. According to this view, variability in cognitive performance as we age may result from gene-environment interactions. This thesis aims to broaden our understanding of such interactions and their role in cognitive aging and dementia.

In the following sections, I will discuss cognitive aging and its neural correlates. I will also give an overview of pathophysiological mechanisms in AD, which is relevant, given that the biomarkers examined are associated with this disease. This will be followed by a description of the genes, inflammatory markers, and environmental factors studied in this thesis.

1.1 COGNITIVE AGING

Aging is accompanied by changes in cognition that may or may not be associated with various disease states. However, even in disease-free conditions, some degree of cognitive decline is a natural part of the aging process. Understanding the cognitive changes that take place in normal aging is essential, not only to benefit the individuals influenced by these alterations, but also to investigate changes that ultimately lead to pathological aging such as dementia. Older adults show impairments in many cognitive domains, including executive functioning, working memory, processing speed, and episodic memory (Park & Schwarz, 1999; Salthouse, 2000). Other areas remain relatively preserved in late life. In the next section I will focus on age-related changes in various memory domains, and the neural correlates of these changes.

Memory can be divided into two major varieties: declarative memory (explicit) that entails conscious recollection of factual knowledge and events, and non-declarative (implicit) memory that involves memory without conscious awareness. Within the non-declarative domain, both priming and procedural memory show relatively little age-related decline (Bäckman, Small, Wahlin, & Larsson, 2000). Priming assesses performance changes of previously encountered stimuli, and procedural memory entails memory of events such as how to ride a bicycle. Within the declarative domain, semantic memory, which encompasses factual knowledge, also remains rather spared in aging (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). In contrast, episodic memory, although relatively stable until the age of 60, is the type of declarative memory that shows the largest degree of decline in aging (Rönnlund et al., 2005).

Episodic memory is the type of memory domain that allows us to consciously recollect and re-experience past events that are unique to us as a person. This is the part of memory that holds the what, when and where of personal events, which allows us to form autobiographical memories keeping us rooted in time and space (Tulving, 1972). It has been described as a form of mental time travel (Tulving, 2002), and decrements in episodic memory performance is not only a cardinal feature of cognitive aging, but also one of the earliest signs of impending AD (Bäckman, Jones, Berger, Laukka, & Small, 2005; Jack et al., 2012). When

probing episodic memory performance, free recall is most impaired in old age, likely because it requires more cognitive resources at encoding and retrieval relative to recognition (Danckert & Craik, 2013). Recognition is less effortful and supported and therefore more preserved in aging. When probing recognition, one can further divide performance into recollection and familiarity in accordance with dual-process models of episodic memory (Yonelinas, 2001). In healthy aging, conscious recollection of an item is more negatively influenced, whereas the sense of familiarity of an item remains well preserved (Koen & Yonelinas, 2016). There has also been increased attention on associative memory, as research indicates that aging is associated with disproportionate deficits in binding pieces of information together in episodic memory (Naveh-Benjamin, 2000). In summary, several measures indicate that episodic memory is sensitive to the effects of aging, which is most likely due to its dependency on the medial temporal lobe (MTL) and the prefrontal cortex (PFC; Cabeza, Nyberg, & Park, 2016) that are particularly affected in old age (Raz et al., 2005).

Neuropsychiatric patients have made significant contributions to our understanding of the organization of memory systems, and the pivotal role that the MTL plays for memory. The work by Brenda Milner on the famous patient H. M. remains the most cited throughout the literature (Scoville & Milner, 1957; Squire, 2009). Suffering from epileptic seizures from young age, H. M's MTL, including his hippocampus (HC), were resected bilaterally in an attempt to control his seizures. The treatment was successful in terms of mitigating the epileptic seizures, but resulted in severe memory impairments. H. M. presented with immediate memory deficits and was not able to remember individuals he had recently encountered: *"Just before coming into the examining room he had been talking to Dr. Karl Pribram, yet he had no recollection of this at all and denied that anyone had spoken to him"* (Scoville & Milner, 1957). Although his performance on the Wechsler-Bellevue Intelligence Scale was comparable to his preoperative state, H. M.´s performance on the Wechsler Memory Scale was far below average. Illustrative of his memory impairment, H. M. had no recollection of any previous attempts of the memory tasks (Scoville & Milner, 1957). Since then, neuropsychologists have studied H. M. and his case has continued to guide the field through the past decades, providing us with vast information about the organization of memory.

Since H. M., the field of neuroimaging has developed, which has made it possible to assess neural correlates of memory in vivo among healthy persons. It has been established that the HC is important for episodic memory, yet the negative association between hippocampal volume and episodic performance has been controversial (Pohlack et al., 2014). Bigger may not always be better, and what is evident is that there is an increase in variability in old age (Van Petten, 2004). Nevertheless, there has also been support for a direct link between HC volume and memory (Head, Rodrigue, Kennedy, & Raz, 2008; Kalpouzos et al., 2009). There are substantial aging effects on the HC, with longitudinal studies showing 1.23% yearly HC decline in healthy older adults. This increases to an average of 1.7% annual decline after the 7th decade of life (Raz & Rodrigue, 2006). This can be compared to the 3-4% annual decline

of the HC that can be seen in AD, and the substantially higher atrophy with up to 8% annual decline in individuals with genetic predisposition to AD (Fox et al., 1996).

Next, we turn the discussion to biomarkers, mechanisms, and genetics relevant to brain aging, cognitive aging, and AD. Although only one study in the thesis (Study III) directly focuses on dementia, especially AD, the relatively lengthy treatment of pathology is motivated by the fact that the genes and biomarkers examined in non-demented aging for the most part originate from work on dementia, especially AD.

1.2 ALZHEIMER'S DISEASE

AD was first described by Alois Alzheimer, whose patient Auguste D presented with memory loss, sleep disturbances, and other psychological symptoms. Upon her passing, Alzheimer viewed the autopsy data and presented a talk about the case in Tübingen in 1906: "*Her memory was most severely disturbed ...Slide preparations made with the Bielschovsky silver method show remarkable changes in the neurofibrils. In the interior of a cell that otherwise still appears normal, one or a few fibrils stand out through their thickness and impregnability.*" – Alzheimer (1907). Later, Perusini (1909) advanced this work by emphasizing the neurofibrillary changes that were first described by Alzheimer. In 1910, the term Alzheimer's Disease was coined in the Handbook of Psychiatry *"Alzheimer described a peculiar group of cases with very severe cellular changes. . . the clinical interpretation of Alzheimer's disease is still unclear"* – Kraepelin (1910)

Thus, already in 1906 one of the main pathological hallmarks of AD was described, even though little was understood about the clinical interpretation of the disease. Today we know more about the clinical presentation but there is still much to discern regarding the pathophysiological changes that ultimately cause the disease. Some prescribe to the amyloid hypothesis, others put emphasis on neurofibrillary tangles, and still others argue that mitochondria and inflammatory processes are key causative factors of AD. Although there has been progress in the field, after decades of research we still have much to learn about the etiology.

AD is the leading cause of dementia, accounting for 50-70% of cases, and is characterized by progressive decline in cognition, primarily within the domains of episodic memory, perceptual speed and executive functioning (Bäckman et al., 2005). The onset is insidious and patients can present as primarily amnestic with deficits in recall of recently acquired information, or have deficits in one additional cognitive domain. Early signs of the disease include, but are not limited to, trouble recalling recent events, mood swings, confusion, disorientation, behavioral changes, and difficulties with activities of daily living (ADL; American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., 1994). With age being a primary risk factor for AD, the increasing aging population suggests that the number of individuals with dementia will increase (for a review, see Winblad et al., 2016), and approximately 66 million people are estimated to have dementia by 2030 (Prince et al., 2013). This in turn is associated with great societal challenges and the

worldwide cost of dementia in 2010 was estimated to be 604 billion US$ (Wimo, Jönsson, Bond, Prince, & Winblad, 2013). This makes the race to find a cure, and to identify groups who may benefit from targeted interventions, increasingly important. Genetic and lifestyle factors may be key in identifying individuals at risk that could benefit from targeted interventions. But first an overview of the primary mechanisms thought to lead to AD.

1.2.1 The role of amyloid in Alzheimer's disease

It is widely accepted that AD is characterized by pathological changes in the brain that commence years before any clinical symptoms are present. Since the amyloid-cascade hypothesis was formulated (Hardy & Allsop, 1991), where amyloid deposition was proposed as the primary event in AD, researches have focused on the role of amyloid in AD. However, both amyloid plaques and neurofibrillary tangles are part of the histopathological signature of AD, and although amyloid has been considered a trigger in AD, abnormal phosphorylation of tau and the formation of neurofibrillary tangles has been described to be the bullet (Bloom et al., 2014). Genetic and postmortem findings support the amyloid hypothesis, yet many amyloid-based therapeutic approaches have failed to show efficacy (Karran & De Strooper, 2016). Moreover, there are some testable predictions of the theory that have not been validated scientifically. For example, individuals can have clinical symptoms of dementia in the absence of amyloid pathology, or vice versa, suggesting that the presence of amyloid in the brain is not sufficient to cause the disease. Findings that up to 47% of cognitively intact individuals have amyloid-positive brain scans, suggests that amyloid deposition may be a part of normal aging (Chételat et al., 2013).

There is a possibility that clinical trials have failed to show efficacy of amyloid-based therapies, because they target individuals too late in their disease progression (Morris, Clark, & Vissel, 2014). An increasing body of evidence shows that amyloid beta (Aβ) and tau interact, and perhaps such mechanisms or other interactions have not been given enough consideration (Bloom et al., 2014). Findings of amyloid in cognitively intact individuals (Chételat et al., 2013) does not negate that amyloid plays an important role in AD. Nonetheless, it is likely that other mechanisms are also involved and influence the onset of AD.

"And while there is fear in the field over the consequences of rejecting it outright, clinging to an inaccurate disease model is the option we should fear most" – Herrup (2015)

1.2.2 Mitochondria

The mitochondrial cascade hypothesis has been proposed as an alternative to the amyloid-cascade hypothesis, and suggests that age-related mitochondrial dysfunction is an important source of the AD pathogenesis. There is genetic and neuropathological research supporting the role of mitochondria and oxidative stress in AD (Devi, Prabhu, Galati, Avadhani, & Anandatheerthavarada, 2006; Hedskog, Zhang, & Ankarcrona, 2012; Lin & Beal, 2006; Reddy & Beal, 2005; Roses et al., 2010). Post-mortem morphological changes of the mitochondria among AD patients have been found in HC, neocortex, and locus coeruleus

(Baloyannis, 2006; Hirai et al., 2001). Interestingly, these changes did not co-occur with amyloid deposition, suggesting that morphological changes within the mitochondria may be an early and primary pathogenic event in AD (Baloyannis, 2006). The mitochondrial import channels may be especially important in this aspect, as amyloid beta precursor protein (APP) has been found lodged in these channels in AD patients. Such mitochondrial APP appears to be especially prevalent in individuals with genetic susceptibility to AD (Devi et al., 2006). The role of mitochondria and oxidative stress has been implicated in many neurodegenerative diseases. However, more research is needed to understand their roles in normal as well as pathological aging. In Study I, we investigate the role of translocase of outer mitochondrial membrane 40 (*TOMM40*) on HC volume and episodic memory performance in normal aging.

1.2.3 Inflammation

Another possible mechanism in AD is inflammation; its presence has been observed in the brain of individuals who subsequently develop AD as early as 20 years prior to diagnosis (Rodriguez-Vieitez et al., 2016). Moreover, inflammatory cytokines, such as c-reactive protein (CRP), and interleukin-6 (IL-6), appear to be upregulated in AD and can be used as blood plasma biomarkers (Schneider, Hampel, & Buerger, 2009). As we age, the immune system becomes increasingly dysfunctional, such that the efficiency in clearing pathogens decreases and senescent cells increase their secretion of pro-inflammatory cytokines (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013).

The few studies that are available suggest that inflammation is associated not only with the risk of dementia, but may contribute to variability in cognitive and brain aging (Marsland et al., 2015). For instance, high levels of IL-6 has been associated with decrements in cognitive performance (Lim, Krajina, & Marsland, 2013), smaller overall gray-matter volume (Marsland et al., 2015), and HC volume in midlife (Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008). These findings suggest that peripheral markers of inflammation are associated with brain integrity and that low-grade systemic inflammation can precede cognitive decline (Marsland et al., 2008).

Chronic peripheral inflammation activates microglia in the brain, and may influence memory and cognition negatively by disrupting neurogenesis in HC (Chesnokova, Pechnick, & Wawrowsky, 2016). Cytokines, including interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), have an influence on synaptic plasticity, neurogenesis, and neuromodulation and, as such, play an important role in the cellular mechanisms involved in learning and memory (McAfoose & Baune, 2009). Granulocyte-colony stimulating factor (G-CSF) is a cytokine that modulates the immune response by inhibiting pro-inflammatory cytokines. It has been shown that high levels of G-CSF are associated with decreased amyloid-deposition in HC, and decreased activity of pro-inflammatory cytokines in plasma (Sanchez-Ramos et al., 2009). Moreover, decreased levels of G-CSF have been observed in AD patients, suggestive of a disturbed immune response (Laske, Stellos, Stransky, Leyhe, & Gawaz, 2009). IL-12p40 may also influence inflammatory processes in the brain, with high levels of IL-12p40 being detrimental to brain aging. Knock-out models of the IL-12p40

receptor complex in mice is associated with decreased amyloid load, reduced neuronal and synaptic loss and reversed cognitive impairment (Tan et al., 2014). Moreover, inhibiting IL-12 signaling pathways is associated with reduction in AD-like pathology and cognitive decline in animal models (vom Berg et al., 2012).

There is limited research on the influence of inflammatory cytokines in healthy aging. The extent to which systemic inflammation influences brain and cognitive aging remains to be elucidated. Study IV of the current thesis examined the role of systemic inflammation in cognitive aging as previous research, albeit limited, indicates that inflammation plays a pivotal role in influencing brain areas known to decline in aging.

1.3 ALZHEIMER´S DISEASE CANDIDATE GENES

Phenotypes such as AD, episodic memory and HC volume are considered to be complex traits, as they are influenced by both genetic and environmental factors. By observing the concordance rate in monozygotic twins, the heritability of AD has been estimated to be up to 58% (Gatz et al., 2006; Pedersen, Gatz, Berg, & Johansson, 2004). For memory and HC volume, the estimated heritability is up to 65% (Blokland, de Zubicaray, McMahon, & Wright, 2012; Mather et al., 2015). These numbers indicate that, although heritability is high, these phenotypes are also under environmental influence. There are several methods for investigating the genetic influence on various phenotypes. Linkage studies examine chromosomal regions and how they segregate within families for certain diseases. Genetic association studies can involve candidate-gene approaches or genome wide association studies (GWAS) to scan for variation in single nucleotide polymorphisms (SNPs) that contribute to a particular phenotype. SNPs represent variation at a specific nucleotide in our DNA, and these are the variations that make up our individual features. GWAS allows us to compare the association between millions of SNPs and phenotypes by comparing disease status (case-control) or by using quantitive traits (i.e. HC volume). This can then be followed up by candidate-gene studies when there is sufficient knowledge about the association of certain SNPs and the phenotype of interest (Goldberg & Weinberger, 2009), which was the method used in this thesis.

The early-onset form of AD (EOAD) runs in families and mutations within three major genetic loci have been associated with EOAD; *APP*, *PSEN1*, and *PSEN2* (see http://www.molgen.vib-ua.be/ADMutations). However, EOAD only accounts for about 1% of the AD cases, and the sporadic late-onset form, referred to as AD throughout this thesis, is the most common form of the disease (Bekris, Yu, Bird, & Tsuang, 2010). GWAS have identified several genetic risk factors for AD (for a review, see Ferencz & Gerritsen, 2015). In the current work, we examine some of the top candidate genes that have been previously associated with AD. Besides being primary candidate genes of AD, the targeted SNPs may also influence cognitive performance, especially episodic memory, in healthy aging (Barral et al., 2012; Nilsson et al., 2006), although the evidence is sparse. In the following section I will give an overview of the primary candidate genes and their phenotypic associations.

1.3.1 *APOE*

There are genetic variations in the population that are common and have a large influence on disease burden, although they do not act in a deterministic fashion. The impact of such loci is deemed high (OR ≥2) or low (OR <2) depending on their association with AD (Winblad et al., 2016). One locus, which has been consistently associated with dementia is *APOE*. *APOE* is located on chromosome 19q13 and comes in three allelic variants, ε2, ε3, and ε4 which have a worldwide frequency of 8.4%, 77.9% and 13.7% respectively (Liu, Kanekiyo, Xu, & Bu, 2013). The ε4 allele has been associated with up to 4 times higher risk of AD (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007), accounting for more than half of the genetic variance in the disease (Ridge et al., 2013). Discovered already in 1991 (Pericak-Vance et al., 1991), it remains one of the major genetic risk factors of AD.

The ε4 allele is also associated with reduced memory and perceptual speed performance (Laukka et al., 2013; Nilsson et al., 2006) and, gray- and white-matter integrity in healthy aging (for a review, see Ferencz, Karlsson, & Kalpouzos, 2012). The less common ε2 allele appears to have a protective effect in AD, and may influence longevity (Raichlen & Alexander, 2014). APOE is involved in the transport of lipids in the central nervous system (CNS), yet the mechanisms by which the lipoprotein influences the brain remain largely unknown. Having an ε4 allele may influence the delivery of cholesterol to the neurons resulting in disturbed lipid homeostasis in the brain (Poirier, 2006), and APOE interacts with amyloid affecting aggregation as well as clearance (Holtzman, 2004). However, already in their early discovery of *APOE*, Roses and colleagues (2006) argued that neither APOE nor amyloid is the central cause of AD. They highlighted the role of APOE in glucose metabolism, and the fact that it binds tighter to amyloid. Amyloid and tau aggregation was suggested to be a downstream event resulting from years of decreased glucose metabolism. Despite the strong association, *APOE* does not explain all of the genetic variation in AD, which suggests that other common variants may play a role in the disease. One such gene, *TOMM40*, has highlighted the important role that mitochondria may play in AD.

1.3.2 *TOMM40*

TOMM40, located on chromosome 19q13 codes the channel forming subunit of the outer mitochondrial membrane that influences the import of protein precursors to the mitochondria (Humphries et al., 2005; Maglott, Ostell, Pruitt, & Tatusova, 2005). Striking at first glance is the close approximation to *APOE*, also located on 19q13. Due to their linkage disequilibrium (LD) on chromosome 19, *TOMM40* and *APOE* have mostly be considered in unison. A closer look at the phylogenetic structure in this region shows that *APOE* ε4 is linked to a long poly-T variant of *TOMM40* (rs10524523), whereas *APOE* ε3 is linked to either a short or very long T variant. The initial studies by Roses and colleagues (2010) used a phylogenetic approach where they found that a long poly-T variant (rs10524523) was associated with higher risk for late onset AD. When assessing individuals with *APOE* ε3/ε4 who developed AD after the age of 60 they found that those who carried an *APOE* ε3 allele in combination with long poly-T length developed AD on average 7 years earlier in comparison to those

who had an *APOE* ε3 allele with short poly-T repeat. Furthermore, this combination was associated with increased tangle formation (Li et al., 2013). However, these findings have not always been replicated (Cruchaga et al., 2011), and the feasibility of this approach has been questioned (Guerreiro & Hardy, 2012). Nonetheless, a recent AD genetic risk algorithm was developed, based on *APOE*, *TOMM40* poly-T length, and age (Lutz, Sundseth, et al., 2016). This combination had higher predicative value than *APOE* alone (Lutz, Sundseth, et al., 2016). Whether or not there is a true independent effect of *TOMM40*, it seems like there is an increased utility of combining *TOMM40* with *APOE* and other risk factors of AD. This suggests that we should consider these genes in unison rather than as independent factors (Lutz, Sundseth, et al., 2016; Lutz, Crenshaw, Welsh-Bohmer, Burns, & Roses, 2016).

In the current thesis, we focus on other *TOMM40* polymorphisms. As with the phylogenetic approach, findings concerning *TOMM40* polymorphisms have been conflicting due to its linkage with *APOE*. Nonetheless, focusing on the haplotype structure of this region may be a better approach; it was demonstrated that a haplotype of rs2075650, rs11556505 (*TOMM40*) and rs429358 (*APOE*) was associated with AD (Potkin et al., 2009). We know that imaging and cognitive markers, such as hippocampal atrophy and episodic memory, are important predictors of AD (Bäckman, 2008; Jack et al., 2012). However, the extent to which variations in *TOMM40* influence hippocampal structure and episodic memory remains less well known. One approach to assess the influence of *TOMM40* on hippocampal volume has been to use hippocampal volume as a quantitative trait in GWAS. This approach has indicated that *TOMM40* rs2075650 is associated with hippocampal volume (Shen et al., 2014). Recently, studies from the Lothian birth cohort have found that *TOMM40* poly-T length was also associated with white-matter integrity (Lyall et al., 2014a), but not cognitive aging (Lyall et al., 2014b). Others have shown an association with episodic memory (Pomara et al., 2011; Yan et al., 2015). However, less is known about the *APOE*-independent influence of *TOMM40* rs11556505 and rs2075650 SNPs on episodic memory and HC volume in old age, which we address in Study I.

1.3.3 PICALM, BIN1, and CLU

GWAS, with up to 17 000 cases and over 30 000 controls, have identified several AD candidate genes (Figure 2; Harold et al., 2009; Lambert, 2013), with *PICALM*, *BIN1* and *CLU* being among the top candidate genes (Bertram et al., 2007). *PICALM,* located on 11q14.2, encodes the clathrin-assembly protein (Maglott et al., 2005). The *PICALM* rs541458 C allele and rs3851179 A allele are associated with decreased risk of AD (Bertram et al., 2007). *PICALM* has been primarily found in endothelial cells, the lining of the blood vessels, and is also present in neurons, astrocytes, and oligodendrocytes. *PICALM* influences clathrin-mediated endocytosis, a process by which ligands, proteins, lipids, growth factors, and neurotransmitters are transported from the extracellular matrix into the cytoplasmic environment. *PICALM* has been suggested to play a role in AD by influencing both amyloid-dependent and independent pathways. The amyloid-independent pathways suggest that

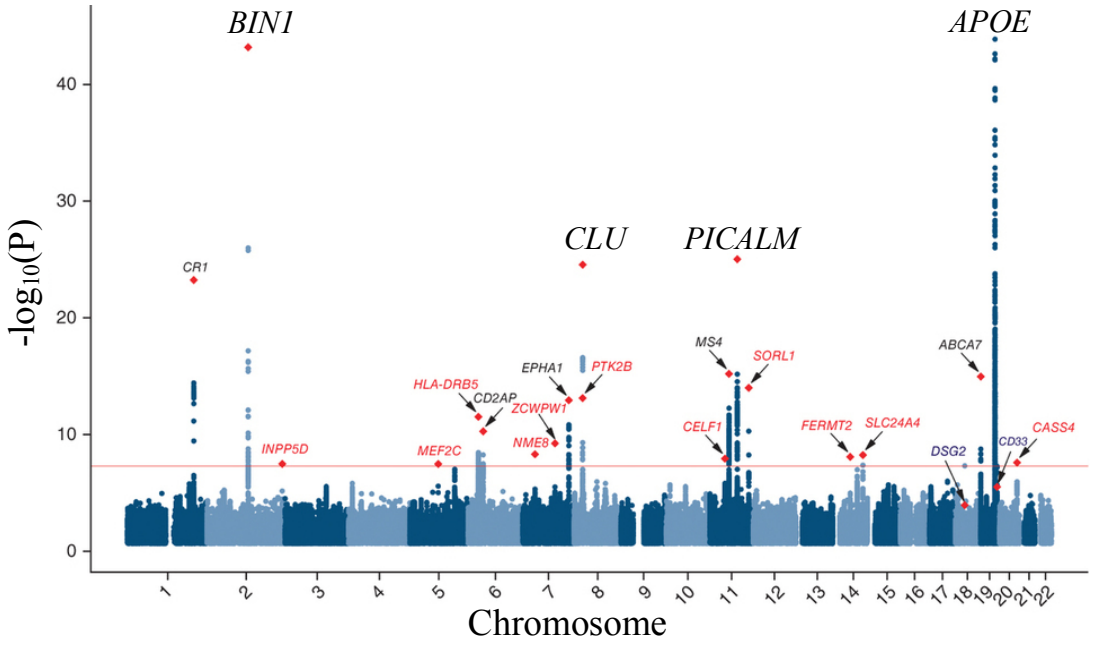

Figure 2. Manhattan plot for genome wide association with AD (Lambert, 2013) indicating *PICALM*, *BIN1* and *CLU* as top candidate genes for the disease.

PICALM may influence lipid metabolism, immune disorders, and iron homeostasis (Xu, Tan, & Yu, 2014). Another potentially interesting pathway by which *PICALM* may exert a negative influence is by allowing the transport of Aß through the blood-brain barrier (BBB, Zhao et al., 2015). *PICALM* also influences hippocampal degeneration (Melville et al., 2012), and entorhinal thickness (Furney et al., 2011), key areas implicated in cognitive aging and AD. Some initial studies suggested that *PICALM* may modulate the effects of *APOE*, with regard to prefrontal volumes and performance on tests of processing speed and working memory (Morgen et al., 2014). Yet, little is known about the *APOE*-independent contribution of *PICALM* to episodic memory, and potential interactions with other top AD candidate genes.

BIN1, located on chromosome 2q14.3, is also expressed in the CNS. It is thought to influence synaptic-vesicle endocytosis, interact with clathrin, and influence apoptotic processes (Maglott et al., 2005). *BIN1* influences similar pathogenic mechanisms as *PICALM*, including lipid metabolism, clearance of amyloid across the BBB, and neurofibrillary tangle formation (Jones, Harold, & Williams, 2010; Zlokovic et al., 1996). After *APOE*, *BIN1* rs744373 is one of the most replicated AD genetic risk polymorphisms, with up to 1.17 higher risk of AD in G allele carriers (Bertram et al., 2007). Despite these findings, little is known about the pathogenic influence of *BIN1* in AD. It has been demonstrated that BIN1 protein expression is elevated in AD brains, especially in HC, and that the elevation coexists with tangle

formation, but not amyloid deposition, suggesting that *BIN1* may also influence amyloid-independent pathways (Holler et al., 2014). Moreover *BIN1* polymorphisms have been associated with several AD biomarkers including atrophy of the HC, elevated tau in CSF, glucose metabolism, but not amyloid deposition (Wang et al., 2016).Yet, little is known of the influence of *BIN1* on episodic memory. Some recent findings implicate *BIN1* loci in working memory performance in healthy young adults (Zhang et al., 2015), and episodic memory performance in type-2 diabetes (Greenbaum et al., 2016).

Finally, the *CLU* gene, located on 8p21.1, codes for the protein clusterin. Described as a "forgotten player" in AD, research showed already 20 years ago that there is an increase in the expression of clusterin in AD (May et al.,1990; Nuutinen, Suuronen, Kauppinen, & Salminen, 2009). The gene product clusterin may have a negative influence on AD pathogenesis. It has been implicated in amyloid-dependent pathways including, clearance, and transport of amyloid across the BBB. Together with APOE, clusterin is considered a major chaperone when it comes to clearing the brain of amyloid. However, it has also been suggested that clusterin is protective and involved in anti-apoptotic processes enhancing cell survival, and the question has been posed if clusterin is a "guardian or enemy" in AD (Nuutinen et al., 2009). It remains to be seen how *CLU* influences episodic memory. So far only one study has found an association between *CLU* and episodic memory performance, and then only in combination with *PICALM* (Barral et al., 2012).

APOE remains the strongest genetic marker for AD, and although *PICALM*, *BIN1* and *CLU* are associated with AD, their impact remains small in comparison. This suggests that we may benefit from considering the combined effects of these polymorphisms on episodic memory and AD. Considering that these SNPs are involved in similar pathogenic mechanisms also speaks in favor for analyzing them in unison. In fact, researchers have started to utilize this type of GRS or multi-locus approach when analyzing the genetic contribution to pathological (Escott-Price et al., 2015; Rodríguez-Rodríguez et al., 2013), and healthy (Barral et al., 2012) aging; however there is limited research on how these specific SNPs influence episodic memory.

Besides the studies in this thesis, and a replication thereof (Papenberg, Becker, et al., 2016), only one other study has associated genotype patterns of *CLU* and *PICALM* with episodic memory performance in normal aging. Here, the combination of the *CLU* rs11136000 T allele together with the *PICALM* rs3851179 G allele was most detrimental to episodic memory performance (Barral et al., 2012). Others have found that this same combination is associated with reduced hippocampal volume in healthy aging (Yang, Li, Liu, Li, & Jiang, 2016). Yet, the same *CLU* allele may also be protective together with the *PICALM* protective A allele (rs3851179), which suggests that more research is needed before we can fully understand the combined effects of these SNPs in normal cognitive aging and dementia. Other studies have also indicated that these SNPs may influence hippocampal volume in a polygenic way (Chauhan et al., 2015; Harrison et al., 2016), which suggests that they may be especially important for episodic memory in aging. However, it remains to be seen

whether a combined risk score based on these genes influences episodic memory and risk of AD, and if this association is independent of *APOE*. Finally, it is of interest to examine whether these associations may be influenced by environmental factors, such as remaining active in old age. In the next section, I will discuss the benefits of physical activity in cognitive and brain aging.

1.4 PHYSICAL ACTIVITY

Physical inactivity is an important modifiable risk factor of AD (Winblad et al., 2016), and it has been shown that a physically active lifestyle can reduce the risk of dementia and AD with up to 45% (Hamer et al., 2009). Although the aging population is increasing there are indications that the incidence of dementia in Western Europe may be decreasing (Qiu, Von Strauss, Bäckman, Winblad, & Fratiglioni, 2013; Wu et al., 2016). This does not mean that we do not face a big societal challenge; the aging population is increasing and the number of individuals affected by dementia and AD is estimated to continue to rise (Winblad et al., 2016). Reducing risk factors for AD (e.g., physical inactivity) with only 10% may prevent up to 1.1 million cases annually. While the ultimate goal is to find a cure for dementia and AD, primary prevention strategies with a life-course perspective may prove to be more fruitful in the foreseeable future (Winblad et al., 2016). Genes are not considered modifiable risk factors of AD, yet they may be more plastic than we initially believed (Belsky et al., 2009). As such, we may benefit from investigating gene-environment interactions in AD, and elucidate the influence of physical activity on genetic risk of dementia and AD.

We have known for centuries that physical activity is beneficial for our health. *"Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save and preserve it."* – Plato 350 BC. According to world health organization (WHO) recommendations, older adults should participate in health and/or fitness enhancing physical activity about 30 minutes daily (Nelson et al., 2007; WHO, 2010). Both health-enhancing (usual paced walks, short bike rides), and fitness-enhancing (brisk walks, jogging) are beneficial for health, but only the latter may influence physical fitness (Rydwik et al., 2013). In this thesis, we use self-reported measures of physical activity, including activities that are both aerobic and non-aerobic in nature. These measures of physical activity are different from physical exercise and exercise interventions, where studies focus on enhancing aerobic capacity in response to an intervention (for a review, see Erickson, Leckie, & Weinstein, 2014). Nonetheless, both measures of physical activity and exercise are associated with health benefits in aging.

An increasing amount of work suggests that physical activity is beneficial for cognitive and brain aging, and indicates that an active lifestyle can prevent neurodegeneration (Erickson et al., 2014; Kramer & Erickson, 2007; Voelcker-Rehage & Windisch, 2013). Still some randomized trials only show modest benefits of physical activity on cognition (Lautenschlager, Cox, & Cyarto, 2012). According to the brain-maintenance view, physical activity supports the aging brain and variability in cognitive performance in old age may be due to differences in genetic and lifestyle factors such as physical activity. In line with this

notion, a physically active lifestyle is positively associated with episodic memory (Klaming, Annese, Veltman, & Comijs, 2016). Further support that physical activity may be especially important for memory comes from imaging studies. These have consistently shown that physical activity and aerobic exercise is associated with increased gray-matter volume, primarily in PFC and HC (Erickson et al., 2009; Kramer & Erickson, 2007). Aerobic exercise in old age was shown to increase the volume of the HC with 2%, which indicates that it has the potential to reverse age-related loss in hippocampal volume with up to 2 years (Erickson et al., 2009).

Exercise may serve to protect against neurodegeneration by reducing oxidative stress (Marosi et al., 2012), inducing neurogenesis (Kempermann, 2008), and modulating angiogenesis (Lista & Sorrentino, 2010). Moreover, physical activity may buffer against neurodegeneration by modulating the effects of inflammation. Indeed, Hamer and colleagues (Hamer et al., 2012) demonstrated that regular engagement in physical activity lowers markers of systemic inflammation in blood, suggesting that physical activity may be beneficial in counteracting a negative inflammatory state often observed in aging and dementia. It remains to be seen whether physical activity interacts with inflammation to influence brain structures in aging.

1.4.1 Gene-lifestyle interactions

As we age and brain resources dwindle, genetic effects on the brain and subsequently cognition become more apparent (Papenberg, Lindenberger, & Bäckman, 2015). Physical activity may be especially beneficial for at-risk individuals in terms of protecting them against cognitive decline. As such, genetic influence on memory in late life, may be counteracted by a physically active lifestyle (Nyberg et al., 2012).

We do not traditionally consider genes as plastic. Yet, the differential susceptibility model posits that genes may be just that. Rather than simply conferring risk to neurodegeneration, individuals who harbor risk genes may be more prone to benefit from positive environmental influences, such as being physically active (Belsky et al., 2009). For example, carriers of *APOE* ε4 alleles who are physically active have less hippocampal atrophy than their sedentary counterparts (Smith et al., 2014). Similar findings have been seen in epidemiological studies, where physical activity modifies the risk of AD among carriers of the *APOE* ε4 allele, suggesting that they may benefit the most from lifestyle interventions (Kivipelto et al., 2008; Rovio et al., 2005). However, not all have been able to confirm this association and it has also been suggested that physical activity may be more beneficial for non-ε4 carriers (Podewils et al., 2005). It remains to be seen how physical activity interacts with other genetic risk loci such as *PICALM*, *BIN1* and *CLU*, in terms of their influence on cognitive aging and dementia. Although it has been shown that these genes are associated with episodic memory performance, it is not known if the effects of *PICALM*, *BIN1* and *CLU* are modified by physical activity.

1.5 SUMMARY AND STUDY OBJECTIVES

An increasing body of research suggests that variability in cognitive performance as we age is a result of complex gene-environment interactions. Yet, there is limited research on some of the most recently discovered candidate genes in terms of episodic memory performance and AD risk in old age, and whether some of these effects are mitigated by physical activity. Moreover, there has not been enough focus in the literature on *APOE*-independent influences of these genes. Whether considered independently or in unison with *APOE*, the influence of other genetic polymorphisms, such as *PICALM*, and *TOMM40*, is important, as they may provide insight into mechanisms relevant to episodic memory and neurodegeneration in aging. Understanding genetic and inflammatory contributions to memory, brain aging, and AD could provide an indication of key mechanisms that ultimately lead to neurodegeneration and AD. Moreover, physical activity remains one of the most important modifiable risk factors for AD, yet its interactions with genetic polymorphisms and inflammatory markers remain largely unexplored.

The current thesis aims to investigate the effects of genetic and inflammatory biomarkers to understand complex phenotypes such as episodic memory, brain aging, and dementia. To understand these phenotypes, we examine AD candidate genes and inflammatory cytokines that have shown promising associations in the literature. Moreover, we aim to assess if there are interactions with physical activity, addressing whether individuals who are most susceptible to neural decline benefit the most from physical activity.

2 AIMS

The general aim of this thesis is to investigate the effects of genetic and inflammatory biomarkers on episodic memory, brain structure and dementia in old age. Moreover, do lifestyle factors such as remaining active in old age interact with any of these factors? The specific aims of each study in this thesis are:

Study I: To estimate the influence of *TOMM40* variants on episodic memory and hippocampal volume in old age.

Study II: To investigate if an aggregate GRS of *PICALM*, *BIN1* and *CLU* variants is associated with episodic memory and if being physically active modifies this association.

Study III: To investigate if an aggregate GRS of *PICALM*, *BIN1* and *CLU* variants is associated with incident dementia and if being physically active modifies this association.

Study IV: To examine the influence of physical activity and inflammatory biomarkers on brain structure and cognitive decline in aging.

3 METHODS

3.1 THE SNAC-K PROJECT

All the studies in the current thesis are based on the population-based SNAC-K project. Data collection for SNAC-K commenced in 2001, with the primary aim to improve health and care for the elderly population and to identify factors associated with healthy aging and dementia. For this purpose, 5111 individuals (≥60 years) from the Kungsholmen municipality of Stockholm, Sweden, were invited to participate. Of these, 4590 were alive and eligible, and 3353 (73%) participated in the baseline assessment that entailed a nurse interview, a medical examination, and a neuropsychological testing session. In total, these examinations lasted approximately 6 hours. The number of individuals who completed the cognitive test battery at baseline was 2848. In addition, a subsample of 555 participants that were eligible for scanning underwent MRI assessment.

The sample was stratified on age (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99+ years). First follow-up for the older cohorts (age 78+ years at baseline) was conducted during 2004-2006 (3-year follow-up); second follow-up for the older cohorts and first follow up for the younger cohorts (age 60-72 years) was performed 2007-2010.

Study I and IV analyzed data from the baseline sample that underwent MRI. Study II used data from the baseline cognitive assessment and in Study III variables collected at baseline were used to predict new cases of dementia at 3 and 6-year follow-up. In all studies, individuals with a dementia diagnosis or other neurological disorders, such as Parkinson's disease, at baseline were excluded.

3.2 COGNITIVE ASSESMENT

The cognitive assessment in SNAC-K lasted approximately 1.5 hours and was administered by trained psychologists in accordance with standardized procedures. In order to minimize practice effects and the effects of fatigue on a particular task, three different versions of the test battery were prepared and administered in two different orders.

Episodic memory was measured using tests of free recall and recognition. Sixteen unrelated nouns were presented to participants visually and verbally. Total number of words recalled during a 2-minute period was used as a measure of free recall. Recognition was assessed using a self-paced yes-no recognition task where participants were presented with 32 nouns (16 old, 16 new). When identifying a word as "old", participants were asked to report if they (a) clearly remembered hearing and/or seeing the presented word in the previous list (recollection), (b) recognized the word, but had no recollection of it (familiarity), or (c) could not determine remembering or recognizing the word (guessing). Recognition and recollection were assessed in terms of discrimination (hits-false alarms).

Semantic memory was measured using vocabulary and general knowledge tests. In the vocabulary task, participants were presented with 30 words and instructed to identify the

corresponding synonyms among 5 alternatives within a time limit of 7 minutes (Dureman, 1960; Nilsson, et al., 1997). The general knowledge task was comprised of 10 questions (e.g., "What is the capital of Uruguay?"), and participants were instructed to choose between two response alternatives (Dahl, Allwood, & Hagberg, 2009). For both tasks, number of correct responses was used as the outcome measure.

Perceptual speed was assessed with the digit cancellation (Zazzo, 1974) and pattern comparison (Salthouse & Babcock, 1991) tasks. For digit cancellation, participants were instructed to cross out the digit "4" from rows of intermixed digits during 30 s. In pattern comparison, participants were asked to judge whether pairs of line segments were the "same" or "different" during 30 s. Number of crossed out "4s" and average correct pattern comparisons from two trials were used as outcome measures.

Verbal fluency was assessed by letter and category fluency tasks (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Participants were asked to generate as many words as possible starting with the letters F and A for letter fluency, and from the categories of animals and professions for category fluency. They were allotted 60 s for each task and the average number of generated words was analyzed.

3.3 DEMENTIA DIAGNOSIS

Dementia diagnosis in SNAC-K was based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., 1994). The diagnosis was performed according to a three-step procedure. The examining physician made a preliminary diagnosis, which was followed by an independent diagnosis based on computerized data. If these diagnoses were incongruent, a supervising physician made a third and final diagnosis. Cognitive measures that aided diagnosis included the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), the Clock test (Manos & Wu, 1994), and questions regarding memory, orientation, executive functioning, interpretation of proverbs, and problem solving. AD was diagnosed according to NINCDS-ADRDA criteria (McKhann et al., 1984). In Study III, we conducted analyses including all incident dementia cases as well as analyses restricted to the incident AD cases. For all other studies in the thesis, those participants who received a dementia diagnosis at baseline were excluded.

3.4 MRI ACQUISITION AND VOLUMETRIC MEASUREMENT

MRI data were acquired on a 1.5 T MRI scanner (Philips Intera, The Netherlands). 3D fast field echo (FFE) T1, axial spin echo (SE) Proton Density/T2, axial fluid-attenuated inversion recovery (FLAIR), and axial diffusion tensor imaging (DTI) were acquired. In this thesis, the axial 3D FFE T1 images repetition time (TR) = 15 ms, echo time (TE) = 7 ms, Flip angle = 15◦, number of axial slices = 128 with thickness = 1.5 mm and in plane resolution 0.94 × 0.94mm^2, no gap, Field of view (FOV) = 240, matrix = 256 × 256) were used.

Manually traced measures of the HC were conducted in HERMES workstation (Nuclear Diagnostics Stockholm, Sweden) and used as an outcome measure in Study I. The delineation of the HC included the HC proper (Ammon´s horn), the dentate gyrus, the subiculum and some white matter (alveus, fimbria; Qiu et al., 2012). HC volumes for both hemispheres were combined and we corrected for head size by adding intracranial volume (ICV) as a covariate.

In Study IV, T1-weighted images were used to quantify gray-matter volumes according to the unified-segmentation approach (Ashburner, 2007) in SPM12b (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 10 (The Mathworks, Inc). Following preprocessing, 8 regions of interest per hemisphere were defined: lateral prefrontal cortex (LPFC), orbitofrontal cortex (OFC), inferior parietal lobule (IPL), inferior temporal cortex (ITC), primary visual cortex (VC), HC, caudate (CD), and putamen (PT). Masks were created based on corresponding Broadmann areas for each region, using the MRIcron atlas for LPFC (Brodmann areas 8, 9, 10, 45, and 46), OFC (Brodmann areas 11 and 47), IPL (Brodmann area 40), and ITC (Brodmann area 20). The WFU Pickatlas AAL was used for the remaining masks. As such, 16 masks were created to extract mean regional volumes for each participant. To increase anatomic validity, the fit of each mask was visually inspected and optimized in terms of clear separation. Volumetric data were corrected for ICV, according to the analysis of covariance method (Raz et al., 2005).

3.5 GENOTYPING

DNA was extracted from peripheral blood samples and genotyping was performed using MALDI-TOF analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet. The following polymorphisms were analyzed in this thesis: *TOMM40* rs11556505 and rs2075650, *PICALM* rs3851179 and rs541458, *CLU* rs11136000, *BIN1* rs744373, and *APOE* rs7412, rs429358. In Studies II and III, we utilized a combined GRS of the following alleles: *PICALM* (rs3851179 G allele, rs541458 T allele), *BIN1* (rs744373 G allele), and *CLU* (rs11136000 T allele). The aggregate GRS was based on the presence of 0, 1 or 2 risk alleles for each polymorphism. Following a median split, groups were divided into low GRS (0-4) and high GRS (5-8) and analyzed accordingly.

3.6 PHYSICAL ACTIVITY

Physical activity was assessed using a self-administered questionnaire (Rydwik et al., 2013). Participants reported if they had been physically active within the past 12 months in terms of levels of intensity (light such as walks or short bike rides, moderate or intense such as brisk walks or jogging) and frequency (<2–3 times/month, 2–3 times/month, several times/week, and every day). Three categories were created to quantify physical activity: (a) inadequate (2–3 times per month in light and/or moderate/intense exercise); (b) health-enhancing (light exercise several times per week or every day); or (c) fitness-enhancing (moderate/intense exercise several times per week or every day), based on recommendations

from the World Health Organization and the American College of Sports Medicine (Nelson et al., 2007; WHO, 2010).

3.7 INFLAMMATORY MARKERS

Blood serum markers of inflammation were extracted from peripheral blood samples (fasting was not compulsory; Papenberg, Ferencz, et al., 2016). IL-1β, IL-6, IL-10, IL-12p40, IL-12p70, G-CSF, and TNF-α were analyzed with a multiplex suspension array system using the Bioplex Luminex 200 instrument (Bio-Rad Laboratories, Hercules, CA) and the MILLIPLEX® MAP Human Cytokine/Chemokine panel (Merck Millipore, Darmstadt, Germany). To control for potential confounding by acute inflammation, CRP was measured using standard procedures (Buckley, Fu, Freeman, Rogers, & Helfand, 2009).

3.8 ADDITIONAL VARIABLES

Independence in terms of ADLs (e.g., dressing, hygiene) and IADLs (e.g., shopping, cooking) was assessed by nurses and analyzed in terms of number of dependencies. The occurrence of chronic diseases was determined by physicians and based on medical history, laboratory data, and current medication use. Disease diagnoses were based on the ICD-10 classification and included, but were not limited to, circulatory diseases, musculoskeletal diseases, and endocrine diseases. Number of chronic diseases was used as a covariate in Study II, where we also adjusted for vascular risk factors such as smoking, high cholesterol, and Body Mass Index (BMI). In Study IV, cardiovascular burden was assessed in terms of aggregates of cardiovascular risk factors (stage-2 hypertension, high cholesterol ≥6.5 mmol/L, obesity ≥30 kg/m2, diabetes, smoking) and cardiovascular diseases (ischemic heart disease, atrial fibrillation, heart failure; Welmer, Angleman, Rydwik, Fratiglioni, & Qiu, 2013). Finally, the MMSE (Folstein et al., 1975) was used for assessment of global cognitive functioning.

3.9 STATISTICAL ANALYSES

Study I and II used ANOVA and $\chi 2$ tests (IBM SPSS 19) to assess group differences in background variables. ANCOVAs were used to investigate main and interaction effects of the independent variables. Several factors were included as covariates including age, sex, education, and ICV in Study I. In Study II, factors associated with cognitive functioning such as smoking, high cholesterol, BMI, ADL, number of chronic diseases, and *APOE* gene status were controlled for. In Study III logistic regressions were performed in SAS to estimate the OR and 95% confidence interval for incident dementia. Here, models were adjusted for age, sex, education, *APOE*, and ADL. Analyses in Study IV were conducted within a structural-equation modeling (SEM) framework using AMOS 7.0 (Arbuckle, 2006) to estimate a model specifying latent gray-matter factors. Inflammatory markers and physical activity were added as predictors in the model and age, sex, education, IADL, cardiovascular risk factors, and CRP levels were added as regressors.

3.10 ETHICAL CONSIDERATIONS

The SNAC-K project complies with the declaration of Helsinki. The ethical committee at Karolinska Institutet approved baseline data collection, and the regional ethical review board approved data collection for follow-up assessments. All participants gave informed consent, and had the option to drop out of the study at any time. If the participant was cognitively impaired (MMSE ≤22), informed consent was obtained from next-of-kin.

4 RESULTS

4.1 STUDY I

Mitochondrial dysfunction has been suggested as a potential pathogenic mechanism in brain aging. Yet, little is known about the influence of *TOMM40* SNPs on episodic memory and volume of the HC in healthy aging. In Study I, we assessed the influence of *TOMM40* polymorphisms (rs11556505 and rs2075650) on episodic memory performance and hippocampal volume in healthy older adults.

Participants: 424 dementia-free individuals ($Range_{age}$ = 60-87, M_{age} = 69.91, SD_{age} = 8.63) from the SNAC-K baseline MRI assessment were included in Study I. Participants were screened for neurological disorders, MMSE ≤ 24, and depression.

Results: There were no main or interaction effects of *TOMM40* polymorphisms on episodic free recall or volume of the HC. Yet, a series of partial correlations showed that there was a significant link between HC volume and episodic memory performance only in those carrying an *APOE* ε4 allele. Stratifying *APOE* across *TOMM40* polymorphisms showed that the association remained significant only in those having the combination of disadvantageous *APOE* ε4, *TOMM40* rs2075650 G, and rs11556505 T alleles.

Conclusions: TOMM40 polymorphisms did not influence episodic memory performance or HC volume in healthy older adults. However, there was an association between episodic memory performance and HC in those carrying disadvantageous alleles of both *APOE* and *TOMM40*. This pattern suggests that *APOE* ε4 carriers with additional *TOMM40* risk alleles may rely more strongly on HC volume for episodic memory performance. These findings suggest that *TOMM40* should be considered in cognitive aging research, in addition to *APOE*.

4.2 STUDY II

PICALM, *BIN1* and *CLU* are top candidate genes for AD and certain SNPs have been associated with reduced episodic memory performance in healthy aging. The susceptibility model holds that individuals with disadvantageous alleles may not only be more vulnerable to certain conditions, but also more prone to benefit from environmental influences, such as being physically active in old age. Here we investigate the effects of a GRS based on *PICALM* (rs3851179, rs541458), *BIN1* (rs744373), and *CLU* (rs11136000) polymorphisms, examining whether a high GRS is associated with episodic memory performance in healthy aging and if there are interactions with physical activity.

Participants: 2480 dementia-free individuals ($Range_{age}$ = 60-100, M_{age} = 72.63, SD_{age} = 10.10) from the SNAC-K baseline neuropsychological assessment were included in Study II. Participants with neurological disorders, MMSE ≤ 24, and preliminary dementia diagnosis at first follow-up were excluded.

Results: There was a main effect of GRS on both free recall and recognition, such that those who had a high GRS performed worse than those who had a low GRS. A similar pattern was evident for physical activity, where individuals who were active outperformed those who were inactive in free recall, but not in overall recognition. Interestingly, there was an interaction between physical activity and GRS, such that the combination of being physically inactive together with having a high GRS was most detrimental to episodic memory performance. Moreover, those who were inactive with a high GRS were also more likely to report a less clear recollection of an item and tended to rely more on familiarity in episodic recognition. Importantly, the effects of GRS on episodic memory were eliminated among those who were physically active. Of note is also that this interactive pattern was only observed for episodic memory. For the tasks assessing semantic memory, verbal fluency, and speed, there were no genetic effects, and there were main effects of physical activity for all measures, except semantic memory.

Conclusions: In line with the susceptibility model, our findings confirmed that individuals with the most disadvantageous alleles benefit the most from environmental influences. Having a high GRS of *PICALM*, *BIN1*, and *CLU* polymorphisms was associated with reduced episodic memory performance in healthy aging. This effect was attenuated by maintaining a physically active lifestyle.

4.3 STUDY III

In Study II, we demonstrated that a high GRS of *PICALM*, *BIN1* and *CLU* SNPs is associated with impaired episodic memory performance. In Study III we tested whether the same GRS, and physical activity predicts incident dementia.

Participants: Individuals ($Range_{age}$ = 60-100, $M_{age\ baseline}$ = 70.54, $SD_{age\ baseline}$ = 9.49) from the SNAC-K baseline assessment who were followed for a 6-year time period were included in Study III. After screening for dementia and other neurological disorders at baseline, the effective sample included 1891 persons. During the 6-year follow-up period, 200 individuals developed dementia (125 received an AD diagnosis) and 1691 remained alive and non-demented.

Results: In line with previous work, physical inactivity was associated with an increased risk of dementia and AD. However, a high GRS of *PICALM*, *BIN1* and *CLU* polymorphisms was not associated with increased dementia risk. Having the combination of a high GRS and being physically inactive was strongly related to incident dementia (OR=2.70, CI=1.56-4.67) and AD (OR=3.58, CI=1.90-6.75). However, there was no significant interaction effect between genetic risk and physical activity with regard to future dementia.

Conclusions: This study shows that physical inactivity is associated with incident dementia. Although the interaction between physical inactivity and genetic risk did not reach statistical significance, future studies may continue to investigate whether an active lifestyle can counteract the negative effects of genetic susceptibility. Preferably, such research should include larger sample sizes and consider additional candidate genes for dementia.

4.4 STUDY IV

Inflammatory factors have been suggested to influence the brain negatively in aging. On the other hand, the brain-maintenance view holds that an active lifestyle in old age could preserve brain integrity and thereby cognition. Here, we investigate the influence of inflammatory biomarkers and physical activity on gray-matter volume and global cognitive decline.

Participants: 414 dementia-free individuals ($Range_{age}$ = 60–87 years, M_{age} = 71.8 years; SD_{age} = 9.0 years) from the SNAC-K baseline MRI assessment were included in Study IV. Participants that were included were free of other disorders, including stroke, epilepsy, and brain tumors.

Results: Participants who were physically inactive had consistently smaller gray-matter volumes. This was true also when controlling for confounders, such as age, sex, education, IADL, as well as cardiovascular risk and disease. Although none of the inflammatory biomarkers were associated with gray-matter volumes, there was an interaction between physical activity and two of the inflammatory markers. Specifically, a high level of IL-12p40 was associated with smaller gray-matter volumes of LPFC and HC, but only in individuals who were physically inactive. High G-CSF, a factor that downregulates inflammation, was associated with larger gray-matter volume of the LPFC and HC in the same group, only when all other inflammatory factors were included in the model. Interestingly, global cognitive decline across a 6-year time period was most evident in those participants who were physically inactive, had high IL-12p40 levels, and showed smaller LPFC and HC volumes.

Conclusions: The observed pattern of data indicates that inflammatory cytokines are most detrimental in combination with physical inactivity in terms of having negative effects on brain volume and cognition.

5 DISCUSSION

5.1 SUMMARY OF FINDINGS

The aim of this doctoral thesis was to investigate the role of genetic and inflammatory biomarkers on cognition, brain aging and dementia. Fundamentally, the goal was to contribute to the understanding of gene-environment interactions in an effort to elucidate the complex phenotypes of cognitive aging and AD. The following are some of the main findings: In Study I, there was some support for the added influence of *TOMM40* polymorphisms, over and above *APOE*, on the link between HC volume and episodic memory performance. Although these findings indicate that *TOMM40* should be considered in addition to *APOE*, more research is needed to confirm an independent association. In Study II we observed direct effects of genes on cognition, where a GRS, based on *PICALM*, *BIN1* and *CLU* alleles, was associated with episodic memory performance in healthy older adults. In Study III, the same risk score was not associated with AD, and although the combination of a high GRS and physical inactivity was most strongly related to dementia and AD, the interaction did not reach significance. In Study II, we found a significant interaction between physical activity and GRS for episodic memory, suggesting that an active lifestyle may especially benefit those who are most susceptible to AD.

The benefits of physical activity in older adults were further demonstrated in Study IV. Here, the effects of inflammation on HC and LPFC volume were observed only in persons who were inactive. This indicates that systemic inflammation may influence brain and cognitive decline in those individuals who are inactive. In summary, this thesis demonstrates the benefits of physical activity in old age as it interacts with genetic and inflammatory biomarkers in aging. Moreover, we demonstrated the benefit of considering the combined effects of genes on cognition, brain integrity, and dementia, whether in GRS constellations or stratified across *APOE* status. Our findings are consistent with the hypothesis that mechanisms such as mitochondrial dysfunction and inflammation may play a role in cognitive aging and AD, which are complex phenotypes influenced by many factors.

5.2 *TOMM40*, MEMORY, AND THE HIPPOCAMPUS

In Study I, our main analyses were not able to demonstrate an independent effect of *APOE*, or *TOMM40* on HC volume and episodic memory performance in older adults. This may have been due to the relatively small and healthy sample especially in the SNAC-K MRI subsample, and that the effect of preclinical dementia was stringently controlled for. The lack of influence of *APOE* is surprising, as the literature supports an influence of *APOE,* especially on gray-matter integrity in aging (for a review, see Ferencz et al., 2012). However, volumetric changes are evident also in old adults with low genetic risk, suggesting that atrophy alone may not be sufficient in distinguishing individuals who will subsequently develop AD (Fjell, McEvoy, Holland, Dale, & Walhovd, 2013). This may explain why there was no direct influence of *APOE* and *TOMM40* on HC volume in Study I. Furthermore, one study suggests that the effects of *TOMM40* may be age-dependent, and occur only before the

age of 60 (Caselli et al., 2012), which is prior to the entry point for individuals in the current study.

Despite the lack of direct effects, there was a positive association between HC volume and episodic memory in *APOE* ε4 carriers with additional *TOMM40* (rs20756505, rs1155650) risk alleles. This suggests that those who are genetically susceptible to AD are more likely to depend on HC volume for episodic memory accuracy. Although there were no *TOMM40*-related structural changes of the HC, our findings are in support of the view that there may be *TOMM40*-related functional changes within the mitochondria of the HC at this stage. This might explain why we observed a combined genetic influence of *APOE* and *TOMM40* on the HC-episodic memory link. Future studies utilizing markers of glucose metabolism and oxidative stress may confirm a role of mitochondrial dysfunction on HC integrity.

Examining the independent or combined effects of *APOE* and *TOMM40* more accurately describe the association from this region, as ascribing the effect to *APOE* and not considering the effects of *TOMM40* may result in overlooking an important association (Roses et al., 2016).

Conclusion: Although there was no direct effect of *TOMM40* on HC volume or episodic memory in healthy aging, we did find an association between volume and performance in *APOE* ε4/*TOMM40* risk allele (rs2075650 G and rs11556505 T) carriers. This could be an early indicator of mitochondrial dysfunction within the HC. Furthermore, it highlights the necessity of considering these genes in combination.

5.3 *PICALM, BIN1, CLU,* AND MEMORY

Study II is the first to demonstrate that a combined GRS of *PICALM*, *BIN1,* and *CLU* risk alleles is associated with worse episodic memory performance in old age, independent of *APOE*. Whereas multilocus genotype patterns of these genes have previously been associated with episodic memory (Barral et al., 2012), we demonstrate that the effect is independent of *APOE* and that a GRS of these genes interacts with physical activity in old age. The association between high genetic risk and episodic memory appears to be robust, as we were recently able to replicate the association in an independent sample (Papenberg, Becker, et al., 2016).

In line with our hypothesis, physical activity interacted with genetic risk on episodic memory, such that those who had a high GRS and were physically active outperformed individuals with a high GRS and inadequate physical activity. When recognition was further probed, the high GRS/inactive participants had less conscious recollection of the items and relied more heavily on familiarity. Recollection and familiarity are distinct memory processes with recollection depending primarily on the integrity of the HC (Yonelinas, 2001). This pattern suggests that a high GRS may be detrimental to HC volume and that physical activity may help preserve it. Indeed, BIN1 is primarily expressed within the hippocampus (Holler et al., 2014), and SNPs of *PICALM* and *BIN1*, that were included in this GRS have been associated with HC and entorhinal cortex volumes (Biffi et al., 2010). Taken together, these findings

suggest that *PICALM*, *BIN1* and *CLU* genes may modulate MTL vulnerability in old age. The effects of high GRS were specific to episodic memory, as perceptual speed, vocabulary, general knowledge, and verbal fluency were not influenced by the GRS. There is always the caveat that common genetic variations account only for a small portion of the explained variance (<1%) in performance. This holds true also for the associations between high GRS and episodic memory in Study II of this thesis. Although the effect sizes on episodic memory are small, their clinical significance may still be of relevance.

Conclusion: Study II confirmed our hypothesis that a high GRS of *PICALM*, *BIN1* and *CLU* risk alleles negatively influences episodic memory performance in old age. The pattern of episodic memory deficits in those with high GRS/physical inactivity suggest that these polymorphisms may be linked to hippocampal integrity in old age. Interestingly, physical activity interacted with GRS and influenced episodic memory performance.

5.4 PLASTICITY GENES

In line with the brain-maintenance view, the results of Study II suggest that individuals who are more susceptible to AD may benefit the most from environmental influences, such as physical activity. This supports the notion that genes associated with an increased risk of AD may not only be vulnerability genes that increase the risk of a disease, but they may also be considered plasticity genes that are more receptive to environmental influence (Belsky et al., 2009). This assertion is not new. Darwin (1809), stated that it is not the strongest who survive, but those who are more responsive to change. It is not customary to consider vulnerability genes as plastic, yet, the differential susceptibility hypothesis suggests that some genes may be just that (Belsky et al., 2009). Rather than simply conferring risk or vulnerability to diseases, participants who harbor unfavorable genetic combinations may be more readily influenced by positive environmental factors such as remaining physically active (Belsky et al., 2009). This has been shown for the *BDNF* gene, where physical activity counteracted the negative effects of the Met allele on working memory performance (Erickson et al., 2013). We have been able to demonstrate similar findings with regard to *PICALM*, *BIN1*, and *CLU* genes, in terms of episodic memory performance. However, as physical activity was not measured objectively, and only cross-sectional associations were examined, we have to be cautious in assuming a direct causal link.

In Study II, we demonstrated an effect of high GRS on episodic memory performance indicating that hippocampal integrity may be compromised in individuals with high genetic risk. A possible explanation for the observed gene-lifestyle interaction is that physical activity may attenuate this association by preserving the integrity of brain areas important to memory, such as the HC and PFC (Rovio et al., 2010). The literature has consistently shown that physical activity and aerobic exercise not only protects against volume loss, but may also reverse age-related HC shrinkage (Erickson et al., 2009, 2014; Kramer & Erickson, 2007). Furthermore, physical activity appears to utilize the brain´s natural capacity for plasticity (Kramer & Erickson, 2007). Our findings in Study II is consistent with the view that the protective effect of physical activity may be especially pronounced

for individuals with high genetic risk. This does not imply that those who have a genetic advantage do not benefit from a physically active lifestyle; however, it suggests that those with high genetic risk may benefit more.

Conclusion: We were able to demonstrate that physical activity, already at a moderate level, is associated with health benefits in terms of counteracting the negative effects of being at high genetic risk of AD on episodic memory. This may be a result of beneficial influence of physical activity in the hippocampal area.

5.5 *PICALM*, *BIN1*, *CLU,* AND ALZHEIMER'S DISEASE

In Study III, there was no effect of a high GRS of *PICALM*, *BIN1* and *CLU* risk alleles on dementia incidence. Physical inactivity, however, was associated with increased risk of developing AD during a 6-year follow-up period. Although stratified analyses indicated that the combination of having a high GRS and physical inactivity was strongly associated with incident dementia, the interaction effect was not reliable.

As the majority of associations of *PICALM*, *BIN1*, and *CLU* alleles with AD come from large GWAS, it is possible that the lack of genetic association in our study reflects low statistical power. Toward this end, note that the same GRS was positively associated with memory in the better-powered Study II. Moreover, heritability estimates based on SNPs are generally considerably lower than those based on twin studies, which reflects complex gene-gene and gene-environment interactions (Reynolds & Finkel, 2015). Furthermore, it is likely that many common genes with small effects act on the polygenic nature of AD. Although polygenic risk scores can double the prediction of AD (Escott-Price et al., 2015; Harrison et al., 2016), the current GRS constellation showed no effects on AD. It is likely that epistatic effects are at play in the disease (Hohman, et al., 2013), meaning that the effect of one gene is dependent upon another in terms of modification. Although the SNPs in the current GRS were chosen based on their associations with AD and relevant biological mechanisms, important genes may be missing from the equation. This signifies the importance of future studies considering multiple gene interactions and overlapping biological mechanisms in creating future risk scores.

Conclusion: The results did not support our hypothesis as a high GRS of *PICALM*, *BIN1* and *CLU* was not associated with incident dementia in our population. Moreover, there was no reliable interaction between high GRS and physical inactivity.

5.6 INFLAMMATORY CYTOKINES

Study IV supports the brain-maintenance view and is in line with the other studies of this thesis showing the benefits of an active lifestyle in old age. In accordance with previous research (Voelcker-Rehage & Windisch, 2013), Study IV shows that physical inactivity is associated with smaller gray-matter volume across several regions including the HC, LPFC, OFC, and the CD. Inflammatory biomarkers were not associated with gray-matter integrity; however, there was an interaction between physical activity and the inflammatory biomarker

IL-12p40. Negative effects of IL-12p40 on hippocampal and LPFC volumes were observed only in participants who were inactive. In the same inactive group, high levels of G-CSF were associated with larger volumes in these regions. This may seem counterintuitive; however, G-CSF has been suggested to downregulate inflammation (Sanchez-Ramos et al., 2009). As such, the association with gray-matter volume in the physically inactive groups may actually reflect a state of inflammation. Notably, the effect of G-CSF was only present when all other markers were included in the model, indicative of a suppression effect. Furthermore, the combination of physical inactivity/high levels of IL-12p40 was associated with global cognitive decline during the 6-year follow-up. In line with the observations in Study II, the HC and the PFC may be especially sensitive to the effects of physical activity, as markers of inflammation only had a negative influence on gray-matter volume in those who were physically inactive. Interestingly, none of the other cytokines (IL-6, IL-10, IL-1β, TNF-α) that have previously been linked to brain and cognition (Marsland et al., 2008; H. Zhang et al., 2016) were associated with brain volume in the current study.

We know that the immune system becomes compromised in aging (López-Otín et al., 2013) and our findings indicate that systemic inflammation may be especially prominent and associated with brain integrity in people who are inactive. The pattern of increased IL-12p40 suggests that there is a state of inflammation that influences HC and PFC volumes, but only in those who are physically inactive. Although there was no overall association between physical activity and inflammatory markers in our study, others have shown that physical activity modulates inflammation by lowering inflammatory markers (Hamer et al., 2012). Mechanisms through which physical activity and exercise may prevent cognitive decline and protect against brain aging include promoting angiogenesis (Lista & Sorrentino, 2010), neurogenesis (Kempermann, 2008), and by reducing oxidative stress (Marosi et al., 2012). As such, it is likely that the benefits of physical activity may act through several different pathways, which might explain why there was no direct association between physical activity and inflammatory levels in this study.

Conclusion: Our findings extend previous research on the benefits of staying physically active in old age. They suggest that the negative effects of inflammatory cytokines on gray-matter volume and cognitive decline are only present in individuals who are inactive. The observed pattern indicates that IL-12p40 could be an early marker of subsequent cognitive decline in combination with physical inactivity.

5.7 ETIOLOGY OF ALZHEIMER'S DISEASE

Taken together, our findings might reflect that there are several pathogenic mechanisms that influence cognitive heterogeneity and dementia in old age. Further research will have to disentangle which specific pathways the genetic and inflammatory biomarkers assessed in this thesis influence. Our findings are compatible with the view that a number of non-amyloid processes may influence memory, brain volume, and AD. This does not mean that amyloid is not involved in the pathological process; it rather implies that other pathological processes are also important. For instance, in Study I, the influence of *TOMM40* on HC volume and

episodic memory, albeit limited, implicates mitochondrial involvement in aging. In Study II and III, the influence of a high GRS on memory and AD, especially in combination with physical inactivity, suggests several amyloid-dependent pathways. The high GRS SNPs examined influence lipid metabolism, immune system response, iron homeostasis, neurofibrillary tangle formation, synaptic vesicle endocytosis, glucose metabolism, and apoptotic processes (Jones et al., 2010; Maglott et al., 2005; Xu et al., 2014; Zlokovic et al., 1996). That said, the genes in this thesis are also involved in amyloid-dependent processes (Xu et al., 2014). Finally, in Study IV, the combined effect of inflammatory cytokines and physical inactivity signifies the importance of considering inflammatory mechanisms as an early and pathogenic hallmark of brain and cognitive aging. Furthermore, the interaction with physical activity implicates yet another set of biological mechanisms that may serve to protect the brain in aging, such as neurogenesis, angiogenesis, and reduction of oxidative stress. The extent to which the genes investigated in this thesis exert their negative effects in these pathways remains unclear. However, for inflammatory markers it is likely that we actually approximate the role that inflammation plays in aging.

Conclusion: Taken together, these findings support the view that several biological mechanisms are important in cognitive and brain aging.

5.8 THE BENEFITS OF PHYSICAL ACTIVITY

Although this thesis was primarily focused on the mitigating role of physical activity and its potential interaction with genetic and inflammatory markers, it should be noted that one of the most consistent finding of the thesis was the benefits of physical activity in old age. This is in line with a vast amount of studies on the benefits of physical activity on cognitive aging (Prakash, Voss, Erickson, & Kramer, 2015) and AD (Kramer & Erickson, 2007).

In Study II, the benefits of physical activity were evident in terms of episodic memory performance. These findings suggest that participating in health- or fitness-enhancing activities several times per week is associated with better episodic memory performance in old age. These findings support previous research suggesting that physical activity preserves memory in aging (Lista & Sorrentino, 2010). Participating in low-intensity activities such as usual paced walks and short bike rides may be sufficient in terms of benefits for episodic memory as we age. Study III further corroborates the benefits of physical activity by demonstrating that individuals who are physically inactive are more likely to develop dementia and AD which is in line with previous reports (Rovio et al., 2005; Tolppanen et al., 2015). Thus, physical activity may continue to serve as an important primary prevention strategy (Winblad et al., 2016).

The findings in Study IV also indicate that it is physical inactivity and a sedentary lifestyle that should be avoided, as the negative effects of inflammation were only seen in those who were inactive. Although no direct influence of physical activity on inflammatory cytokines was observed, these findings suggest that the effects of inflammation may be especially detrimental in individuals who are inactive. Interestingly, in Study IV we were able to

replicate previous work on the benefits of staying active by showing an association between physical activity and regional gray-matter volumes (Rovio et al., 2010; Voelcker-rehage & Windisch, 2013). Individuals who were inactive showed consistently smaller gray-matter volumes across the brain.

Conclusion: The studies of the current thesis support the benefits of physical activity in older adults. We demonstrate that physical activity already at low levels of intensity is beneficial in terms of memory and brain aging. Moreover, a sedentary lifestyle is associated with an increased risk of developing dementia and AD. These findings support the view that we should continue to promote physical activity in line with WHO recommendations, to reduce the risk of dementia, and maintain memory functioning and brain health in aging.

5.9 IMPLICATIONS FOR PREVENTION STRATEGIES

Our findings are consistent with the hypothesis that several factors influence the heterogeneity of memory performance, brain aging, and dementia risk, which makes it imperative to consider multiple factors when designing future intervention studies. Randomized controlled trials with multi-domain lifestyle interventions are already well on their way (Ngandu et al., 2015). Our findings further highlight the importance of considering other genetic influences, besides *APOE*, in future clinical trials and interventions. The vast number of clinical trials that have failed may target individuals too late in the disease process. With that in mind, genetic and inflammatory biomarkers could identify at-risk individuals early in the disease process. Our findings also suggest that some may benefit more from remaining active in old age. Randomized controlled trials will be needed to determine if the benefits of physical activity in this thesis can be replicated. This work would benefit from adding biomarkers of, for instance, oxidative stress that were not measured in this thesis. To combat the dementia epidemic, we need to target such modifiable risk factors early. Although genes are not traditionally considered modifiable risk factors, our data suggest that they may be plastic. Recent estimations indicate that utilizing genetic risk scores could lower the costs of clinical trials, by enriching the trials with individuals most likely to develop dementia (Hu et al., 2013).

Conclusion: Our findings highlight the benefit of considering genetic and inflammatory biomarkers in future clinical trials for AD, in combination with environmental influences to target at-risk individuals early in the disease progression.

5.10 LIMITATIONS

A main limitation of this work is the cross-sectional nature of some of the empirical studies. For instance, we would benefit from knowing if the genes examined in this thesis are associated with brain and cognitive changes. Moreover, it is likely that measures of physical activity and inflammation change over time, and it would have been preferable to also assess these measures longitudinally to examine if there is a direct influence of physical activity on inflammation.

Another limitation concerns the lack of objective assessment of physical activity. It has been shown that subjective and objective measures of physical activity can differ (Dyrstad, Hansen, Holme, & Anderssen, 2014), which may be especially critical in participants with poor memory performance. The observational nature of the studies in this thesis warrants for caution when interpreting the causality of physical activity associations. Intervention studies will have to confirm potential gene-environment interactions in this regard. Furthermore, there is also the possibility that lack of physical activity is a result of other functional problems, limiting participation. However, the associations in this thesis remained after we controlled for various confounders such as ADL, and chronic diseases.

In terms of structural imaging of the brain, it is clearly desirable to use more advanced MRI protocols with higher resolution than what was available in SNAC-K. However, the longitudinal nature of the SNAC-K project limits our ability to update scanner protocols.

Concerning generalizability of the current data, note that the findings are based on an urban-dwelling, highly educated Swedish population. In terms of dementia, it is possible that the results of Study III were influenced by survival bias as physical inactivity is associated with mortality (Groot et al., 2004). However, as pointed out by others, if participants who had deceased were more likely to have high genetic risk and be physically inactive, it is more likely that we underestimated the effects of genes and physical activity on dementia in our sample (Kivipelto et al., 2008). Future studies should consider also the diagnostic, genetic, and lifestyle status of those who have deceased.

5.11 FUTURE DIRECTIONS

We have been able to demonstrate that there are several genetic, inflammatory, and environmental markers that influence cognitive heterogeneity, brain integrity, and risk of dementia. Our results support the notion that normal and pathological aging is a multifactorial process involving mitochondrial, inflammatory, and most likely amyloid processes. Besides systemic inflammation, none of these other pathogenic markers were measured in this thesis. Thus, it is not possible to ascertain the biological underpinnings of the genetic effects in this thesis. Future studies would benefit from assessing, for example, markers of oxidative stress in unison with genetic variation.

In terms of genetic associations, future studies will continue to benefit from considering multiple genes in unison and polygenic AD scores in order to understand the polygenic structure of cognitive aging and dementia (Escott-Price et al., 2015; Harrison et al., 2016). Such analyses allow us to assess the SNPs that may contribute to the polygenic makeup of cognitive aging and AD, but that fail to meet the accepted p-value threshold for GWAS. It was recently shown that, even after excluding SNPs that are in LD, as many as 24 genomic regions were associated with AD (Escott-Price et al., 2015). Moreover, there is increasing support for the notion that episodic memory is a polygenic behavioral trait (Papassotiropoulos & de Quervain, 2011). As such, rather than focusing on single SNPs or even genetic-risk scores, creating individual genetic risk profiles will be more accurate in terms of predicting

disease. The likelihood that episodic memory and AD are complex phenotypes influenced by many different genes is reflected also in the small effects of the SNPs in this thesis. Although memory and AD are highly heritable, the contribution of each SNP is relatively small. A recent GWAS with quantitative traits identified several new loci associated with HC volume and shape that predicted AD (Hibar et al., 2017). These findings support the notion that common variants with small effect sizes contribute to complex phenotypes such as AD. Others suggest we should move the focus from common variants with small effect sizes and try to identify rare variants with high penetrance in next generation sequencing (Ridge et al., 2013).

Traditionally, genes are not considered as biomarkers, yet they may be stable predictors of AD. Ultimately, genetic risk algorithms could be further developed to include genetic, lifestyle and inflammatory biomarkers to identify individuals at high risk. Efforts to develop such biomarkers have commenced, focusing on *TOMM40* and *APOE* (Lutz, Sundseth, et al., 2016). We maintain that to benefit from such strategies, we must shift the focus from single-locus genetic approaches to examine the combined effects of genes in unison. For research purposes, these measures would preferably be combined with objective measures of physical activity. To further enhance our understanding of genetic influences in cognitive aging it will be necessary to assess potential pleiotropic effects of SNPs from a life-course perspective. According to the resource-modulation hypothesis the effects of genetic variation is limited in younger adults, but magnified in old age (Papenberg et al., 2015). Such effects have already been demonstrated for *APOE* ε4 carriers (for a review see Papenberg et al., 2015). It remains to be seen if there are any pleiotropic effects of the SNPs studied in this thesis.

One potential mechanisms by which genes are plastic is through epigenetic mechanisms. To understand how physical activity may influence the effects of genes, epigenetic research will become increasingly important. Some such studies are already well on the way, and focus on how physical activity may be involved in gene expression by changing DNA methylation (Horsburgh, Robson-Ansley, Adams, & Smith, 2015). While still in their early stages, such studies will become increasingly important especially for understanding how physical activity can mitigate the influence of inflammation. Moreover, it may be important to consider personality factors as a potential influence as recent research shows that genes may interact with some personality traits (Saptoka, Wiebe, Small, & Dixon, 2016).

Although we have demonstrated that physical activity is beneficial in terms of brain-maintenance in aging, and that genes may be plastic, future longitudinal studies as well as intervention studies are necessary to confirm such associations.

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Zlokovic, B., Martel, C. L., Matsubara, E., Mccomb, J. G., Zheng, G., McCluskey, R. T., Frangione, B., & Ghiso, J. (1996). Glycoprotein 330/megalin: probable role in receptor-mediated transport of apolipoprotein J alone and in a complex with Alzheimer disease amyloid beta at the blood-brain and blood-cerebrospinal fluid barriers. *Proceedings of the National Academy of Sciences, 93,* 4229–4234.

8 APPENDIX

LIST OF DISSERTATIONS FROM THE AGING RESEARCH CENTER AND THE STOCKHOLM GERONTOLOGY RESEARCH CENTER, 1991-2016

1991

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

1992

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

1993

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

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

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

1994

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

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

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

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

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

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

1996

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

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

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

1997

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

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

1998

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

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

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

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

1999

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

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

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

2000

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

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

2001

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

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

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

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

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

2004

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

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

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

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

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

2005

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

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

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

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

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

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

2006

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

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

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

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

2007

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

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

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

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

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

2008

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

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

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

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

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

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

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

2009

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

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

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

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

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

2010

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

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

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

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

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

2014

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

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

2015

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

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

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

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

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

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

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

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

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

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