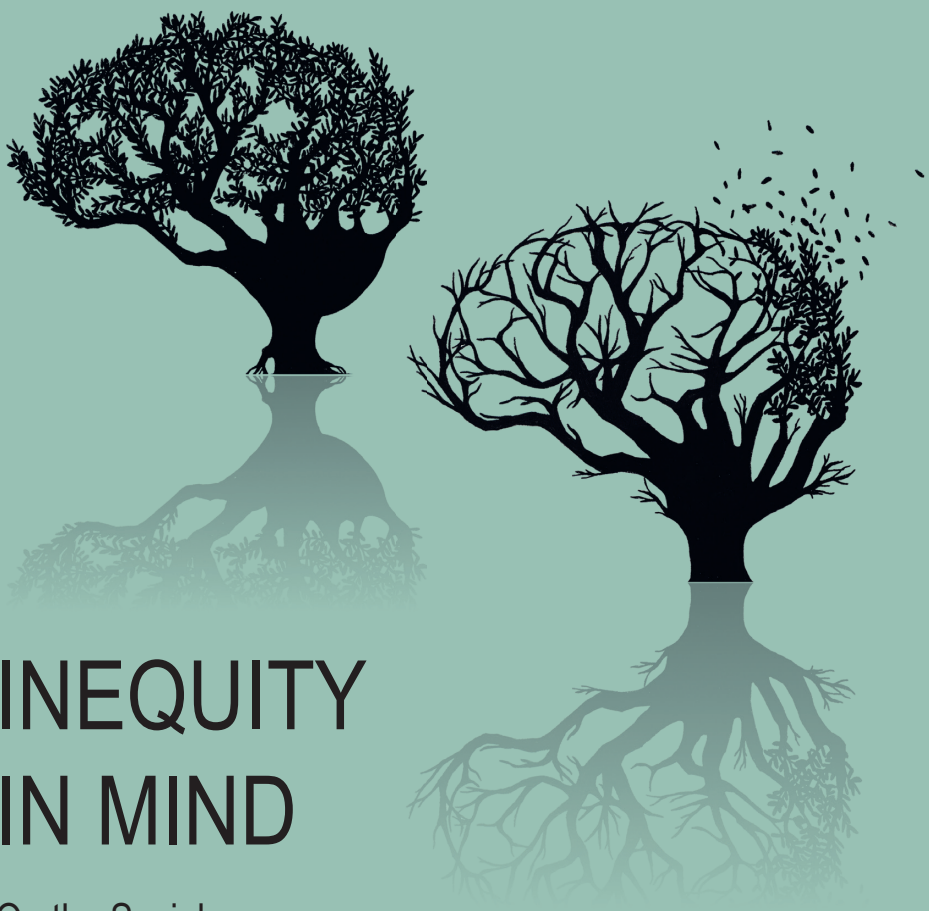

INEQUITY IN MIND

On the Social and Genetic Risk Factors of Dementia and Their Interactions

Caroline Hasselgren

Inequity in Mind

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Not every puzzle is intended to be solved. Some are in place to test your limits. Others are, in fact, not puzzles at all.

Vera Nazarian

Abstract

The present thesis seeks to further explain the occurrence of Alzheimer's disease and other dementias by studying the long-term impact of class- and gender-based inequities as well as the extent to which they potentially moderate genetic risk. Central to this endeavour is the recognition of social inequity as multifaceted, and of potential intersections between different drivers of structural (dis)advantage in relation to individual health prospects. The main point of departure is that even though the causes of dementia are heterogeneous and cannot be reduced to either genetic or environmental factors, dementia is, just like many of its potential risk/protective factors, unevenly distributed in the population. Nevertheless, our knowledge of whether and how systems of structural inequity intersect and interact with individual genetic endowments in the development of disease is still scarce.

The thesis encompasses four empirical studies, all of which should be considered examples of interdisciplinary efforts to incorporate theory and expertise from different fields in order to create a more holistic understanding of dementia aetiology. The analyses are based on data derived from the longitudinal *Gothenburg H70 Birth Cohort Study (H70)* and the *Prospective Populations Study on Women (PPSW)* from Gothenburg, Sweden. The baseline sample (N=1019) was first examined in 2000 and followed up in 2005 and 2009.

Study I lays the foundation upon which the other studies rest. It does so by asking whether socio-economic status (SES) could in fact moderate the increased risk of dementia that carrying one or more copies of the *APOE* (apolipoprotein E) ε4 allele implies. Having identified that high SES seems to buffer the effect of *APOE* ε4 among men but not among women, Study II and III set out to explore two mechanisms that could possibly shed further light on the link between socio-economic (dis)advantage and dementia risk as well as on the previously identified sex difference: work environment exposures and access to social networks. The findings of Study II suggest that work control is the most influential aspect of the work environment, with respect to moderation of genetic endowments, but that it is only protective among men. While no significant gene-social network interactions were revealed in Study III, the results indicate that there might be important differences between men and women in the impact of social networks on dementia risk. Finally, Study IV tests the assumption that the higher lifetime risk of dementia among women could, at least in part, be the result of differences in educational attainment and/or in experiences of general psychological distress. The results confirm that education ought to be considered a 'gendered' dementia risk factor and propose that psychological distress constitutes a potential, and hitherto rarely acknowledged, pathway between dementia and female sex, on the one hand, and dementia and low educational attainment, on the other.

In light of the findings presented in this thesis, it is evident that dementia is an emergent phenomenon that must not be reduced to the sum of its parts, especially considering the results suggesting that genetic endowments can actually be moderated by

externally imposed factors. Additionally, all four studies underline that the risk/protective factors that are more proximate to the individual, such as work environment exposures, social networks or distress, must not be studied as if they were distinct from the social structures that 'put people at risk of risks'. Consequently, I argue, class and sex/gender must be attended to as fundamental, and intersecting, causes of dementia if we are to better understand why some individuals develop the disease, while others do not.

Contents

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Hasselgren C., Ekbrand H., Fässberg M.M., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). *APOE* ε4 and the long arm of social inequity: Estimated effects of socio-economic status and sex on the timing of dementia onset. *Ageing & Society,* 39(9): 1951-1975.

II. Hasselgren C., Dellve L., Ekbrand H., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). Socioeconomic status, gender and dementia: The influence of work environment exposures and their interactions with *APOE* ε4. *Social Science & Medicine (SSM) Population Health,* 5: 171-179.

III. Wu J., Hasselgren C., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). The impact of social networks and *APOE* ε4 on dementia among older adults: Tests of possible interactions. *Aging & Mental Health.* Advance online publication, https://doi.org/10.1080/13607863.2018.1531368.

IV. Hasselgren C., Ekbrand H., Halleröd B., Fässberg M.M., Zettergren A., Johansson L., Skoog I & Dellve L. (submitted manuscript). Sex differences in dementia: On the potentially mediating effects of educational attainment and experiences of psychological distress.

Authors' contributions

Study I: *CH* (first author) was responsible for conception and study design, processed the data and carried out the statistical analysis (together with *HE*) as well as drafted and finalized the manuscript. *BH, HE, IS* and *MMF* supervised the first author. *MMF* contributed specifically in the sample selection process. *BH* contributed specifically in the drafting of the manuscript. *IS* was responsible for data acquisition and assessed information obtained from the neuropsychiatric examinations in order to diagnose dementia. *KB*, *AZ* and *HZ* were responsible for the genotyping procedures. All authors have reviewed and revised the manuscript as well as provided useful comments and insights in relation to their specific field of expertise. All authors have approved the final manuscript.

Study II: *CH* (first author) was responsible for conception and study design, processed the data and carried out the statistical analysis as well as drafted and finalized the manuscript. *LD, HE, BH* and *IS* supervised the first author. *IS* was further responsible for data acquisition and assessed information obtained from the neuropsychiatric examinations in order to diagnose dementia. *KB*, *AZ* and *HZ* were responsible for the genotyping procedures. All authors have reviewed and revised the manuscript as well as provided useful comments and insights in relation to their specific field of expertise. All authors have approved the final manuscript.

Study III: *CH* (co-author), *JW* and *BH* designed the study. *CH* contributed particularly to the methodological design. *JW* and *CH* carried out the statistical analysis. *JW*, *CH* and *BH* interpreted the results and *JW*, partly in collaboration with *CH*, drafted the manuscript. *IS* supervised *CH* and was further responsible for data acquisition and assessing information obtained from the neuropsychiatric examinations in order to diagnose dementia. *KB*, *AZ* and *HZ* were responsible for the genotyping procedures. All authors have reviewed and revised the manuscript as well as provided useful comments and insights in relation to their specific field of expertise. All authors have approved the final manuscript.

Study IV: *CH* (first author) was responsible for the conception and design of the study, processed the data and carried out the statistical analysis as well as drafted and finalized the manuscript. *LD, HE, BH, IS* and *MMF* supervised the first author. *IS* was further responsible for data acquisition and assessed information obtained from the neuropsychiatric examinations in order to diagnose dementia. *AZ* and *LJ* contributed to data acquisition and *AZ* was specifically involved in the compilation of genetic data. All authors have reviewed and revised the manuscript as well as provided useful comments and insights in relation to their specific field of expertise. All authors have approved the final manuscript.

List of figures

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E
DLB	Dementia with Lewy bodies
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders
EGP	Erikson Goldthorpe Portocarero
FCT	Fundamental Cause Theory
FTD	Frontotemporal dementia
H70	Gothenburg H70 Birth Cohort Study
JEM	Job Exposure Matrix
MMSE	Mini Mental State Examination
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PPSW	Prospective Populations Study on Women
SEI	Swedish Socio-economic Classification
SES	Socio-economic status
SNPs	Single nucleotide polymorphisms
VaD	Vascular dementia
WLSMV	Weighted least squares means and variance adjusted

Förord [acknowledgements]

Det känns både bra och läskigt att skriva det, men nu är avhandlingen faktiskt klar. Och dessutom tycks jag ha kommit ut hyfsat helskinnad på andra sidan! Detta tack vare en lång rad människor som på ett eller annat vis varit avgörande för att jag sitter här idag och filar på det här förordet. Först och främst tack till alla deltagare i H70 och Kvinno-undersökningen – utan er, ingen avhandling! Tack också till *Sten A Olssons stiftelse för forskning och kultur* för finansiering, och till *AGECAP - Centrum för åldrande och hälsa* samt *SWEAH - Nationella forskarskolan för åldrande och hälsa* för tvärvetenskapliga kunskaps-utbyten och delfinansiering.

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Caroline Hasselgren
Göteborg, augusti 2019

1
Introduction

There is much that is fundamentally unfair about dementia and its impact upon individuals and societies. It selectively impacts upon the old and frail, women, those with less education, and fewer assets. It dims the voices of those affected, just when they might have most to tell us about their experiences [...].
Alzheimer's Disease International, 2015

The present thesis seeks to explore the occurrence of Alzheimer's disease and other dementias by studying the long-term impact of class- and gender-based inequities as well as the extent to which they potentially moderate genetic risk. Central to this endeavour is the recognition of social inequity as multifaceted, and of potential intersections between different drivers of structural (dis)advantage in relation to health, in general, and to dementia, in particular. The main point of departure is that even though the causes of dementia are heterogeneous and cannot be reduced to either genetic or environmental factors, dementia is, just like many of its potential causes, unevenly distributed in the population. Nevertheless, our knowledge of whether and how systems of structural inequity intersect and interact with individual genetic endowments in the development of disease is still scarce.

Why study dementia?

The word dementia originates from the Latin words *de-* [out of] and *mens* [mind]. It is the umbrella term for a range of chiefly age-related disorders that occur as a result of damage to, or destruction of, neurons in the brain (Livingston et al., 2017). Dementia is a devastating condition that significantly impairs the individual's ability to perform everyday activities, and thus one of the major causes of disability and dependency among older adults worldwide (World Health Organization, 2012). Hitherto, it has lacked effective prevention, treatment and cure. At the same time, the lack of awareness and understanding seen in many countries causes stigmatization as well as barriers to diagnosis and care (Lord and Cruchaga, 2014; World Health Organization, 2012). Hence, as longevity continues to increase in all regions of the world, dementia has become a public health issue of major concern to all ageing societies (Winblad et al., 2016; World Health Organization, 2012). In 2016, Alzheimer's Disease International reported that the number of people suffering from dementia disorders worldwide is over 47 million. This number

is projected to almost triple by 2050, which means that the societal economic burden of dementia, estimated at $US 818 billion globally in 2016, will continue to grow. Given that the global increase in life expectancy is most notable in low- and middle-income countries, they are likely to experience the greatest increase in dementia prevalence. At the same time, many of these countries lack sufficient economic and professional resources to cater for the health and care needs that follow such profound demographic and epidemiological changes (Prince et al., 2016).

Evidently, the challenges posed by dementia extend from the individual, to societies, and to the world. This implies that the search for treatments, and not least protective factors, is of the utmost importance. In the present thesis, it is argued that recognizing dementia as a condition imprinted with multi-layered injustice is crucial to this endeavour. Additionally, dementia disorders must not be regarded as an object of study reserved for the medical sciences alone. In order to fully grasp its complexity – its diverse causes and consequences, knowledge from various disciplines, including sociology, is needed. More specifically, sociologists have the possibility to contribute to dementia research by offering a theoretical apparatus that sheds further light on the intricacy of intertwined structural constraints as well as their far-reaching impact on individuals' health prospects.

Dementia disorders – a brief background

Dementia is the umbrella term for a range of neurological disorders, all of which are associated with distinct symptoms and brain abnormalities. In order to provide some background to the current object of study, the subsequent sections describe the most common types of dementia, including their respective pathologies and symptoms. Before that, however, it should be noted that recent evidence indicates that a majority of individuals with dementia, particularly among the oldest-old, have brain abnormalities that can be attributed to more than one cause (Attems and Jellinger, 2013; James et al., 2016; Jellinger, 2007; Kapasi et al., 2017; Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 2001; Schneider et al., 2007; Schneider et al., 2009). This means that mixed pathologies (referred to as 'mixed dementia') are likely to be more common than pure ones, and thus that estimates of the proportion of cases attributable to each subtype must be interpreted with caution (World Health Organization, 2012).

Alzheimer's Disease

The most common cause of dementia is Alzheimer's disease (AD), which accounts for approximately 50-70 per cent of all cases (Winblad et al., 2016). AD is a slowly progressing disorder in which pathological brain changes are likely to start developing years, or even decades, before clinical symptoms occur (Jack et al., 2010; Sperling et al., 2011). Pathologically, AD is characterized by the build-up of beta-amyloid plaques, abnormal clusters of protein fragments between nerve cells in the brain, as well as by twisted strands

(neurofibrillary tangles) of the protein *tau* inside of neurons. These changes disrupt normal cell activity, which, successively, results in the damage and death of neurons (Figure 1).

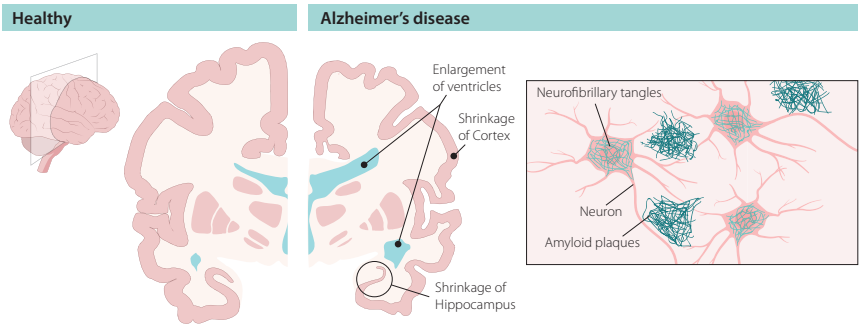

Figure 1. *Brain changes in Alzheimer's disease*[1]

Early symptoms of AD include, e.g., difficulties remembering recent conversations, names or events, and depression. As the disease progresses, communication is often impaired, while at the same time confusion, disorientation and behavioural changes occur. Eventually, the affected individual might also experience difficulties swallowing, speaking and walking (Alzheimer's Association, 2019). Genetically, AD can be subdivided into a rare, autosomal dominant[2] form and a sporadic form. The former is estimated to account for approximately one per cent or less of cases, and usually affect individuals younger than age 65 (Cuyvers and Sleegers, 2016; Van Cauwenberghe et al., 2016). Thus, the vast majority of AD cases are sporadic, i.e., the causes are multifactorial and the disease occurs through a complex interplay between genetic susceptibility and environmental exposures. Most sporadic AD cases (approx. 95 per cent) occur in individuals aged 65 or older (Scheltens et al., 2016; Winblad et al., 2016).

Vascular dementia

Vascular dementia (VaD) occurs as a result of cerebrovascular pathologies, primarily infarcts (regions of tissue loss) and white-matter lesions caused by ischemia[3] (Gorelick et al., 2011; van der Flier et al., 2018). Such vascular changes are seldom the sole cause of dementia, but are estimated to be present among up to 50 per cent or more of individuals diagnosed with the disease (Brenowitz et al., 2017; Kapasi et al., 2017; Schneider et al.,

[1] Illustration by Mattias Karlén.
[2] The disorder affects everyone who inherits the mutation for the trait as long as they live a normal lifespan. Any affected parent has a 50 per cent risk of passing on the disease to his or her child.
[3] A restriction in blood supply that causes a shortage of oxygen.

2007). In most cases, they occur in combination with AD pathology. In contrast to AD, where memory loss is often associated with the early stages of disease process, more common symptoms of VaD are impaired judgment, inability to make decisions, and deteriorating motor function (Alzheimer's Association, 2019).

Lewy body dementias

Lewy body dementias is the umbrella term for dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The presence of Lewy bodies, i.e., abnormal aggregations of the protein alpha-synuclein inside brain neurons, is a pathological hallmark of Parkinson's disease (PD) as well as a common cause of dementia (Alzheimer's Association, 2019; Emre et al., 2007; Jones and O'Brien, 2014; Walker et al., 2015). Dementia is highly prevalent in patients with PD, and findings from a recent large autopsy study suggest that although less than 10 per cent of individuals with neuropathological brain changes show signs of Lewy body pathology alone, they often co-exist with AD pathology (Brenowitz et al., 2017; Walker et al., 2015). DLB and PDD differ foremost regarding the order in which cognitive and motor symptoms occur. DLB typically involves some of the cognitive changes characteristic of AD, but affected individuals are also likely to experience Parkinson-like motor symptoms, sleep disturbances and visual hallucinations. In contrast, PDD refers to when dementia is diagnosed in the context of already established PD (Alzheimer's Association, 2019; Walker et al., 2015).

Frontotemporal dementia

The term frontotemporal dementia (FTD) refers to a group of disorders that cause progressive nerve cell loss primarily in the front (frontal lobe) and side regions (temporal lobes) of the brain. The nerve cell damage eventually leads to loss of function in these regions, which results in either deteriorating social function and changes in personality (behavioural FTD) or in declining language skills (primary progressive aphasia, which further can be divided into several subtypes) (Ahmed et al., 2014; Bang et al., 2015). FTD usually occurs at younger ages (<65), and although estimates of the relative frequency and prevalence of FTD vary widely between studies (Hogan et al., 2016), it is currently considered a leading type of early-onset dementia (Bang et al., 2015).

Risk factors for AD and other dementias

As noted above, the vast majority of dementia cases cannot be attributed entirely to either heredity or environmental exposures, which means that the causes are multifactorial (Blennow and Wallin, 1992; Cacabelos et al., 2012; Kivipelto et al., 2018; Livingston et al., 2017; Verghese et al., 2011; Whalley et al., 2006). In this section, I will briefly sketch an overview of potential risk factors, genetic as well as social, while also discussing the idea that these may not simply have independent effects on disease onset.

Genetic risk – the *APOE* ε4 allele

The *APOE* (apolipoprotein E) gene provides the blueprint for a cholesterol carrying protein that is involved in lipid transport and injury repair in the brain. All individuals inherit one of three variants (alleles) of this gene from each parent: ε2, ε3 or ε4. To date, the *APOE* ε4 allele is considered the major genetic risk factor for late onset sporadic AD[4]. It is relatively common in the population[5] and has a strong impact on disease risk, *inter alia* because it interferes with Aβ clearance from the brain. Compared to ε3 homozygotes, ε4 carriers run a three- (heterozygotes) to fifteenfold (homozygotes) risk of developing AD (Alzheimer's Association, 2019; Blennow et al., 2006; Liu et al., 2013; Scheltens et al., 2016; Winblad et al., 2016). While the association between *APOE* ε4 and AD has been verified in numerous studies, its impact in relation to other dementia subtypes is less well-established. However, it has recently been suggested that *APOE* ε4 could also be associated with, e.g., VaD and/or DLB (Keogh et al., 2016; Liu et al., 2012; Rohn, 2014; Skillbäck et al., 2018; Tsuang et al., 2013).

The *APOE* ε4 allele is a non-causative mutation, which means that not all people who carry the allele develop dementia, whereas others, despite lacking this risk factor, do (Blennow et al., 2006; Rohn, 2014; Scheltens et al., 2016; Tsuang et al., 2013; Verghese et al., 2011). Naturally, this raises questions regarding what factors outside the genome could potentially increase or decrease disease susceptibility. This issue is particularly pertinent given recent findings suggesting that elimination of some of the most influential modifiable risk factors could reduce dementia incidence by as much as 30-35 per cent (de Bruijn et al., 2015; Livingston et al., 2017).

The social gradient in dementia

It is well established that poor social and economic conditions have a negative impact on health and mortality (Link and Phelan, 1995; Marmot, 2004; Marmot and Brunner, 2005; Phelan et al., 2004; Wilkinson and Marmot, 2003). Like most diseases, dementia has a social gradient. Two of the most common indicators of social class, albeit seldom referred to as such, found in studies of dementia are education and occupational class. In this section, I review research related to each of these indicators as well as to potentially mediating factors and pathological pathways suggested to explain their association with disease risk.

Low educational attainment is one of the most thoroughly investigated risk factors for dementia, in general, and for AD, in particular (Caamaño-Isorna et al., 2006; Meng and D'Arcy, 2013; Ngandu et al., 2007; Qiu et al., 2010; Wang et al., 2012a). In fact, recent figures from the *Lancet Commissions* suggest that elimination of the risk factor 'no education beyond primary' could prevent as much as eight per cent of new dementia cases

[4] Advances in genomics technologies during recent decades have enabled the identification of other susceptibility genes. However, further explorations of such genetic risk factors are beyond the scope of this thesis.
[5] Although the ε4 allele frequency varies across ethnic groups, the worldwide prevalence has been estimated at approximately 14 per cent (ALZGENE, 2010; Farrer et al., 1997).

(Livingston et al., 2017). With regard to occupational class, previous studies are scarcer and their results rather inconclusive. For instance, some studies have suggested that education and occupational class may separately reduce the risk of dementia (Qiu et al., 2003; Sattler et al., 2012), while others have indicated that the effect of the latter is attributable to differences in educational attainment (Evans et al., 1997; Helmer et al., 2001; Karp et al., 2004). Nevertheless, a number of studies have attempted to decompose the potential effects of occupational class, and the majority of these have focused on exploring the potentially protective effects of task complexity. For instance, it has been suggested that high occupational complexity with regard to people, data and/or things could reduce the risk of dementia (Andel et al., 2005; Dekhtyar et al., 2015; Karp et al., 2009; Kröger et al., 2008) and that work activities such as 'information processing' and 'pattern detection' could delay the time of its clinical manifestation (Then et al., 2017). Moreover, although work-related psychosocial stress has previously been linked to dementia/AD (Andel et al., 2012; Elovainio et al., 2009; Pan et al., 2019; Sindi et al., 2016; Then et al., 2014; Wang et al., 2012b), knowledge concerning the potential impact of other psychosocial work exposures is still limited and extant findings need to be validated.

The presumably protective function of higher education and/or of occupying certain occupational class positions is generally explained by the *cognitive reserve hypothesis,* which suggests that the kind of intellectual stimulation inherent in activities such as reading, information processing and pattern detection creates a virtual 'buffer' in the brain, which prevents symptoms of degenerative brain changes (Sattler et al., 2012; Then et al., 2017; Verghese et al., 2011; Winblad et al., 2016). This 'buffer' is thought to occur as a result of increased synapse density and regeneration of neurons in the brain as well as by improved efficacy and flexibility in the neuronal networks (Stern, 2002; Stern, 2012). There is, however, reason to believe that this is not the whole story, especially considering that class is also closely related to a number of other well-known dementia risk factors.

One such example is depression, which is currently considered a probable risk factor (Barnes et al., 2012; Diniz et al., 2013; Dotson et al., 2010, see also Livingston, 2017) and/or a preclinical sign of dementia (Singh-Manoux et al., 2017). It is hypothesized to increase dementia risk through its effect on stress hormones, neuronal growth factors, and hippocampal volume (Livingston et al., 2017) and is also known to be more common in socio-economically disadvantaged groups (Ferrari et al., 2013a; Huurre et al., 2007; Stansfeld et al., 2003; World Health Organization, 2014). Likewise, longstanding exposure to unfavourable, material and/or psychosocial conditions is often assumed to cause sustained stress reactions, and stress is therefore generally considered an important pathophysiological pathway linking socio-economic (dis)advantage to health and longevity (Marmot, 2004; Wilkinson and Marmot, 2003). In line with this, studies conducted among Swedish women have found that psychosocial stressors in mid-life and long-standing distress are associated with dementia (Johansson et al., 2013; Johansson et al., 2010; Johansson et al., 2012). Other studies have suggested that this also applies to work-related stress (Andel et al., 2012; Pan et al., 2019; Sindi et al., 2016; Then et al., 2014; Wang et al., 2012b). The association between stress and dementia is often attributed to

the impact of stress on cardiovascular risk factors, such as hypertension (Kivipelto et al., 2001; Skoog et al., 1996). Stress is also known to heighten levels of glucocorticoid hormones in the blood. This has been suggested to cause both damage to the hippocampus and reductions in grey matter volume (Bremner, 2006; Gianaros et al., 2007; Lupien et al., 1999; Sapolsky, 1996; Sindi et al., 2017) as well as build-up of beta-amyloid peptide and tau-protein in the brain (Dong et al., 2004; Green et al., 2006). An argument similar to those presented above can be made for a range of other lifestyle risk factors such as physical inactivity, obesity, and smoking: All of these follow social gradients (see, e.g., Marmot and Bell, 2012) and are well-established cardiovascular dementia risk factors (Livingston et al., 2017).

Finally, numerous studies, using various indicators of individual social networks and focusing on different aspects thereof, have demonstrated associations with dementia risk (see, e.g., Amieva et al., 2010; Béland et al., 2005; Crooks et al., 2008; Fratiglioni et al., 2004; Kuiper et al., 2015; Kuiper et al., 2016; Livingston et al., 2017; Saczynski et al., 2006). Just like depression, social isolation could be a prodrome of dementia. However, emerging evidence suggests that it is also an independent risk factor (Amieva et al., 2010; Kuiper et al., 2015; Livingston et al., 2017). Its impact is often explained with reference to, e.g., the potential for the intellectual stimulation as well as support (and thereby reduction of stress) that is embedded in social relationships (see, e.g., Kuiper et al., 2015). At the same time, access to social support is known to follow a social gradient, in favour of individuals occupying higher positions in the social hierarchy (Gecková et al., 2003; Mickelson and Kubzansky, 2003).

In conclusion, it is argued here that many non-genetic risk/protective factors for dementia, such as work environment exposures, mental health and access to social networks/support, are often examined individually, while the fact that many of them are also related to social class is generally overlooked. This suggests that there is a need to increase our knowledge of the multidimensional impact of social inequity on dementia risk, i.e., of how different risk factors are related to each other and, as we shall see below, how they potentially moderate genetic risk.

Sex differences in dementia

Estimates of sex differences in the prevalence and incidence rates of AD and other dementias appear to vary by type, age group and geographical region (Andersen et al., 1999; Fratiglioni et al., 2000; Fratiglioni and Qiu, 2013; Nebel et al., 2018; Ruitenberg et al., 2001; Winblad et al., 2016). Nevertheless, it is well-established that women have a greater lifetime risk, defined as 'the probability that someone of a given age [...] will develop a condition during his or her remaining life span' (Alzheimer's Association, 2019: 19), of developing AD or any dementia. For example, at age 65, approximately 20 per cent of all women, but only 14 per cent of all men, are projected to develop a dementia disorder during the remainder of their lifespan (Nebel et al., 2018; Seshadri et al., 1997; Seshadri

and Wolf, 2007). The prevailing view has long been that these differences are mainly attributable to differences in life expectancy, i.e., to the fact that women tend to live longer than men. Although research on alternative explanations is still limited, it has lately been suggested that variation in other biological and social factors is likely to contribute to these disparities (Alzheimer's Association, 2019; Mazure and Swendsen, 2016; Nebel et al., 2018; Rocca et al., 2014).

In a recently published call to action statement written by representatives from the Society for Women's Health Research Interdisciplinary Network on AD (Nebel et al., 2018), it is suggested that there are primarily three ways in which sex/gender can affect disease risk. First, there are risk factors that are equally common among women and men, but have a stronger effect in one sex. For instance, there are studies indicating that the risk increase implied by the *APOE* ε4 allele could be greater among women (Altmann et al., 2014; Farrer et al., 1997). Second, there are risk/protective factors that, despite having similar effects in both sexes, are more common among either men or women. One such example is education, in which substantial differences in access have existed between men and women throughout history. In a similar vein, women are known to suffer a greater burden of depression, anxiety and stress-related complaints (Matud, 2004; McDonough and Walters, 2001; World Health Organization, 2001). Finally, Nebel et al. (2018) noted that some potential risk factors are in fact restricted to one sex, such as earlier age at menopause, which has been linked to dementia in some studies (Bove et al., 2014; Rocca et al., 2007). All in all, the present review of potential sex differences in dementia risk proposes that more research on the matter is needed. In particular, these differences must be studied in relation to other systems of structural (dis)advantage.

Interacting risk factors?

As noted above, risk factors contributing to the development of AD and other dementias are hypothesized to 'operate' in tandem rather than independently. In fact, even though an individual's genome is given, its expression may vary due to the impact of exogenous social or environmental factors (see, e.g., Ferrari et al., 2013b). Such potentially pathogenic changes in gene expression are usually termed *epigenetics* – the name implying that something 'above' the genome itself affects the way in which genes express themselves without actually changing the underlying DNA sequence. Despite this, research on the epigenetic processes related to AD is still scarce, especially in comparison to such research on other diseases. This depends, among other things, on the fact that brain tissue contains multiple cell-types, all with specific alteration patterns, which complicates the biological interpretation of epigenetic changes (Lord and Cruchaga, 2014; Lunnon and Mill, 2013). Currently, the number of studies focusing specifically on gene-social environment interactions, even without explicitly addressing epigenetic changes, is still limited and the results are inconclusive.

For example, it has been suggested that while higher education reduces the risk of developing dementia among both *APOE* ε4 carriers and non-carriers, there are no interaction effects between these two risk factors (Meng and D'Arcy, 2013). In contrast, others propose that education (Arenaza-Urquijo et al., 2015; Ferrari et al., 2013b; Wang et al., 2012a) and engagement in 'cognitive reserve-enhancing' activities (Dekhtyar et al., 2019) could reduce the risk of dementia or postpone cognitive changes related to *APOE* ε4. In a similar vein, relatively few studies have examined the possibility of gene-social network interactions, and among these studies, the findings are inconsistent. For instance, neither Brenowitz et al. (2014) nor Zuelsdorff et al. (2013) could confirm interaction effects in relation to cognitive function. In contrast, the findings presented by Poey et al. (2017) suggest, e.g., that perceived social support as well as feelings of loneliness could moderate the effect of *APOE* ε4 on both dementia and/or cognitive impairment. Likewise, Niti et al. (2008) found that the protective effect of participation in social activities (e.g., religious services, social group activities) on cognitive decline was particularly pronounced in APOE ε4 carriers.

In relation to the current state of research, and to the inconsistencies outlined above, it is evident that further research on the ways in which the social environment and genetics interact is greatly needed in relation to dementia disorders. What is needed in particular are studies that also address the possibility of sex differences in moderation patterns (Altmann et al., 2014; Bennett et al., 2014; Lord and Cruchaga, 2014; Lunnon et al., 2014; Nebel et al., 2018).

Aims and objectives

This thesis aims to further explain the occurrence of AD and other dementias by studying the long-term impact of class- and gender-based inequities, as well as by exploring whether these inequities, and their related mechanisms, could moderate genetic risk. Following this line of inquiry, the thesis revolves around two distinct, albeit related, themes: (1) Potential moderation of genetic risk in dementia and (2) Possible intersections between class and sex/gender in disease development. These two themes are summarized in the following research questions:

I. To what extent does class moderate genetic risk in the development of dementia (Study I)? Can *APOE* ε4-environment interactions be observed in relation to potentially intermediate risk factors such as work environment exposures and access to social networks (Studies II & III)?

II. To what degree do class- and gender-based inequities intersect in relation to dementia risk? How can such interactions be understood in light of, e.g., gender differences in work environment exposures and general psychological well-being (Study I-II & IV)?

Outline of the thesis

The present chapter has provided a brief background to why dementia needs to be the focus of further investigation as well as to the aetiology of its different subtypes. Further, I have presented an overview of the current state of research and, more specifically, of research dealing with genetic and social risk factors, including their potential interactions. Finally, I have described the overarching aim of the thesis and its related research questions. **Chapter II** begins with a review of some of the most commonly employed explanations for why inequities in health arise. I further discuss why these explanations ought to be regarded as complementary rather than mutually exclusive and conclude by examining two main drivers of social inequities in health: class and sex/gender. In **Chapter III**, I discuss the importance of joint interdisciplinary efforts in dementia research and, additionally, address a pertinent question: 'So what if genes interact with the social environment – is this knowledge key to achieving social and/or political change (*if* that is what we are aiming for)?'. **Chapter IV** provides a detailed description of the data used in the four studies, including a review of the neuropsychiatric examinations and diagnostic procedures employed. In this chapter, I also discuss the statistical methods used and identify a number of methodological limitations. In **Chapter V**, I provide brief summaries of the four empirical studies. Finally, in **Chapter VI**, I discuss the main findings and conclude by synthesizing the results and considering some possible directions for future research.

2

The sociology of health inequity

No person, I think, ever saw a herd of buffalo, of which a few were fat and the great majority lean. No person ever saw a flock of birds, of which two or three were swimming in grease, and the others all skin and bone.
Henry George, 1885

The association between position in the social hierarchy and health is well established and continues to engage scholars from various disciplines, including medicine, sociology, and public health. Throughout the years, a plethora of explanatory models, with somewhat different theoretical foci, have aimed to explain these disparities in health and mortality. The following chapter is devoted to such explanations as well as to considerations of how inequity arises 'in the first place'. However, before going further into these themes, a definition of concepts is in order. I use the term *health inequity* as distinct from *health inequality*. This divide is common in the literature and aims to draw a line between the more normative connotations of the former concept and the chiefly descriptive features of the second. Hence, the notion of health inequity aims to describe differences in health that are 'politically, socially and economically unacceptable' (my translation) (Rostila and Toivanen, 2012: 20), which by extension implies that it is possible, and commendable, to take action to reduce them.

Explaining health inequity – main theoretical strands

It is clear that countless attempts have been made to provide explanations for *why* inequities in health arise, while at the same time none of the most common approaches offer a comprehensive answer to this question. Nevertheless, in popular as well as academic debates, one or the other explanation is occasionally put forth as being more likely than the others. In fact, debates concerning the relative importance of different approaches have come at a high price, i.e., a lack of critical discussions on the question of what causes differences in exposure to risks in the first place (see, e.g., Link and Phelan, 1995). However, to promote a better understanding of why different approaches to health inequity must not be considered mutually exclusive, it is important to first review them individually, particularly because their distinctive relevance 'underline[s] the complexities of causation when dealing with social determinants of health' (Siegrist and Marmot, 2006: 7).

Social mobility explanations

Contemporary explanations for health inequities can be roughly divided into two categories pertaining to the question of direction of causality (Elstad, 2000). The first category is often referred to as *social mobility explanations,* the central tenet of which is that individuals are 'sorted' into different social positions based on their, allegedly, innate characteristics. Accordingly, an individual's health is assumed to determine the social position in which he or she ends up (health selection) and/or factors predictive of ill health are assumed to predict future social position (indirect health selection) (West, 1991). With regard to the former suggestion, there is little doubt that illness might cause downward social mobility. However, direct health selection is unlikely to be an exhaustive explanation for inequities in health (Bartley and Plewis, 1997; Blane et al., 1999; Blane et al., 1993; Marmot, 2004; Marmot et al., 1997). Concerning indirect health selection, a similar conclusion can be drawn, as previous findings indicate that the social gradient in health remains even after controlling for factors such as cognitive ability or family background (Batty et al., 2006; see, e.g., Link et al., 2008; Marmot et al., 1997).

Social causation explanations

In contrast to social mobility explanations, *social causation explanations* assume that individuals are born with more or less the same outset for health/ill health but, as a consequence of their social position, are exposed to things that are either beneficial or adverse to health (Elstad, 2000). Among the social causation explanations, three main theoretical currents can be distinguished (Elstad, 2000; Rostila and Toivanen, 2012).

First, drawing largely on the Marxist tradition, the *materialist/structuralist explanation* (Lynch et al., 2000; Smith et al., 1994) for health inequity identifies the physical environment and other material resources as the major determinants of health. Hence, in its most basic form, it assumes that grand social forces allocate individuals to different social positions that are in turn characterized by differences in, e.g., exposure to hazardous working conditions, lack of clean water, poor nutrition or lack of adequate medical care. The conditions that confront the individual are merely the consequence of a macro-social process external to her, and thus unavoidable. Given the extensive social developments that have taken place in the Western world during the 20th century, the materialist/structuralist explanation has been put under scrutiny. First and foremost, critics argue that if the causes of health inequity were purely material in nature, this inequity would not exist above the threshold of absolute material deprivation (Elstad, 2000). However, large-scale epidemiological studies conducted during the past decades have revealed that this is not the case (see, e.g., Marmot, 2005; Marmot and Brunner, 2005). While such findings have certainly posed a challenge to the materialist/structuralist approach, this explanation has by no means been abandoned altogether, primarily because the criticism is considered to rest upon an overly narrow definition of 'materialist' (Siegrist and Marmot, 2006). For example, as argued by Blane et al. (1997: 385): 'some psychosocial

hazards, such as those associated with particular work regimes or labour market positions, are externally imposed and, in this sense, materialist'.

As the name implies, the *behaviour/lifestyle explanation* asserts that health disparities arise as a consequence of dissimilarities in behaviour between different social groups. For example, it has repeatedly been shown that, e.g., smoking and malnutrition are more common in socially disadvantaged groups. Because such 'behaviours' are also influential determinants of mortality and morbidity, these differences are considered to form the basis of health inequity. Consequently, this approach is sometimes referred to as the *risk factor model* (Link and Phelan, 2010). While social causation is indeed emphasized in this approach, it is usually conceptualized differently than in the materialist/structuralist explanation. For example, it is assumed that differences in behaviour/lifestyle emerge as a consequence of the different social positions individuals occupy. However, the question of *why* adverse health behaviours are more common in certain groups is often answered with reference to the varying knowledge and beliefs about health individuals in different social groups possess. Hence, individual and group agency is usually granted a more prominent position within this explanatory approach (Elstad, 2000). The behavioural/lifestyle explanation has received extensive criticism over the years, e.g., for focusing too much on factors more 'proximate' to disease and thereby contributing to an 'individualization' of risk (Carter, 2015; Elstad, 2000; Townsend, 1990).

While the materialist/structuralist and behavioural/lifestyle explanations dominated the field of research on health inequity until the 1980s, the *psychosocial explanation* began to gain ground during the 1990s. This development can be traced back to persisting health inequity across many Western societies despite decades of improvement in living standards, on the one hand, and the emergence of epidemiological evidence indicating that lifestyle factors can only partly explain health inequities, on the other (see, e.g., Carroll et al., 1996; Evans, 1994; Marmot, 2004). Thus, in order to fully explain health inequity above the threshold of absolute material deprivation, proponents of the psychosocial approach advocate focusing on individuals' social environments. For instance, it has been argued that, because humans are inherently social beings, they will always relate to their social environments, which will in turn evokes different psychological reactions. In less advantaged groups, these reactions will predictably comprise stress and frustration that, drawing on the behaviours/lifestyle model, either spur 'unhealthy behaviours' or trigger physiological processes that increase disease susceptibility (e.g., hypertension or immunosuppression) (Marmot, 2004; Wilkinson and Marmot, 2003). Moreover, an individual's class position is usually considered closely related to her *social capital* (Bourdieu, 1984; Kawachi et al., 1997; Rostila, 2013). While social capital could be related to all of the three explanatory traditions outlined above (Rostila, 2013), it deserves some attention here owing to its emphasis on the significance of social relationships. In its most basic form, the notion of social capital 'expresses the idea that there are tangible resources embedded in social relationships, available for members to access' (Kawachi and Berkman, 2014: 291, see also Bäck, 2012; Portes, 2000; Rostila, 2011). At the individual level, potentially health-promoting resources of social capital include, but are not limited

to, acquisition of relevant information as well as financial and affective support. When instead analysed as a property of a whole network, social capital may exert influence on the health of members through, e.g., transmission of behavioural norms or mobilization of collective action in times of crisis (Kawachi and Berkman, 2014; Rostila, 2011).

Despite the growing interest in, and wide acceptance of, psychosocial explanations for health inequity during recent decades, the relative explanatory power of such factors remains a contested issue. On the one hand, vast empirical evidence supports the idea that health disparities above the threshold of absolute material deprivation must be approached by attending to individuals' social environments (see, e.g., Marmot and Wilkinson, 2001; Wilkinson and Pickett, 2006). On the other hand, although psychosocial factors do indeed contribute significantly to health, as do lifestyle and material factors, some studies have shown that their contribution is generally modest (Aldabe et al., 2011; Lynch et al., 2001; van Oort et al., 2005).

Explaining explanations – Fundamental cause theory?

The fundamental cause theory (FCT) of health inequities was first formulated in the 1990s, largely in opposition to the then-prevailing 'risk factor approach' (see above) that predominated in much of the medical and epidemiological research (House, 2002). As indicated in Chapter I, I maintain that the focus on individual-level risk factors has been immensely influential also in studies of dementia – at the expense of attempts to explain what unites these factors.

According to Link and Phelan (2010: 3), the risk factor approach '[…] precedes according to a seemingly persuasive logic: social conditions are related to health because of their influence on a host of risk factors that lie between [them] and disease in a chain of causality'. Following this line of thought, interventions targeting intermediate, modifiable risk factors are considered key to remedying health inequities. However, this logic comes up short in particularly one aspect: namely that the association between social position and health holds for a wide range of diseases and remains stable over time, i.e., even when intervening mechanisms vary or change completely (Link and Phelan, 1995; Link and Phelan, 2010; Phelan et al., 2004). Public health policies that focus on providing information on risk/protective factors will not suffice to eradicate health inequities insofar as they do not also target factors that influence individuals' possibilities to, e.g., acquire new knowledge or make use of new technologies (Link and Phelan, 2010). Social inequity must therefore, it is argued, be regarded as a *fundamental* cause of disease – simply because the more affluent will always have better access to resources that can be used to avoid disease risk, regardless of what the risk/protective factors are at the time (Link and Phelan, 1995; Phelan et al., 2004).

Within FCT, it is by no means assumed that 'disease […] flow[s] directly from income, education or occupational status into the body'. Neither do proponents of this approach deny that public health initiatives based on the risk factor approach have been very successful in improving overall public health. However:

> [I]n the process of elucidating the mechanisms connecting social conditions to health and illness – an important and desirable activity – we may, over time, lose interest in and come to neglect the importance of the social condition whose effect on health we originally sought to explain (Link and Phelan 1995: 81).

Consequently, FCT underlines the significance of not only focusing on risk factors *per se*, but also on the system(s) that underlie differences in exposure to risks. In line with this, Link and Phelan have recently extended their original formulation of FCT by acknowledging that class is by no means the only social structure operating as a fundamental cause. Rather, all social positions that are 'intimately linked to resources of money, knowledge, power, prestige, and beneficial social connections over time', such as sex/gender, ethnicity or sexual orientation, should be considered probable fundamental causes (Phelan and Link, 2013: 113).

To sum up, it is argued here that FCT has one major virtue in relation to the other social causation explanations outlined in this chapter: It does not deny the role of either material, behavioural/lifestyle, or psychosocial factors in the emergence of health inequities. Instead, it synthesizes the other approaches by suggesting that their associated mechanisms operate in tandem and that their relative importance may vary across time and place. In the following sections, I discuss the two fundamental causes that are of principal interest in the present thesis, i.e., class and sex/gender.

Fundamental drivers of (health) inequity

On the concept of class

So far in this thesis, I have used the concepts of class and socio-economic status[6] (henceforth referred to as SES) as if they were more or less interchangeable, although (evidently) they are not. Thus, some clarifications are now in order. In much of the empirical work targeting health inequity, SES has been, more or less explicitly depending on the discipline, used synonymously with class. It is usually operationalized as either education, income, occupation or as a composite of these measures (see, e.g., Winkleby et al., 1992). However, SES cannot simply be equated with the broader term class, at least not beyond the merely gradational definition of the latter concept (see, e.g., Olin Wright, 2005a).

[6] The concept of socio-economic status has been criticized for obscuring 'the distinctions between two different aspects of socioeconomic position: (a) actual resources, and (b) status, meaning prestige- or rank-related characteristics' (Krieger et al., 1997: 346). Nevertheless, because it is the most commonly used term, it is used here as well as in the four empirical studies to refer to both of these aspects jointly.

In fact, socio-economic indicators such as those outlined above provide only 'nominal classifications of a population according to a dimension of stratification' (Sørensen, 2000: 1526). As such, they neither propose how nor why the basis on which these classifications rest come into being (ibid.). From this follows an inevitable question – namely: What is class?

Without a doubt, the concept of class has been subject to vast theoretical as well as empirical inquiry, not least within sociology. Nevertheless, popular as well as academic usages remain imbued with ambiguities (Olin Wright, 2005b). In the present thesis, class is understood in line with the (neo-)Weberian approach. Hence, it is assumed that the market in capitalist societies 'distributes life chances according to the resources [e.g. education, skill or property] that individuals bring to it' (Breen, 2005: 32). In turn, life chances can be understood as individuals' chances of achieving, or gaining access to, various valued outcomes, such as good health or employment prospects (Breen, 2005; Weber, 1978 [1922]: 302). By identifying the market as a determinant of life chances, the Weberian, like the Marxist, class analysis differs markedly from merely gradational approaches. The difference lies in the fact that class is not defined solely on the basis of empirically observed disparities in, e.g., income (see Sørensen above). Rather, the analysis of class begins with an identification of the social order (or relations) that determine individuals' access to economic assets (Breen, 2005; Olin Wright, 2005a).

In line with this, the neo-Weberian class analysis, which is usually associated with the Eriksson–Goldthorpe-Portocarero (EGP) scheme (Erikson and Goldthorpe, 1992a; Erikson et al., 1979, see also Breen, 2005), identifies employment relations as the foundation of class, for the simple reason that similar positions on the labour market generate similarities in life chances and living conditions (Goldthorpe, 2007). The differentiation between classes in the EGP scheme rests on two main distinctions. The first distinguishes those who own the means of production from those who do not. The second concerns different employee-employer relationships and seeks to apprehend the distinct levels of qualification and supervision that generally characterize different labour market positions. Accordingly, employees are differentiated as either having a 'labour contract', where the wage-for-effort exchange is very specific and the worker is closely supervised (typically manual- and non-manual workers), or a 'service contract' that involves more diffuse exchanges, making monitoring more difficult (Breen, 2005; Goldthorpe, 2007). In the present studies, I use the Swedish standards for Socio-Economic Classification (SEI) to operationalize class (Statistics Sweden, 1982). The SEI closely resembles the EGP scheme and has thus been suggested to work as a viable 'proxy' (Bihagen, 2007b; Tåhlin, 2007), even though the schemes partly differ in their theoretical basis. More specifically, 'skill' is a key discriminant criterion between classes in the SEI, whereas the EGP rests primarily on the distinction between employment relations (see above) (Lambert and Bihagen, 2014; Tåhlin, 2007). However, as argued by Thålin (2007: 558), these differences have not been 'very consequential for operationalizations'.

I would like to end this section by returning to the distinction between SES and class introduced above. Henceforth, I will refer to SES when discussing the findings of

empirical studies in which this term is used instead of class, including the four studies that make up the present thesis. The concept of class, however, will be used when discussing its impact on life chances and health more broadly. First and foremost, this admittedly pragmatic choice was motivated by the fact SES appears to the more commonly used concept in studies focused on health inequity, particularly within epidemiology. However, it should be underlined that the use of this term does not exclude the possibility of also recognizing that differences in access to resources, and thereby life chances, did not arise out of nothing. In relation to this, it should again be stressed that in studies targeting health inequity, different indicators of class/SES, e.g., income, education and occupational class, are often used interchangeably. Insomuch as these measures are causally related and 'reflect overlapping resources in terms of social standing' (Torssander and Erikson, 2010: 465), this can be considered justified. Nevertheless, it is still plausible that they could be linked to health via partly different mechanisms, which means that different indicators are occasionally needed (Lahelma et al., 2004; Torssander and Erikson, 2010). For example, because parents' class background has a strong impact on their children's educational choices, educational attainment not only provides information about, e.g., capacity to manage education and acquired knowledge/abilities, but also upbringing conditions (Bihagen, 2007a; Erikson and Goldthorpe, 1992a; Erikson and Jonsson, 1996; Halleröd and Gustafsson, 2011; Nordlander, 2015). Education is further a strong predictor of individuals' future labour market positions, which, in turn, affect their economic prospects, their exposure to various working conditions as well as how they, potentially, act in accordance with class-specific values and beliefs (Bihagen, 2000; Bihagen and Halleröd, 2000). All of these aspects can, as discussed previously in this chapter, be linked to health and mortality, albeit in slightly different ways.

On the concepts of sex/gender

Previous research on health inequities has revealed a noteworthy paradox: Although women tend to outlive men in developed nations, the former group continuously reports higher rates of morbidity across a wide range of indicators such as self-assessed health or limiting long-term illness (see, e.g., Alberts et al., 2014; Bambra et al., 2009). Accordingly, sex/gender is currently viewed as a central determinant of health (Marmot et al., 2008; World Health Organization, 2014; World Health Organization, 2016), and differences in educational and occupational opportunities are considered one of the major drivers underlying these differences (see, e.g., World Health Organization, 2016). With that said, a definition of concepts is needed before going on to discuss how class and sex/gender intersect to cause disparities in health outcomes.

A common divide in the sociological, as well as the epidemiological, literature is the distinction made between *sex* (referring to the assignment of an individual as male or female based on the possession of male/female genitalia) and gender (referring to 'the beliefs, values and expectations attached to sex categories, and the social relations and ordered practices which they legitimate') (New, 2005: 64, see also West & Zimmerman, 1987). In line with this, it is assumed here that sex is ontologically prior to gender, but

also that neither category is reducible to, nor entirely determined by, the other (New, 2005). Rather, they are intrinsically linked, which means that the distinction between them is foremost made for analytical purposes. In line with this, I use the term 'sex' as I refer to contexts/empirical investigations where individuals have been classified as either male or female solely based on certain biological features. In contrast, I use gender when referring to the expectations, norms, relations and inequities for which sex, and alleged sexual difference, serves as a 'basis' or referent. In the subsequent section, I provide some examples of ways in which class and gender inequities intersect in relation to health and mortality.

Intersecting drivers of inequity

Large-scale differences have existed between men and women in terms of access to education throughout history. In Sweden, for instance, men were overrepresented in post-secondary education as late as until the mid-1990s (Statistics Sweden, 2008). Provided that education is currently recognized as a key determinant of health, these disparities are crucial to understanding how sex differences in health arise, particularly in older cohorts (World Health Organization, 2016). Likewise, although women's labour market participation increased substantially in Sweden and elsewhere during the 20th century (Statistics Sweden, 2011), differences persist in relation to time spent in paid versus unpaid work (Statistics Sweden, 1992; Statistics Sweden, 2012). For instance, in 1970 – when the majority of participants in the present study sample were in their forties – the employment rates among Swedish men and women in this age group were 96.6 and 69.5 per cent, respectively (Statistics Sweden, 1973). Still today, reduced labour force participation among women, deriving from norms prescribing that women take the main responsibility for childcare and domestic chores, has a strong impact on their access to economic resources, job security, future pensions as well as possibilities of role enhancement (e.g., enhanced social integration, prestige and recognition), and thereby on their health prospects (see, e.g., Blau and Kahn, 2017; Deere and Doss, 2006; Moen et al., 1995; Rozario et al., 2004; World Health Organization, 2016).

By the same token, women who work full-time are likely to experience a double burden of professional and domestic engagements that must be taken into consideration (see, e.g, Griffin et al., 2002), especially given that the combination of high workloads in both paid and unpaid work has repeatedly been found to predict various forms of psychological strain and ill health (Arber et al., 1985; Floderus et al., 2009; Hall, 1992; Krantz et al., 2005). Finally, the gendered division of (paid) labour must be acknowledged. It is well-established that the occupations in which women predominate, such as human service professions, pay less than those with a lower share of women, also when controlling for education and skill level (England, 2010; Levanon et al., 2009). As stated above, these differences ultimately confine women's access to economic resources and thus their comparative chances of attaining good health. Additionally, stressors such as emotional demands, violence/threats of violence, and thereby affective and stress-related

complaints, are known to be widespread in sectors where women predominate (Brotheridge and Grandey, 2002; Hochschild, 2003; Johnson et al., 2005; Stansfeld et al., 2011; Swedish Work Environment Authority, 2016; Wieclaw et al., 2006). Similar differences exist in relation to other work environment exposures as well. For example, work control, which is one of the most thoroughly investigated dimensions of the psychosocial work environment and an important predictor of stress and health, has repeatedly been reported to be higher among men (Hall, 1989; Matthews et al., 1998; Swedish Work Environment Authority, 2016; Swedish Work Environment Authority, 2018).

3

On transcending disciplinary divides

We must never confuse a part, however well we understand it, for the whole.
Anthony Walsh, 2009

As of today, it is widely recognized that social and biological factors operate in tandem to cause health/ill health, which underlines the importance of simultaneously attending to factors at different 'levels of influence' when aiming to improve our knowledge on health and illness across the lifespan. I, and others with me, argue that these developments are imperative if we are to transcend historical disciplinary divides, such as that between the medical and the social sciences. This chapter aims to discuss why interdisciplinary efforts are crucial in dementia research and, additionally, asks a pertinent question: 'So what if genes interact with the social environment – do we need this knowledge to bring about social and political changes (*if* that is what we are aiming for)'?

Entering the post-'nature vs. nurture' era

In a recently published anthology entitled *Social Neuroscience: Brain, Mind and Society* (2015), psychiatrist and co-editor Matcheri S. Keshavan rightfully note that the fields of neuroscience and social science 'were often in different silos over much of the twentieth century' (p. 29). In their introductory chapter, Keshavan, together with co-editors Russel K. Schutt (sociology) and Larry J. Seidman (psychology), go on to state that 'despite interdisciplinary consensus that humans are social animals', their three respective disciplines have 'taken markedly different stances toward the practical salience and the causal direction of the brain-mind-society link' (p. 2). In fact, they argue that many scholars have regrettably denied the existence of this link and/or rejected to investigate it altogether.

However, recent advances in research on, e.g., *epigenetics* (see above) and *neuroplasticity*[7] have offered the empirical support needed to finally put an end to the protracted 'nature vs. nurture' debate. In line with this, the present thesis assumes that dementia is an *emergent* phenomenon that cannot be reduced to the sum of its parts. Rather, it is considered the

[7] 'The ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections' (Cramer et al., 2011: 1592).

outcome of mechanisms operating at, and across, different levels of reality (e.g., the biological and the social). This means that theories, methods or concepts corresponding to each level are required if we are to better grasp the multifactorial nature of dementia. In other words, interdisciplinary efforts are key if we wish to circumvent the reductionist trap of seeking *a priori* explanations for phenomena based on mechanisms that exist on only one particular level of reality (Bhaskar and Danermark, 2006; Danermark, 2009). These aspirations, or the plea for more interdisciplinary dementia research, should not be confused with an attempt to provide an 'absolute truth' – rather it is about searching for a more holistic or inclusive understanding of a complex phenomenon. Likewise, it should be underlined that while interdisciplinary efforts are crucial in dementia research, 'any viable vision of an interdisciplinary system relies on the continued existence and vitality of disciplines' (Jacobs, 2017) – simply because fruitful knowledge exchanges *between* disciplines presuppose a solid, *intra*-disciplinary knowledge base.

So what?

So far in this chapter, and more or less implicitly throughout this thesis, I have argued that researching gene-environment interactions is tantamount to rejecting previous, more deterministic approaches to health, in general, and to dementia, in particular. However, this standpoint and scientific discoveries of interactions between the individual's social circumstances and her genome have by no means escaped criticism. In this current debate, it appears as if two main lines of critique can be distinguished.

First, voices of legitimate concern have been raised regarding the danger of an 'excessive focus on biological factors of any sort to explain differential social outcomes to the exclusion of structural and institutional sources of vulnerability' – a focus that advances in genetic medicine might endorse (Angel, 2011a; Angel, 2011b: 644). In this context, I would argue that sociologists, and social scientists in general, have important contributions to make, in particular by offering a theoretical apparatus that allows a nuancing of what constitutes 'the social', for example, by drawing attention to the complexity of intertwined structural constraints/opportunities and by problematizing the often taken-for-granted socio-political categorizations used in much of the medical research (see, e.g., Fotaki, 2011; Freese, 2008; Shanahan and Hofer, 2005). Accordingly, it is crucial that social scientists not 'throw out the proverbial baby (genetics) with the bathwater (biological determinism)' (Fotaki, 2011: 641), but instead assist in debunking the social part of the gene-environment interaction and strive to delineate the mechanisms through which it gets under the skin (see, e.g., Fotaki, 2011; Shanahan and Hofer, 2005).

The second line of critique concerns, at its core, the alleged lack of policy relevance. For instance, and despite acknowledging that the identification of risk profiles including biomarkers for specific diseases might indeed be fruitful, Angel (2011a: 634) noted that it is currently unclear how 'genetics can inform social policy'. With reference to a widely

cited paper targeting the potentially moderating effect of genotype on sensitivity to childhood maltreatment (Caspi et al., 2002), he stated:

> [K]nowing that certain children are at elevated risk of developing antisocial behavioral traits if they are abused provides little useful policy-relevant information. Child abuse should be socially condemned, outlawed, and punished regardless of the genetic vulnerability of the victim (Angel, 2011a: 634).

In a similar vein, and with reference to Lundborg and Stenberg (2009), who discuss how recent discoveries of gene-environment interactions could be an impetus for more egalitarian social policies, Angel (2011: 634a) objected by stating, 'certainly, one would never advocate that resilient children who can be identified through genetic testing should be abandoned to poverty'. At the core of Angel's objections, we find an admittedly reasonable question, i.e., whether the detection of such interactions is really necessary to motivate political changes intended to, e.g., reduce poverty or outlaw child abuse, particularly as many (albeit not necessarily all) would agree that these are 'bad things' and given that there is already vast empirical evidence to support policies aimed at their elimination.

To some extent, this makes sense. However, I would argue that Angel's general claim comes up short in primarily three respects. First, it should be stressed that scientific freedom and basic research driven by a desire to understand the world around us is key to progressive knowledge developments and to enable unforeseen, yet potentially indispensable, scientific discoveries (remember penicillin, right?). Consequently, although I disagree with the aforementioned line of critique, research in general must never be deemed irrelevant merely because it is not considered immediately 'useful' to policy-making. Second, returning to the example of child abuse, it is of course true that it should be condemned 'regardless of the genetic vulnerability of the victim'. Nevertheless, in its present form, Angel's argument rests primarily on moral grounds and, more importantly, appears to assume that moral principles are universal. One could, however, easily imagine a situation where a certain phenomenon would be considered immoral and unethical by some, yet morally defensible or even desirable by others. Take social inequality for example. As noted by Olin Wright (2005a: 186), some would argue that class differences are not 'morally objectionable so long as individuals have equal opportunity for achieving [status and material] rewards', while others would deem them unjust and detrimental to societies at large. Finally, the question of alleged policy irrelevance remains: Given the vast body of empirical findings supporting the fact that inequity has adverse effects on health, do social scientists really need genetics to promote, for instance, the advocacy of more egalitarian social policies (Angel, 2011a; Angel, 2011b)? My answer would be yes, and no. One could argue that previous research on health inequities should be sufficient impetus for policies aimed at their reduction. Indeed, such policies do exist, yet large-scale health inequity still persists. In part, this might be attributable to the fact that the magnitude of the impact of inequity on health remains to be fully explored, particularly in relation to past and recent discoveries across different disciplines. For example, if social

(dis)advantage can actually moderate genetic endowments, new possibilities are actualized of reducing the occurrence of diseases, such as dementia, that (1) entail both individual suffering and huge social costs and (2) have previously been considered largely dependent on individuals' genetic make-up.

At its core, the argument put forth in this chapter is fairly straightforward: By rejecting simplistic and deterministic explanations, may they be sociological, biological or something else, the impact of any claim is likely to be improved as its scope expands. Hence, if we seek to effectively tackle complex and urgent global challenges, such as climate change, inequity or the aftermaths of an ageing population, scholars from different disciplines need to 'join forces' (see, e.g., Bhaskar, 2010), and as stated in the introductory quote, never confuse a part for the whole.

4
Data and methods

Data and participants

The data used in the present thesis are derived from the longitudinal *Gothenburg H70 Birth Cohort Study (H70)* and the *Prospective Populations Study on Women (PPSW)* that were initiated in Gothenburg, Sweden in 1971 and 1968, respectively. Since then, these studies have longitudinally examined representative birth cohorts of older adults living in Gothenburg (Karlsson et al., 2009), with the overarching aim to 'examine the impact of mental, somatic and social health on the functional ability and well-being of individuals aged 70 years and above' (Rydberg Sterner et al., 2018: 2).

All participants in the H70/PPSW studies were sampled from the Swedish population register and systematically selected on the basis of birth dates. Both people living in private households and in residential care were included. As illustrated below (Figure 2), the PPSW was initiated in 1968 and included 1,467 women. In 1980 and 1992, more women were recruited, and 1,032 women were still alive on September 1, 2000. During that same year, a new cohort of 70-year-olds (born in 1930) was sampled to the H70 study (n = 540), meaning that the total number of potential study participants living in Sweden on September 1, 2000, was 1,572. Of these, 50 died before they could be examined, 21 had emigrated and six were non-Swedish speaking, leaving a total of 1,495 eligible participants. Among the women who had previously been part of the PPSW, the total number of eligible study participants was 964, and 691 individuals agreed to partake in a new psychiatric follow-up examination (response rate 71.7%). With regard to the newly recruited men and women, 531 individuals were eligible for examination, and 328 (99 men and 229 women, response rate 61.8%) agreed to participate (Karlsson et al., 2009). In comparison to individuals who declined to participate in the study, participants were more often women and more likely to survive to November 2003. Likewise, they were less likely to be registered with a psychiatric diagnosis or stroke. In contrast, no significant differences between participants and non-participants regarding birth year, age or hospital discharge diagnoses of dementia were observed. For a more detailed description of these analyses, see Karlsson et al. (2009). The baseline sample (N = 1,019) was re-examined in 2005 and in 2009.

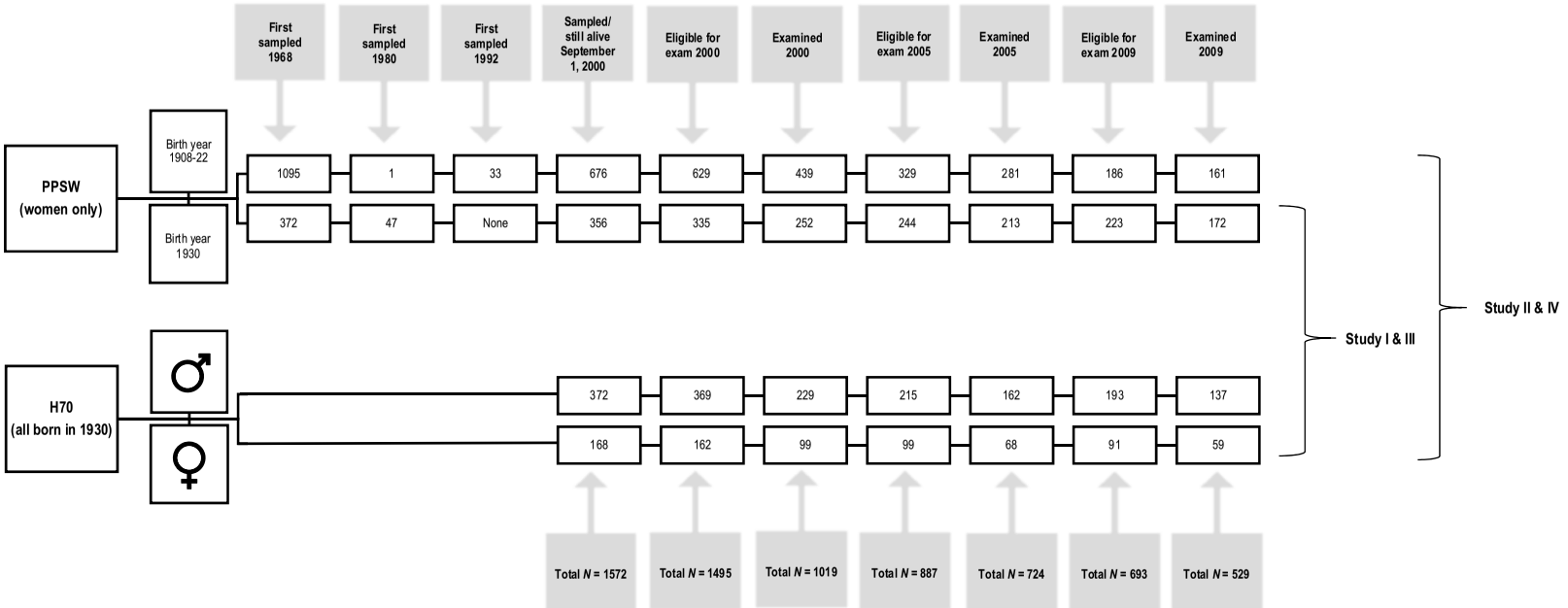

Figure 2. *Overview of data and sampling*

In 2005, 887 individuals were eligible for examination (i.e., still alive and living in Sweden, could be reached and had no language difficulties), and 724 of them agreed to participate in the follow-up (response rate 81.6%). In 2009, 693 individuals were eligible for examination, and 529 agreed to participate (response rate 76.3%).

Examinations

In line with the multidisciplinary approach of H70/PPSW studies, special efforts were made to enable the examination of interactions between factors on different levels of influence, e.g., the societal, the psychological and the biological, on individual health and well-being. Thus, at each study wave, participants underwent a comprehensive examination comprising psychiatric, cognitive and physical investigations, sampling of blood and cerebrospinal fluid as well as computed tomography and magnetic resonance imaging of the brain. The examination further included interviews concerning, e.g., the participant's social relations, general health and functional ability (Rydberg Sterner et al., 2018). Below, the neuropsychiatric examination is described in more detail.

Neuropsychiatric examination

At each study wave, participants went through a semi-structured neuropsychiatric examination, performed by a trained psychiatric research nurse. The examination was conducted at an outpatient department or in the participant's home. It included ratings of common symptoms and signs of dementia (e.g., assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs, following commands, naming ability and language). For a more detailed description of these procedures, see Guo et al. (2007) and Skoog et al. (1993). In addition, semi-structured interviews with a close informant were performed and comprised questions regarding changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living, and, in cases of dementia, age of onset and disease course (Karlsson et al., 2009; Skoog et al., 2015).

Dementia diagnosis

Dementia was diagnosed by geriatric psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised (DSM-III-R) (APA, 1987). The diagnoses were based on symptoms rated during the neuropsychiatric examinations as well as on information from the close informant interviews, as previously described elsewhere (Guo et al., 2007; Skoog et al., 1993). For individuals lost to follow-up, incident dementia cases (until 2012) were diagnosed on the basis of information from medical records, evaluated by geriatric psychiatrists, or from the Swedish Hospital Discharge Register (Guo et al., 2007). Age at onset was determined based on information from the hospital discharge register and the examinations, as well as on information provided by

close informants. If unavailable from any of these sources, age at onset was defined as the midpoint between the last examination without a dementia diagnosis and the first with such a diagnosis (Najar et al., 2019).

Genotyping

The SNPs (single nucleotide polymorphisms) rs7412 and rs429358 in *APOE* (gene map locus 19q13.2) were genotyped using the KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK) or by mini-sequencing, as previously described in detail (Blennow et al., 2000). Genotype data for these two SNPs were used to define ε2, ε3, and ε4 alleles. Because the ε4 is the only allele associated with an *increased* risk of dementia/AD, all analyses focused solely on this variant.

Operationalization of main independent variables

Socio-economic status

In the present thesis, two measures are used to indicate SES: occupational class and education. Information on lifetime principal occupation was obtained through the interviews at baseline and/or in conjunction with the follow-up examinations. Women who stated that they had primarily engaged in domestic work during working age were excluded. The responses were coded in accordance with the Swedish standards for Socio-economic Classification (SEI) (Statistics Sweden, 1982). Based on the initial classifications, three aggregated occupational groups were specified: (1) *Blue collar*, which corresponds to manual workers (un-skilled, semi-skilled and skilled), (2) *Lower white collar*, which includes assistant, non-manual employees, with or without subordinates, in occupations that normally require two, but not three years of post-comprehensive schooling, and (3) *white collar and self-employed*, which corresponds to intermediate/higher non-manual workers and professionals in occupations that require three, but not six, years of post-comprehensive education, as well as upper-level executives, self-employed and farmers[8]. With regard to education, respondents were asked to specify their level/type of educational attainment at baseline. For those who did not, information was, if available, obtained from the follow-up examinations. Based on these responses, three educational categories were specified: (1) *Primary*, which corresponds to elementary school/vocational school, (2) *Lower secondary*, which refers to girls' school (preparatory, vocational or theoretical education for girls constituting a continuation of elementary school)/junior secondary school or folk high school, and (3) *Secondary/university*, which corresponds to high school/university.

[8] For a more detailed discussion of potential limitations associated with these categorisations, see p. 33-34.

Work environment exposures

In order to estimate participants' exposure to different work environment exposures, we used the validated Job Exposure Matrix (JEM) (Johnson et al., 1990; Johnson and Stewart, 1993). The data on which the JEM is based were originally sampled through the annual Swedish Survey of Living Conditions in 1977 and 1979. By using factor analyses to combine sets of questions pertaining to work environment, Johnson et al. (1990) identified five work exposure factors: *work control, support, psychological demands, physical demands* and *job hazards*. The original dataset was subsequently used to create mean occupational estimates for each factor. Accordingly, a wide range of occupations were assigned scores corresponding to each of the five factors. The scores range from 0 to 10, and higher scores indicate higher levels of exposure. Given substantial gender differences in terms of work content, the matrix includes separate scales for men and women (Johnson et al., 1990), which, in practice, implies that a man and a woman holding the same occupation would be assigned different JEM scores. By manually combining these JEM scores with data on respondents' life time principal occupation obtained from the H70/PPSW examinations, we were able to estimate their exposure to each of the five work environment characteristics. Even though the JEM is stratified according to duration of time spent in the occupation as well as age at the time the occupation was held, it also includes combined scores for each occupation (all duration, all ages). These were used in the present study for reasons related to data availability.

Social networks

For reasons related to data availability, we were not able to study social capital, which would have been desirable considering its relation to social class and the many ways in which it can influence health (see Chapter 2). Instead, Study III focuses on individual social networks, which is one component of the broader notion of social capital (Rostila, 2011). During the baseline examination, participants were asked to answer a range of questions concerning their social networks. Inspired in part by the convoy model of social relations (Fiori et al., 2007; Kahn and Antonucci, 1980), which underlines their multidimensionality by identifying three key aspects of individual networks (structure, function and subjective evaluations of quality), seven of these questions were included in the analysis. Unfortunately, the available data did not include questions related to the functions of social networks (specifically support and reciprocity), which means that the variables used only concern network structure and/or quality. By combining these variables through factor analysis, two latent variables were retained and used in the succeeding analyses: *close social networks* and *distant social networks*. The former was constructed from the following two survey questions: (1): 'Do you have an intimate person with whom you can talk about anything?' and (2) 'Do you have more than one intimate person?' The latter was constructed from the following five questions: (1) 'Do you and your neighbours visit each other to say hello?', (2) 'Do you stop and talk with your neighbours when you meet?', (3) 'Do you think you have enough contact with your

neighbours?', (4) 'Do you think you have enough contact with people other than your children or neighbours?', (5) 'Do you receive visits from or visit people other than your children or neighbours?'.

Psychological distress

General psychological distress was indicated by a latent variable constructed from the covariance between seven manifest items (all measured at baseline). The first, *Previous depression*, is self-reported and indicates whether or not an individual had suffered from depression prior to the baseline examination. The second item, *Have experienced one or more period(s) of stress in life,* was constructed from the following survey question: 'Have you experienced any period of stress (one month or longer) in relation to circumstances in everyday life, such as work, health or family situation? By stress we mean feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances'. The third and fourth indicator, *Satisfaction with social situation* and *Self-esteem*, was obtained from a battery of questions in one of the baseline questionnaires where participants were asked to rate their satisfaction in relation to different life domains on a seven-point scale ranging from 'very good, could not be better' to 'very bad'. The fifth and final indicator, *Longstanding feelings of loneliness*, was based on the following question: 'Do you feel lonely?'. The respondents could also specify for how long they had been feeling lonely.

Statistical methods

The empirical studies utilized a range of different statistical methods and the analyses were mainly conducted in STATA (versions 14 and 15). R and MPlus (version 8) were also used for specific purposes in Study I and IV, respectively. Below, I provide a brief summary of the specific techniques used in each paper.

In **Study I and III**, Cox proportional hazards regression was employed, which can be grouped under the umbrella term survival analysis. The common denominator for these modelling techniques is that they are focused on 'whether and when an event takes place' (Guo, 2010: 3). An advantage of Cox regression (and survival analysis in general) compared to ordinary regression techniques is that it accommodates right-censored cases, which means that it accounts for the fact that individuals who never suffer the event of interest still contribute survival time (Flynn, 2012; Guo, 2010). This was considered advantageous given the relatively small sample size and few dementia cases. As in all survival analysis, the dependent variable is survival time, and in the present studies, it measured years-at-risk for dementia starting from age 65. Consequently, and because differences in age of diagnosis exist between cohorts in the full baseline sample, these studies only utilize data from individuals born in 1930 (Figure 2). The values of the beta-coefficients are estimated through Partial Likelihood Estimation (Allison, 2014; Box-Steffensmeier and Jones, 2004), which depends only on the order, not the exact time, in

which events occurs. Hazard ratios, which is a relative measure indicating the difference in hazard rates between (e.g.) two groups, and/or predicted survival times, were reported.

In **Study II**, the main outcome variable was dichotomous (indicating whether an individual had been diagnosed with dementia prior to, or during, year 2012). The analyses were thus based on data from the full baseline sample (Figure 2). Further, binary logistic regression was used, which is advantageous in the sense that it does not assume a linear relationship between the outcome variable and the predictors (Long and Freese, 2006). Odds ratios, representing 'the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure' (Szumilas, 2010: 227), were reported.

In **Study III**, seven variables were combined through exploratory factor analysis in order to enable a better conceptual understanding of relationships among potential indicators of individual social networks. In line with this, the retained factors should thus be considered 'unobservable latent variables that influence more than one measured variable in a battery and are [thus] presumed to account for the correlations (covariances) among the measured variables' (Fabrigar et al., 1999: 275).

Studies I-III all set out to explore *moderation*, i.e., whether the effect of *APOE* ε4 could be altered by externally imposed factors. This was done by including multiplicative gene*environment interaction terms in the multivariate models. While this technique is advantageous in the sense that it enables us to estimate the extent to which the effect of *APOE* ε4 is dependent on some other factor, including categorical by categorical interactions makes interpretation more complicated. In part, this depends on the fact that there is no longer a single reference category or base level (as is the case when a regular dummy variable is included). For example, and considering the interaction term SES**APOE* ε4, all combinations including the reference category for any of these predictors are treated as base (StataCorp, 2013). Further, multiplicative interaction models differ from linear-additive regression models because the coefficient of any constitutive term X cannot be interpreted as an unconditional marginal effect. Instead, when an interaction term X*Z is included, the beta coefficient of this term indicates only the effect of a one-unit change in X on Y when the conditioning variable (Z) is zero (Brambor et al., 2006). Taken together, the specific features of the interaction models described above imply that it is not possible to draw any substantial conclusions based solely on the estimates from the traditional results table. Thus, in Paper I-III, post hoc computations were performed on all interaction models in order to predict and compare the effect of *APOE* ε4 at different levels of the moderating variable in question.

In **Study IV**, data from the full baseline sample (Figure 2) were used. Confirmatory factor analysis (CFA) was used to identify a latent construct in the data, and structural equation modelling was employed to study mediation, i.e., the hypothesized relationships between female sex, educational attainment, psychological distress and dementia (see, e.g., Byrne, 2013). One key advantage of the latent variable approach, compared to using e.g. an additive index, is that latent variables comprise *only* the covariance between the manifest indicators. All residual variances are estimated separately, which means that

latent constructs are, in a sense, 'error free' (see, e.g., Halleröd and Seldén, 2013). Moreover, the residuals can be incorporated into the model. Given the specific features of the observed indicator variables, the weighted least squares means and variance adjusted (WLSMV) estimator was used in all analyses (Beauducel and Herzberg, 2006; Brown, 2015). Because the WLSMV estimator is computationally limited in handling missingness that has not occurred completely at random, missing values were imputed using Bayesian analysis (Asparouhov and Muthén, 2010a; Asparouhov and Muthén, 2010b)

Methodological strengths and limitations

Below, I review some of the main methodological strengths and limitations of the thesis. Some of these apply to all of the studies and some of them are unique to one or more studies. However, before going into the more specific strengths and limitations, I would like to highlight a principal strength of the thesis, which is the prospective population design of the H70/PPSW studies, the richness and amount of data collected, and the extensive neuropsychiatric examinations through which dementia was diagnosed.

Sample size

Despite the richness of the data collected, the sample size, and particularly the number of dementia cases, is relatively small in all four studies (not least among males). Because of the small number of dementia cases and/or lack of information, we did not distinguish between dementia subtypes in any of the four studies. This is a significant limitation, as *APOE* ε4 is foremost considered a risk factor for AD. For other dementia subtypes, associations are less well-established, even though some studies have suggested that the ε4 allele could also be associated with, e.g., VaD (Liu et al. 2012; Rohn, 2014) and DLB (Keogh et al., 2016). AD is, however, the most common subtype, and recent findings have demonstrated that many people with dementia have brain abnormalities that can be attributed to more than one cause – implying that mixed pathologies might in fact be more common than 'pure' ones (Attems and Jellinger, 2013; James et al., 2016; Jellinger, 2007; Kapasi et al., 2017; Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 2001; Schneider et al., 2007; Schneider et al., 2009). Nevertheless, the limitations related to sample size imply that the results must be interpreted with caution and, additionally, underline the continuing need for large longitudinal studies with long(er) follow-ups.

Reverse causality

Reverse causality is a significant issue when studying factors that could be both risk factors for, and/or pre-diagnostic signs of, dementia, such as social isolation or depression. This issue is primarily relevant to Study III and IV. In both cases, we attempted to reduce the possibility of such bias by excluding individuals who were diagnosed with dementia at

baseline or prior to the baseline examination. Additionally, in Study IV, we excluded individuals who had been diagnosed during the first year after baseline and/or or had a baseline Mini Mental State Examination (MMSE) score of less than 24 (see, e.g., Karp et al., 2006; Stephan et al., 2013; Wang et al., 2002). Another strength in the latter study is that the issue of reverse causality was addressed more explicitly through sequential exclusion of dementia cases and repetition of the analyses at different time points.

Selection bias

Selection bias occurs when 'individuals with certain characteristics are underrepresented in the sample' studied (Kelfve, 2017: 8). Generally speaking, such underrepresentation, resulting either from sample exclusion or nonresponse, is known to be correlated with both age, health, functional ability, SES and sex (see, e.g., Hardy et al., 2009; Kelfve et al., 2013). Studying health outcomes, specifically with a focus on health inequity, in older populations thus entails a range of specific challenges. As described in more detail above, a substantial issue in studies targeting health inequity in older cohorts is *non-random mortality selection* (sometimes referred to as *cohort inversion*) (Dupre, 2007; Dupre, 2008; Noymer, 2001; Shuey and Willson, 2008; Willson et al., 2007). It occurs as a result of higher mortality rates in young ages among the less affluent and/or those with poorer health. Consequently, individuals who survive until old age are generally healthier than those who do not, which may result in a systematic underestimation of the association between SES and health as the cohort ages (Dupre, 2007; Dupre, 2008; Kelfve, 2017). Therefore, longitudinal study designs that incorporate time, such as those in Paper I and III, are often preferable to cross-sectional ones. Finally, and in relation to the issues of sample exclusion and non-response, it is worth underlining that one advantage of H70/PPSW studies is the inclusion of individuals living in institutions as well as the use of proxy interviews (referred to above as 'close informant interviews') (see, e.g., Kelfve, 2017).

Misclassification

In relation to the present studies, some specific issues relating to misclassification must be addressed. Misclassification refers to 'when sensitivity and/or specificity of the procedure to detect exposure and/or effect is not perfect' (Delgado-Rodriguez and Llorca, 2004: 638).

Socio-economic status

Information on principal lifetime occupation, as well as level of educational attainment, was self-reported and collected retrospectively, which is a possible source of recall bias (Last et al., 2001). In relation to occupational class, another potential issue is the use of the Swedish standards for Socio-Economic Classification (SEI). These classifications are currently considered somewhat 'outdated' because of changes in the educational system as well as in the amount of schooling required for different occupations that have taken place during recent decades. This was, however, considered relatively un-problematic, and

even a possible advantage, considering when the majority of study participants (born in 1930) were active in the labour market. However, somewhat more problematic is the relatively crude classification of socio-economic groups in which only three groups were specified (see above). For example, the third group, *white-collar and self-employed*, not only includes intermediate/higher non-manual workers, professionals and upper-level executives, but also self-employed individuals and farmers. First and foremost, this merging of occupational categories was motivated by the small sample size and, by extension, group size. While it does constitute a potential threat to the validity of this measure, it should be underlined that the number of self-employed individuals was small (2.6%, $N = 22$) and the number of farmers even smaller (0.1%, $N = 1$). Another plausible issue related to the operationalization of SES concerns the use of individual, rather than household, measures. Because men, particularly in previous generations, were usually more strongly attached to the labour market than women were, it is possible that household class would have been a more efficient, or at least complementary, measure to asses SES in the present studies (see, e.g., Erikson, 1984; Erikson and Goldthorpe, 1992b; Hellevik, 1988). Unfortunately, however, respondents in the H70/PPSW studies were not asked about the occupational history of their spouse.

Work environment exposures

The job exposure matrix that was used to assess individuals' exposure to different work environment factors (Study II) offers relatively 'crude' measurements in the sense that it only provides aggregate estimates (occupational means). This is a potential weakness, as subjective experiences of one's work environment might, depending on the exposure in question, be equally or even more important to health than actual working conditions. On the other hand, the use of occupational averages is potentially advantageous in the sense that estimates are not affected by individual differences in, e.g., personality and general well-being. Moreover, and even though the JEM is stratified according to length of time spent in the occupation as well as age at the time the occupation was held, we used the combined score for reasons related to data availability (see above). In relation to exposure duration, it should be noted that even though women who stated that they had primarily been engaged in domestic work during working ages were excluded from the analyses, women who did work may still have spent longer periods than men outside the labour market.

Social networks and psychological distress

The operationalization of measures and the quality of the factor indicators used in Study III and IV must also be acknowledged. With regard to the former, a potential source of non-validity is the difficulty of delineating the extent to which individuals' assessment of their social relations at one specific time point provides a 'general' description of their social networks throughout life, particularly given the changes in social relations that ageing might entail. By the same token, it should be stressed that all indicators of

psychological distress used in Study IV were self-reported, which means that the information on, e.g., previous depression was not based on clinical data. This is a possible source of systematic misclassification, *inter alia*, in the sense than women might be more prone to reporting mental ill health or symptoms thereof (Piccinelli and Wilkinson, 2000).

Confounding bias

A confounder can be defined as 'a variable related to two factors of interest that falsely obscures or accentuates the relationship between them' (MacKinnon et al., 2000: 174). Just like in all of the present studies, this is usually dealt with through the inclusion of confounding variables (or controls). In the present thesis, a number of lifestyle-related risk factors for dementia, e.g., physical inactivity, obesity, smoking, diabetes and hypertension (Livingston et al., 2017), were not added as controls in the statistical models. The reason for this is twofold. First and foremost, all of these factors follow social gradients, i.e., they are largely determined by individuals' SES (see, e.g., Brunner et al., 1997; Marmot and Bell, 2012). By extension, this means that by controlling for such 'proximate' risk factors, researchers run the risk of underestimating or obscuring the impact of SES on health (see, e.g., Link and Phelan, 1995; Phelan et al., 2004). With that said, excluding them implies, naturally, that it is not possible to obtain any estimates of their *relative impact* as potential mediators. Yet this was not within the scope of any of the studies. Second, Study I-III set out to explicitly examine interaction effects. Thus, adding further controls would have complicated the interpretation of these potential effects considerably (see above).

Ethical considerations

The extensive examinations that participants in the H70/PPSW studies undergo raises a number of ethical concerns. First, participants are asked to respond to a range of potentially sensitive questions concerning, e.g., psychiatric symptoms and sexuality. Second, they are asked to donate blood for genetic analyses and the studies entail reviews of medical records. Third, participants' intellectual function is tested and information regarding their psychiatric functional capacity is obtained from a proxy informant, i.e., from someone other than the respondents themselves. While the examinations as such do not involve any medical risks, all of these procedures could be perceived as an infringement of personal integrity. By extension, this makes information about freedom to participate, as well as about the right to terminate participation, imperative. This information, as well as information about the purpose of the study, was provided in written form. Subsequently, informed consent, also in written form, was attained from all participants. In cases of severe cognitive impairment, proxy consent was obtained from a next-of-kin (see Swedish Reserach Council, 2017; World Medical Association, 2013). Of equal importance in this context is anonymity and confidentiality (ibid.). Consequently, it should be noted that those who work with the studies must observe professional secrecy

and that collected data are stored at Sahlgrenska University hospital in accordance with permission from The Swedish Data Protection Authority. Thus, the data cannot, and must not, be accessed by unauthorized individuals and are only used for research purposes. Moreover, all analyses are conducted using anonymized data and only group-level results are reported. All blood samples are stored in a biobank and handled in accordance with *Lag om biobanker i hälso- och sjukvården m.m* [Law on biobanks in the health care sector] (SFS 2002:297). Thus, they are anonymized and can only be used for purposes for which participants have given their consent. Another key aspect of counteracting experiences of privacy infringement is sensitivity and responsiveness on the part of the interviewers. In relation to this, it should be underlined that all examinations were carried out by trained research nurses. Upon detection of disease, or risk factors for disease, that required further investigation or treatment, participants were offered additional help. Furthermore, being close, or related, to someone with dementia is often perceived as both difficult and stressful. However, the close informant interviews offer relatives an opportunity to discuss these difficulties with an expert who, in turn, has the ability to provide further advice and information. Finally, it should be stressed that all H70/PPSW examination waves were approved by the regional Ethical Review Board for medical research in Gothenburg, Sweden: 2000 (ref: Ö402-99), 2004 (ref: T453 04), 2009 (ref: 075-09).

5
Summary of findings

In this chapter, I review the main findings of the present thesis by providing brief summaries of the four empirical studies upon which it is based. More specifically, the studies relate to the main research questions (see Chapter 1) of the thesis, and build upon each other, as follows: Study I lays the foundation upon which the other studies rest. It does so by asking whether SES could in fact moderate the increased risk of dementia that carrying one or more copies of the *APOE* ε4 allele implies. It also addresses the question of whether such possible moderations follow a similar pattern among men and women. Having identified that high SES seems to buffer the effect of *APOE* ε4 among men but not among women, Study II and III set out to explore two mechanisms that could possibly shed further light on the link between socio-economic (dis)advantage and dementia risk, as well as on the previously identified sex differences: work environment exposures and social networks. Further, both of these studies investigate the possibility of gene-mechanism interactions. Finally, Study IV tests the assumption that the well-established sex difference in lifetime risk of dementia could partly be the result of differences in educational attainment and/or in experiences of *general psychological distress,* rather than simply a consequence of women's longer life expectancy.

Study I

Hasselgren C., Ekbrand H., Fässberg M.M., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). *APOE* ε4 and the long arm of social inequity: Estimated effects of socio-economic status and sex on the timing of dementia onset. *Ageing & Society,* 39(9): 1951-1975.

The risk of developing dementia is unevenly distributed in the population. Individuals with low SES are at greater risk of developing different forms of this disease, and low SES has also been suggested to disproportionally affect women, especially among the oldest old. Furthermore, individuals carrying the *APOE* ε4 allele are known to run a three- to fifteenfold risk of developing dementia. Nevertheless, studies of whether, and how, social inequities interact with individual genetic endowments in the development of dementia are still scarce. Thus, we examined: 1) whether SES (here indicated by education and occupational class) could moderate the effect of *APOE* ε4 allele and 2) the extent to which

such socio-economic moderations differed between men and women. The analyses were based on a sample of 580 individuals from the H70/PPSW studies, and data were analysed using Cox proportional hazards regression.

In general, the results suggest that there is an interaction effect between SES and *APOE* ε4 in relation to dementia onset, at least among men. More specifically, they indicate that susceptibility to dementia among male *APOE* ε4 carriers is dependent on SES, as indicated by the fact that it was only detectable among individuals with a primary-level education and/or in blue-collar occupations. In contrast, among women, the difference in effect between carriers/non-carriers was not as clearly related to SES. Women who had been employed in white-collar occupations, and who did not carry the *APOE* ε4 allele, generally developed dementia later in life compared to blue-collar workers and ε4 carriers. However, among women who carried the allele, the time to disease onset in the white-collar groups was on a par with that of women in blue-collar occupations.

Two potential explanations for the differing results among men and women were identified. First, and particularly for a cohort born in 1930, large systematic differences existed in men's and women's labour market/educational trajectories. Consequently, women's own occupational class or educational level might not necessarily capture their 'actual' SES, implying that commonly used socio-economic indicators could be less well suited to studying such differences in older women's health. Second, it is likely that the advantages accompanying certain socio-economic positions were greater for men than they were for women. For example, while many potential dementia risk factors are generally more common among blue-collar workers than among white-collar workers, they are also more common among women than among men *within* practically all SES groups.

Study II

Hasselgren C., Dellve L., Ekbrand H., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). Socioeconomic status, gender and dementia: The influence of work environment exposures and their interactions with *APOE* ε4. *Social Science & Medicine (SSM) Population Health,* 5: 171-179.

Most individuals spend a vast amount of time at work throughout life, and given the considerable SES and sex differences in work environment exposures, we hypothesized that the social gradient in dementia could, at least partly, be attributed to differences in work environment. Consequently, we explored the relationships between dementia and five work exposure characteristics (work control, support, psychological demands, physical demands and job hazards), all of which are known to be unevenly distributed between different socio-economic groups, as well as between men and women. Specifically, we examined whether any of these exposures could moderate the impact of the *APOE* ε4 allele, and whether sex differences existed in this respect. The empirical analyses were based on data from the H70/PPSW studies (*N*=1019), in which all

participants were asked to specify their main occupation in free text. Subsequently, these data were linked to the validated Job Exposure Matrix (JEM). All multivariate analyses were conducted using binary logistic regression and focused specifically on gene-work exposure interactions.

The results suggest that holding a high-control profession is potentially protective for men, but not for women. For instance, among males, the effect of *APOE* ε4 was only significant at lower levels of control, which implies that male carriers could be 'protected' by previous abilities to exert control over their work situation. The pattern observed among women was directly the opposite, i.e., the effect of *APOE* ε4 was only significant at higher levels of control. In both cases, these results remained significant when controlling for both occupational class and education.

Considering some of the potential pathological pathways between work exposures and dementia, it appears reasonable that work control stands out (among men) as a protective factor. In fact, previous studies have repeatedly linked work control to other known dementia risk/protective factors (e.g., stress and skill discretion). With reference to the results obtained among women, it should be noted that, in the present sample, human service workers make up a large proportion of the women in the 'high control' group. However, reportedly important stressors in these professions, such as emotional demands, are not included in the JEM. It is thus possible that although these women were exposed to certain favourable conditions in the labour market, they were also exposed to unmeasured, adverse ones. Further, it is reasonable to assume that women in this generation, even those who worked full-time in professional occupations, were expected to shoulder the main responsibility for domestic chores. Ultimately, this may have resulted in a greater total workload and thereby in elevated stress levels.

Study III

Wu J, Hasselgren C., Zettergren A., Zetterberg H., Blennow K., Skoog I., & Halleröd B. (2018). The impact of social networks and *APOE* ε4 on dementia among older adults: Tests of possible interactions. *Aging & Mental Health.* Advance online publication, https://doi.org/10.1080/13607863.2018.1531368

As of today, social isolation is considered an influential dementia risk factor. Yet, studies that jointly examine the influence of the *APOE* e4 allele and social networks, as well as potential interactions between these, are few and their results somewhat inconclusive. Moreover, social support seems to follow social gradients – in favour of, e.g., women and individuals occupying higher positions in the social hierarchy. Thus, in Study III, we examined whether social networks could moderate the adverse effect of the *APOE* e4 allele and, also, whether sex-specific patterns existed in this respect. We utilized data from a sample of 580 individuals obtained through the H70/PPSW studies. Exploratory factor analysis was performed to enable a better conceptual understanding of the relations

between different indicators of social networks. Subsequently, multivariate analyses were conducted using Cox proportional hazards regression. Following the factor analysis, two underlying factors were retained: 1) presence of a close social network and 2) presence of a distant social network.

Results from the multivariate analyses indicated that, in the total sample, the presence of a close social network could have an inverse effect on age of dementia onset, also when controlling for all covariates except education. However, when the sample was stratified by sex, a different image emerged. Among women, only the presence of a distant social network was estimated to postpone onset (also under control for covariates), whereas among men the significant associations between close social networks and dementia did not remain after controlling for covariates. However, no significant sex-network interactions could be confirmed, and no interactions between social networks and the *APOE* e4 allele were detected.

In line with earlier findings, our results generally confirmed the importance of social networks in postponing dementia onset. As previously suggested, these associations could possibly be attributed to, e.g., the fact that social support has a positive impact on individuals' emotional state by lowering stress levels, and thereby preventing cardiovascular risk. In addition, the results obtained indicate that the impact of having a social network on dementia risk may differ among men and women. Even though significant interaction effects between sex and social networks could not be corroborated, which means that the observed differences must be interpreted with caution, they correspond well with findings from other studies targeting sex differences in social relations. For example, despite the fact that women are known to have larger networks and more close friends than men do, women more often report feeling lonely and, additionally, appear to perceive loneliness as a more severe problem than men do.

Study IV

Hasselgren C., Ekbrand H., Halleröd B., Fässberg M.M., Zettergren A., Johansson L., Skoog I & Dellve L. (submitted manuscript). Sex differences in dementia: On the potentially mediating effects of educational attainment and experiences of psychological distress

Old-age dementias are known to disproportionally affect members of disadvantaged groups, such as women and individuals with low educational attainment. Because age is a major dementia risk factor, the higher lifetime risk among women has mainly been attributed to their longer life expectancy. However, considering historical inequities in terms of access to education between the sexes, as well as the sex and socio-economic gradients in many dementia risk factors, the impact of sex, and subsequent gender inequity, is likely to be more multifaceted than this explanation implies. Accordingly, we used confirmatory factor analysis and structural equation modelling to test whether

differences in educational attainment and experiences of *general psychological distress* could mediate the association between female sex and dementia. Data were obtained from the H70/PPSW studies (n=892).

While the results could not corroborate the notion that education directly mediates the effect of sex on dementia, level of distress was predicted both by female sex and by education and, in turn, shown to be significantly associated with dementia, even when controlling for confounders. However, when time from baseline to diagnosis was increased (by sequential exclusion of dementia cases), the effect of distress on dementia was no longer significant.

Overall, the findings of the fourth study suggest, in line with previous research, that social (dis)advantage, in this case indicated by female sex, predicts general psychological distress. Even though it cannot be concluded with certainty that distress mediates the effects of female sex on dementia (because reverse causality cannot be definitely ruled out at this point), this hypothesis was partly supported by the data. Consequently, while the need for longitudinal studies with longer follow-up must be underlined, the present study contributes to the current state of research by suggesting a rarely acknowledged pathway between dementia and one of its main structural determinants. As such, it also highlights the importance of studies promoting a more nuanced understanding of how and why social inequity influences dementia risk later in life.

6
Concluding remarks

The overarching aim of this thesis has been to further explain the occurrence of Alzheimer's disease and other dementias by studying the long-term impact of class- and gender-based inequities, as well as by exploring whether their related mechanisms could moderate genetic risk. Central to this endeavour has been the recognition of social inequity as multifaceted, and of potential intersections between different drivers of structural (dis)advantage. All four studies on which the thesis is based should be considered examples of an interdisciplinary effort to incorporate knowledge, theory and expertise from different fields so as to create a more holistic understanding of dementia aetiology. Considered jointly, the results underline that intersections between systems of structural inequity, such as that between class and gender, must be taken into consideration if we are to better understand the complexity of dementia disorders. Additionally, they suggest that genetic endowments can actually be moderated by externally imposed factors. In this chapter, I will discuss and further exemplify these results in relation to the four studies. Accordingly, I begin by returning to the two central themes around which this thesis revolves (see Chapter I), as well as their respective research questions. I discuss each of them in turn and conclude by synthesizing the main findings and considering some possible directions for future research.

Moderation of genetic risk in dementia – the potential influence of class and its associated mechanisms

Of central interest to the present thesis has been the question of whether externally imposed factors, such as class and its associated mechanisms, can moderate genetic risk in the development of dementia. This question originally draws on the observation that a vast number of studies have examined the impact of SES (in this context most often indicated by education) in relation to dementia risk, thereby establishing it as one of the major protective factors (see, e.g., de Bruijn et al., 2015; Livingston et al., 2017). Likewise, after decades of research, compelling evidence exists showing that the *APOE* ε4 allele substantially increases dementia risk (Livingston et al., 2017). Nevertheless, although studies examining whether these risk/protective factors can actually moderate each other do exist, they still remain scarce and results are inconclusive. Additionally, very few of the studies that specifically target such potential moderations of genetic risk have explicitly

examined whether there are gendered patterns in this respect. This is particularly noteworthy, I argue, considering the well-documented intersection between class and gender in relation to health and mortality.

The findings obtained through Study I indicate that high SES moderates, or 'buffers', the effect of *APOE* ε4 by postponing onset among male, but not female, carriers. By extension, this suggests that the disadvantages accumulated by men with low SES could potentially 'trigger' the genetic predisposition to dementia or, conversely, that the advantages accompanying high SES are likely to compensate for the increased genetic risk implied by *APOE* ε4. A similar sex difference in moderation patterns was observed in Study II, where we sought to shed further light on the complex relationship between SES and dementia by investigating the impact of range of work exposures as well as their possible interactions with genetic risk. In short, the findings suggest that work control is the most influential aspect of the work environment, with respect to moderation of genetic endowments. However, as described in the previous chapter, the observed moderation patterns were the direct opposite among men and women. In contrast, Study III, where we examined the impact of access to social networks, another well-established risk factor for dementia as well as a suggested pathway between class and health, did not reveal any significant gene-environment interactions. Nevertheless, the study suggests that there might be important differences between men and women in the impact of social networks on dementia risk.

To conclude, both Study I and II add to the current state of research by suggesting that SES, and related work exposures, could moderate genetic risk. While this does not qualify as a discovery of epigenetic changes (see p. 8), it should still be considered yet another important step away from biological determinism. Further, these findings underline that the health advantages of occupying certain socio-economic positions may be fewer among women than among men, not least in older cohorts. Thus, both these studies, as well as Study III, underline that risk/protective factors that are more proximate to the individual, such as work environment exposures, social networks or distress, must not be studied as if they were distinct from the underlying systems of structural (dis)advantage that 'put people at risk of risks' (Link and Phelan, 1995; Phelan et al., 2004). This theme will be further elaborated in the succeeding section, where I argue that class and sex/gender should be considered fundamental causes of dementia.

Intersecting systems of (dis)advantage in dementia risk

A central premise guiding all the work resulting in this thesis has been that the risk factors for dementia, or any other disease for that matter, must be studied in relation to the social structures that underlie differences in risk exposure. In line with this, I have repeatedly stressed that all social positions that are 'intimately linked to resources of money, knowledge, power, prestige, and beneficial social connections over time', such as class or sex/gender, should be considered *fundamental causes* of disease (Link and Phelan, 1995;

Phelan and Link, 2013: 113; Phelan et al., 2004). Further, and of equal importance, is the recognition of intersections between such drivers of inequity. In relation to this, I have also argued that the focus on risk factors more 'proximate' to the individual has been very influential in dementia research, at the expense of attempts to explore what unites these factors. More specifically, this means that few studies explicitly acknowledge the fact that most modifiable dementia risk factors are unevenly distributed in the population with respect to, e.g., class and sex/gender.

Both Study I and Study II indicate, as described in more detail above, that high SES as well as potentially mediating mechanisms between SES and dementia do not protect women to the same extent as they protect men. Considering that class and gender are known to intersect, in general, as well as in relation to health, this is not surprising. For instance, and regardless of SES, throughout history women have encountered norms prescribing that they should assume primarily responsibility for childcare and domestic chores. By extension, this is likely to reduce their labour force participation, which in turn has a range of potentially adverse effects on their health prospects, e.g., by limiting their job security and their access to economic resources, as well as by confining their opportunities for role enhancement (see, e.g., Blau and Kahn, 2017; Deere and Doss, 2006; Moen et al., 1995; Rozario et al., 2004; World Health Organization, 2016). By the same token, women who work full-time are, and have been, more likely to experience a greater *total* work load than men, because they usually spend more time on unpaid, domestic work. Ultimately, factors such as those described above are likely to contribute to the greater, and well-documented, burden of stress and mental ill health among women (Arber et al., 1985; Floderus et al., 2009; Griffin et al., 2002; Hall, 1992; Krantz et al., 2005). Accordingly, although these results should be interpreted with caution, Study IV proposes that psychological distress constitutes a potential, and hitherto rarely acknowledged, pathway between dementia and female sex, on the one hand, and dementia and low educational attainment, on the other. Additionally, the findings of this study confirm that education ought to be considered a 'gendered' dementia risk factor because of the vast, systematic inequities that have existed between men and women in terms of educational opportunities throughout history.

Taken together, these results support the idea that the higher lifetime risk of dementia observed among women is not, as previously thought, attributable primarily to differences in life expectancy (see, e.g., Mazure and Swendsen, 2016; Nebel et al., 2018; Rocca et al., 2014). Similarly, they suggest that the impact of education on dementia risk is likely to go beyond the positive brain changes usually associated with the cognitive *reserve hypothesis* (Stern, 2002; Stern, 2012), particularly because education is a strong predictor of individuals' future labour market position and thus of their economic prospects, their exposure to different working conditions, their access to social connections and their lifestyle-related behaviours (see, e.g., Bihagen, 2000; Bihagen and Halleröd, 2000; Link and Phelan, 1995; Phelan and Link, 2013; Phelan et al., 2004). Consequently, the results of the present thesis suggest that recognizing class and sex/gender as fundamental, and

intersecting, causes of dementia is of the outmost importance if we are to better understand why some individuals develop the disease, while others do not.

The 'so what?' question revisited

All four studies, together with the introductory parts of the thesis, answer some questions, while at the same time posing a range of new ones. Notwithstanding, they offer insights into a number of seldomly recognized intra-disciplinary 'blind-spots'. In relation to this, I would like to return to the 'so what?' question posed in Chapter III by arguing that the findings of the present studies demonstrate some potential insights that medical and social scientists alike could gain if they were to engage in interdisciplinary dementia research. First, in light of the results presented in this thesis, as well as elsewhere, it is evident that dementia is an emergent phenomenon that must not be reduced to the sum of its parts. Accordingly, overly simplistic and deterministic explanations that aspire to explain its diverse causes and consequences must be avoided. More specifically, the present findings provide a fairly concrete example of how 'household' sociological knowledge, such as there being an intersection between systems of structural (dis)advantage, can provide new and deepened insights in other fields of research. In turn, this underlines the fact that sociologists have important contributions to make in relation to other disciplines, such as medicine, by offering a theoretical apparatus that could promote a more nuanced view of 'the social' and thereby prevent oversimplifications of its complexity (see, e.g., Fotaki, 2011; Freese, 2008; Shanahan and Hofer, 2005). Likewise, it is clear that if such contributions are to be possible and gain influence in other fields, sociologists, and social scientists in general, are equally dependent on the 'household knowledge' of other disciplines, in my case medicine and genetics. While it should again be stressed that not all research *can* or *should* be interdisciplinary, it is, as argued in Chapter III, of key importance not to throw out the 'proverbial baby' (humility in the face of complexity) with the bathwater (disciplinary battles and differences).

Directions for further research

With regard to directions for further research, I would like to make three principal points. First, it is evident that more studies focused on the uneven distribution of risk are needed in relation to dementia. More specifically, further elaborations of class and sex/gender as fundamental causes of disease are necessary. For example, none of the studies in the present thesis have explored the unequal distribution of lifestyle-related risks and, thereby, the extent to which such factors could mediate the effect of class or sex/gender on dementia. Of equal importance is the exploration of other such structural determinants of risk exposure, such as ethnicity or sexual orientation. Second, in more general terms, I argue that it is key to adopt such more holistic approaches to risk, health and morbidity in relation to other diseases as well. For such efforts to be successful, it is, as noted above,

my belief that researchers from different disciplines must 'join forces'. Finally, as noted in Chapter II and IV, although the associations between class/gender and health have been subject to extensive scientific inquiry, more research targeting the issue of how this relationship varies over time is crucial. This is particularly pertinent if we are to promote a better understanding of potential bias resulting from, e.g., selective mortality, and thereby the extent to which researchers run the risk of underestimating the 'true' impact of inequity on health and morbidity.

Sammanfattning på svenska [Summary in Swedish]

Den demografiska strukturen i stora delar av världen, inklusive Sverige, genomgår just nu stora förändringar och andelen äldre (över 65 år) i befolkningen växer i en aldrig tidigare skådad takt. Detta innebär att alltfler individer kommer att utveckla en demenssjukdom under sin livstid, vilket i sin tur leder till ökat lidande för både drabbade och anhöriga såväl som till nya samhällsekonomiska utmaningar. Frågan om hur demens kan förebyggas är därmed av största vikt för alla åldrande samhällen.

Idag vet vi att de flesta demenssjukdomar är multifaktoriella och uppstår till följd av ett samspel mellan genetiska- och yttre (inklusive sociala) riskfaktorer. Vi vet dock betydligt mindre om hur olika riskfaktorer modifierar varandra – dvs. kan yttre, sociala faktorer skydda individer som till följd av sin genuppsättning löper större risk att drabbas? Vi vet också att många modifierbara riskfaktorer för demens, såsom exempelvis låg utbildning, depression och socialt utanförskap, uppvisar starka samband med både kön och/eller klass. Trots detta saknas kunskap och medvetenhet om hur olika former av strukturell ojämlikhet, enskilt såväl som i samverkan, påverkar risken att drabbas av demens. I föreliggande avhandling studeras uppkomsten av Alzheimers sjukdom och andra demenssjukdomar med särskilt fokus på de långsiktiga effekterna av klass- och könsbaserade ojämlikheter. Vidare undersöks huruvida ojämlikheten och dess relaterade mekanismer kan 'buffra' den genetiska risk som finns förknippad med genvarianten *APOE* (apolipoprotein E) ε4.

Avhandlingen omfattar fyra empiriska studier. Samtliga dessa bör betraktas som exempel på tvärvetenskapliga strävanden mot en mer holistisk förståelse för demenssjukdomarnas etiologi. Analyserna baseras på data från två svenska, longitudinella populationsstudier genomförda i Göteborg: H70-undersökningen och Kvinnoundersökningen.

Studie I lägger grunden för de tre nästkommande genom att undersöka huruvida socioekonomisk status (SES) kan modifiera den förhöjda risk att utveckla demens som genvarianten *APOE* ε4 medför. Resultaten indikerar att hög SES tycks 'buffra' effekten av *APOE* ε4 bland män, men att denna faktor inte har samma 'kompensatoriska förmåga' hos kvinnor. Baserat på dessa resultat, undersöker Studie II och Studie III två potentiella, mellanliggande mekanismer med syfte att fördjupa förståelsen för sambandet mellan SES och demens, såväl som för den tidigare observerade skillnaden mellan män och kvinnor: arbetsmiljöfaktorer samt tillgång till sociala nätverk. Resultaten indikerar att kontroll i arbetet är den mest betydelsefulla arbetsmiljöfaktorn, med avseende på modifiering av genetisk risk. Dock tycks kontroll endast fungera som en skyddande faktor bland män. De resultat som presenteras i Studie III tyder på att effekten av *APOE* ε4 inte kan modifieras av tillgång till olika typer av sociala nätverk. Däremot indikerar de att det kan

finnas viktiga könsskillnader vad gäller betydelsen av desamma för risken att utveckla demens. Slutligen undersöker Studie IV huruvida den högre livstidsrisken för demens bland kvinnor kan härledas till skillnader i (1) utbildning och (2) förekomst av psykisk ohälsa. För det första bekräftar resultaten av denna studie att utbildning bör betraktas som en 'könad' riskfaktor för demens. Vidare indikerar de att skillnader i förekomsten av psykisk ohälsa skulle kunna utgöra en möjlig, och sällan uppmärksammad, förklaring till varför kvinnor, såväl som personer med lägre utbildning, löper större risk att utveckla demens under sin livstid.

Sammantaget indikerar de resultat som presenteras i avhandlingen att modifierbara (sociala) faktorer faktiskt kan påverka, och reducera, effekten av den genetiska riskfaktorn *APOE* ε4. Likaså betonas vikten av att uppmärksamma hur sociala strukturer ger upphov till en ojämlik fördelning av risk på individnivå, såsom exempelvis låg utbildning, bristande arbetsmiljöförhållanden, socialt utanförskap eller psykisk ohälsa. I sin tur understryker detta betydelsen av att noga beakta den komplexitet som kännetecknar demenssjukdomarnas etiologi om vi bättre vill förstå varför vissa individer drabbas och andra inte. För att detta skall kunna vara möjligt behövs kunskap från, och samarbete mellan, olika discipliner.

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The word dementia originates from the Latin words de- [out of] and mens [mind]. It is the umbrella term for a range of chiefly age-related disorders that occur as a result of damage to, or destruction of, neurons in the brain. Dementia is a devastating condition that hitherto lacks effective prevention, treatment and cure. Thus, as longevity continues to increase in all regions of the world, it has become a public health issue of major concern to all ageing societies. The vast majority of dementia cases occur through a complex interplay between genetic susceptibility and environmental exposures. The present thesis seeks to further explain the occurrence of Alzheimer's disease and other dementias by studying the long-term impact of class- and gender-based inequities as well as the extent to which they potentially moderate genetic risk. The thesis encompasses four empirical studies based on data from Swedish prospective cohort studies - all of which should be considered examples of interdisciplinary efforts to incorporate theory and expertise from different fields in order to create a more holistic understanding of dementia aetiology.

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