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THE ROLE OF SLEEP AND SHIFT WORK IN DEMENTIA AND COGNITIVE AGING: AN EPIDEMIOLOGICAL APPROACH

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The role of sleep and shift work in dementia and cognitive aging: An epidemiological approach

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Stockholm 2018

"I love sleep. My life has a tendency to fall apart when I'm awake, you know?"

Ernest Hemingway

ABSTRACT

Dementia is a syndrome that afflicts older persons and is characterized by progressive deterioration in memory and other cognitive functions, behavior, and the ability to perform day-to-day activities. Older adults, and even more so those suffering from dementia, often experience disturbances in the sleep-wake cycle. This thesis sought to investigate the long-term effect of sleep and shift work (SW), which can affect sleep patterns and sleep quality, in dementia and cognitive aging using prospective and longitudinal studies of the Swedish Twin Registry (STR).

Study I prospectively explored whether sleep characteristics such as time in bed (TIB), rising time, bedtime, sleep quality, non-restorative sleep, and snoring in late life were associated with dementia incidence while accounting for baseline cognitive functioning. The study was based on a sample of 11,247 participants aged 65 and older. Short (≤6 hours) and extended (>9 hours) TIB as well as late rising time (rising 8:00 AM or later) were associated with higher dementia incidence in the following 17 years. After stratifying by baseline cognitive status, only the association between short TIB and dementia remained in those cognitively intact at baseline. Altogether, the findings suggest that extended TIB and late rising represent prodromal features whereas short TIB appeared to be a risk factor for dementia.

Study II employed quantitative genetic methods to investigate the relative importance of genetic influences for late-life sleep characteristics, dementia and Alzheimer's disease (AD), and whether dementia-related sleep characteristics modified genetic influences on dementia and AD in a sample of 10,894 twins. Genetic influences accounted for about half of the variation in liability to dementia and AD, and for late rise time and bedtime. For the other sleep phenotypes assessed, non-shared environment contributed a larger part of the phenotypic variation. TIB and late rising were associated with dementia incidence, but these sleep traits did not moderate the genetic influences on dementia and AD.

Study III examined the association between SW and dementia incidence. The study was based on two cohorts: one cohort comprised 13,283 individuals with information on any-type SW and another cohort comprised 41,199 individuals with information on night work (NW), with follow-up time spanning 41 and 14 years, respectively. History of SW, including NW, was associated with higher dementia incidence. Further, longer duration of SW and NW appeared to be associated with greater risk of dementia.

Study IV estimated the impact of SW on change in cognitive performance before and after retirement. The study included 595 individuals at least 50 years of age at baseline who had been employed and who had undergone up to 9 assessments of cognitive performance over a period of 27 years. Latent growth curve modeling showed that SW and NW during mid-life were not associated with greater rate of change in any of the cognitive domains (verbal, spatial, memory, and processing speed) later in life.

In summary, the work in this thesis has combined unique population-based data sources and modern epidemiological methods to evaluate the role of sleep and SW in dementia and cognitive aging. While SW did not appear to explain differences in rate of normative cognitive change in later life, findings indicate that SW and sleep characteristics are associated with increased risk of dementia.

LIST OF SCIENTIFIC PAPERS

I. **Bokenberger K**, Ström P, Johansson A, Gatz M, Dahl Aslan AK, Pedersen NL, Åkerstedt T. Association Between Sleep Characteristics and Incident Dementia Accounting for Baseline Cognitive Status: A Prospective Population-Based Study. *J Gerontol A Biol Sci Med Sci*. 2017 Jan;72(1):134-139; doi: 10.1093/gerona/glw127

II. **Bokenberger K**, Kuja-Halkola R, Åkerstedt T, Dahl Aslan AK, Pedersen NL. Sleep Characteristics and Dementia: Genetic and Environmental Influences. *(Manuscript)*

III. **Bokenberger K**, Sjölander A, Dahl Aslan AK, Åkerstedt T, Pedersen NL. Shift work and Risk of Incident Dementia: A Study of Two Population-based Cohorts. *(Submitted)*

IV. **Bokenberger K**, Ström P, Dahl Aslan AK, Åkerstedt T, Pedersen NL. Shift work and cognitive aging: A longitudinal study. *Scand J Work Environ Health*. 2017 Sep 1;43(5):485-493. doi: 10.5271/sjweh.3638

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid-β
AD	Alzheimer's disease
AIC	Akaike information criterion
APOE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical
BDRS	Blessed Dementia Rating Scale
BMI	Body mass index, kg/m^2
CDR	Causes of Death Register
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiologic Studies Depression
CI	Confidence interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DSM	Diagnostic and Statistical Manual
DZ	Dizygotic
GENDER	Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly
HARMONY	Study of Dementia in Swedish Twins
HR	Hazard ratio
ICD	International Classification of Disease
IPT	In-person testing
KSQ	Karolinska Sleep Questionnaire
LGCM	Latent Growth Curve Modeling
LRT	Likelihood ratio test
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MZ	Monozygotic
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS/AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NPR	National Patient Register
NREM/REM	Non-rapid eye movement / Rapid eye movement
NW	Night work
OCTO-Twin	Origins of variance in the Old-Old: Octogenarian Twins Study
OR	Odds ratio
PDR	Prescribed Drug Register
SALT	Screening Across the Lifespan Twin Study
SATSA	Swedish Adoption/Twin Study of Aging
SD	Standard deviation
SE	Standard error
SEM	Structural equation modeling
SES	Socioeconomic status
STR	Swedish Twin Registry
SW	Shift work
TIB	Time in bed
VaD	Vascular dementia

1 INTRODUCTION

As the aging population continues to grow, as does the impetus to understand what leads one to age well and another less so. In this thesis, particular interest surrounds why one's cognition remains relatively intact and at the other end of the spectrum another's takes a pathological turn. While genetic factors to some degree influence the variation in cognitive abilities[1, 2] and dementia[3] in later life, the balance that is explained by environmental factors remains partly unknown.

Dementia is characterized by debilitating cognitive and functional decline and poses a major burden for the dementia-afflicted patient, family caregivers, healthcare professionals, and the society at large.[4, 5] It was estimated in 2017 that close to 50 million people of all ages worldwide were living with dementia; this number is expected to jump to about 130 million in 2050.[5] The economic toll related to dementia is also steep with a projected global cost of above 1 trillion US dollars.[5] In light of these startling numbers, recent reports suggest that the age-specific prevalence (proportion of cases) as well as incidence (the rate of occurrence of new cases) of dementia is declining[6-8], which may have been in part due to rising educational levels and lifestyle changes, among other factors. What we do know is that these changes have not been due to drug treatments for halting the progression and reversing the functional effects of dementia, as such treatments so far do not exist despite decades of research and billions of dollars devoted to drug discovery.[9, 10] Overall, the changing trends of dementia incidence are encouraging, though it should be borne in mind that as long as the elderly population increases so will the absolute number of people with dementia. While dementia is highly prevalent in the elderly population, the majority experience cognitive decline without signs of pathology, also referred to as cognitive aging. Population aging means that it is also increasingly important to pinpoint factors that may accelerate cognitive aging. Although there is a huge research effort to determine factors associated with cognitive health in older age, only a small part of the variance in cognitive aging and dementia has been explained.

A factor that has been explored in relation to risk of dementia (but shown inconsistent findings), and one that is potentially modifiable, is sleep. In 2015, results from a survey on brain health administered by the American Association of Retired Persons indicated that 84% of adults aged 50 and older were interested in learning more about sleep in relation to brain health.[11] This is unsurprising given that this rejuvenating feature takes up approximately a third of our lives, and that the quantity and quality of sleep tends to decrease in older age[12] and particularly for persons with dementia.[13] Another third of our lives is spent at work (in working populations). An employment practice that in many cases directly impacts sleep is shift work (SW),[14] in which a fifth of the global workforce is engaged.[15]

This thesis comprises 4 studies that all utilize an epidemiological approach to understand how sleep and SW are associated with dementia and cognitive aging.

2 BACKGROUND

2.1 A BRIEF INTRODUCTION TO EPIDEMIOLOGY

Epidemiology is "the study of the distribution and determinants of disease frequency in human populations and the application of this study to control health problems."[16] Classical applications of epidemiology focus on descriptive investigations while modern applications emphasize the search for causes and effects of health-related factors and outcomes, the latter of which has led to the development of models of causation and have been used in the work within this thesis.

2.1.1 Causal inference and DAGs

When one thinks of causation in epidemiological research, the Bradford Hill Criteria and its nine aspects of association come to mind.[17] Since the publication of these causal guidelines in 1965, which have been useful for its intended purpose, additional tools for causal inference have come into play. A handy tool used for establishing as well as visualizing directions of supposed relationships between an exposure, an outcome, and other related factors is the Directed Acyclic Graph (DAG) (Figure 2.1).

To put this into context, let us apply the DAG to the analysis of the association between shift work (**exposure**) and dementia (**outcome**). An arrow indicates an association as well as the (assumed) direction of association between two variables. Whether the association is positive or negative, or to what extent the association is positive or negative (magnitude) is not shown in the DAG. A **confounder**, such as education in this example, is a factor that influences both the exposure and the outcome. To detect whether an association between the exposure and the outcome is influenced by a confounder, we need to condition on the confounding variable, i.e. by means of statistical adjustment, stratification, or sample restriction, which would close the path through the confounder.

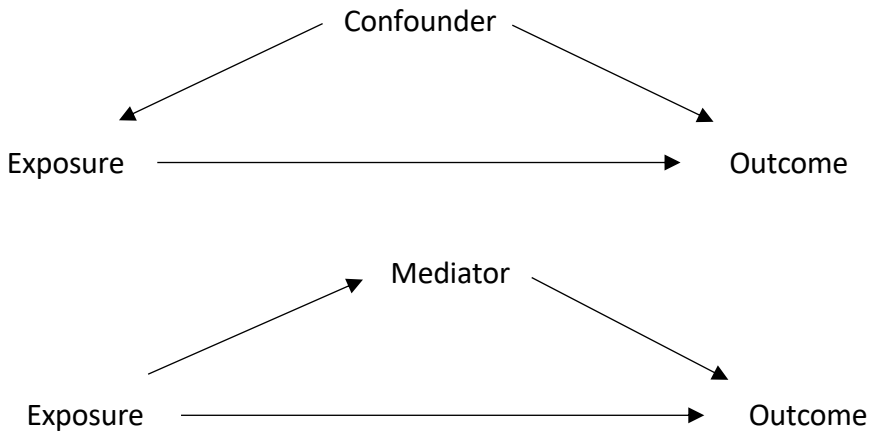


Figure 2.1. DAG illustrating directions of associations with a confounder (top) and mediator (bottom).

A **mediator**, such as cardiovascular disease (CVD) in this example, lies in the causal pathway between the exposure and outcome. One may choose not to adjust for the mediator in order to identify the total effect of the exposure on the outcome. It is also possible to adjust for the mediator to estimate the direct effect of the exposure on the outcome. But one must be aware that adjusting for a mediator may, in the presence of unmeasured confounding between the mediator and the outcome, open up the path through that unmeasured confounder, which may lead to spurious associations. In the absence of mediator-outcome confounding, adjusting for a mediator would theoretically attenuate the association between the exposure and the outcome.

A single factor may increase the risk of an outcome, but rarely does the causal mechanism leading to the outcome involve a single factor, but rather a multitude of factors. When the effect of the exposure on the outcome differs as a function of another factor (**moderator** or **effect modifier**), such an effect is referred to as **interaction** or **effect modification**. Overall, the development of a disease or outcome is an intricate and multifactorial process, and dementia and cognitive aging are not exceptions to the rule.

2.2 DEMENTIA

Dementia is a syndrome that encompasses a group of a chronic and debilitating diseases characterized by the progressive deterioration of cognitive processes such as memory, language, judgment, and behavior to the extent that normal activities of daily living are hindered.[18] Depending on the dementia subtype, there are different pathogeneses of cerebral atrophy.

The two major subtypes of dementia include Alzheimer's disease (AD) and vascular dementia (VaD), in which AD represents approximately 70% of all cases while VaD accounts for 20 to 30%. Other causes of dementia include dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).[19]

AD is a neurodegenerative disease and is characterized by two abnormal structures that are thought to develop independently of each other: extracellular amyloid plaques, also called senile plaques, which accumulate in the brain due to defective clearance of beta amyloid (Aβ) upon cleavage malfunction from the larger amyloid precursor protein; and, intracellular neurofibrillary tangles that are made up of tangles of hyperphosphorylated tau (p-tau) protein. Abundance of both aberrant structures in the brain leads to loss of connection between neurons, thereby diminishing cell function and giving rise to cell death.[20] Interestingly, while plaques and tangles have been considered hallmarks of AD, some studies have indicated that not all persons diagnosed with AD showed plaques and tangles, and not all persons with AD pathology at death were cognitively impaired for their age when they were alive.[21-23] AD may be further differentiated into early-onset (onset age between 30 to 60 years) and late-onset AD (onset age after 60 to 65 years). Early-onset AD represents about 4% of AD cases and is typically familial autosomal dominant, meaning that its occurrence is caused by inheriting a copy of a mutated gene. Up to 10% of early-onset AD cases are explained by mutations in any of the following three genes: amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), or presenilin-2

(*PSEN2*).[24] Late-onset AD on the other hand is to a large extent sporadic (no family history of AD).[24]

The second most common form, VaD, also known as vascular cognitive impairment, is loss of cognitive functioning resulting from cerebrovascular disease such as stroke, which leads to the development of vascular brain lesions.[25]

Fundamentally, where neuronal death stems from misfolding of proteins in the brain in AD, cell damage in VaD is caused by lack of oxygen due to disturbance in the blood supply to the brain.[26] In practice, however, the delineation between subtypes is not quite as clear-cut. During a visit to the memory clinic, one physician, when asked about the prevalence of VaD, replied with some skepticism, "Is there really such a thing?" To him and others tasked with making a differential diagnosis, discerning isolated VaD from AD is a challenging endeavor as a diagnosis of VaD would require that there is an absence of degenerative pathology (which is difficult to ascertain pre-mortem). Then there is mixed dementia (also called multifactorial dementia) which is the coexistence of AD and VaD (as well as with other causes of dementia) wherein most dementias fall on a spectrum between AD and VaD.[27, 28] A recent review reported that the prevalence of mixed dementia pathology could be up to 74%.[27]

Due to the substantial overlap between different subtypes and the challenges in differential diagnosis, we focused on all-cause dementia in older age as the outcome of interest. In *Study II* where we estimated genetic influences for various phenotypes, all-cause dementia as well as AD were examined.

2.3 COGNITIVE AGING

Older persons who are not diagnosed with dementia also experience normative cognitive aging, also called age-related cognitive decline, non-pathological aging, or simply cognitive aging.[29, 30] This condition is defined as having a measurable decline in cognitive performance due to natural maturational processes in which cognitive factors such as verbal abilities, spatial abilities, memory, and processing speed are affected, but not to the extent wherein daily functional independence is compromised.[29, 31]

The level and rate of decline of various cognitive domains vary between individuals, and by age, with certain domains being more age-sensitive than others.[32] Verbal ability is the ability of using and understanding language. Performance in verbal abilities increases until midlife, is stable thereafter, and begins to slowly decline around the age of 70.[33] Performance in verbal ability may be assessed with tests involving synonyms and antonyms, analogies, and other tests for measuring one's ability to understand verbal information.[34] Spatial ability is the ability one can understand, judge, and remember the spatial relations among objects, and be able to visualize objects in the mind. An example would be reading a map and being able to navigate oneself. This cognitive factor starts to decline during middle age is assessed for example using figure logic, block design, and card rotations tests.[35] Memory comprises different domains. Short-term memory (also called working memory) such as remembering a sequence of numbers in a short span of

time remains stable into very late life. Tests such as forward and backward digit span memory assess working memory. Long-term memory in itself can be divided into two subtypes. One is the unconscious preservation of memory of skills, sometimes referred to as implicit long-term memory, such as driving a car or playing the piano, which remains stable into late adulthood and declines slowly. The other is the conscious recollection of knowledge, which is also known as explicit long-term memory; this begins to worsen earlier in life but at a slow rate, and then at a faster rate later in old age.[36] Tests involving picture memory, names and faces, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list were used in the studies in this thesis to assess long-term memory.[35] Processing speed measures how fast one can process information and perform mental operations. The slowing of processing speed occurs earlier beginning at age 30.[37, 38] This can be measured using symbol digit and figure identification tests.[35, 38] While it is possible for different cognitive domains to be tapped by different tests, the domains are not isolated islands. For example, verbal ability relies on the ability to retrieve information from long-term memory, and processing speed predicts decline in other domains.[38] A global score of cognitive ability can be derived from a combination of these cognitive domains.

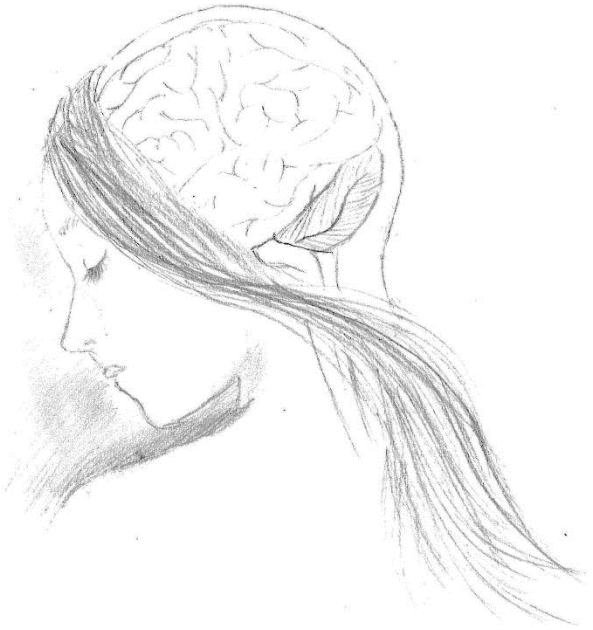
2.4 ETIOLOGY OF DEMENTIA AND COGNITIVE DECLINE

Old age is the strongest risk factor for dementia. After the age of 65, the risk of AD doubles every 5 years.[39] Senescence, while highly related to dementia, is not a causal factor as not everyone develops dementia; therefore, dementia is not a normal part of the aging process. Twin studies have demonstrated that the heritability for dementia and AD is estimated to be about 50% to 80%.[40-42] The presence of the Ɛ4 allele of the apolipoprotein E (*APOE*) gene represents the strongest genetic risk factor for AD.[43]

Besides old age and genetic susceptibility, research has shown that higher educational attainment is associated with higher cognitive ability[44] and lower risk of dementia in old age.[45, 46] This association may be explained by the cognitive reserve hypothesis, that is, individuals with higher levels of education may have enhanced neural compensatory ability, thereby mitigating the burden of brain pathology.[45, 47] Socioeconomic status (SES), which is highly correlated with education, is another factor associated with dementia. Higher educational attainment has been shown to be a protective factor for dementia, and this may be due to lower-level occupations typically being associated with behaviors and lifestyles that are related to higher dementia risk.[48]

Reports on the association between sex and dementia risk is mixed. Previous studies have shown that, among the very old, being female is a risk factor for AD, but not for VaD. This is perhaps explained by longer survival among women and earlier cardiovascular-related deaths among men leading to a survival bias.[49] Well-researched lifestyle factors in midlife related to cognitive decline and dementia include physical activity, cigarette smoking, and alcohol consumption.[39, 50] Medical conditions associated with both VaD and AD include depression, stroke and non-stroke CVD, and CVD risk factors such as hypertension, obesity, hyperlipidemia, type II diabetes and other metabolic disorders.[50]

2.5 SLEEP



An important and potentially modifiable factor that may influence cognitive function and risk of dementia is sleep. Characteristics of interest include quantity and quality of sleep, chronotype (a person's propensity to sleep at a particular time within a 24-hour period), and disordered breathing. Sleep architecture for persons with cognitive impairment or diagnosed with dementia differs from cognitively intact individuals.

A normal sleep cycle in adults lasts for approximately 90 minutes. Within each cycle, a person goes through four stages of sleep. The first three essentially dreamless stages of sleep (N1-N3) occur during non-rapid eye movement (NREM) sleep. The last stage of sleep during which dreams mainly occur is called rapid eye movement (REM) sleep.[51, 52] Humans shift from very light sleep during N1 to basic sleep during N2, and then to very deep sleep during N3. N3 sleep is often referred to as slow wave sleep (SWS) due to the presence of delta amplitude waves seen during this stage in electroencephalography (EEG) recordings. It is during SWS when neuronal regeneration and cellular repair occurs. The last NREM stage begins to decrease after middle age and is reported to be nonexistent after age 90.[12]

Normal aging is accompanied by physiologic changes in sleep[53] and is associated with greater sleep latency (the length of time it takes to transition from wakefulness to sleep), sleep fragmentation, earlier awakening due to phase advance of the circadian clock, increases in stage N1 and N2 sleep,[52] decreases in stage N3,[54] and higher prevalence of daytime napping.[53, 55]

Older individuals with cognitive impairment or diagnosed with dementia tend to experience similar age-related sleep changes such as greater difficulties falling asleep and restlessness during the night to the extent that sleep is disrupted. This then leads to noticeable sleepiness during the daytime,[52] which is associated with a decreased likelihood of being able to perform activities of daily living.[56] In addition to daytime sleepiness, some patients with dementia experience sundowning, which is the exhibition of behavioral problems such as confusion, restlessness and agitation that begins at dusk and lasts into the night.[52]

Atypical characteristics of sleep such as disturbances affecting sleep duration and quality in persons with cognitive impairment is perhaps due to impaired circadian rhythms. The circadian system is one of two body systems that regulates the sleep-wake cycle, the other system being sleep-wake homeostasis, wherein homeostatic sleep pressure increases with every waking hour, and decreases once asleep.[57] Circadian rhythms oscillate with a period that is approximately 24 hours, hence the term 'circadian', which is derived from the Latin *circa* ("around") and *diem* ("day"). They are mainly operated by an endogenous biological clock located in the suprachiasmatic nucleus within the hypothalamus, and are sensitive to so-called Zeitgebers (literally meaning "time giver" in German), which are exogenous stimuli such as light, temperature, noise, food availability, and social cues, to name a few.[58] These Zeitgebers entrain the biological clock to the 24-hour light/dark cycle of the Earth. Interestingly, in the absence of entrainment from Zeitgebers, the endogenously generated circadian rhythms would continue on a period that is just over 24 hours on average (though this would make for a rather dreary existence). With the help (or interference) of Zeitgebers, circadian rhythms can be entrained or reset.

The resetting period involves desynchronization of endogenous circadian rhythms and exogenous factors, which is often seen in shift-workers and persons experiencing jet lag. It is hypothesized that disturbances in circadian rhythms may be involved in various disorders and disease processes, including type II diabetes, obesity, and CVD by directly mediating glucose and lipid metabolism.[58]

Regarding the relationship between sleep and cognition, research has shown that reduction of sleep acutely[59] or chronically [60] will lead to pronounced increases of sleepiness and impaired cognitive performance, including working memory performance. Disordered sleep has also been reported to be highly prevalent in persons with mild cognitive impairment and dementia.[61-64] Much research has been done on investigating the adverse acute effects of interrupted and deprived sleep on cognitive performance that is measured hours or days later.[65] While there have been studies examining the longer-term effects of sleep on late life cognition and dementia development, there has been greater focus on sleep-disordered breathing and sleep quantity and quality—with conflicting findings—and very little on chronotype.[66, 67]

Studies examining sleep prior to or during the preclinical phase of dementia, which could extend beyond 20 years,[68] while taking into account initial cognitive function are important for providing a better understanding of whether the sleep trait of interest is a risk factor or risk marker.

2.6 SHIFT WORK (SW)

SW is a necessary employment practice that has emerged as a consequence of society's demand for 24-hour service[69] and has been around ever since the invention of the lightbulb in the 1800s, which allowed for work to continue or begin after the setting of the sun.[70] Approximately one in five of the working population in high and middle-income countries are shift-workers,[69] and about 30% of rotating and night shift-workers experience chronic insomnia and excessive sleepiness.[71] In Sweden, 22.5% of the working population work shifts and 16% work night shifts.[72]

In broad terms, according to the National Sleep Foundation, SW is "work that takes place on a schedule outside the traditional 9AM - 5PM day."[73] Work schedules that include shifts can include fixed night or evening shift schedules, rotational shift schedules, and on-call schedules.[74] Such schedules are typically implemented in, for example, security industries, the healthcare sector, factory work, and jobs in construction, roadwork, and power plants.

Rotational SW covers a variety of work schedules. A common rotational schedule used in Europe entails clockwise rotation from morning to afternoon to night shifts, with no more than three successive nights per block. For instance, this means working 7AM - 3PM for three shifts, 3PM - 11PM for three shifts, 11PM - 7AM for three shifts, and then 3 days off to recuperate from the sleep-wake cycle shifts.[75] The reason for having short blocks is to avoid drastic resetting of the biological clock, though research has shown that there is loss of 1 to 4 hours of sleep per night during the 3-day recuperation period.[76] A 'fixed' or 'permanent' shift schedule is when a person (usually a crew of workers) works the same shift all the time. Historically, to not have shift changes at all was the circadian gold standard based on the idea that a fixed shift schedule imitated a typical day work schedule with fixed work hours during the day. In reality, however, very few working permanent shifts, particularly the night shift—evocatively known as the 'graveyard shift'—can manage a complete circadian shift since most cannot opt out of family and social functions that fall during daytime hours. [76]

In this thesis, both a broad and narrow definition of SW is used. SW refers to any type of schedule that alternates between temporal positions, and this may include rotating SW, which contains night shifts. Night shift work or simply 'night work' (NW) refers to permanent night work or work that is part of a rotating schedule that includes night work.

Working during irregular or unusual hours is known to affect sleep patterns and even cause sleep disorders.[14, 77] SW, particularly if including night work (NW), is related to future increases in sleepiness[78], and both night and morning shifts have been reported to reduce sleep by about 1.5 to 2 hours[79, 80]. Excessive sleepiness, shortened sleep time, and insomnia characterize a circadian rhythm disorder specific to shift-workers that is known as shift work sleep disorder.[71] When sleep disturbances occur amongst shift-workers, this may instigate insulin resistance, glucose intolerance, higher body mass index (BMI) and adverse neurocognitive consequences.[58] Considering animal studies

that have shown circadian disruption to suppress hippocampal neurogenesis[81], it is plausible for there to be deleterious cognitive effects due to chronic exposure to SW.

So far, however, the effects of SW on cognition years later are less clear. A previous cross-sectional study with a sample of 3,237 workers observed SW to be related to substantially lower cognitive performance.[82] A more recent prospective study focusing on the male subset of the same French cohort noted similar findings.[83] Men currently or previously exposed to any atypical work schedule scored lower on memory, speed, and global cognitive performance compared to men never exposed to any SW. Exposure to more than 10 years of rotating SW predicted lower global cognitive performance scores compared to those with no rotating SW experience.[83] Another study by Devore and colleagues examined the effects of rotating night SW in midlife on mean cognition levels and rate of cognitive decline over a 6-year period, but no association was observed based on the study's sample of 16,190 female participants from the Nurses' Health Study.[84]

3 AIMS

The overall objective of this work is to contribute to a better understanding of how sleep and SW influence incidence of dementia and cognitive aging in late life.

Specific aims

1. ***Study I:*** To study whether sleep characteristics predict risk of dementia while accounting for baseline cognitive functioning.

2. ***Study II:*** To estimate the relative importance of genetic influences for late-life sleep characteristics, dementia and AD, and to examine whether dementia-related sleep characteristics modify the importance of genetic influences on dementia and AD.

3. ***Study III:*** To investigate whether SW is associated with an increased risk of dementia.

4. ***Study IV:*** To examine whether SW is associated with cognitive aging among persons not diagnosed with dementia.

4 DATA SOURCES AND MEASURES

The saying is that Sweden is a gold mine for epidemiological research. This stems from the abundance of national population registers and the unique personal identification number (PIN) that is allocated to each of the 10 million inhabitants in Sweden. The PIN is a 10-digit number, with the first 6 digits representing one's date of birth (YYMMDD) and the last 4 digits as a unique identifier that indicates the place of birth and sex of the individual (an even third digit indicates female; an odd number indicates male). The PIN is the basis of all Swedish public administration and it is this unique identifier that enables linkage of data from different register sources.[85] By using register data with the help of the PIN, one can conduct a population-based cohort study with minimal risk of loss to follow-up, selection bias, and recall bias.

In this chapter, registers and the register-based studies of aging used in this thesis are described.

4.1 THE SWEDISH TWIN REGISTRY

The Swedish Twin Registry (STR) is the largest and one of the oldest population-based registry of twins in the world and is a collection of different birth-year based cohorts.[86] In total, the registry includes 194,842 twins born between 1886 and 2008.[87] A main reason for the establishment of the STR in the late 1950s was to investigate associations between environmental exposures such as smoking and chronic diseases such as lung cancer while controlling for familial effects.[86] As one can imagine, a great deal of human effort and coordination went into establishing the STR, which was maintained at Karolinska Insitutet (KI). In the beginning, the STR contacted all parishes in Sweden about multiple births that occurred during 1886-1925; twins born during this time are referred to as the old STR cohort. Later in 1970, information on all twins born 1926-1967 were gathered from the National Board of Health and Welfare (in Swedish: Socialstyrelsen).[86] Twins born during 1926-1958 are referred to as the middle STR cohort. The studies in this thesis focus on the old and middle cohorts of the STR.

Zygosity assignments

Zygosity assignments were made by genotyping, by being opposite sex, or based on a question about intrapair similarities ("During childhood, were you and your twin partner *as similar as two berries* [equivalent to the English phrase, *two peas in a pod*] or not more alike than siblings in general?").[87] If both members of a pair responded that they were similar, then the pair was classified as MZ. Twins from the old and middle STR cohort with undetermined zygosity and who had participated in SALT (see below) were given the question: "How often do strangers have difficulty distinguishing between you and your twin partner when you were children?" Twins who had replied that they were mixed up by strangers were classified as MZ.

4.1.1 STR studies of aging

Since the inception of the STR, the registry has acted as a valuable resource for medical research, including aging research. For instance, a series of sub-studies of aging based on the old and/or middle STR cohorts have hatched forth, including cross-sectional studies such as the STR 1973 questionnaire study, SALT, HARMONY, and TwinGene, and longitudinal studies such as SATSA, OCTO-Twin, and Gender.[86] These STR-based studies provide the basis for this thesis. An overview of these studies is illustrated in Figure 4.1.

4.1.2 STR-1973

KI has administered questionnaires that include demographic, medical, and environmental exposure variables to specific age-based STR cohorts since the 1960s. Questionnaires in 1961, 1963, 1967, and 1970 were sent out to the old cohort. In 1973, a questionnaire, which asked about work-related exposures such as SW, was sent out to all like-sexed pairs in the middle cohort (N=36,536), of whom 36,429 responded.[86] This cohort is referred to as the STR-1973 cohort, and is one of the cohorts that was followed up in *Study III*.

4.1.3 SALT and HARMONY

SALT

A more recent STR wave contacted individuals of same- and opposite-sex twin pairs via a telephone interview, called the Screening Across the Lifespan Twin study (SALT), in 1998-2002 that targeted all twins born in 1958 or earlier.[86, 88] Thus, STR-1973 twins who survived to 1998 are included in the SALT cohort. A total of 61,767 individuals were invited and 44,825 responded. The telephone interview followed a structured questionnaire that included questions about illnesses and health, prescription and nonprescription medication use, occupation, education and lifestyle factors. Certain items were only administered to participants 65 and older, such as items concerning sleep and memory. Permission to review medical records was also asked.

HARMONY

SALT twins who were alive and aged 65 and older at the time of the interview were administered a cognitive screening module called the TELE. This was the basis of the Study of Dementia in Swedish Twins study, commonly referred to as the HARMONY study (based on the Swedish words for "health" [Hälsa], "genes" [Arv], "environment" [Miljö], "and" [Och], and "new" [NY]). The aim of HARMONY was to ascertain cases of dementia in all twins who were 65 and over at the time.[89] Details regarding clinical ascertainment of dementia in HARMONY are described later in Section 4.4.2.

Data on sleep habits from SALT were used in *Study I* and *Study II* and as a covariate in a sensitivity analysis in *Study III*. Data on cognitive functioning from HARMONY was used in *Study I*. Dementia ascertainment data from HARMONY were used in *Study I, Study II,* and *Study III*.

4.1.4 TwinGene

TwinGene is a cross-sectional study of older twins born 1911-1958 who had participated in SALT and in which both members of the pair were alive at the time the study was conducted in 2004-2008.[87] A total of 10,714 individuals were successfully genotyped using Illumina OmniExpress. Genotype imputation was performed based on the data from the 1000 Genomes Project.[90] Thus, *APOE* genotype information was available from TwinGene, which was used in a subsample analysis in *Study III*.

4.1.5 SATSA

The Swedish Adoption/Twin Study of Aging (SATSA) is a longitudinal study of aging, with the base population made up of twins from the old and middle STR cohort who were separated before the age of 11 and reared apart, and a matched control sample of twins reared together based on sex, date of birth, and county of birth.[91, 92] The main reason for the separation of twins was illness or death of parents or economic hardship.

Data collection for SATSA began in 1984 with a questionnaire (Q1) and ended in 2014. Of the 2,845 individuals from the base sample who were mailed the Q1 questionnaire in 1984, 2,019 individuals responded.[35] In addition to the questionnaire component, SATSA included an in-person-testing (IPT) component. Altogether there was a total of 9 questionnaire waves and 10 IPT waves. The mean baseline age in 1984 was 60.3 (SD 14.0).

The questionnaire included questions concerning health, sociodemographic factors, lifestyle factors, and work environment exposure such as SW. Questionnaires were mailed out in 1984, 1987, 1990, 1993, 2004, 2007, 2010, 2012, and 2014.

The IPT involved an extensive cognitive battery, health examinations, and collection of biological samples. IPT assessments were conducted in 1986-88, 1989-91, 1992-94, 1995-98, 1999-2000, 2002-04, 2005-07, 2008-10, 2010-12, and 2012-14, and were administered at primary care centers or offsite in the participant's place of residence, wherever convenient. Data collection was done by trained registered nurses. To be considered for IPT participation, both members of a pair had to have responded to Q1, and they had to be at least 50 years of age. A total of 645 individuals participated at the first IPT occasion (IPT1). Thereafter, those who had participated in IPT1, or those who had turned 50 during the study period, were invited to take part in subsequent IPTs up to IPT5. For IPT4, a subset of IPT participants (n=40) were interviewed due to funding considerations. There were 859 individuals who had participated in at least one IPT. SATSA has a good response rate with more than 90% of participants having returned for each IPT wave with the exception of IPT4, and not counting those who had died during the course of the study. Over 76% of the sample has participated in at least three IPT waves.

Data and documentation for the first 6 questionnaire waves and 7 IPT waves of SATSA are publicly available at the National Archive of Computerized Data on Aging (URL: https://www.icpsr.umich.edu/icpsrweb/DSDR/studies/3843).[93]

In Study *IV*, information on SW (available at Q1) and cognitive performance (measured in IPT1-9) were used, Clinical diagnoses of dementia were made in SATSA, and these data supplemented register data on dementia and AD in *Study II*.

4.1.6 OCTO-Twin

The Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-Twin) study concerned individual differences among older aged adults.[94] OCTO-Twin is similar in design to SATSA and includes questionnaires and IPTs, including cognitive assessments. The base population was like-sexed twin pairs drawn from the old cohort of the STR. A total of 702 individuals (351 complete pairs) participated at baseline. The mean baseline age was 83.6 years (SD 3.2). Participants in OCTO-Twin were invited to take part in 5 IPTs at rolling 2-year intervals. Clinical diagnoses of dementia were done in this OCTO-Twin subset; these data supplemented register data on dementia and AD in *Study II*.

4.1.7 GENDER

Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly, more often referred to as the GENDER study, followed opposite-sexed twin pairs born 1906-1925 drawn from the old cohort of the STR.[95] The objective of Gender was to investigate differences in gender in various measures of health and cognitive function. Of the 1,843 individuals who responded to the baseline questionnaire, a subsample of 498 individuals (249 twin pairs) aged 70-79 years participated in GENDER's first IPT beginning in 1995. Altogether there were 3 waves of IPTs that were administered on a 4-year rolling schedule between 1995 and 2005. The IPT component in Gender included cognitive assessments and were much like that in SATSA and OCTO-Twin.[96] Dementia was ascertained clinically in GENDER, and these information were used towards the construction of the dementia and AD variables in *Study II*.

Generally, SATSA, OCTO-Twin, and GENDER were consistent in terms of information collected.

4.2 THE SWEDISH MILITARY SERVICE CONSCRIPTION REGISTER

Until 2007, military conscription was compulsory for all Swedish men. Around the age of 18-20, all men participated in conscription tests that included assessments of exercise and lung capacity, BMI, mental health, and cognitive ability.[97] Exam results have been documented electronically since 1969. Regarding the cognitive component, verbal ability, spatial ability, logic inductive and technical ability were evaluated. Raw scores from these four tests were standardized into z scores. A general cognitive ability score was generated by summing the scores together, resulting in a total score ranging 1 to 40 points, with a higher score demonstrating stronger cognitive performance.[101]

In *Study IV*, a sensitivity analysis was performed on a subset of men born in 1936-1948 who had participated in SATSA and undergone military conscription and thus had data on early adult cognitive ability.

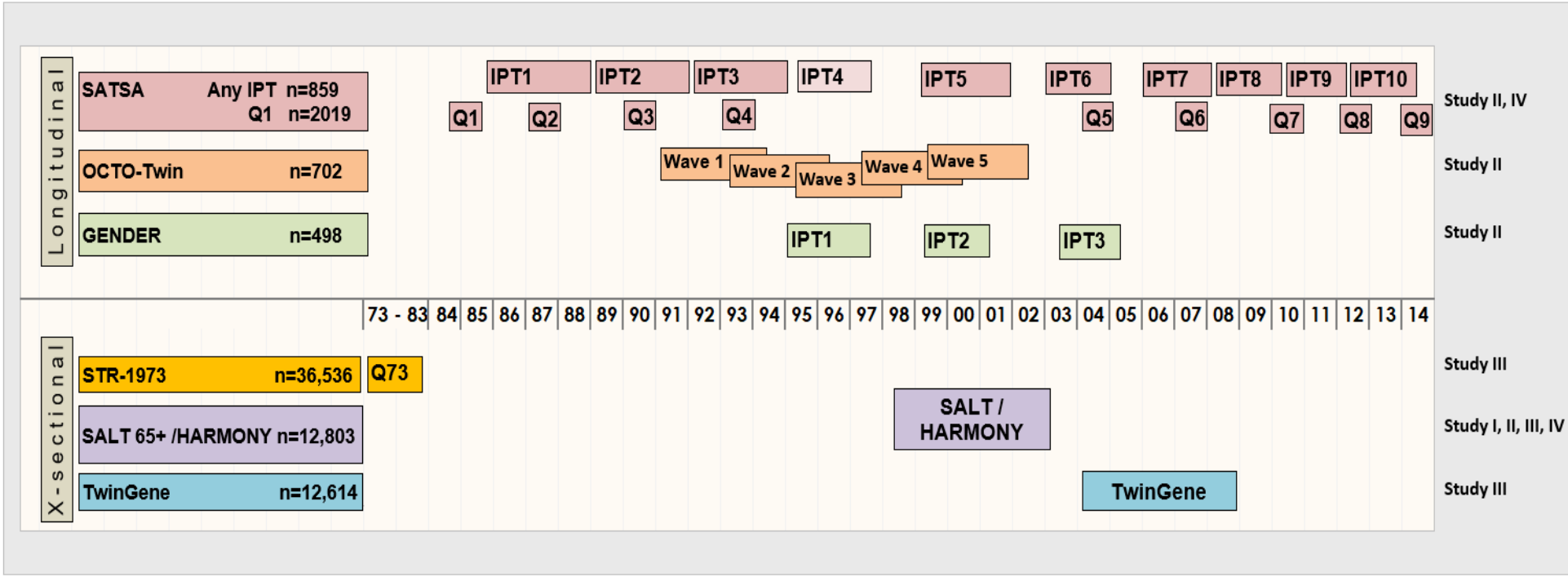


Figure 4.1. Overview of studies of the Swedish Twin Registry that provide the basis of this thesis. Modified from Karlsson 2017.[98]
Study I includes data from SALT/HARMONY.
Study II includes data from SALT/HARMONY, SATSA, OCTO-Twin, and GENDER.
Study III includes data from SALT/HARMONY, STR-1973, and TwinGene.
Study IV includes data from SATSA and SALT.

4.3 NATIONAL HEALTHCARE REGISTERS

With the PIN, the STR and its sub-studies can also be linked to a number of population health registers, namely the National Patient Register, the Prescribed Drug Register, and the Causes of Death Register, from which data used in this work are extracted from.

4.3.1 National Patient Register

Follow-up of the health of the Swedish population has been maintained by the National Board of Health and Welfare since 1964, which was when the National Patient Register (NPR) was established.[99] For everyone living in Sweden, the NPR collects information on hospitalization for diseases coded as the International Classification of Diseases (ICD) codes relevant at the time, as well information on dates of admission and discharge. In the NPR, inpatient care, i.e. overnight hospitalizations, was recorded since the beginning in 1964, psychiatric care recorded since 1973, and outpatient visits from hospital-based or specialist clinics since 2001. Primary care is not recorded in the NPR.[100] There was incomplete geographical coverage of patient care in the 1960s, with only 6-12 counties in Sweden included in the NPR (Sweden is divided into 21 counties).[101] By 1987 and onwards, coverage of care was nationwide.

4.3.2 Prescribed Drug Register

The Swedish Prescribed Drug Register (PDR) is a relatively newer register that was initiated on July 1, 2005.[102] The PDR contains information on all prescribed pharmaceuticals dispensed to all Swedish residents. The National Corporation of Swedish Pharmacies, a company owned by the Swedish state, is responsible for the data collection for the PDR. The data are then transferred to the National Board of Health and Welfare each month. For each observation, the register includes, but is not limited to, the date the drug was dispensed, the substance and brand name of the dispensed item, and the dispensed amount and expenditure.[102] The PDR does not include data on over the counter medications. All drugs follow the Anatomical Therapeutic Chemical (ATC) classification system. For the purposes of the work in this thesis, the PDR serves as an additional source of data on dementia as well as on use of hypnotics and sedatives.

4.3.3 Causes of Death Register

The Causes of Death Register holds information on deaths for all residents of Sweden, regardless of whether the death was in Sweden or abroad.[103, 104] Stillborn deaths and individuals who died in Sweden but do not hold a permanent residency are not registered in the CDR. The National Board of Health and Welfare has been responsible for maintaining the CDR since 1952, which has established nationwide coverage since 1961. Information such as age and date of death, the underlying cause of death, and the contributing cause(s) of death are entered into the CDR. New deaths are registered on a continual basis.

4.4 DEMENTIA ASCERTAINMENT

Data on incident dementia (after study baseline) came mainly from the national health registers described above, and were used to construct the dementia variables in *Study I*, *Study II*, and *Study III*. Register-based dementia diagnoses were supplemented with additional clinical diagnoses made in the STR sub-studies of aging in *Study II* (conducted last, chronologically).

4.4.1 Ascertainment of dementia from registers (*Study I, Study II, Study III*)

Incident cases of dementia were ascertained via record linkage between the STR with the NPR, PDR, and CDR. At the time the four studies of this thesis were performed, NPR data were available for 1967-2014, PDR data were available for 2005-2014, and CDR data were available for 1952-2014. Note that since this thesis concerns incident cases of dementia (*Study I, Study II, Study III*), and that the earliest study baseline was in 1973 (*Study III*), only register-based dementia data starting from 1973 were extracted. Therefore, ICD-8 (1969-1986), ICD-9 (1987-1996), and ICD-10 (1997-current) codes were used to identify cases of all-cause dementia and specific dementia subtypes (Table 4.4.1a).

From the NPR, data on hospital admission date (inpatient) or date of dementia diagnosis (outpatient) was used to construct the variable for date/age of dementia onset. Both primary and additional diagnoses were used. From the PDR, the date the dementia medication (class N06D) was dispensed was considered as the date of AD onset, since the anti-dementia drugs prescribed in Sweden are specific for managing mild to severe AD.[105] The full list of the medications used to derive the AD variable is shown in Table 4.4.1b. From the CDR, data on the date of death with dementia as the primary or contributing cause of death was extracted. If there was information on dementia dates from multiple register sources, the earliest date was used for the date of dementia onset variable.

Dementia diagnoses from the NPR and CDR have been validated against clinical diagnoses identified from six Swedish population-based studies.[106] For all-cause dementia diagnoses in the NPR and CDR combined, the sensitivity—which is how well the registers can detect dementia cases and is calculated as the number of cases ascertained in the registers divided by the number of cases identified in the population-based studies—was 63%. The specificity—which is how well the registers can detect non-dementia cases and was calculated as the number of non-cases ascertained in the registers divided by the amount of non-cases identified in the population-based studies—was 99.8%.[106] The work within this thesis was mainly concerned with all-cause dementia.

Table 4.4.1a. ICD codes for identification of dementia. Modified from Karlsson 2017.[98]

ICD / Dementia	ICD-8 1969-1986	ICD-9 1987-1996	ICD-10 1997-current
Alzheimer's disease	290	290A/B	F00
		331A	G30
Vascular dementia	293.0, 293.1	290E	F01
Other dementia		290X/W	F02-03
		294B	G311
		331B/C/X	G318A
			F051

Table 4.4.1b. ATC codes for anti-dementia drugs in Sweden.

ATC code	Group name	Drug name in Sweden
N06D	Acetylcholinesterase (AChE) inhibitors (for mild to moderate AD)	• Donepezil • Galantamine • Rivastigmine
	NMDA receptor antagonist memantine (for moderate to severe AD)	• Memantine

4.4.2 Clinical ascertainment of dementia from STR sub-studies (*Study II*)

For the clinical ascertainment of dementia in the four STR studies (HARMONY, SATSA, OCTO-Twin, and GENDER), the general procedure is to: 1) administer a cognitive screening, and 2) perform a clinical evaluation for those who screened positive for dementia or conduct a consensus conference, in which a group of specialists review all relevant study protocols and medical records to come to a differential diagnosis.

Cognitive screening

In SATSA, OCTO-Twin, and Gender, the MMSE as well as other cognitive tests including tests of spatial ability, processing speed, verbal ability, and memory were used for neuropsychological assessment of cognitive function.[35, 94, 95] In HARMONY, the TELE was used as a telephone cognitive screening tool.[89] As part of the TELE, participants were given a 10-item mental status questionnaire (MSQ), asked to recall three words, were presented three pairs of words and were asked to explain why they were similar, and questioned about health and daily functioning. In the event that the twin performed poorly on the TELE, an informant supplied information about the twin with the BRDS, which assessed to what extent the twin's cognitive status interfered with everyday functioning. An ordinal cognitive scale ranging from intact cognition (0) to cognitive dysfunction (3) was created based on information from the TELE and BDRS.[89] A description of the ordinal cognitive scale can be found in Table 4.4.2. HARMONY participants who received a score of 3 indicating cognitive dysfunction were referred to a full clinical work-up.

Table 4.4.2. Ordinal cognitive scale in HARMONY based on the TELE and informant interviews.[89]

Cognitively intact (0)	Minor errors (1)	Poor performance (2)	Cognitive Dysfunction (3)
Completed TELE interview with no impairment in any domain.	Completed TELE interview but with impairment in one domain (MSQ, similarities, or three-word recall).	Presence of errors in more than one domain of the TELE or the twin was unable to be interviewed but informant did not indicate that the twin had functional impairment.	Presence of more than two errors on the MSQ items, a BDRS score of at least 1.5 based on the informant interview, or the twin reported having functional impairment.

Clinical work-up and diagnosis

In HARMONY and up to the fourth wave of SATSA, twins who screened positive for dementia were referred to a full clinical work-up which generally followed the CERAD protocol.[107] The work-up involved a team that included a nurse and a physician who performed a physical and neurological assessment, administered a neuropsychological battery, reviewed medical records, looked at onset and progression of memory or cognitive symptoms, collected blood for lab analysis, and referred some individuals for neuroimaging.[89] Additionally in HARMONY, informants of the twin answered a Clinical Dementia Rating scale[108] as well as a Neuropsychiatric Inventory concerning behavioral symptoms.[109] In OCTO-Twin and Gender, and from the fifth IPT occasion in SATSA, ascertainment of dementia was based on psychological and physical health evaluations, decline in cognitive performance between waves, nurse's impressions, and review of medical records including medical history and prescribed and non-prescribed drug use.

Across the four STR studies, a dementia diagnosis was set during a multidisciplinary consensus conference according to DSM-III-R or DSM-IV criteria. A differential diagnosis was made based on NINCDS/ADRDA criteria for AD,[110] and based on NINDS-AIREN criteria for VaD.[25]

4.5 COGNITIVE MEASURES IN SATSA (*STUDY IV*)

In SATSA, five cognitive composite factors – verbal abilities, memory, spatial abilities, processing, speed, and a general cognitive factor – were generated based on tests in a cognitive battery.

Table 4.6 lists the specific tests, which had reliabilities ranging between .82 to .96,[1] that were related to each cognitive factor as revealed by principal component analysis. Each test in the principal component analysis was standardized to the mean and standard deviation of IPT1 test scores. For ease of interpretation, the cognitive factor scores were transformed into T scores that had a mean of 50 and a standard deviation of 10. The individual cognitive tests were available at all IPT waves, and it was therefore possible to model trajectories of performance over time for each of these cognitive factors, which was done in *Study IV*.

Table 4.6. Five cognitive factors in SATSA (used in *Study IV*).

	Verbal	Spatial	Memory	Processing speed	General cognitive ability
Cognitive tests	-Information -Synonyms -Analogies	-Block design -Card rotations (2-minute version)	-Picture memory -Digit span forward & backward	-Symbol digit -Figure identification	-All tests

4.6 EXPOSURE VARIABLES

4.6.1 Sleep characteristics (*Study I* and *Study II*)

All information on sleep habits was self-reported and came from the Karolinska Sleep Questionnaire (KSQ), which was included in the SALT interview.

Six sleep measures were used mainly in *Study I* and *Study II*, and as a covariate in *Study III*. Table 4.7 lists the six sleep measures as well as the specific KSQ sleep items that were used to construct the sleep measures.

By design, five items (rise time, bedtime, disturbed sleep, difficulty falling asleep, and waking up too early in the morning) were administered to all SALT participants 65 and over. The other sleep items (repeated nighttime awakenings, not feeling rested upon awakening, difficulties awakening, and heavy snoring) were administered to a smaller subset of this 65+ year sample, identified randomly, due to funding considerations.

Rise time (rising 8AM or later vs. earlier rising) and **bedtime** (going to bed 11PM or later vs. earlier bedtime) were dichotomized measures, with the 75th percentile rise time or bedtime value in the *Study I* population determining the cut-off point. This was done in order to detect delayed sleep phase rhythms. In *Study I*, sensitivity analyses on the association between rise time and bedtime with incident dementia was performed based on rise time and bedtime variables dichotomized at 70th, 75th, and 80th percentile cut points; similar findings were yielded compared to that from main analyses, indicating that the effects of late rise time and bedtime were not spurious.

A **time in bed (TIB)** variable was calculated based on rise time and bedtime information. TIB was grouped as ≤ 6 hours (short), between 6 and 9 hours (reference), and >9 hours (long) based on the distribution of the study population in *Study I* and a meta-analysis that developed age-specific normative sleep values.[12] This measure is similar to sleep duration. A notable difference is that TIB length is typically longer on average than the length of sleep duration because TIB includes the sleep latency period as well as the time awake when night-time awakenings occur.

To capture different dimensions of poor sleep, two validated sleep indices were used: the **Sleep Quality Index** and the **Non-Restorative Sleep Index**.[111] The Sleep Quality Index is based on four KSQ items (see Table 4.7) and is used for capturing nocturnal symptoms of insomnia; these items were determined according to DSM-IV criteria of insomnia.[111] The Non-Restorative Sleep Index is based on two KSQ items (Table 4.7) and is for capturing the extent to which sleep is refreshing.

Heavy snoring was used as a marker of sleep-disordered breathing. A caveat with this measure is that one may not be aware of one's snoring status unless living with others.

Table 4.7. Sleep variables used in *Study I and II*.

Items about sleep habits from the Karolinska Sleep Questionnaire (KSQ)	Sleep variables based on KSQ items on the left
D*uring the last 6 months…* What time do you usually get up? Get up at [time] _____ What time do you usually go to bed? Go to bed [time] _____	Time in bed (TIB) Short = < 6 hours Middle = ≥6 to 9 hours Long = ≥ 9 hours Rise time Rising time < 8AM Rising time ≥ 8AM Bedtime Bedtime < 11PM Bedtime ≥ 11PM
How often, *during the last 6 months,* have you been affected by this problem? …Waking up too early and not being able to sleep again. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4) …Feeling of not having had enough sleep upon awakening. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4) …Experience disturbed or uneasy sleep. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4) …Repeatedly waking up during the night and having difficulties falling back asleep. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4)	Sleep Quality Index *(Range 0 to 4; Higher score = poorer sleep quality)*
How often, *during the last 6 months,* have you been affected by this problem? …Having trouble waking up in the morning. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4) …Do not feel restored/rested upon awakening. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4)	Non-Restorative Sleep Index *(Range 0-4; Higher score = less restorative sleep)*
How often, *during the last 6 months,* have you been affected by this problem? …Experience heavy snoring. Never (0) Seldom (1) Sometimes (2) Usually (3) Always (4)	Heavy snoring No Yes

4.6.2 Shift work and night work (*Study III* and *Study IV*)

SATSA – SW of all types (Study IV)

In SATSA, at Q1 baseline in 1984, participants were asked if they worked shifts for the greater part of their life. Those who indicated that they had worked shifts were also able to give an open-ended response regarding the number of years that they had worked shifts. Participants were also asked if they had worked shifts in the last 12 months, i.e. their current shift work status. A general SW status variable (ever/never) and a SW experience variable with 4 categories (0 years; 1-9 years; 10-19 years; 20 or more years) were created. The SW variable from SATSA was the main exposure variable in *Study IV*.

SALT – Night work (Study I, Study III and Study IV)

The NW measure from the SALT questionnaire in 1998-2002 was based on the open-ended item, "During about how many years have you had working hours that meant that you at least sometimes worked at night?" NW was grouped as ever/never and categorized into 4 levels (0 years; 1-9 years; 10-19 years; 20 or more years). NW was one of the main exposure variables in the main analysis in *Study III*, used in a subsample analysis in *Study IV*, and included as a covariate in a preliminary model in *Study I*.

STR-1973 – SW of all types (Study III)

In the STR questionnaire in 1973, the middle STR cohort was asked, "Do you work or have you worked shifts?" One was able to respond No or Yes, and specify for how long time in years one had worked shifts. This variable was treated as an ever/never variable as well as a categorical variable (0 years; 1-9 years; 10-19 years; 20 or more years). The SW variable from the 1973 STR questionnaire was one of the main exposure variables in *Study III*.

Overlap of participants in SATSA, SALT and STR-1973

The overlap of participants in SATSA and SALT made it possible to check if participants who had responded that they worked nights in SALT, had also responded that they had worked any-type SW in SATSA (*Study IV*). Of the SATSA individuals who had responded that they worked nights in SALT (n=47), 100% of these individuals had responded that they worked shifts in SATSA.

There was also an overlap of participants in STR-1973 and SALT. One of the main limitations with the SW measures is that SW is measured at only one occasion in each study. This means that SW exposure is assumed to be fixed when in reality this may not have been the case. With the overlap of participants between studies and with two study sources of SW data, we were able to draw some scenarios concerning the length of exposure time (in years) to SW, or allow for SW exposure status to vary over time, which were done in *Study III*.

4.7 OTHER VARIABLES

Age and sex were included as covariates in all final statistical models in the 4 studies in this thesis.

Highest educational attainment was included as a covariate in all final models in *Study I, Study III,* and *Study IV*. While it is compulsory to attend school for years 1-9 today in Sweden,[112] for the study population made up of individuals born between 1886 and 1958, compulsory 'basic' or 'elementary' school ("folkskola" in Swedish) was 6 or 7 years of education.[113] Thus, education was treated as a binary variable based on the distribution of educational attainment levels and earlier work on risk of cognitive decline and dementia in this older-aged cohort[113] and was coded as '≤7 years educations / >7 years education' in *Study I* and *Study III,* and equivalently as 'elementary education/higher education' in *Study IV*.

Covariates for behavioral, lifestyle, and work environment factors were based on baseline questionnaire data (SATSA, SALT, or STR-1973, whichever relevant) and included: smoking (ever/never), habitual alcohol consumption (consumed alcohol during the last month vs. no alcohol consumption during the last month), physical exercise (hardly any exercise, light exercise, moderate exercise, intense exercise), and BMI (kg/m^2) with categories:: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).

Manual work status was grouped as manual and non-manual work based on self-reported occupation. A scale for complexity of work was created based upon the self-reported occupation that the individual had for the greater part of his/her working life. Occupations were coded according to categories of the 1980 Swedish Population and Housing Census, which was then matched based on occupational descriptions to the 1970 U.S. Census occupational classification system for which a score matrix was available and used to derive scores for work complexity ranging between 0 and 10.[114] Higher scores reflected greater work complexity.

Covariates for medical conditions and medication use were generally derived from baseline questionnaire data and included:

- CVD, defined as ever having had angina pectoris, heart failure, high cholesterol, claudication or intermittent claudication, thrombosis, ischemic or hemorrhagic stroke, transient ischemic attack, cardiac, valvular murmurs or narrowing of the carotid arteries, and irregular heartbeat (yes/no).
- Stroke, ischemic or hemorrhagic (ever/never).
- Diabetes, Type I or II (yes/no).
- History of cancer (yes/no).
- Chronic obstructive pulmonary disease (yes/no) which was constructed based on whether one coughed with or without phlegm, or had bronchitis or emphysema.
- Depression scale based on the 11-item short form of CES-D.
- Hypnotics and sedatives use, including sleep medications (ever/never).

For CVD, stroke, diabetes, and use of hypnotics and sedatives, these questionnaire-based data were supplemented with register data.

- Non-stroke CVD based on ICD codes from the NPR: 420, 450, 453.33(ICD-7); 410-414, 440, 443.90 (ICD-8); 410-414, 440, 443X (ICD-9); 984, 3068, 3080, 3127, 3141, 3158, FNC, FND, FNE, FNG00, FNG02, FNG05 (ICD-10).
- Stroke based on ICD codes from the NPR: 330, 331.00, 331.01, 331.09, 331.99, 332.00, 332.00-19, 332.29, 334.00-98 (ICD-7); 430, 431, 433, 434, 436 (ICD-8); 430, 431, 434, 436 (ICD-9); I60, I61, I63, I64 (ICD-10).
- Diabetes based on ICD codes from the NPR: 260.09, 260.20, 260.21, 260.29, 260.30, 260.40, 260.49, 260.99 (ICD-7); 250.00-09 (ICD-8); 250A-H, 250X (ICD-9), E10, E11, E12, E13, E14 (ICD-10).
- Hypnotics and sedatives use based on the ATC code of N05C from the PDR.

APOE genotype data came from TwinGene, and *APOE* status was categorized as *APOE* ε4 carrier versus *APOE* non-ε4 carrier.

5 METHODS

5.1 STATISTICAL METHODS

5.1.1 Cox proportional-hazards regression (*Study I, Study II, Study III*)

The Cox model is a type of survival model well-known for its application to time-to-event data.[115] Briefly, the Cox model is a semi-parametric model which allows for the distribution of the underlying baseline hazard to be unspecified or not directly estimated. The formula for the Cox proportional-hazards model is as follows:

$$h(t;x_i) = h_0(t)\exp(\beta' x_i)$$

where t is time, $h_0(t)$ is the baseline hazard function, x represents covariates and β represents their estimated coefficients. The effect estimate is the hazard rate or simply the hazard, which refers to the probability that an individual has an event at time t. A hazard ratio (HR), then, is the hazard in the exposed divided by the hazard in the unexposed.

The model is based on the proportional-hazards assumption, which stipulates that the *relative hazards* is constant between exposed and unexposed groups over time. However, the *magnitude* of the hazards may vary over time, i.e. if the hazards in the exposed group increases over time, then the hazards in the unexposed group also increases proportionally along with it. The assumption can be tested using Schoenfeld residual tests and visually inspected via log-log survival plots. In all studies that employed Cox models, no statistically significant violations of the proportional-hazards assumption were observed.

Additionally, to deal with the heteroscedasticity of data arising from relatedness (dependence) between members of a twinship, we included cluster-robust standard errors.

5.1.2 Twin methodology – Co-twin control design (*Study I* and *Study III*)

In twin methodology, rather than treating the relatedness between members of a twin pair as a nuisance, here we take advantage of their unique relationship.

The co-twin control method is an elegant research design for detecting the extent to which an association between an environmental risk factor and an outcome variable is due to familial confounding (shared early environmental or genetic factors influencing both the risk factor and outcome). If the association between a risk factor and an outcome attenuates or disappears in within-pair analyses, this would indicate presence of familial confounding. If the association further attenuates in within-pair analyses fitted to a subset of MZ twins (who share the same genome), this would provide additional support of genetic confounding, thereby providing a clearer picture of the extent to which causal

inferences can be drawn. A caveat, however, is that the method requires an adequate number of complete twin pairs, especially if the effect size of the risk factor is small.

The co-twin control design can be applied to different types of regression models, including survival models. This is done by conditioning the model on pair membership. In a survival model setting as in *Study I* and *Study III*, twin pairs discordant for the outcome could mean that a) one twin developed dementia and the co-twin did not develop dementia during the study period, or b) both twins developed dementia, with one twin having developed dementia at an earlier or later age than the co-twin during the study period.

5.1.3 Twin methodology – Quantitative genetic design (*Study II*)

Quantitative genetic designs further utilize the similarity, or the *correlation* statistically speaking, between members of twin pairs to quantify contributions of genetic and environmental factors to a trait. Quantitative genetic analyses are often performed within a structural equation modeling (SEM) framework to model variance and covariance matrices, which are then decomposed into latent (unmeasured) genetic and environmental components.

Twin modelling: Univariate twin model

In a classical univariate twin model for estimating heritability (the proportion of variance due to genetic variance), variance decomposition relies on the assumption that MZ twins share 100% of their genes, DZ twins share on average 50% of their segregating genes, that twin pairs share 100% of shared (or in common) familial environment, and that genetic and environmental components are independent. Thus, within-pair genetic correlations are assumed to be 1 for MZ twins and 0.5 for DZ twins, and that the shared environmental correlation is 1 for both types of twins.

A phenotype is assumed to be influenced by genetic and environmental effects. Specifically, the total phenotypic variance within the population may be decomposed into the following biometric components: additive genetic effects (A), non-additive (dominance) genetic effects (D), shared or 'common' environmental effects (C), and non-shared or 'unique' environmental effects (E). Shared environment is any environmental effect that makes twins in a pair similar to each other in terms of the phenotype such as parents, childhood SES, neighborhood, and so on. Non-shared environment is everything else and contributes to differences among family members, such as differential parenting, peers, school teachers, et cetera. Measurement error, assumed to be random, also goes into the non-shared environment term which is by definition uncorrelated between members within a pair. While four sources of variance are quantifiable, only three variance components may be estimated simultaneously using twin modelling. In *Study II*, we elected not to consider component D because the investigated traits indicated no evidence of dominant genetic influences (phenotypic correlations in MZ pairs were not

more than twice that of DZ pairs). Further, the component of A is a good approximation of genetic effects (A+D). Resulting from this is an ACE model.

In quantitative genetic model fitting, the first step is to fit a saturated model in which there are no constraints on mean, variance, and covariance structures, i.e. means and variances for MZ and DZ twins as well as for each twin within a pair are estimated. By building a saturated model, we may test whether means and variances are equal by twin order and by zygosity using the likelihood ratio test (LRT). Next, genetic twin models such as the ACE model, which is a sub-model or 'nested' model of the saturated model, may be compared to the saturated model using LRT. The ACE model can then be compared to an even more parsimonious model such as the AE model. These model fitting steps were undertaken in *Study II*, where estimates were mainly based on AE models since we noted that the additional parameter of C generally did not improve the model fit.

The total phenotypic variance is the sum of genetic and environmental variance components. These components are *proportions* of variance in a phenotype and thus reflect the relative importance of the component. For binary traits, the components sum up to 1. Taking the AE model as an example:

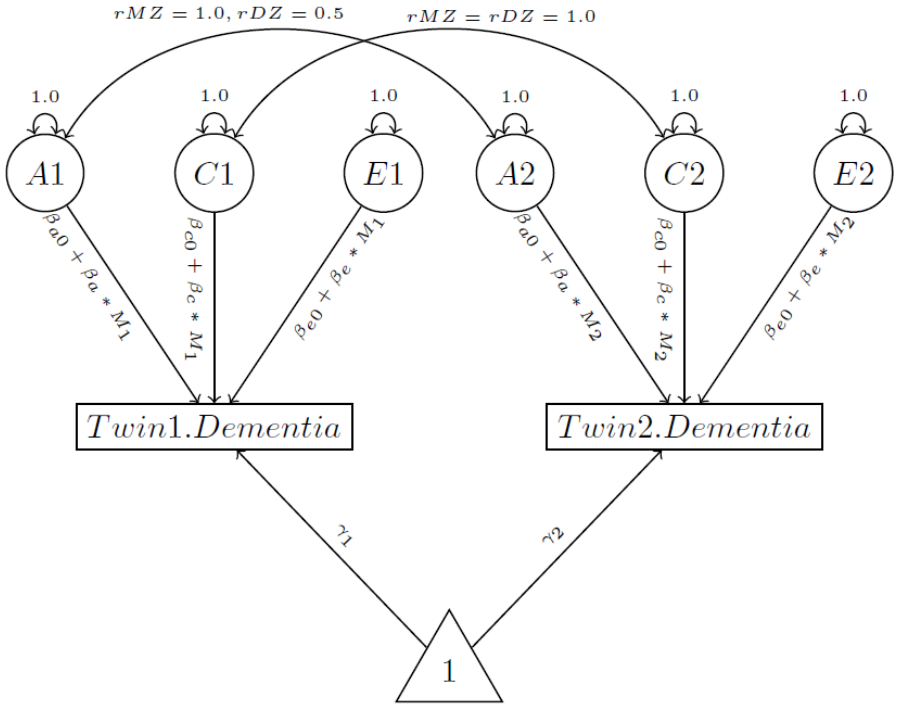
$$Var(P) = Var(A) + Var(E)$$

By definition, heritability (h^2) is then the proportion of variance (the similarities or differences) in a trait that is attributed to genes. It is *not* the proportion of a trait attributed to genes.

$$h^2 = \frac{Var(A)}{Var(P)}$$

Twin modelling: Moderation model

The univariate twin model can also be extended to include a moderator, which results in what we call a univariate moderation twin model, or simply a moderation model. A moderation model addresses whether Trait A (i.e. sleep) moderates genetic and environmental variance components underlying Trait B (i.e. dementia). Figure 5.1.3 illustrates a path diagram of the ACE twin moderation model used in *Study II*.



$$\gamma_1 = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Sex + \beta_4 M_1 + \beta_5 M_2$$

$$\gamma_2 = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Sex + \beta_4 M_2 + \beta_5 M_1$$

Figure 5.1.3. Univariate ACE moderation twin model estimating the sleep-moderator effect on genetic and environmental influences on dementia/AD.
Note: A = additive genetic influences; C = common environmental influences; E = unique environmental influences; rMZ = correlation in MZ twins; rDZ = correlation in DZ twins. Means and variances were specified separately. In the means model, for each twin, linear and quadratic age, sex, and the moderator (M_1) of twin 1 and the moderator (M_2) of the co-twin was controlled for. For the variances, genetic, shared and non-shared components of variance were allowed to differ as a function of moderator M_1 or M_2.

5.1.4 Liability threshold model (*Study II*)

For all binary traits under study, ACE and AE twin models were combined with a liability threshold model.

For example, dementia is a dichotomous measure; one either has a diagnosis of dementia or does not. The liability threshold model assumes that binary traits are affected by numerous factors with small effects that sum up to a liability score. Thus, there is an

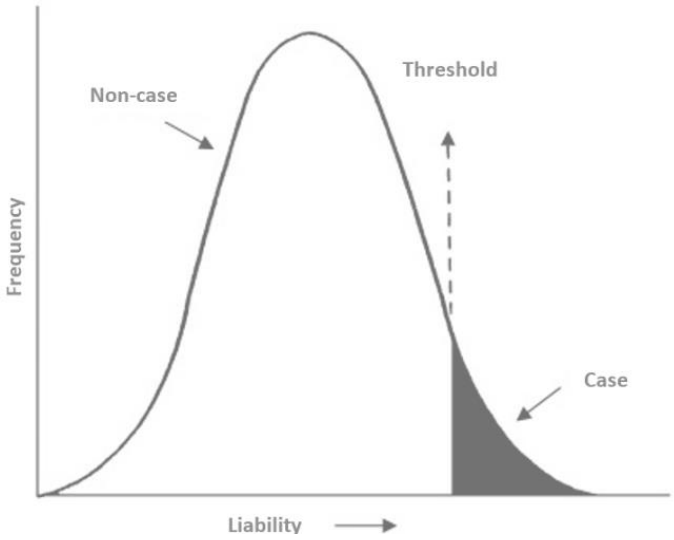


Figure 5.1.4. Liability threshold model.

underlying normal distribution of liability for dementia in the population with one threshold for binary traits (for traits with ordinal groupings, there is more than one threshold). When a certain threshold is reached, i.e. when clinical symptoms of dementia appear and persist, it is at this cut-off when a non-case becomes a case. The further to the right of the liability threshold, the more severe the dementia (Figure 5.1.4).

Thus, with the appropriate tools genetically informative twin data are helpful for understanding genetic and environmental influences on phenotypic variation.

5.1.5 Latent Growth Curve Modeling (*Study IV*)

Latent Growth Curve Modeling (LGCM) is a longitudinal analysis technique for estimating change (or specifically growth or decline) over time.[116] It can also be thought of as a mixed model that estimates fixed and random (latent) effects.

The first step of LGCM entails establishing the optimal fit of the model, that is, one that best captures the collection of individual change over time. This can be done by comparing the fit of two or more models based on, for example, Akaike Information Criterion (AIC) fit estimates. In *Study IV*, the fit of a one-slope model was compared to that of a two-slope model with retirement age as centering age. In the one-slope model, or the linear model, an intercept and a slope (Slope 1) was included, with Slope 1 defined as the rate of cognitive change per year spanning across the entire measurement period. In the two-slope model, also called a piecewise model or spline model, an intercept and two slopes (Slope 1 and Slope 2) were included, with Slope 2 defined as the additional rate of cognitive change per year after retirement age. Based on a comparison of AIC fit estimates (the smaller the better fitting), the two-slope model was determined to be better fitting for all cognitive factors.

The second step is to include predictors as well as other covariates of interest into the model. This results in a conditional growth model since parameter estimates are now adjusted for covariates.

In summary, fixed effects are represented by the mean intercept and the mean slopes, and random effects are the variance of individual trajectories around these means. Together, fixed and random effects provide a picture of growth (or decline) that takes into account between-individual differences and within-individual variation.

5.2 OVERVIEW OF METHODS BY STUDY

5.2.1 *Study I* – The prospective study on sleep characteristics and incident dementia

5.2.1.1 Study population

Study I explored the association between sleep-related characteristics and incident dementia while accounting for baseline cognitive function. The study base comprised like and unlike-sexed twins from the old and middle STR cohort who were born 1958 or earlier and who had participated in the SALT interview in 1998-2002. Since by design only SALT participants who were 65 and older at the time of interview (N=12,803) were administered questions about sleep, the age range of the study population at baseline was between 65-99 years, effectively truncating the cohort to those born 1933 or earlier. The study population in *Study I* is illustrated in the flowchart in Figure 5.2.1.1. Altogether, 11,247 individuals responded to at least one of the sleep questions, and 4,716 responded to all sleep questions. As mentioned earlier, some of the sleep questions were not administrated to all persons aged 65 and over due to funding considerations, hence the low response rate to all sleep questions.

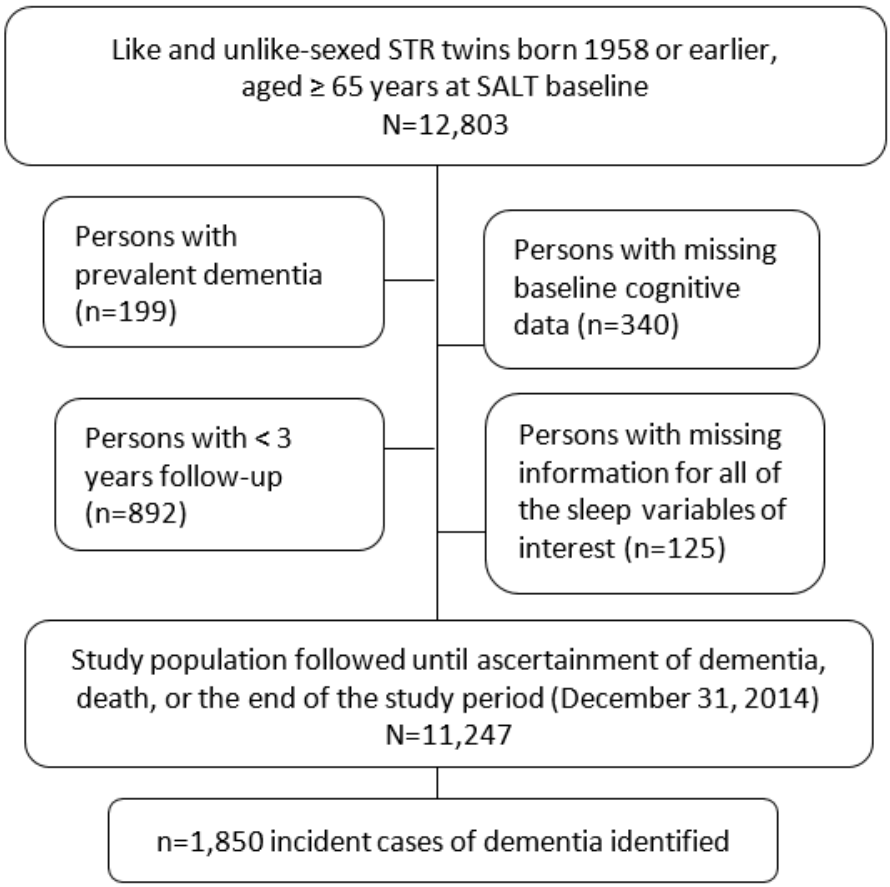


Figure 5.2.1.1. Flow chart of participant selection and exclusion process (*Study I*).

5.2.1.2 Study design

Study I is a prospective population-based study. Participants were interviewed at baseline in 1998-2002 and followed until a dementia diagnosis (ascertained in the NPR, PDR, and CDR), death, or end of follow-up (December 31, 2014), whichever came first (Figure 5.2.1.2).

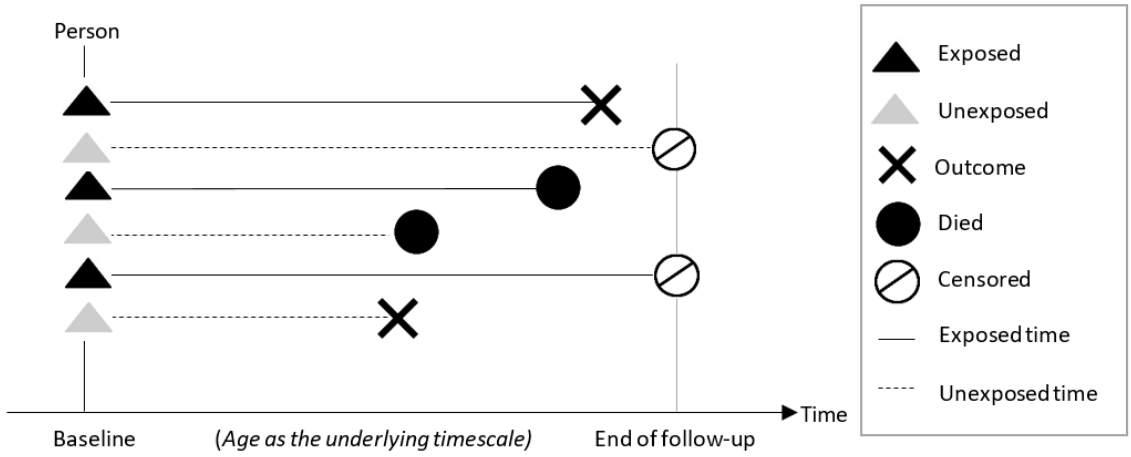


Figure 5.2.1.2. Prospective cohort design with time-to-event data.

5.2.1.3 Exposure and outcome measures

Exposure: Six sleep-related measures (TIB, rising time, bedtime, sleep quality, non-restorative sleep, and heavy snoring) were assessed as exposures. These measures were based on KSQ items included in the SALT interview. A TIB measure including daytime nap time was created for a sensitivity analysis.

Outcome: Incident dementia. Dementia data were ascertained from register sources (the NPR, PDR, or CDR).

5.2.1.4 Statistical analysis

Cox proportional-hazards regression was performed to estimate HRs with 95% CIs for the associations between the 6 sleep characteristics and incident dementia. Age was the underlying time scale. Follow-up time, sex, education, and baseline cognitive functioning (TELE score) were adjusted for in final Cox models. Covariates for smoking, habitual alcohol consumption, physical exercise, BMI, type II diabetes, sleep medication use, NW status, cancer, CVD, and COPD were included in preliminary models, but dropped in final models due to unchanging estimates and to maintain model parsimony.

Multivariable adjusted Cox models were also stratified by baseline cognitive status to assess how HR estimates of associations changed across ordinal levels of baseline cognition.

Co-twin control analysis on a sample of twins discordant for both exposure and outcome was performed to control for familial effects. These models were fitted to all twin pairs (to control for familial confounding), as well as to a subset of monozygotic twin pairs (to control for genetic confounding).

Additional sensitivity analyses entailed Cox analyses using slightly differing study populations depending on exclusions based on follow-up time.

In all models excepting the co-twin control model, cluster-robust standard errors were used to correct for dependence between pair members.

Data analyses were performed in SAS 9.4 and STATA 13.

5.2.2 ***Study II*** **– The twin study estimating genetic and environmental influences**

5.2.2.1 Study population

Study II deals with quantifying genetic and environmental influences on phenotypes for late-life sleep and dementia, as well as testing for moderating effects of sleep on the genetic and environmental influences on dementia and AD. The study population in *Study II* is similar to that in *Study I*, with small differences in inclusion criteria (Figure 5.2.1.1 And Figure 5.2.2.2).

5.2.2.2 Study design

Study II primarily uses a classical twin design to assess the extent to which genetic and environmental factors contribute to a trait. Using the structural equation modeling approach, variances for a trait can be decomposed into latent variables that represent unobserved genetic and environmental contribution. The prospective cohort study design was also employed in *Study II* to confirm the association between the sleep characteristics and incident dementia.

5.2.2.3 Phenotypes

The phenotypes assessed in *Study II* included incident dementia, incident AD, and six late-life sleep characteristics. The sleep characteristics (TIB, rising time, bedtime, sleep quality, non-restorative sleep, and heavy snoring) are the same as those in *Study I.* Regarding the TIB measure, TIB was treated as a binary variable instead of a categorical variable. Thus, we had a long TIB variable which was grouped as 'long TIB' (>9 hours) versus 'moderate TIB' (≤6 to 9 hours). Short TIB was not assessed due to insufficient power. TIB was treated as such in *Study II* in order to comply with assumptions under the liability threshold model. The liability threshold model is necessary for converting binary or categorical data into a latent liability score.

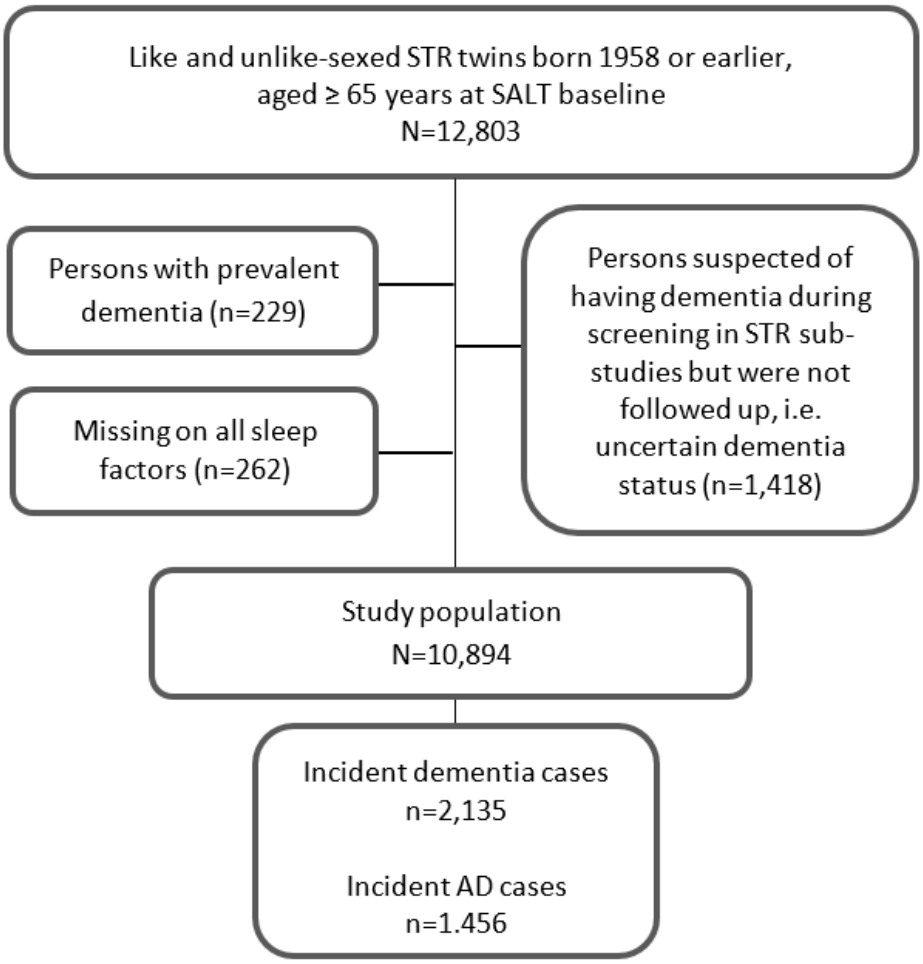


Figure 5.2.2.2. Flow chart of participant selection and exclusion process (*Study II*).

5.2.2.4 Statistical analysis

Within-pair correlations were computed to get a sense of whether there were genetic influences for dementia, AD, and sleep traits. Quantitative genetic analysis, in the form of univariate AE and ACE twin models, were performed to estimate genetic influences (heritability) and environmental influences on the traits. AE models, compared to ACE models, were more parsimonious and generally fit the data better according to likelihood ratio test and AIC fit statistics.

Cox proportional-hazards regression was done to estimate HRs of associations between the sleep traits and dementia (and to confirm the associations reported in *Study I*) as well as between the sleep traits and AD. Cross-twin cross-trait correlations, i.e. correlation between trait 1 (sleep) in one twin with trait 2 (dementia) in the co-twin, were computed and suggested limited genetic correlation between the sleep traits with dementia and AD.

Based on Cox model and cross-twin cross-trait correlation findings, univariate ACE and AE twin moderation models were fitted to assess whether a given sleep parameter moderated the genetic and environmental effects on dementia and AD risk (Figure 5.1.3.) In other words, the moderation models assessed whether the phenotypic variance of the outcome (liability for dementia and AD) explained by genetic (A), shared environment

(C), and non-shared environment (E) differed by level of the moderator (sleep phenotype, namely long TIB and late rising).

For all models, the estimation of the threshold of a trait, i.e. the means (continuous variable) or prevalences (binary variable) of a trait, was adjusted for age and sex. Data management was performed in SAS 9.4, and quantitative genetic analyses in OpenMx and mets packages in R 3.4.1.

5.2.3 *Study III* – The prospective study on SW and incident dementia

5.2.3.1 Study population

Study III examined the association between SW and incident dementia based on two STR cohorts: the STR-1973 cohort and the SALT cohort. The two study populations were analyzed separately in main analyses. As there was overlap of participants between the STR studies (N=8,904), the two were combined into one sample in sensitivity analyses.

To ensure that there was sufficient job experience at the time of responding to the questionnaire, individuals younger than 30 years were excluded from the STR-1973 sample (n=19,178), which was on average younger than the SALT cohort.

As this study was concerned with incident dementia in relation to SW, individuals with prevalent dementia or baseline cognitive dysfunction were excluded, as were those who did not work or those who reported having worked shifts when they were younger than 17, which may have been invalid responses.

Compared to *Study I* and *Study II*, the study population in *Study III* was younger at baseline (mean 37.8 years, SD 5.4 in STR-1973; mean 58.5 years, SD 10.4 in SALT). Thus, the prevalence of dementia in *Study III* was lower (7.4% in STR-1973 and 4.8% in SALT).

Subsamples of the STR-1973 and SALT cohorts participated in TwinGene and therefore had data on *APOE* genotype.

Flow charts of the participant selection process based on the STR-1973 cohort are depicted in Figure 5.2.3.1a and the SALT cohort in Figure5.2.3.1b.

5.2.3.2 Study design

Study III employed a prospective population-based cohort design using time-to-event data (Figure 5.2.1.2). Participants in the STR-1973 cohort were followed from baseline in 1973 until a dementia diagnosis, death, or end of follow-up in December 31, 2014. The median follow-up time was 41.2 years. Participants in the SALT cohort were followed from baseline in 1998-2002 until a dementia diagnosis, death or end of follow-up in December 31, 2014. The median follow-up time was 14.1 years.

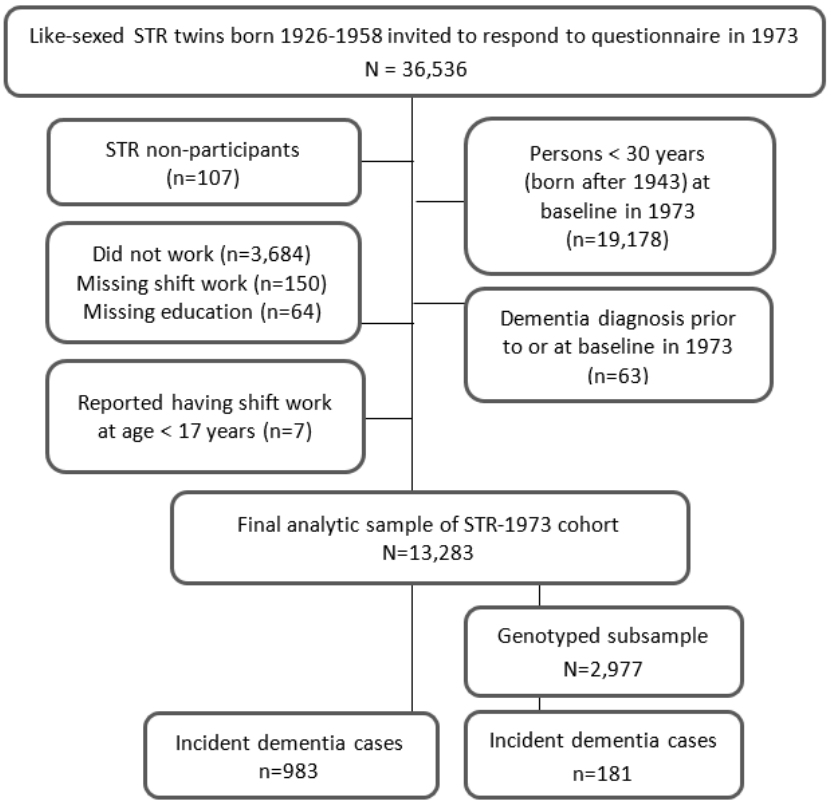


Figure 5.2.3.1a. Flow chart of participant selection and exclusion process for the STR-1973 cohort (*Study III*).

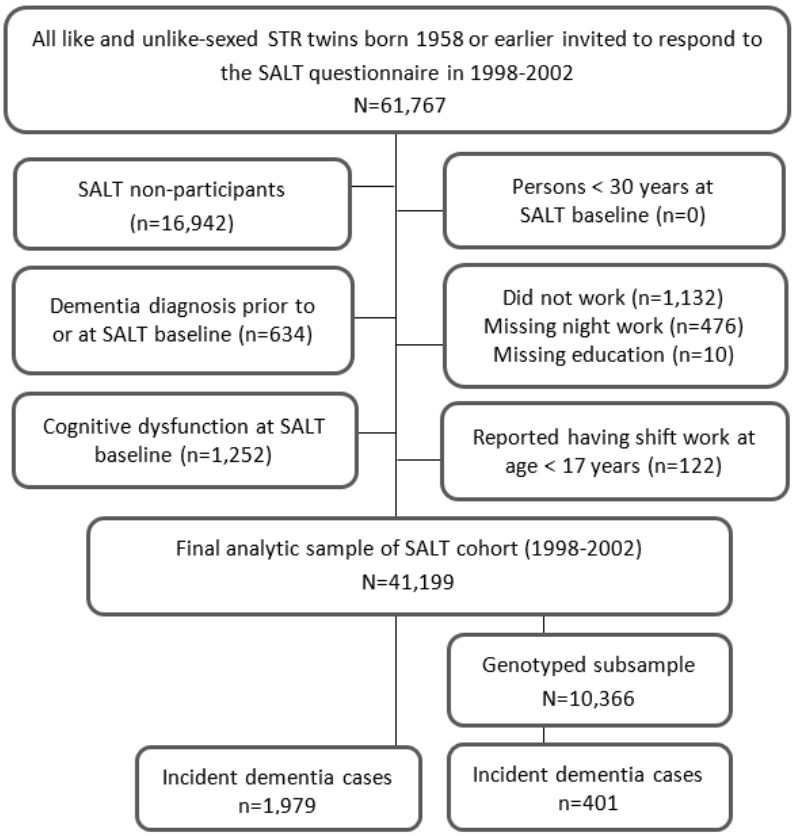


Figure 5.2.3.1b. Flow chart of participant selection and exclusion process for the SALT cohort (*Study III*).

5.2.3.3 Exposure and outcome measures

Exposure: Status and duration of SW in general were assessed in the STR-1973 cohort. Status and duration of NW were assessed in the SALT cohort.

Outcome: Incident all-cause dementia and AD were examined as outcomes in this study.

5.2.3.4 Statistical analysis

Cox models with age as the underlying timescale was applied to estimate HRs for dementia. A cluster sandwich estimator was used to correct for relatedness between members of a twin pair. Since the mean baseline age in the STR-1973 sample was 38 years and 58 years in the SALT sample, there were a few individuals who received a dementia diagnosis under age 65. These cases were considered as early-onset familial cases. Instead of excluding these individuals from the sample, which would be like looking into the future, we allowed these individuals to contribute person-years as non-cases up until the point they received the dementia diagnosis at an age younger than 65.

Main analyses

Two sets of main analyses using Cox models were conducted. In the first set of analyses, SW status and duration of SW were examined in relation to incident dementia. For this analysis, the STR-1973 cohort were followed from baseline in 1973. The second set of analyses examined NW status and duration of NW in relation to incident dementia. For this analysis, the SALT cohort were followed from baseline in 1998-2002. Age, sex, education, diabetes, CVD and stroke were controlled for in final models. Diabetes, CVD and stroke that occurred before a dementia diagnosis were allowed to vary with time; all other potential confounders were time-invariant. SW and NW duration variables were transformed into restricted cubic spline variables with three knots (1, 10, and 20 years) in Cox models.

Sensitivity analyses

Given the overlap of participants in STR-1973 and SALT, it was possible to combine SW information from both study sources. Three sensitivity analyses were undertaken to investigate how well the main findings would hold up depending on how the SW measure was treated. Based on a sample of individuals who had participated in both STR-1973 and SALT, these were the different possible scenarios of SW exposure that were put forth:

- Given that follow-up began in 1973, if one responded that they had SW in the 1973 questionnaire and did not respond that they worked nights in SALT in 1998-2002, SW status was treated as time-varying. For those who had participated in STR-1973 and not in SALT, SW was treated as a fixed variable.
- Given that follow-up began in 1998-2002 at the time of the SALT interview, for those who had participated in both STR-1973 and SALT, the response in SALT determined the SW exposure duration if we assume that the duration reported in SALT included the duration reported in STR-1973. For those who participated in

only one of the studies, SW duration information was based on the study that one had participated in.

- In the third scenario, given that follow-up time began in 1998-2002 when the SALT interview occurred, for individuals who participated in both STR-1973 and SALT, SW duration was the sum of SW durations reported in both studies. And again, for those who participated in just one of the studies, SW duration was based on whichever study one had participated in.

There was also the matter of possible cohort effects, and thus a final sensitivity analysis was done that entailed restricting the SALT sample to include individuals born 1926-1958, so as to be comparable to the STR-1973 sample born 1926-1958.

Additional analyses

In the genotyped subsamples, *APOE* status was include in Cox models.

Similar to *Study I*, co-twin control analyses were applied to a sample of twins discordant for exposure (SW/NW) and outcome (incident dementia). The model was fit to all twin pairs (including DZs and MZs) as well as to a subset of MZ twin pairs.

Data management was done in SAS 9.4 and data analyses in STATA 14.1.

5.2.4 ***Study IV*** **– The longitudinal study on SW and cognitive aging**

5.2.4.1 Study population

Study IV deals with the relationship between SW and normative cognitive aging. Participants were drawn from the IPT phase of the population-based SATSA. A total of 859 individuals had participated in at least one out of nine IPT waves. Participants with dementia at baseline were excluded; for those who developed dementia later in the course of follow-up, data points after the diagnosis were dropped from the longitudinal data analysis. After exclusion criteria were applied, the resulting main sample with complete data included 595 participants.

Of the 595 participants with data on any-type SW status (of whom 106 had SW history), a subset of participants born 1958 or earlier (n=320) had also participated in SALT and therefore had data on NW. All individuals who responded in SALT that they worked nights had also responded that they were shift-workers in SATSA (n=47). Additionally, there was a subsample of 77 men born 1936 and 1948 who had undergone military conscription when they were approximately 18-20 years of age and thus had data on early adult general cognitive ability. The flowchart of the study population is depicted in Figure 5.2.4.1.

5.2.4.2 Study design

A longitudinal study design was used in *Study IV*. The main analytic sample of 595 participants were followed up for a mean of 17.6 years (SD 8.8) during 1984-2012.

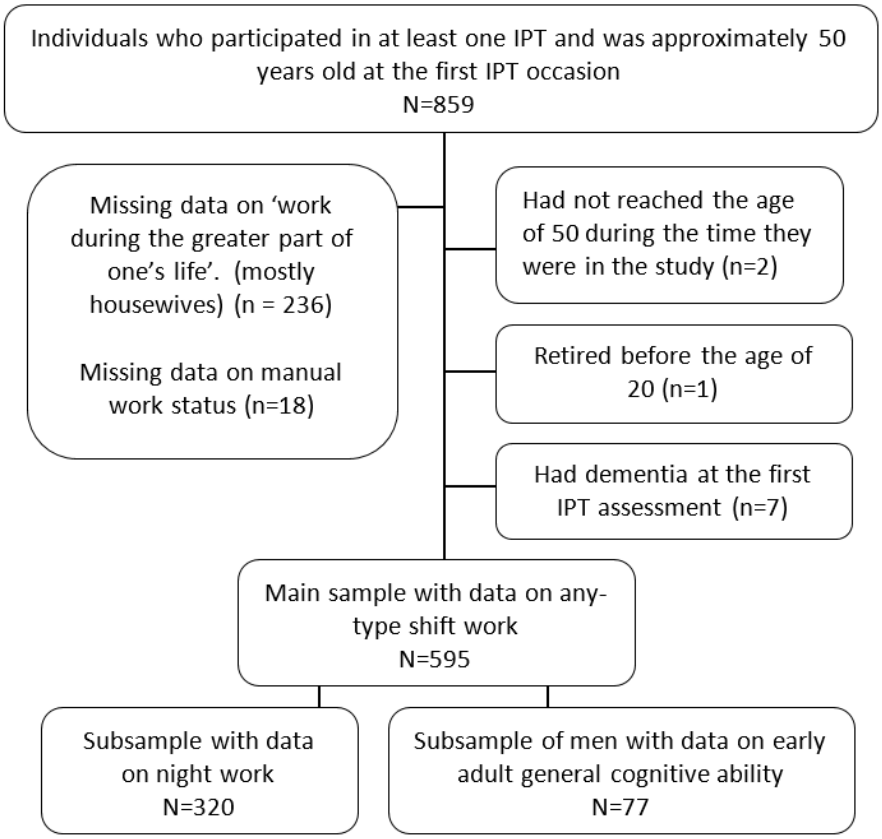


Figure 5.2.4.1. Flow chart of participant selection and exclusion process (*Study IV*).

5.2.4.3 Exposure and outcome measures

Exposure: SW of any type was the exposure variable of interest in the full sample. This data came from baseline Q1 in 1984. A NW measure based on SALT data from 1998-2002 was examined in a subsample analysis. A binary (yes/no) and categorical (0 years; 1-9 years; 10-19 years; 20 or more years) measure of SW and NW were assessed.

Outcome: Outcome measures included the mean cognitive performance at retirement age and the rate of cognitive performance change for five components (verbal, memory, spatial, and processing speed abilities).

5.2.4.4 Statistical analysis

The main analysis entailed a LGCM for estimating the effect of any-type SW on mean cognitive performance at retirement, and on change in cognitive performance across the mid to late adult life course. This was done for each of the five cognitive components. The LGCM includes an intercept and two slopes, which fitted the data better compared to a model with an intercept and one slope, as determined by AIC fit estimates (Table 5.2.4.4).

The intercept is fixed at retirement age, which is set as centering age. The first slope represents the rate of cognitive change per year across the whole measurement period, and the second slope represents the additional rate of cognitive change per year beyond retirement.

Table 5.2.4.4. Comparison of AIC fit estimates for each cognitive factor

Cognitive Measure	One-Slope Model: Intercept and 1 slope	Two-Slope Model: Intercept and 2 slopes
	AIC estimate	AIC estimate
Verbal	13,499	13,440
Spatial abilities	14,110	14,060
Memory	15,810	15,789
Processing speed	15,193	15,119
Global cognitive ability	12,865	12,564

Note: Smaller AIC estimate indicates better fitting model.

In a subsample of men, selection effects, i.e. the possibility that those with higher cognitive ability selected themselves into jobs entailing SW or not, were tested. T-tests, with a significance threshold set at $p = 0.05$, were used to compared mean early adult cognitive scores between shift-workers and day-workers, within low and high education groups.

An additional subsample analysis was done to examine the association between NW and cognitive performance.

Data management and analyses was done in SAS 9.4 (*proc mixed* command for LGCM).

6 MAIN FINDINGS AND DISCUSSION

Table 6. Overview of the 4 studies within this thesis.

Study	I	II	III	IV
Aim	Examine association between late-life sleep characteristics and incident dementia.	Estimate heritability for sleep characteristics, dementia and AD, and to examine whether dementia-related sleep characteristics modify genetic influences on dementia and AD.	Investigate association between mid-life SW and incident dementia.	Estimate impact of mid-life SW on cognitive aging in late life.
Data sources	SALT, NPR, PDR, CDR	SALT, NPR, PDR, CDR, SATSA, OCTO-Twin, Gender	SALT, STR-1973, NPR, PDR, CDR, TwinGene	SATSA, SALT, Conscription Register
Study population	Like and unlike-sexed STR twins born 1958 or earlier, ≥65 years and dementia free at SALT baseline	Like and unlike-sexed STR twins born 1958 or earlier, ≥65 years and dementia free at SALT baseline	Like and unlike-sexed STR twins born 1958 or earlier, ≥30 and dementia free at STR-1973 or SALT baseline	Like-sexed STR twins born 1958 or earlier, ≥50 years and dementia free at the first IPT occasion in SATSA
Baseline age (Mean, SD)	72.5 (SD 5.9)	72.6 (SD 6.0)	STR-1973: 37.8 (SD 5.4) SALT: 58.5 (SD 10.4)	58.2 (SD 10.5)
Design	Prospective cohort; co-twin control	Prospective cohort; classical twin design	Prospective cohort; co-twin control	Longitudinal
Follow-up time	17 years	17 years	STR-1973:42 years SALT: 17 years	27 years
Exposure	Sleep characteristics (TIB, late rising, late bedtime, sleep quality, non-restorative sleep, snoring)	Sleep characteristics (TIB, late rising, late bedtime, sleep quality, non-restorative sleep, snoring)	SW, NW	SW, NW
Outcome	Incident dementia	Incident dementia and AD	Incident dementia	5 cognitive factors (verbal, memory, spatial, processing speed, global)
Statistical methods	Cox regression, ordinal logistic regression	Cox regression, quantitative genetic analysis	Cox regression	LGCM
Covariates in final model	Age, sex, education, and baseline cognitive function	Age and sex	Age, sex, education, diabetes, CVD, and stroke	Age, sex, education, and occupational status
Main findings	Short TIB was associated with 40% increased dementia incidence based on full sample analysis. Long TIB and late rising were associated with higher dementia incidence (HR=1.47 and HR=1.59, respectively) among those with baseline cognitive dysfunction, suggesting these characteristics were prodromal.	Heritability was 47% for dementia and 54% for AD. For late rising and late bedtime, heritability was about 50%, and between 13-31% for long TIB, sleep quality, non-restorative sleep, and snoring. While long TIB and late rising were associated with higher dementia incidence, these sleep traits did not moderate genetic effects for liability of dementia and AD.	SW of any type (HR=1.36) and NW (HR=1.12) were associated with higher dementia incidence. Longer duration of SW and NW predicted higher dementia risk. Among *APOE* ε4 carriers, those with ≥20 years of SW and NW had a 2 to 4-fold greater dementia risk compared to day-workers.	SW of any type or NW during midlife did not affect the level of performance at retirement or the rate of change for any of the cognitive factors in later life.

6.1 *STUDY I* – THE ASSOCIATION BETWEEN SLEEP CHARACTERISTICS AND INCIDENT DEMENTIA

6.1.1 Main findings

Participants had a mean baseline age of 72.5 years (SD 5.9) and were followed up for a median of 14.3 years. The incidence rate of dementia was 10.3 per 1,000 person-years in this study population aged 65 years and older. Out of 11,247 participants, 1,850 (16.4%) cases of incident dementia were identified during the 17-year study period.

Based on multivariable adjusted analysis of the full sample, TIB and rising time were associated with dementia incidence. TIB showed a U-shaped association with dementia incidence, such that short (HR=1.40, 95% CI=1.06-1.85) and long TIB (1.11, 95% CI=1.00-1.24) were related to higher rates of dementia. In a sensitivity analysis a TIB measure including daytime nap time was examined, but estimates remained unchanged. Those habitually rising from bed 8AM or later, compared to earlier risers, showed a 12% (95% CI=1.01-1.24) higher risk of dementia. Bedtime, sleep quality, non-restorative sleep, and snoring were not predictive of incident dementia.

We then tested the association between sleep characteristics and incident dementia, stratified by baseline cognitive status. Among those cognitively intact at baseline, the association between short TIB and incident dementia became more pronounced, though with wider confidence intervals (HR=1.74, 95% CI=1.19-2.55). In those with poorest baseline cognitive status, long TIB (HR=1.47, 95%=1.08-2.00) and late rise time (HR=1.59, 95% CI=1.15-2.20) were associated with greater risk of dementia. Results from full sample analyses are illustrated in Figure 6.1a, and results from stratified sample analyses are illustrated in Figure 6.1b.

Co-twin control analyses generally produced associations with wide confidence intervals that included the null, with no discernable pattern of findings, i.e. associations were not stronger based on a sample of only MZ twin pairs compared to a sample of all twin pairs. Thus, one cannot draw conclusions on whether familial factors confounded the associations between sleep characteristics and incident dementia.

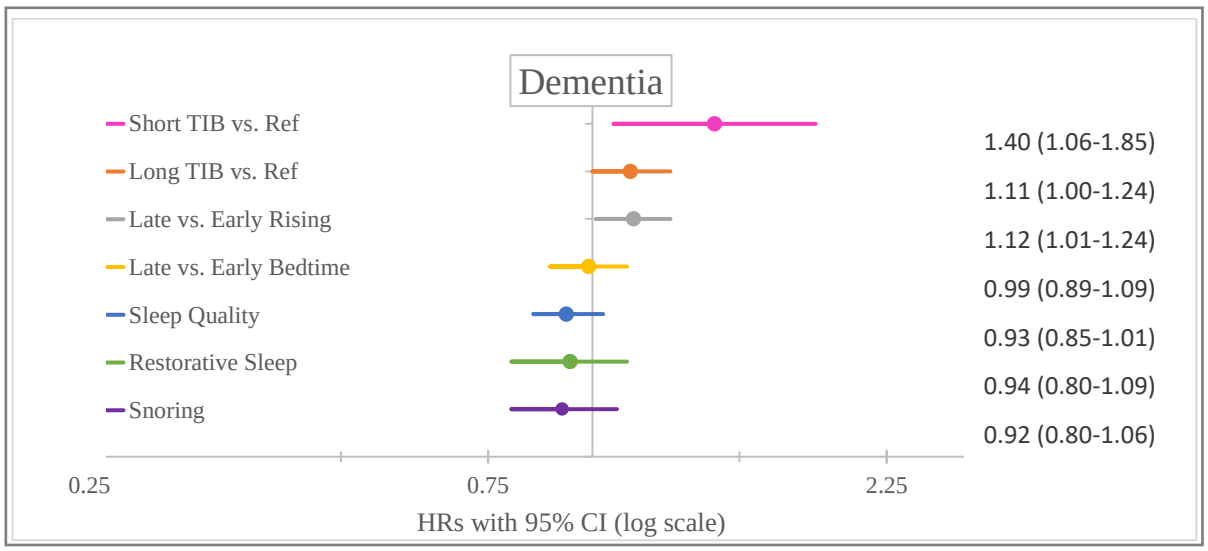


Figure 6.1a. Forest plot of HR associations between sleep characteristics and incident dementia based on full sample analysis.

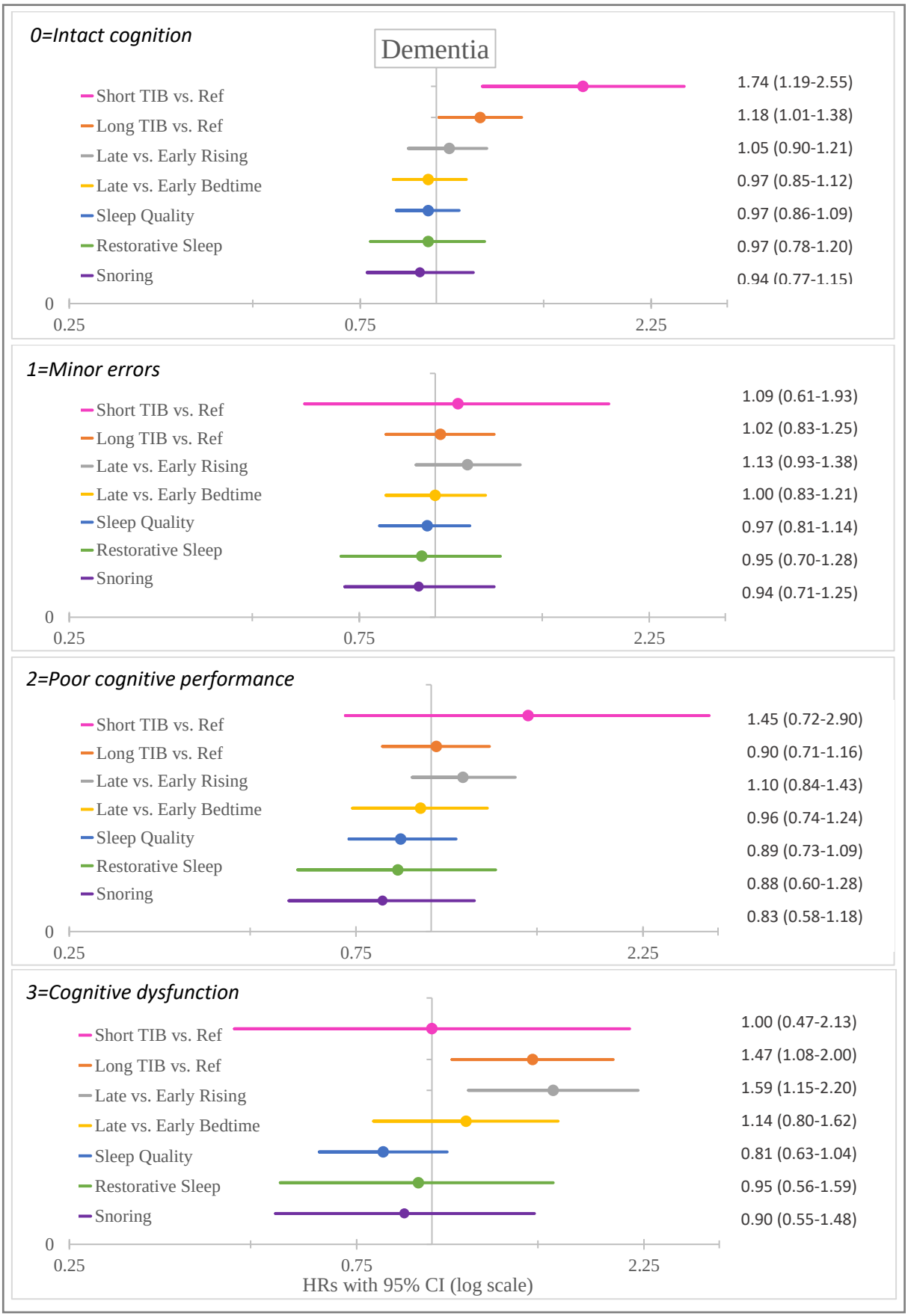


Figure 6.1b. Forest plot of HR associations between sleep characteristics and incident dementia, stratified by baseline cognitive status.

6.1.2 Discussion

Study I extends prior studies on sleep characteristics in relation to subsequent risk of dementia. The U-shaped associations between TIB and increased dementia incidence agree with previous research showing positive associations between extreme sleep durations and elevated dementia risk.[66] Mechanisms explaining the risk conferred by short sleep have been proposed. Studies based on mouse models have demonstrated that Aβ levels in brain interstitial fluid increase with longer time spent awake,[117] and that rate of Aβ clearance is decreased during the wake state compared to the sleep or anesthetized state.[118] Thus, short sleepers, who by default spend more time awake, may present with more amyloid accumulation that precedes amyloid plaque formation—a classic feature of AD. Short sleep has also been associated with subsequent ventricular enlargement[119] and frontotemporal cortical thinning[120] in those with dementia compared to healthy aged counterparts.

The mechanism underlying long sleep and dementia risk is less clear. However, our study demonstrated that the association between long sleep and heightened risk of dementia was particularly strong in those exhibiting cognitive impairment at baseline, giving indication that long sleep may be marker rather than a contributor of pathological cognitive processes.

Adding to a previous study that observed delayed peak circadian rhythm activity timing was associated with higher odds of mild cognitive impairment and dementia,[121] the present study found that rising later in the morning compared to rising earlier was predictive of higher dementia incidence. On the other hand, later bedtime, which one would think goes hand in hand with later rising, was not significantly predictive. But considering there was variation in TIB, which was constructed from the variables for rising time and bedtime, it would make sense that early risers are not necessarily early sleepers. Rise time may be a better phenotypic representation of circadian rhythms as there are fewer external influencing factors and therefore more consistent than bedtimes within an individual. For bedtime, beyond the influence of circadian rhythms and sleep pressure are exogenous cues like artificial light and social activities. This may have led to a higher likelihood of reporting inaccurate bedtimes, which could lead to misclassification of the non-differential type, and thus have resulted in null findings.

Our findings concerning sleep quality and dementia incidence agrees with previous studies that reported null findings[119, 122, 123], but not with others that did find an association.[124-126] This study also did not find snoring and sleep restoration to be predictive of incident dementia. Misclassification of exposure could be a possible culprit for the lack of association (see chapter 8 on methodological considerations).

Overall, *Study I* showed that short and long TIB as well as late rising time among older adults were associated with greater dementia incidence in the following 17 years. The pattern of findings suggests that very long sleep and delayed rising represent prodromal dementia, whereas short TIB plays a contributory role for dementia.

6.2 *STUDY II* – SLEEP CHARACTERISTICS AND DEMENTIA: GENETIC AND ENVIRONMENTAL INFLUENCES

6.2.1 Main findings

For the 10,894 participants in this study, the mean baseline age in 1998-2002 was 72.6 (SD 6.0). During the study period, 2,135 (19.6%) developed dementia, of whom 1,456 were AD cases (68.2%).

The first part of *Study II* probed the balance between genetic and environmental contributions for a trait (dementia, AD, and late-life sleep traits). Within-pair correlations were generally twice as strong in MZ pairs as that in DZ pairs, indicating presence of genetic influences for all traits under study. For short TIB, although the within-MZ-pair correlation was high (.59) compared to the within-DZ-pair correlation (-.01), these coefficients were based only on 3 complete MZ twin pairs and 1 complete DZ twin pair concordant for short TIB. Given that there were so few observations with this phenotype, short TIB was not (and could not be) examined further in quantitative models. AE models provided further evidence of genetic influences on the traits (Figure 6.2). Heritability for dementia, AD, late rising and late bedtime was approximately 50%, indicating substantial genetic effects for the dementia outcomes and chronotype-related traits. For the other sleep traits of non-restorative sleep, sleep quality, and snoring, heritability ranged between 13-31%, characterizing the importance of environment factors for these sleep traits.

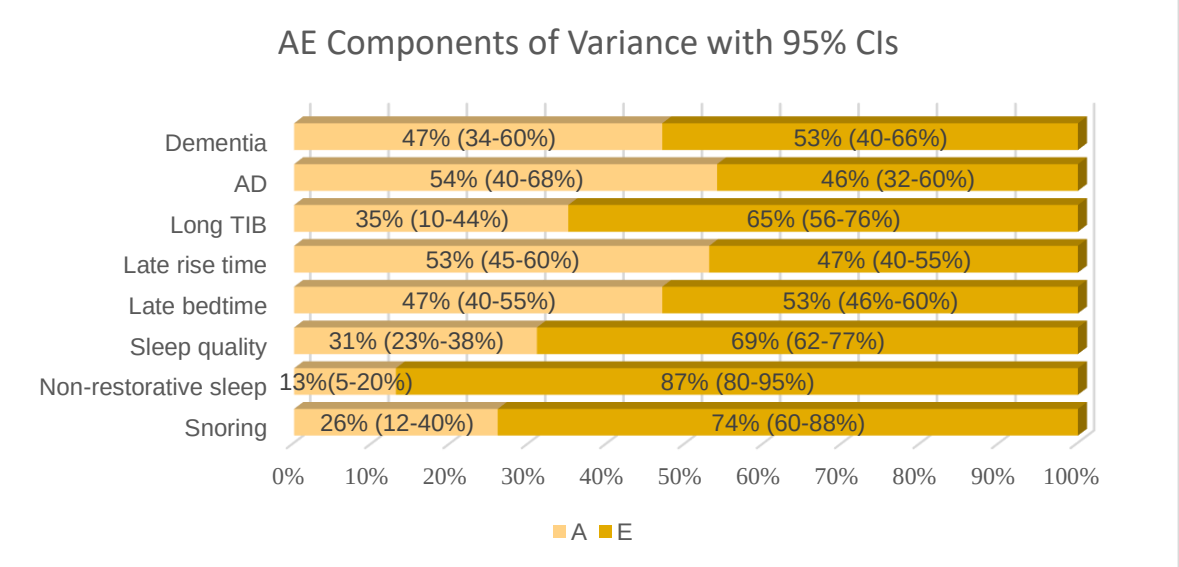


Figure 6.2. AE components of variance with 95% CIs for dementia, AD, and sleep traits.

The second part of *Study II* investigated sleep measures as a moderator on the genetic and environmental influences on dementia and AD liability. Before performing twin moderation analysis to investigate this question, we confirmed the associations between long TIB (HR=1.19, 95% CI=1.08-1.82) and late rising (HR=1.11, 95% CI=1.00-1.22) with incident dementia, which were similar in magnitude to that in *Study I*. The sleep measures were also analyzed in relation to incident AD. Similar associations were observed (Table 6.2), wherein long TIB (HR=1.35, 95% CI=1.11-1.40) and late rising (HR=1.11, 95% CI=1.01-1.23) were associated with higher risk of AD. We also checked cross-twin cross-trait correlations, which were low – about .10 or less – and were not discernably higher in MZ twins than in DZ twins. This suggests minor or absence of additive genetic influences to the contribution of the covariation between a given sleep trait and dementia or AD, i.e. the two traits are unlikely to share common genetic roots.

Table 6.2
Associations between sleep measures and incident dementia and AD based on Cox models.

	Dementia	AD
	HR (95% CI)	HR (95% CI)
Time in bed		
Short (≤ 6 hours)	1.40 (1.08-1.82)	0.99 (0.69-1.42)
Reference	1.00	1.00
Long (> 9 hours)	1.19 (1.08-1.31)	1.25 (1.11-1.40)
Rise time		
Earlier than 8AM	1.00	1.00
8AM or later	1.11 (1.00-1.22)	1.11 (1.01-1.23)
Bedtime		
Earlier than 11PM	1.00	1.00
11PM or later	0.92 (0.83-1.03)	0.92 (0.83-1.03)
Sleep quality index	0.93 (0.86-1.01)	0.93 (0.86-1.01)
Non-restorative sleep index	0.92 (0.79-1.07)	0.92 (0.80-1.07)
Heavy snoring		
No	1.00	1.00
Yes	0.90 (0.79-1.03)	0.90 (0.79-1.02)

Note: Model is adjusted for sex with age as the underlying timescale, with robust standard errors. Analyses of TIB, rise and bedtime were based on a sample of N=10,894. The sleep quality index, non-restorative sleep index, and heavy snoring were based on smaller samples of N=5,278, N=5,308, and N=4,686, respectively. Note: Higher scores on the sleep quality index and non-restorative sleep index indicate poorer quality or less restorative sleep, respectively.

Since long TIB and late rising were associated with incident dementia and AD, these traits were assessed as moderators in separate moderation models. After implementing a rigorous procedure of ACE and AE model fitting which entailed comparing a number of nested models, we observed that models with moderation on the variance did not fit significantly better compared to models without moderation on the variance. Taking the late rising phenotype as an example, this means that the *proportion of variance* in dementia or AD attributable to *genetic* and *environmental variance* did not differ between late risers and early risers. Thus, we did not find evidence of moderation effects of long TIB or late rising on the genetic and environmental influences on liability of dementia or AD.

6.2.2 Discussion

Our heritability estimates of about 50% for incident AD and incident dementia is in line with those previous studies.[3, 41, 42] Our findings concerning rising time and bedtime, together with findings from previous studies on diurnal preference,[127] suggest that chronotype-related phenotypes are equally influenced by genetic and environmental effects. Heritability for late bedtime was slightly lower than for late rising, which we suspect may be due to random error. For instance if we assume that, within an individual, bedtime is more susceptible to exogenous cues, i.e. light emitted from a smartphone or laptop, this may contribute to more inter-individual variation in bedtimes. Comparatively, rise times, other than perhaps waking up to use the bathroom, may be more driven by circadian rhythms. For the other late-life sleep traits under study—long TIB, sleep quality, non-restorative sleep, and heavy snoring—our study and others[128-131] point to the relative importance of environmental factors in explaining the phenotypic variances.

This is the first study to examine sleep habits, specifically long TIB and late rising, as moderators of genetic influences on dementia and AD liability. As we did not observe moderation effects, this indicates a lack of gene-environment interaction influencing liability of AD or dementia. Taken together with findings from *Study I*, long TIB and late rising are unlikely factors augmenting dementia susceptibility, but rather prodromal manifestations of preclinical dementia. Short TIB, on the other hand, appeared to fit the role of a risk factor for dementia and AD; unfortunately, too few observations with short TIB meant moderation analysis for short TIB and dementia/AD was unachievable.

6.3 *STUDY III* – THE ASSOCIATION BETWEEN SW AND INCIDENT DEMENTIA

6.3.1 Main findings

For the STR-1973 cohort, the mean baseline age of the 13,283 participants aged 30 years and older was 37.8 years (SD 5.4). The incidence rate of dementia was 2 per 1000 person-years, and a total of 983 (7.4%) incident dementia cases were identified during the study period between 1973 and 2014 (median follow-up time of 41.2 years (range 0.01 to 42.0 years) for the STR-1973 cohort.

For the SALT cohort (N=41,199), the mean baseline age was 58.5 years (SD 10.4). In this sample, the incidence rate was 3.6 per 1000 person-years, and a total of 1,979 cases (4.8%) were identified between 1998 and 2014. The lower incidence proportion detected in the SALT sample is likely owed to the fact that individuals with baseline cognitive dysfunction were excluded from the SALT sample.

Having ever been exposed to SW or NW was associated with increased dementia rates (Figure 6.3). For SW, a very slight attenuation was noted in the (final) model additionally adjusted for diabetes, CVD and stroke (HR=1.36, 95% CI=1.15-1.60) compared to the model adjusted only for age and sex (HR=1.41, 95% CI=1.19-1.66). Adjustment for these cardiometabolic factors did not attenuate the association for NW and dementia incidence.

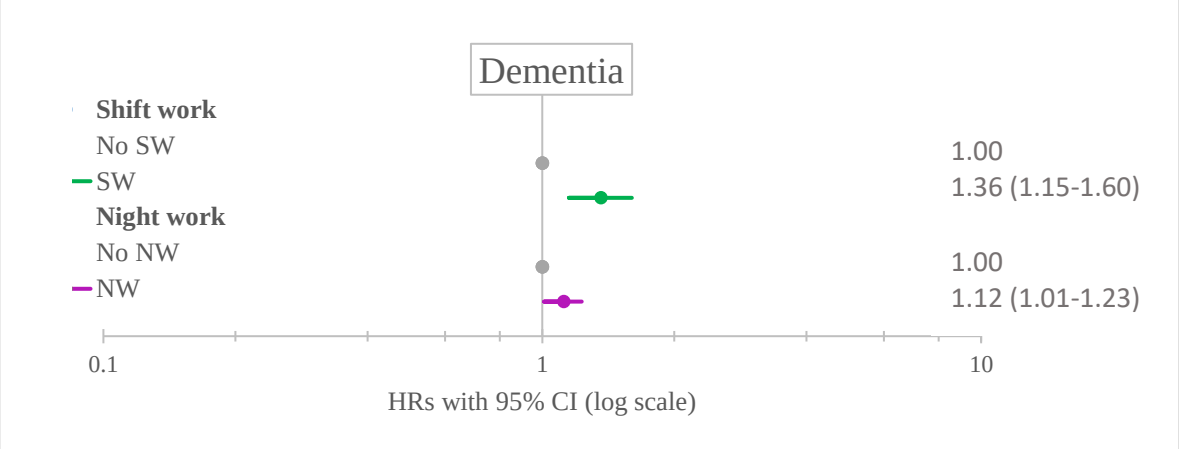


Figure 6.3. HR estimates of associations for SW and incident dementia from main analyses based on the STR-1973 cohort and the SALT cohort.

Sensitivity analyses based on SW measures derived from SW and NW information from both STR-1973 and SALT yielded similar estimates, with HRs ranging from 1.13 to 1.18, with confidence intervals of similar width and not including the null. Further, similar HR estimates were produced from a sensitivity analysis of the SALT cohort restricted to those born after 1925 (in an effort to be more comparable to the STR-1973 cohort).

Duration of SW and NW showed modest dose-response associations with dementia incidence, with longer number of years of SW or NW conferred higher dementia risk (Figure 6.4 and Figure 6.5, respectively). In Figure 7.5, which is based on the STR-1973 sample, we see the gradual increase in dementia rates with increasing duration of SW. The risk drops slightly just shy of 20 years SW duration, which we suspect is ascribed to fewer observations having so many years of SW exposure.

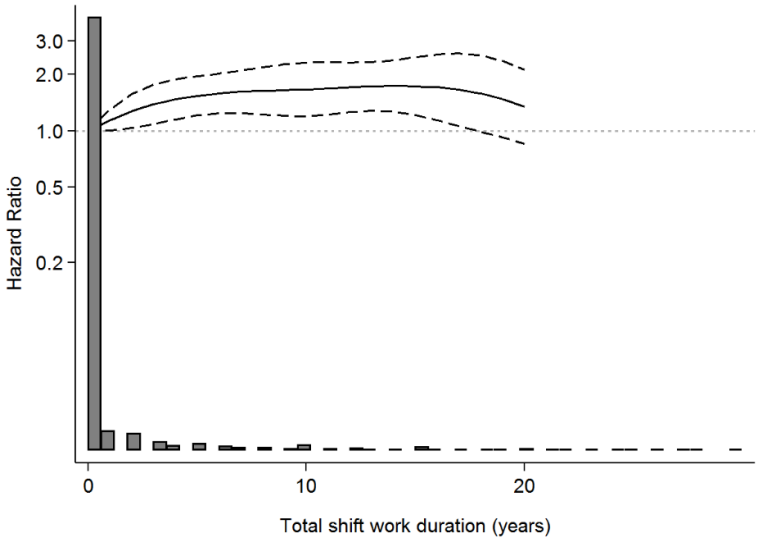


Figure 6.4. Cubic spline model for the association between SW duration and incident dementia, based on the STR-1973 sample (N=13,283), with the sample distribution of the total number of years of SW. Model adjusted for age, sex, education, diabetes, CVD and stroke.

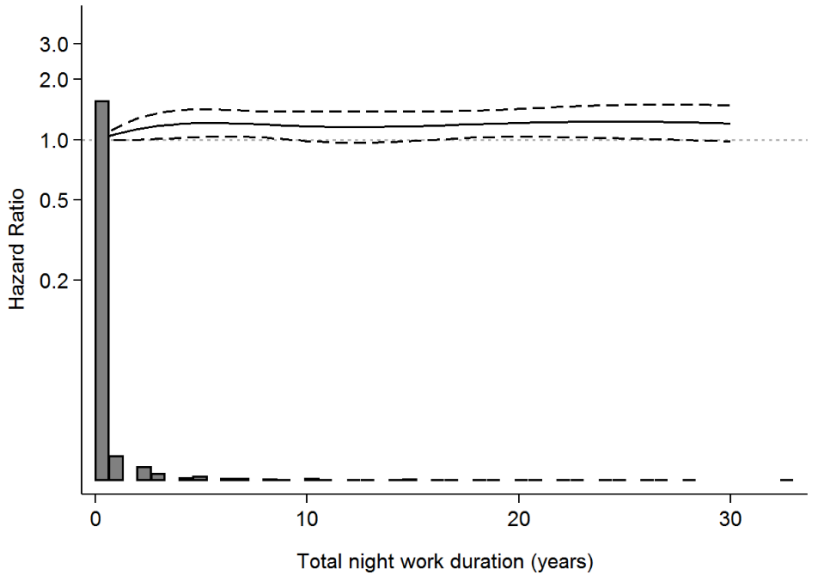


Figure 6.5. Cubic spline model for the association between NW duration and incident dementia, based on the SALT sample (N=41,199), with the sample distribution of the total number of years of NW. Model adjusted for age, sex, education, diabetes, CVD and stroke.

Findings from interaction analyses based on genotyped subsamples of *APOE* gene polymorphism with SW status and duration are shown in Figure 6.6, and with NW status and duration in Figure 6.7. An interaction between *APOE* ε4 with NW but not with SW with regards to incident dementia was observed. In the *APOE* ε4 carrier group, NW compared to day work was associated with a 41% (95% CI=1.08-1.92) increased hazards of dementia.

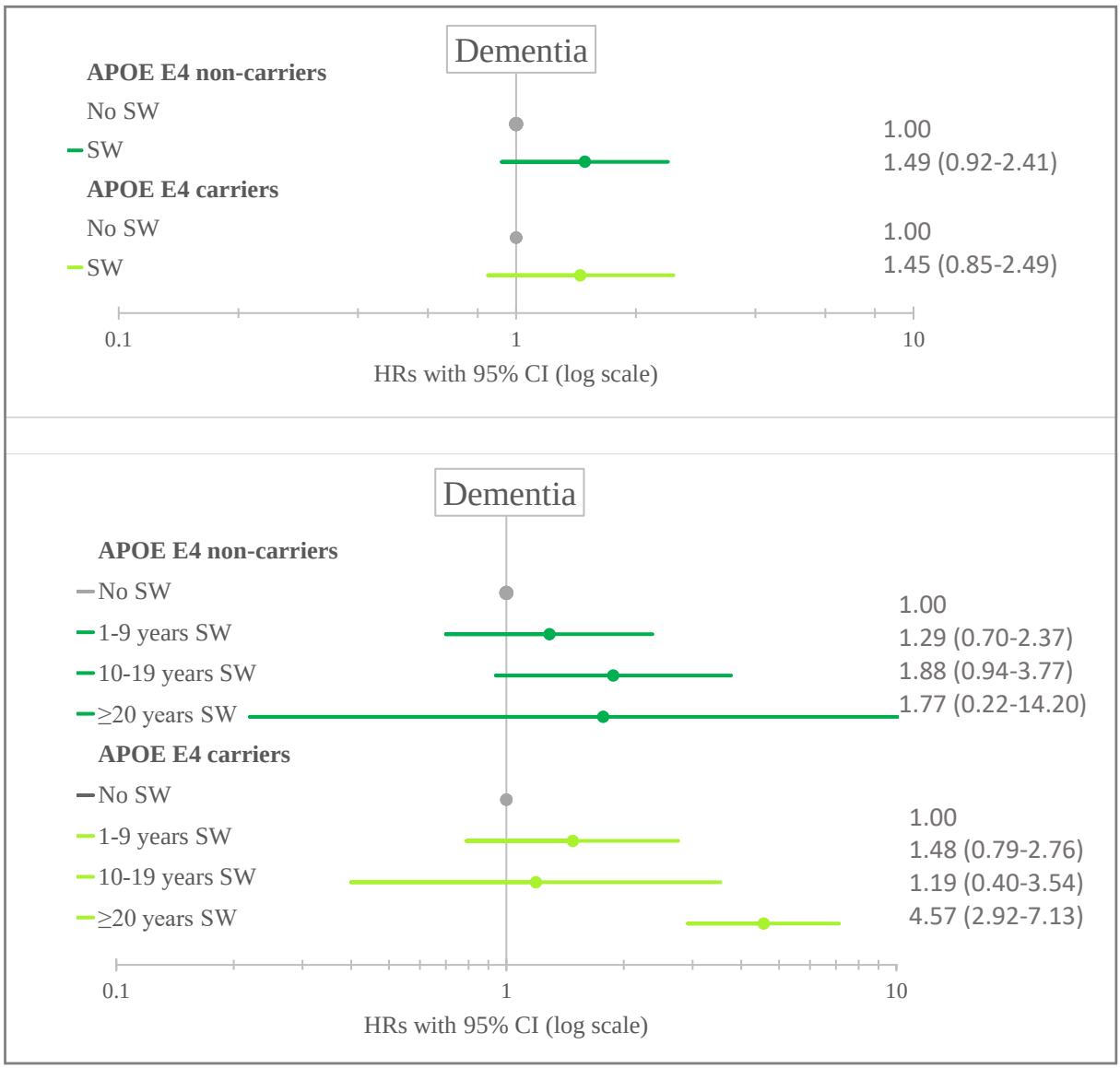


Figure 6.6. HR estimates of associations. Interactions of SW and SW duration with *APOE*.

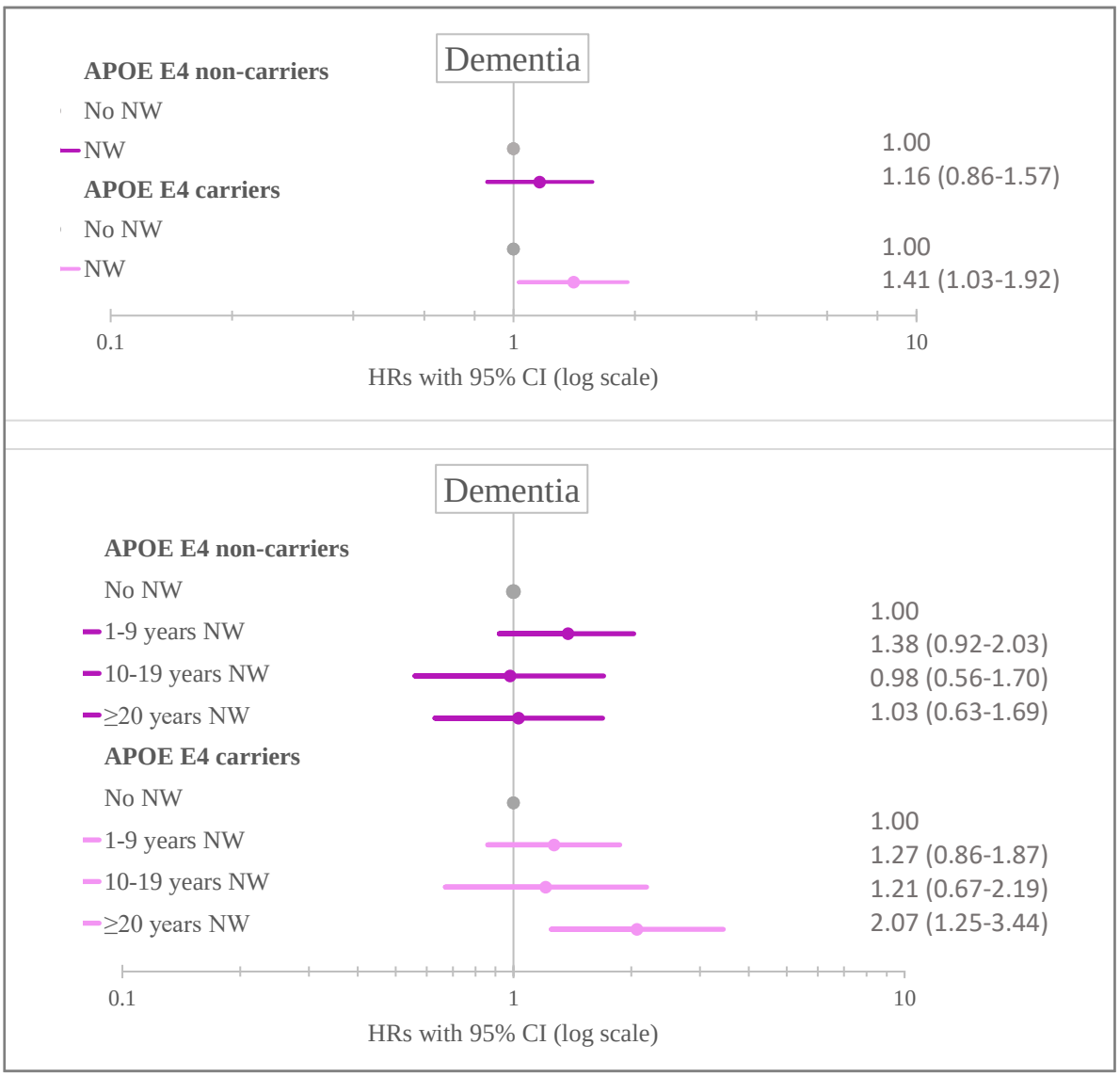


Figure 6.7. HR estimates of associations. Interactions of NW and NW duration with *APOE*.

The interaction effect was even more apparent when examining SW duration and NW duration. Among ε4 carriers in the STR-1973 subsample, those exposed to SW for 20 years or more (n=5) had a 4-fold risk of dementia (Figure 6.6). Among ε4 carriers in the SALT subsample, NW duration of 20 years or more (n=225) was associated with a 2-fold risk (Figure 6.7). All 5 of those with 20+ years of SW at the time in 1973 had also participated in SALT two decades later, and had responded that they had worked nights. Thus the 4-fold risk effect observed in the STR-1973 subsample analysis may have been specific to NW.

Co-twin control analyses produced similar findings corresponding to that in main analyses not conditioned on twin pair registration. Based on only MZ twins, co-twin control analysis yielded an HR of 1.12 (95% CI=0.58-2.15) for the association between SW and incident dementia, which is lower than that based on co-twin control analysis fitted to all twin pairs (HR=1.40, 95% CI=0.98-2.03) and cohort level analysis (HR=1.36, 95% CI=1.15-1.60). The HR of association between NW and incident dementia based on the MZ-only co-twin control model was 1.01 (95% CI=0.55-1.85)

compared to that from the within-pair analysis fitted to all twin pairs (HR=1.12, 95% CI=1.01-1.23) and cohort level analysis (HR=1.28, 95% CI=1.00-1.64).

With regards to the co-twin control findings, the attenuation in associations in the MZ subset (compared to that in cohort level analyses) suggests potential familial confounding. However, since co-twin control confidence intervals were wide and overlapping with those from cohort level analysis, the findings may not be wholly reliable.

6.3.2 Discussion

To the best of our knowledge, there has so far only been one previous study that has investigated the association between SW and risk of dementia. In that study, which was based on a sample of 4,766 men from the Copenhagen Male Study who, the authors did not observe an association between SW (defined as SW including NW) and risk of dementia,[132] which is contrary to our study's findings. A possible explanation for the divergent findings may be due to the lower life expectancy since 1980 in Danes, particularly Danish men, compared to Swedes for practically all age groups and birth cohorts.[133, 134] Thus it is possible that Danish men may not be living long enough due to dying from other causes such as lung cancer or heart disease to a greater extent than Swedes of either sex. Our results are in line with an earlier study based on a Danish cohort of 18,015 female nurses, also of prospective design, which reported that evening and rotating SW compared to day work was associated with a 4-fold and 5-fold risk, respectively, of mortality due to all-cause dementia including AD.[135] A difference between the two Danish studies is that one was based on a sample of men, and the other of women. In our final models, sex was controlled for, though there was hardly any difference in findings regardless of whether or not sex was included as a covariate. Nevertheless, including both men and women in the study population offers greater generalizability of findings.

Plausible mechanisms underlying the risk of dementia conferred by SW may have to do with forced desynchronization of the circadian clock, thereby eliciting a cascade of effects. Sleep restriction has been shown in *Study I* and other previous research[66] to be linked to increased risk of dementia. Perturbations of our internal circadian clock caused by altered sleep times and eating schedules may have deleterious effects on metabolic and endocrine functions, and present as reduced glucose tolerance and diabetes.[136, 137] In diabetes, high glucose levels increase oxidative stress, which is toxic to neurons, and high insulin levels may impair Aβ clearance from the brain.[138] Relatedly, shift work via circadian rhythm disturbance may break down vascular integrity; this hypothesis is supported by a highly controlled laboratory study that showed circadian misalignment per se increased blood pressure and inflammatory markers such C-reactive protein and interleukin-6 over a 24-hour period in healthy adults.[139] Heart disease, stroke and cardiovascular risk factors, including diabetes, manifesting during midlife have been linked to future development of dementia.[140] Working on a shift schedule has been shown to instigate changes in lifestyle like reduced physical activity.[141] Social and domestic life tends to suffer in shift-workers, which can lead to

poorer psychological wellbeing.[142] Such lifestyle factors and social aspects can bring about or exacerbate cardiometabolic factors, and in turn, lead to poorer cognitive profile. The slight attenuation upon adjustment for diabetes, CVD and stroke suggests these factors may partially mediate the association between SW and dementia risk.

The mechanism explaining the interaction effect between *APOE* and SW/NW with respect to dementia risk is unknown, but one could speculate. A hypothesis is that SW, perhaps via restricted sleep, may modify the effect of *APOE* genotype on AD and all-cause dementia. APOE has an important function binding and transporting lipids,[143] and the *APOE* ε4 isoform, a well-established genetic risk factor for sporadic AD, has been shown to be less efficient at binding cholesterol and implicated in impaired Aβ clearance.[144] One previous study reported that better sleep consolidation—the extent to which sleep is interrupted (or not interrupted) by arousals—attenuated the influence of *APOE* ε4 on risk of AD and neurofibrillary tangle pathology.[145] In *Study III*, while one of the aims was to examine short sleep as a moderator of genetic influences on dementia and AD liability, we were ultimately hindered by a lack of data on complete twin pairs concordant for short sleep.

Evidence on the association between SW and risk of dementia is still preliminary, and as this is the one of the first studies to report a connection between shift work and increased incidence of dementia, further research on this topic is warranted.

6.4 *STUDY IV* – THE IMPACT OF SW ON COGNITIVE AGING

6.4.1 Main findings

In this longitudinal study, 595 participants (mean age at baseline in 1984=58.2, SD 10.5) were followed for up to 27 years (median of 19.2 years). Of these, 106 (18.3%) individuals were identified as shift-workers. SW was not associated with mean cognitive performance at retirement or with cognitive change before and after retirement for any of the 5 composite factors (verbal, spatial, memory, processing speed, global) even after adjustment for age, sex, manual work status, and education. Duration of SW was also not associated with cognitive level and rate of change.

Findings were similar when NW was examined in relation to cognitive performance level and rate of change based on analyses of a subsample (n=320; mean age at baseline in 1984=55.0, SD 8.8; mean age at SALT interview in 1998-2002=69.2 years, SD 8.7), of whom 47 (14.7%) were identified as night-workers. Regarding the 47 shift-workers who indicated that they worked nights, the mean age at the time of the SALT interview in 1998-2002 when they responded about NW history was 69.7 (SD 8.7) and the mean duration of NW reported was 14.4 years (SD=12.3). Thus, one can infer that exposure to NW for these 47 individuals was during mid-life. LGCM estimates of associations with standard errors are displayed in Table 6.4. Trajectories of cognitive factors plotted on LGCM-based scores estimated as a function of shift work are illustrated in the left column of Figure 6.8.

We noted an interaction between SW and education on cognitive performance at retirement for all 5 cognitive factors. As shown in the right column of Figure 6.9, among those with higher levels of educational attainment, day-workers scored higher on average for all cognitive factors at retirement than shift-workers, which was expected. Curiously, in the group with less education, day-workers performed relatively poorly compared to shift-workers. The reasoning behind this latter finding was not immediately apparent, so to dig deeper we performed sensitivity analyses based on a subsample of 77 men who had data on early adult cognitive ability. This subsample analysis revealed that within the group *with lower education* (n=33), the mean early adult cognitive ability was higher for shift-workers (n=8; mean=19.4, SD 5.4) than for day-workers (n=25; mean=16.8, SD 5.3) (p=0.23). Within the group that was higher educated (n=44), the early adult cognitive scores were lower for shift-workers (n=10; mean=19.5, SD 5.6) than for day-workers (n=34; mean=22.0, SD 5.23). Although the subsample findings were not significant at an alpha level of .05, the pattern of findings suggests selection effects were present. For instance, those with lower education but higher intelligence may have selected jobs with low education requirements that were more mentally demanding, and such jobs may have involved shift work. Moreover, the fact that there was no interaction on the slopes, i.e. the rate of cognitive change, which captures within-person change, adds to the suspicion that the interaction findings were driven by selection effects

Table 6.4. Latent Growth Curve Model estimates of association between SW or NW with level and change in cognitive performance[a]

Effect		Verbal		Spatial		Memory		Processing Speed		Global	
		Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
	Shift work[†]										
$Intercept_{RA}$	0=No (Reference)	51.66***	2.16	64.66***	2.73	50.86***	2.59	59.78***	2.49	57.99***	2.33
	1=Yes[b]	1.33	0.86	0.01	1.07	0.88	0.99	0.01	0.97	0.35	0.93
Linear Age_{S1}	0=No (Reference)	-0.04	0.24	0.85*	0.34	0.64	0.40	0.69	0.37	0.57*	0.24
	1=Yes[c]	0.04	0.07	-0.06	0.10	-0.18	0.11	-0.13	0.12	-0.12	0.07
Linear Age_{S2}	0=No (Reference)	0.69*	0.28	-0.46	0.43	0.26	0.48	-0.31	0.45	0.26	0.31
	1=Yes[d]	-0.12	0.09	0.12	0.14	0.29	0.15	0.21	0.14	0.20	0.10
	Night work[‡]										
$Intercept_{RA}$	0=No (Reference)	46.83***	2.71	58.62***	3.69	50.04***	3.32	59.03***	3.25	54.12***	3.14
	1=Yes[b]	0.43	0.14	-2.00	1.55	0.94	1.36	-1.67	1.34	-0.92	1.32
Linear Age_{S1}	0=No (Reference)	0.23	0.30	0.46	0.45	0.30	0.53	0.82	0.48	0.38	0.30
	1=Yes[c]	-0.03	0.08	0.04	0.13	-0.16	0.14	-0.20	0.14	-0.12	0.09
Linear Age_{S2}	0=No (Reference)	0.23	0.35	0.30	0.56	0.78	0.63	-0.42	0.57	0.49	0.38
	1=Yes[d]	-0.02	0.11	0.04	0.18	0.30	0.19	0.24	0.18	0.17	0.13

Abbreviations: Est., estimate. SE, standard error.
Significance levels: *p<0.05, **p<0.01, ***p<0.001. An asterisk for $Intercept_{RA}$ indicates the value is significantly different from 0. An asterisk for slope (Linear Age_{S1} or Linear Age_{S2}) indicates the slope is significantly different from 0.
[†]Associations between SW with cognitive level and change based on full sample (N=595).
[‡]Associations between NW with cognitive level and change based on subsample (N=320).
[a] All models are adjusted for baseline age, sex, education, and occupational status.
[b] Effect of SW or NW on mean performance level ($Intercept_{RA}$) at retirement age compared to reference.
[c] Effect of SW or NW on rate of change per year in cognitive performance across the entire measurement period (Linear Age_{S1}) compared to reference.
[d] Effect of SW or NW on additional rate of change per year in cognitive performance after retirement age (Linear Age_{S2}) compared to reference.

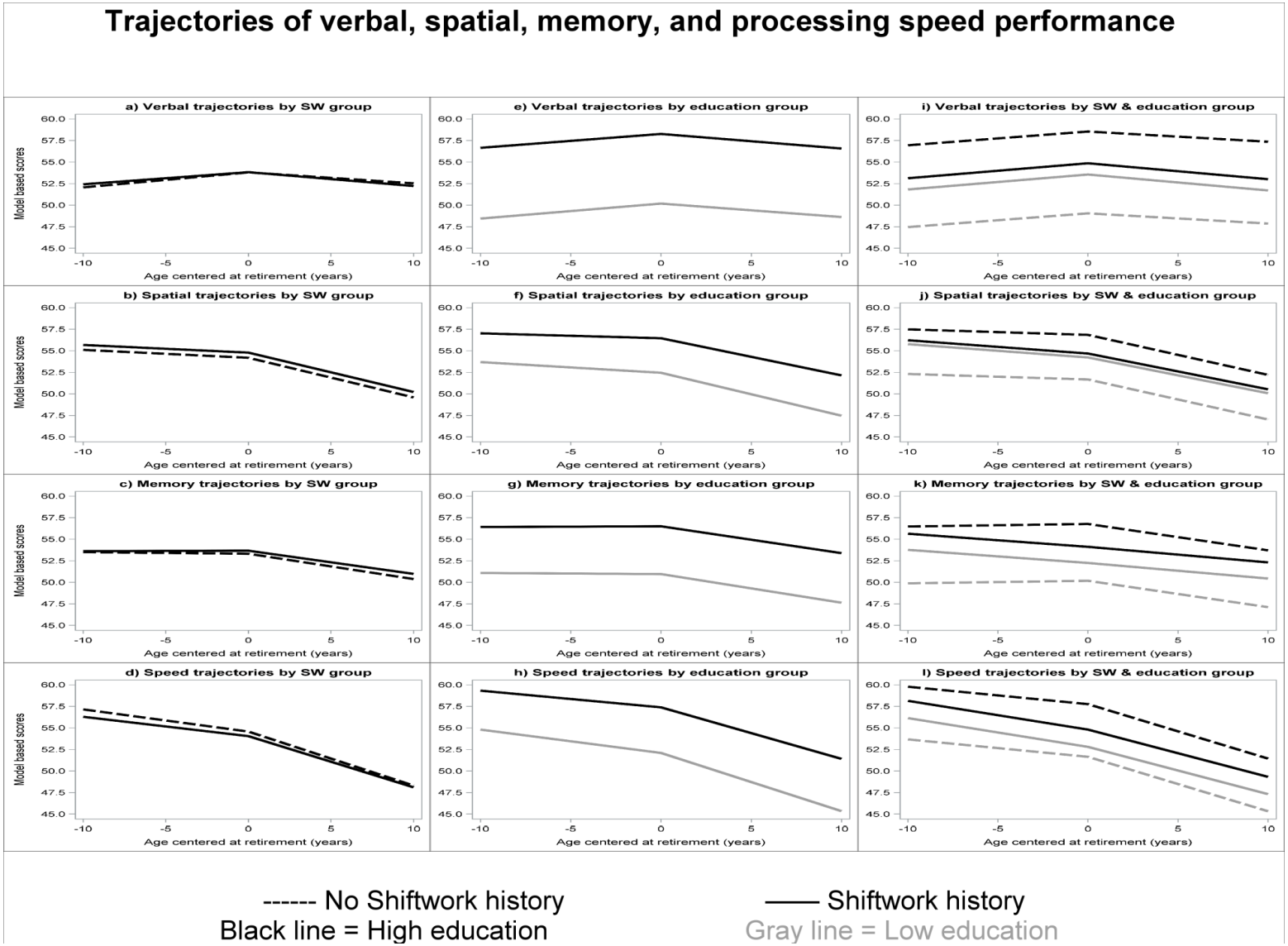


Figure 6.9. Trajectories of verbal, spatial, memory, and processing speed performance plotted on unadjusted LGCM scores at the intercept (retirement age) and at 10 years before and after retirement age.

Trajectories are plotted by SW status (left column), education level (middle column), and SW and education status (right column).

6.4.2 **Discussion**

Earlier studies that have examined the association between SW and later cognition in middle and older-aged adults have so far provided different pieces of evidence. The findings revealed in the present study are consistent with a previous prospective study based on the Nurses' Health Study cohort that did not find an association between mid-life SW history with later life cognitive status and decline.[84] In contrast, two other studies reported positive findings for the association between SW and cognitive performance. A French study reported that current or past exposure to rotating SW versus never having been exposed to SW was associated with lower cognitive scores for memory, speed, and global performance.[83] However, this was based on differences in mean cognitive performance scores and not on differences in rate of performance change. This makes the results less clear-cut since mean differences does not capture within-individual variation over time. The investigators also observed that among former shift-workers, those who had stopped working shifts earlier performed better on cognitive tests than those who stopped working shifts more recently.[83] A recent Swedish study using a cross-sectional design reported similar findings to the French study. Recent former shift-workers who had worked shifts within the past 5 years as well as current shift-workers demonstrated poorer executive cognitive function compared to day-workers; but no differences in executive cognitive function was observed between former shift-workers who had stopped working shifts more than 5 years ago and day-workers.[146] Altogether, this would suggest that shift work may have acute and possibly reversible adverse effects, but not long-term effects if one stops working shifts.

A general difference from *Study III* is that earlier studies did not account for dementia and thus cannot rule out the potential effect of underlying pathological processes. We acknowledge that such processes cannot be entirely ruled out in *Study IV* given the long preclinical phase dementia (and that in some cases underlying neuropathology does not guarantee dementia development), but efforts to study normative cognitive aging were made by excluding those with baseline dementia as well as observation points relating to occasions following a dementia diagnosis.

7 GENERAL DISCUSSION

A considerable amount of research has been undertaken to gauge how aspects of sleep relate to later life cognition and dementia. However, there is variation in sleep characteristics studied, with more investigations on sleep quantity, quality and disordered breathing, and less on chronotype-related features such as rising time and bedtime. Moreover, findings have been inconsistent among studies. Comparatively lacking is the research done on SW and its long-term cognitive effects. The studies in this thesis add to the discussion on the role of sleep as well as SW in later life cognition.

In *Study I*, after accounting for baseline cognition, short TIB fit the role of a risk factor for dementia while long TIB and late rising appeared to signify prodromal dementia. Short TIB as a risk factor may be interpreted as such: short TIB may initiate development of dementia, or that it may accelerate progression of existing pathology. We also wondered if the association between short TIB and dementia could be explained by genetic factors in common to both traits, or if short sleep perhaps potentiated genes influencing dementia risk. All scenarios are biologically plausible. The intention was to examine the last question using quantitative genetic models in *Study II*; unfortunately, this was not possible as only 3 MZ twin pairs were concordant for short sleep. But since there are MZ twins discordant for short sleep, it cannot only be genetics influencing one to have short sleep. Clearly more research, particularly with larger samples, is needed.

Long TIB and late rising, on the other hand may be markers of incipient dementia. Rather than being risk factors in the sense that long TIB and late rising per se would *cause* development of dementia, which is not unthinkable but mechanistically mysterious, these characteristics of sleep in older individuals may be neurobehavioral manifestations of preclinical dementia. The lack of moderation of long TIB and late rising on the genetic influences on dementia liability as shown in *Study II* supports the premise of these sleep traits as markers of ongoing pathological processes. Delayed rising may signify circadian rhythm irregularities and fragmented sleep (that is perhaps underestimated by self-report), which are more prevalent and severe in patients with dementia compared to healthy controls,[147-149] and are implicated in neurodegenerative processes.[148] Long TIB, too, may be driven by early neurodegeneration. This was suggested by a study that showed prolonged sleep duration of more than 9 hours (relative to sleeping 6-9 hours) was associated with smaller total cerebral brain volume.[150] Long sleep and late rising may also be due to disordered breathing during sleep, depression, alcohol consumption, and underlying disease processes.[151] However, adjustment for various potential confounders such as depression, COPD, CVD, cancer history, type II diabetes, BMI, smoking, alcohol use, sleep medication use, and NW did not influence the association between long TIB and dementia incidence. Having found an effect of NW on risk of dementia in *Study III*, it was at first curious that adjustment for NW did not significantly influence the association between the investigated sleep characteristics and incident dementia. However, since sleep was assessed at age 65 or beyond, sleep habits may have changed before and after retirement. Perhaps it would have been a different story had we examined sleep habits during *midlife* with respect to dementia risk, and adjusted for NW, or vice versa.

Directly impacting sleep is SW, which is a term with fairly negative connotations, likely due to the myriad of physical symptoms and disorders that have been reported to be associated with this type of work schedule. As for cognitive effects, it is virtually undisputed that a shift schedule, particularly when including night shifts, acutely impairs cognitive performance—and certainly, most of us can recognize that disoriented feeling and loss of concentration that comes with jetlag. Considering this, it is rather surprising how sparse the literature is on the chronic cognitive effects of SW. This is where *Study III* and *Study IV* come into play.

The findings in *Study III* and *Study IV* were illuminating, but did not perfectly align with expectations—though such an occurrence rarely happens in research it seems. In *Study III*, SW and NW during midlife were associated with increased incidence of dementia. In *Study IV*, based on a sample of participants with no dementia and with data points from the time a person developed dementia excluded, we found that midlife SW did not influence age-related cognitive change. Findings from earlier research on the long-term cognitive effects of SW have also been somewhat conflicting. The point of divergence may lie in the concept of SW recency. In previous studies, associations between SW and cognitive performance were particularly strong when the focus was on 'recent shift-workers'—that is, shift-workers who had worked shifts during the previous 5 years. Importantly, former shift-workers who had ceased working shifts at least 5 years ago showed similar cognitive performance levels compared to those who had never worked shifts.[83, 146] And that among those with SW history, former shift-workers who exited SW within the past 5 years performed better than those who had exited SW earlier.[83] Data on recency of SW exposure as well as longitudinal data on SW were not available in *Study III* and *Study IV*, and represents a limitation as we could not account for the possible reversibility factor of SW. Differences in cognitive change tend to be subtle, and is all the more difficult to capture in smaller samples.

But how do the findings in *Study IV* (where there was no evidence of an association between SW and late life normative cognitive functioning) reconcile with those we saw in *Study III* (where we saw a positive association between SW and risk of dementia)? The possible reasons for the divergent findings are listed as follows:

- ***Duration of SW*** – Longer duration of SW was associated with modestly higher dementia incidence (*Study III*). If we expect a small effect size of long SW duration on cogntive change, the SATSA sample and the number of shift-workers with 20+ years of SW history in this sample may not have been large enough to capture small effects (*Study IV*). In *Study III*, differences in SW duration might also explain why the risk effect of 'general' SW history (measured in 1973; mean STR-1973 cohort baseline age=38 years) was larger than that of NW history (measured in 1998-2002; mean SALT cohort baseline age=58 years). Some of those with a SW history in 1973 likely continued working shifts after the measurement timepoint, meaning they might have been exposed to SW for well beyond 20 years and thus showed higher risk of dementia.

- ***Cohort effects and riskiness of SW*** – The type of schedule (counterclockwise rotation or permanent night shifts vs. clockwise rotation, for example) together with fewer regulations surrounding SW might have driven risk of dementia upwards in the STR-1973 cohort compared to the later SALT cohort. This, in addition to other cohort effects (famine, influenza outbreak, poorer healthcare, et cetera) could also explain why the risk estimate of SW history (based on the STR-1973 cohort) was higher than that of NW history (based on the SALT cohort).
- ***Age at exposure to SW*** – We did not have information on age at exposure to SW, but if we assume those with 20+ years of SW also were those who worked shifts when older, it could be that exposure to SW at an older age is riskier than exposure to SW at a younger age. This premise is supported by an earlier study based on the Nurse's Health Study cohort that suggested that working night shifts before age 25 was associated with a more adverse risk profile for chronic diseases compared to night shift work later in life.[152] Closely related is *recency of SW exposure,* which was associated with cognitive performance in previous studies. Perhaps those who were still working shifts were likely those exposed to SW at a later age, and that those who stopped working shifts were liklely those who stopped SW at an earlier age. So one might wonder how those who worked shifts for 20 years in total until the age of 65 fared in terms of cognitive performance and dementia risk compared to those who worked shifts for 20 years in total until the age of 45 and then switched to day work.
- ***Differential impact of SW on normative cognitive aging versus pathological cognitive aging*** – This is hinted by the interaction findings of SW**APOE* genotype with respect to risk of dementia (*Study III*), which points towards SW exacerbating underlying genetic vulnerability, not unlike one of the hypothesized mechanisms explaining how short TIB may contribute to greater dementia incidence (*Study I*). While it is an intriguing thought that there may be a differential impact of SW on pathological versus non-pathological cognitive decline, testing this hypothesis is not straightforward since it is possible that individuals who do not outwardly exhibit cognitive decline may have underlying AD-like pathology.
- ***The trifecta*** – What if we are not seeing an effect of SW on cognitive aging because to see an effect would require: a) long duration of SW, b) exposure to SW at older age, and c) being *APOE* Ɛ4 positive. This is perhaps a too simplistic reasoning, and there are likely other factors at play, but dementia and cognitive aging are multifactorial processes, so wouldn't it make sense that these components together would drive the risk for dementia upwards (and perhaps accelerate non-pathological cognitive decline)?

When taken together, perhaps *Study III* and *Study IV* are not contradictory, but rather complementary. The saying is trite, but truly, more studies are needed to better understand the role of sleep and SW in dementia and cognitive aging. Overall, the findings from epidemiological studies within and beyond this thesis paint a complex picture of how sleep and SW relate to later life cognition—But what one can take away is this: A confluence of factors contribute towards or act as markers of risk of dementia and cognition in old age; among these may very well be SW and atypical sleep.

8 METHODOLOGICAL CONSIDERATIONS

All studies in this thesis utilized information from well-established population-based cohorts. The possibility of following participants on disease and vital status via register linkage represents a major strength of these studies. Nevertheless, epidemiological research is not without limitations. Some methodological issues were brought up in the general discussion within the last chapter. In this chapter, methodological weaknesses common in epidemiological studies are acknowledged; by doing so, we may improve upon future scientific work.

8.1 STUDY POPULATION, SELECTION BIAS, AND GENERALIZABILITY

Findings from population-based cohort studies can be generalized to the broader population as the selection of study participants is assumed to be random. Further, in the older birth cohorts of the STR, the willingness to participate in studies was higher than it is today. However, selection bias may still occur, particularly in studies of aging where individuals not only need to be in good enough health and willing to participate, but also need to have survived to a certain age to qualify for study inclusion. During the recruitment of the cohorts, it is likely that non-responders were older and in poorer health than responders, which would result in a study population that is healthier than the general population.[153]

A comment on the slight study population differences in Study I and Study II:

Although both *Study I* and *Study II* were based on the SALT cohort, study populations were not identical due to differences in exclusion criteria. Those who received a dementia diagnosis within 3 years proximal to baseline were excluded in *Study I*. However, sensitivity analyses were performed on samples that excluded those who developed dementia within 1 year, 2 years or 4 years from baseline, and results remained unchanged. Thus, in *Study II*, we did not exclude individuals with short follow-up time. Another difference between the two studies was that we decided to supplement register data on dementia diagnoses with dementia data from the STR sub-studies of aging in *Study II* (which was the last study performed, chronologically). In the STR sub-studies, there were some who screened positive for dementia but did not participate in the clinical work-up; since dementia status for these persons was uncertain, they were excluded. Reassuringly, no matter which study population the analyses were based on, HR estimates of associations between sleep and incident dementia remained stable.

8.2 CONFOUNDING AND REVERSE CAUSATION

As with any observational study, confounding is a major concern. In each of the studies, we have taken care to adjust for potential confounders. Many of the times, the final model is not one that includes as many covariates as possible, but one that includes those based on subject matter knowledge; these covariates are generally the ones that do influence the association when tested in a statistical model.

All the studies in this thesis aimed to understand the effect of sleep or SW on cognitive aging and risk of dementia, which implies a direction of causation. Assessing causality is especially challenging when the outcomes of interest are long-term processes, and even more so for dementia for which the preclinical stage is unknown.

The same applies for SW and late life cognition—does working shifts lead to poorer cognitive function in late life, or does cognitive ability lead one to select a job with SW and is thus what predicts late life cognitive function? In *Study IV*, there was that peculiar interaction between SW and education, wherein lower-educated shift-workers showed better late life cognitive performance than lower-educated day-workers. Selection effects were suspected, and a sensitivity check indicated that early adult cognitive ability was higher in lower-educated shift-workers than in lower-educated day-workers (and also that early adult cognitive ability was higher in higher-educated day-workers than in higher-education shift-workers).

With regards to SW and dementia, it does not seem logical that dementia would cause SW—but confounding is a major issue. Is it the adverse effect of SW or is it individual factors affecting one to work shifts that are associated with risk of dementia? What drives one to work shifts may be tied to SES, for example. Thus, SES indicators such as education and manual work status were adjusted for in models.

8.3 POTENTIAL MISCLASSIFICATION

Misclassification of dementia

A limitation of *Study I*, *Study II*, and *Study III* has to do with the fact that dementia was identified from Swedish health registers, which could result in misclassification of dementia. Since only inpatient and outpatient data were included in the NPR, but not primary care data, the cases captured in the register may have been the more severe cases and persons receiving their diagnoses at younger ages as these cases may have been more likely to have been admitted to a hospital or require specialist care. In terms of detection of cases of dementia, the NPR and CDR combined have moderate sensitivity (63%) and high specificity (99.8%).[106] That is, there are a moderate number of false negative cases, i.e. moderate probability of detecting dementia cases in registers—and a very low number of false positive cases, i.e. a high probability of detecting non-cases in registers. Misclassification of dementia due to low sensitivity, if unrelated to the exposure, would bias the association towards the null. A higher degree of misclassification was observed for differential diagnoses of dementia than for all-cause dementia, which was a primary reason for why all-cause dementia was examined as the outcome of interest in the relevant studies within this thesis. Dementia data were also pulled from the PDR. As of yet there has not been a validation study of dementia identified via the PDR, though anti-dementia drugs are highly specific for the treatment of AD (symptoms). However, it is possible dementia medications were prescribed to persons with mild cognitive impairment, which may have decreased the specificity of dementia diagnoses based on all three registers.

In *Study II* (which was chronologically the last study performed) we retrieved data on dementia not only from registers but also from four STR sub-studies, and the clinical dementia diagnoses available in these sub-studies were the reference gold standard the register-based diagnoses were compared against.[106] As mentioned earlier, findings remained stable regardless of slight differences to the analytic sample or if dementia status was based on only register data or if it was supplemented with data from STR sub-studies. The poor capture rate of the registry-based diagnoses may also have led to inflation of the non-shared environment term and thus contributed to the somewhat lower heritability estimates than previously reported based on the STR data.

Given the insidious onset of dementia, it is also worth mentioning that age of dementia diagnosis does not necessarily indicate age of dementia onset. Indeed, the long preclinical and asymptomatic stage of AD would certainly suggest that there is a delay between age at onset and age at diagnosis. In *Study I*, this delay was accounted for when we tested associations on different samples based on different follow-up time criteria.

Misclassification of sleep

We cannot rule out the possibility of misclassification of sleep characteristics which were based on self-reported data. While subjective measures of sleep correlate with the corresponding objective measures of sleep, the correlation is not perfect.[154] All sleep characteristics assessed had to do with habitual sleep experiences during the past 6 months. Recalling bedtimes might have been trickier as bedtimes are more likely to be determined by exogenous factors while rising times serve as a better indicator of endogenous circadian rhythms. Thus, self-reported bedtimes may have been more susceptible to random error, and thus resulted in null associations with dementia risk. The sleep quality and non-restorative sleep indices have been shown to have good criterion validity and internal consistency,[111] but as these were based on self-reported data there is still a possibility of random measurement error. The measure for snoring (yes/no) was admittedly a crude measure for capturing snoring status and particularly sleep-disordered breathing, and thus may have led to non-differential misclassification, which in turn contributed towards null findings.

Misclassification of SW

SW history and duration of SW history was assessed at a single measurement occasion (baseline), which may have led to misclassification of SW history status and length of SW exposure. This is perhaps less of an issue for the ever/never SW measure as day-workers were probably unlikely to switch to a SW schedule at a later age, but more problematic for duration of SW since some shift-workers likely continued to work shifts beyond baseline. To decrease the risk of misclassification, in *Study III* we utilized information about SW status and duration measured at different time points from two study sources, thereby allowing for SW status to be time-varying as well as allowing for different scenarios regarding length of SW exposure.

There are different facets of SW that we would have liked to have captured. While we had data on years of SW exposure, we were not able to capture intensity of SW, i.e. number of shifts per month. A strength was that we had a measure of NW; however, we were not able to measure whether the NW was permanent or part of a rotational work schedule, i.e. the shift system. This is a limitation of not only *Study III* and *Study IV* but also of previous studies[82, 83, 132, 146] that have not been able to consider all these different pieces of SW in relation to late life cognition or risk of dementia.

8.4 ETHICAL CONSIDERATIONS

Ethical considerations in medical research are taken seriously in Sweden; the right to be informed in understandable terms about the research one is participating in, as well as the right to decline to participate in research is written in Swedish Law. In all STR sub-studies, informed consent was obtained from participants. With regards to use of register-based data, informed consent is not required, but approval is needed from the ethics committee. Ethical considerations of using register data in medical research has been explored at length,[85] with the conclusion that register-based research is of important value to society, and that the benefits of its use outweighs the potential harm.

Ethical permits obtained for each of the studies:

Study I – Dnr 00-132 and 97-051

Study II – Dnr 00-132 and 97-051.

Study III – Dnr 00-132 and 97-051

Study IV – Dnr 84:61, 98-319, and 2010/657-31/3

When working with large amounts of data as one does in epidemiological research, ethical considerations are mainly concerned with the ensuring integrity of participants and data security. Great care is taken in protecting the privacy of study participants. Data that is available to researchers do not include the PIN, names, addresses or any other personal identifiers. Findings based on these data are presented as aggregate findings (i.e. characteristics of the group and not of the individual). Additionally, for each project in this thesis, access to data and documentation is restricted to only those involved in the project.

9 IMPLICATIONS FOR PRACTICE AND FOR FUTURE RESEARCH

The work described in this thesis has provided additional pieces of understanding on the role of sleep and SW in cognitive health later in life, but there are still pieces of the puzzle missing.

Regarding the association between chronotype and dementia, there have only been two studies—*Study I* and one other[121]—that have investigated and demonstrated the connection between delayed habitual rising[155] or rhythms[121] with subsequent risk of dementia; thus, more studies are called for.

Collectively, *Study I* and previous research findings offer compelling evidence—epidemiological and otherwise—of short sleep conferring risk of dementia. We hoped to dig deeper, but due to lack of data, we were unable to answer the question of whether short sleep interacted with genes influencing dementia, or if there was genetic overlap between the two. This is important for understanding the mechanisms underpinning the association which could serve as a basis for future research or interventions. So although the studies in this thesis were based on large samples, future studies with larger samples, using quantitative genetic models, are needed to further investigate if short sleep and risk of dementia share underlying genetic etiology, or if short sleep potentiates genes influencing dementia liability.

In a clinical setting, an assessment of sleep habits among older aged patients would be useful, especially as part of a cognitive screening protocol. Short sleepers may be offered interventions such as cognitive behavioral therapy for insomnia (CBT-I).[156] Patients with habitually long sleep (beyond 9 hours) or late rising times (later than 8AM) may give indication of underlying health issues or prodromal features of neurodegenerative disease, and thus allow for appropriate treatment earlier on and potentially delay cognitive impairment.

A number of studies of sleep and subsequent dementia risk have been examined in study populations where participants are aged 65 and above. The literature would benefit from prospective studies following adults at an earlier age on sleep habits, SW status, and cognitive and dementia development. As a complement to subjective measures of sleep, objective measures would offer deeper insight, but of course objective measures of sleep on a large scale is understandably hard to come by.

In contrast to sleep, there is very little in the literature on SW and its impact on later life cognition. *Study III* and *Study IV* have only scratched the surface of this topic, and further studies are needed to elucidate the long-term effect of SW on pathological versus non-pathological cognitive aging. The interesting interaction finding of SW and *APOE* ε4 with respect to dementia incidence in *Study III* needs to be replicated in future studies. The age at which SW was performed may contribute to an adverse cognitive profile, and this

detail has not yet been examined. Additionally, the possibility of cohort effects influencing SW could suggest that the burden of dementia is even greater in lower-income aging populations where occupational health and safety standards are poorly enforced.

There is still work to be done, and the practical implications for cognitive health in old age arising from epidemiological research—past, present and future—on the role that SW and sleep plays—as a contributory factor or marker—are considerable.

10 CONCLUSIONS

With the help of unique data sources and a variety of epidemiological methods, the studies within this thesis highlight the role of sleep and SW in late life cognition and dementia, specifically:

I. Short and long TIB as well as late rising time among older adults are associated with increased incidence of dementia. Long sleep and delayed rising may be markers of prodromal dementia, whereas short TIB fits the role of a risk factor for dementia.

II. Long TIB and late rising, while associated with greater dementia and AD incidence, does not potentiate genetic influences of dementia and AD liability.

III. Midlife SW, including NW, compared to day work is associated with elevated dementia incidence. Additionally, a modest dose-response association is shown, with longer duration of SW and NW predicting higher dementia risk.

IV. Normative cognitive aging differs in extent between individuals, but history of midlife SW does not appear to explain differences in rate of cognitive change in later life.

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