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IMPACT OF PSYCHOSOCIAL WORKING CONDITIONS ON HEALTH IN OLDER AGE

Kuan-Yu Pan

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Impact of psychosocial working conditions on health in older age

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Kuan-Yu Pan

Principal Supervisor
Professor Hui-Xin Wang, Ph.D.
Stockholm University
Faculty of Social Science
Stress Research Institute
and Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Co-supervisors
Associate Professor Weili Xu, M.D., Ph.D.
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Professor Laura Fratiglioni, M.D., Ph.D.
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Assistent Professor Francesca Mangialasche, M.D., Ph.D.
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Clinical Geriatrics
and Aging Research Center

Opponent
Professor Marianna Virtanen, Ph.D.
Uppsala University
Department of Public Health and Caring Sciences

Examination Board
Professor Kristina Alexanderson, Ph.D.
Karolinska Institutet
Department of Clinical Neuroscience
Division of Insurance Medicine

Professor Mikael Rostila, Ph.D.
Stockholm University
Department of Public Health Sciences
Centre for Health Equity Studies

Associate Professor Kirsten Nabe-Nielsen, Ph.D.
University of Copenhagen
Department of Public Health
Center for Health and Society

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Inghesalen, Widerströmska Huset, Karolinska Institutet, Tomtebodavägen 18A, Solna

To my family

The Constitution of World Health Organization states, “The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.”

The truth is that Taiwan, my beloved motherland that has one of the most advanced and accessible health care systems in the world, is still facing an enormous obstacle to attend the World Health Assembly. I hereby take the opportunity to raise the awareness of it.

ABSTRACT

Work takes up a large proportion of time in our adult lives, thus possibly making it an important determinant of health. This doctoral thesis aimed to investigate the impact of psychosocial working conditions on health in older age, including metabolic and cognitive health, and disability. Psychosocial working conditions were defined in accordance with the job demand-control model and classified into four scenarios: high strain (high demands, low control), low strain (low demands, high control), passive job (low demands, low control), and active job (high demands, high control). The four studies in this thesis were based on data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).

Study I. This study used six-year follow-up data and examined the association between work-related stress, characterized by high strain, and the risk of diabetes. High strain was related to an increased risk of diabetes among people aged 60 years at baseline, especially in women, but not in men. Having more than 14 years of work experience in high strain increased the risk of diabetes among women aged 60 years.

Study II. The association between demand-control status and cognitive decline over the nine-year follow-up period was examined. Compared to active jobs, low strain, high strain, and passive jobs were all associated with faster cognitive decline. Longer duration of work in low strain, high strain, or passive jobs was associated with an accelerated rate of cognitive decline, whereas longer duration of active jobs was related to slower cognitive decline.

Study III. This study examined the association of demand-control combinations with dementia using 12-year follow-up data. Passive jobs were associated with a higher risk of dementia among the younger-old individuals (aged ≤72 years), but not among the older-old (aged ≥78 years). Long work duration of more than ten years in passive jobs increased the risk of dementia among the younger-old.

Study IV. The relationship between demand-control categories and disability trajectories over 12 years of follow-up was investigated. Compared to active jobs, low strain, high strain, and passive jobs were all related to a faster rate of disability progression. These associations were mediated 38% by cognitive decline and 18% by chronic disease accumulation.

Conclusion. The findings from this thesis underscore the importance of psychosocial working conditions for health in older age. High strain increases the risk of diabetes among women in their early 60s; passive jobs increase the risk of dementia among the younger-old individuals. Having non-active jobs, including high strain, low strain, and passive jobs, accelerates the speed of cognitive decline and disability progression in later life. In addition, duration of work plays a role in the associations between psychosocial working conditions and health outcomes. Both cognitive decline and chronic disease accumulation can partially mediate the association between psychosocial working conditions and disability progression.

Key words: psychosocial working conditions, job demand, job control, type 2 diabetes, cognitive decline, dementia, disability, cohort study, epidemiology

SAMMANFATTNING

Arbete tar upp en stor del av tiden i våra vuxna liv och kan därmed vara viktig för vår hälsa. Denna doktorsavhandling syftar till att undersöka sambandet mellan psykosociala arbetsförhållanden och hälsan bland äldre, med hänsyn till metabolisk, kognitiv hälsa och funktionshinder. Psykosociala arbetsförhållanden definierades i enlighet med krav-kontrollmodellens fyra kategorier: spända (höga krav, lågt beslutsutrymme), avspända (låga krav, högt beslutsutrymme), passivt jobb (låga krav, lågt beslutsutrymme) och aktivt jobb (höga krav, högt beslutsutrymme). De fyra studierna i denna avhandling baseras på data från Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).

Studie I. Denna studie använde sex års uppföljningsdata och undersökte sambandet mellan arbetsrelaterad stress (mätt som spända förhållanden) och risken för diabetes. Spända förhållanden var relaterat till ökad risk för diabetes bland 60-åringar vid första intervjutillfället, särskilt bland kvinnor men inte bland män. Mer än 14 års arbete med spända förhållanden ökade risken för diabetes bland kvinnor som var 60 år.

Studie II. Sambandet mellan krav-kontroll status och kognitiv försämring under nio år undersöktes. Jobb med spända eller avspända förhållanden samt passiva jobb var förknippade med snabbare kognitiv försämring jämfört med aktiva jobb. Längre tid med ett jobb med spända eller avspända förhållanden samt passiva jobb var förknippad med snabbare kognitiv försämring, medan längre tid med ett aktivt jobb var relaterat till långsammare kognitiv försämring.

Studie III. Denna studie undersökte sambandet mellan kategorierna från krav-kontrollmodellen och demens under 12 år. Passiva jobb var förknippade med en högre risk för demens bland yngre-äldre (≥72 år) men inte bland de äldre-äldre (≥78 år). Lång tid (>10 år) med ett passivt jobb ökade risken för demens bland de yngre-äldre.

Studie IV. Sambandet mellan krav-kontroll kategorierna och funktionsnedsättning under 12 års undersöktes. Jobb med spända eller avspända förhållanden och passiva jobb var relaterade till en snabbare ackumulering av funktionshinder jämfört med aktiva jobb. Detta samband förklarades med 38% av kognitiv försämring och 18% av kroniska sjukdomar.

Slutsats. Resultaten från denna avhandling understryker vikten av psykosociala arbetsförhållanden för äldres hälsa. Spända arbetsförhållanden ökar risken för diabetes bland kvinnor i 60 års ålder och passiva jobb ökar risken för demens bland de yngre-äldre personerna. Att inte ha ett aktivt jobb (dvs. spända eller avspända förhållanden samt passiva jobb) ökar takten på kognitiv försämring och funktionsnedsättning senare i livet. Hur lång tid personer arbetat med ogynnsamma arbetsförhållanden påverkar sambandet med hälsa senare i livet. Både kognitiv försämring och ackumulering av kroniska sjukdomar kan delvis förklara sambandet mellan psykosociala arbetsförhållanden och funktionsnedsättning.

Nyckelord: psykosociala arbetsförhållanden, arbetsbelastning, krav-kontroll, typ 2-diabetes, kognitiv försämring, demens, funktionshinder, kohortstudie, epidemiologi

摘要

工作佔據我們一生當中的許多時間，因此可能對健康影響甚鉅。此博士論文旨在研究工作中的心理社會要素對老年代謝健康、認知能力，以及獨立生活功能的影響。根據工作要求—掌控模型，工作的社會心理條件可分為以下四種狀況：高張型（高要求、低掌控）、低張型（低要求、高掌控）、被動型（低要求、低掌控）和主動型（高要求、高掌控）。此論文包含四項獨立研究，其所使用的資料源於瑞典國家老化與照護研究中，在斯德哥爾摩 Kungsholmen 地區執行的子研究 (SNAC-K)。

第一項研究使用六年的追蹤資料以探討工作壓力對老年糖尿病風險的影響。結果顯示，相較於未從事高張型工作的人，曾從事高張型工作的六十歲的參與者有較高的糖尿病風險，而此關係在女性中尤其顯著，但未見於男性。此外，曾從事高張型工作長達十四年以上的六十歲女性，其罹患糖尿病的風險增加。

第二項研究分析工作中的社會心理要素與認知功能下降速率的關係。從九年的追蹤資料中我們發現，相較於從事主動型工作的人，從事高張型、低張型或被動型工作的人都有較快的認知下降速率。再者，在整個工作生涯中，從事高張型、低張型或被動型工作較長時間的人，比任職於這些工作較短時間的人，有較快的認知功能下降；反之，較長時間從事主動型工作的人，其認知下降的速率較緩。

第三項研究探討工作的心理社會要素對失智症的影響。十二年的追蹤資料顯示，相較於主動型工作者，從事被動型工作的較年輕的研究參與者（六十至七十二歲）有較高的失智症患病風險，而此關係不見於較老的參與者（七十八歲以上）。同時，在較年輕的參與者中，從事被動型工作十年以上者，其罹患失智症的風險提高。

第四項研究調查工作中的社會心理要素與日常生活功能退化速率的關係。依據十二年的追蹤數據我們發現，相較於從事主動型工作的人，從事高張型、低張型或被動型工作的人都有較快的獨立生活功能退化速率。另外，此關係中，百分之三十八是透過認知退化造成，而百分之十八是透過慢性疾病累積導致。

結論：工作中的社會心理要素對老年的健康有相當重要的影響。高張型工作提高六十歲女性的糖尿病患病風險，而被動型工作提高六十至七十二歲的老年人的失智症罹病風險。此外，從事高張型、低張型或被動型工作的人較從事主動型工作者，有較快的認知功能下降及獨立生活功能退化。再者，在工作社會心理要素與老年健康的關係中，工作時間長短扮演重要的角色。最後，從事高張型、低張型或被動型工作所造成的較快速的獨立生活能力退化，部份肇因於認知功能的下降以及慢性疾病的增加。

關鍵字：工作社會心理要素，工作要求，工作掌控，二型糖尿病，認知退化，失智症，獨立生活功能退化，世代追蹤研究，流行病學

LIST OF SCIENTIFIC PAPERS

I. **Pan KY**, Xu W, Mangialasche F, Fratiglioni L, Wang HX. Work-related psychosocial stress and the risk of type 2 diabetes in later life. *J Intern Med* 2017; 281:601-610. doi: 0.1111/joim.12615

II. **Pan KY**, Xu W, Mangialasche F, Dekhtyar S, Fratiglioni L, Wang HX. Working life psychosocial conditions in relation to late-life cognitive decline: a population-based cohort study. *J Alzheimers Dis* 2019; 67:315-325. doi: 10.3233/JAD-180870

III. **Pan KY**, Xu W, Mangialasche F, Grande G, Fratiglioni L, Wang HX. Passive job and dementia risk in older adults: the role of Apolipoprotein E. *Under review*

IV. **Pan KY**, Xu W, Mangialasche F, Wang R, Dekhtyar S, Calderón-Larrañaga A, Fratiglioni L, Wang HX. Psychosocial working conditions and trajectories of disability in old age: the mediating role of cognitive decline and chronic disease accumulation. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of daily living
APOE	Apolipoprotein E gene
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disorder
HbA1c	Glycated hemoglobin
HPA	Hypothalamic Pituitary Adrenal
HR	Hazard ratio
IADL	Instrumental activities of daily living
ICD	International Classification of Disease
IL	Interleukin
KP	Kungsholmen Project
MMSE	Mini-Mental State Examination
NYK	Nordisk yrkesklassificering
OR	Odds ratio
SES	Socioeconomic status
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SNS	Sympathetic nervous system
TNF	Tumor necrosis factor
VRF	Vascular risk factor

1 INTRODUCTION

1.1 POPULATION AGING AND HEALTH OUTCOMES

The world's aging population has been growing significantly since the mid-twentieth century (1, 2). From 1950 to 2013, the number of people aged 60 years or older had increased from 205 million to 841 million. In the coming decades, the number is projected to more than double, reaching 2 billion by 2050 (3). This demographic transition driven by increasing life expectancy is a success in human history because it reflects the improvement in living conditions and health care systems. However, aging is accompanied by multiple pathological changes, from cell to organ, increasing the risk of diseases which in turn can lead to functional decline and disability (4). With the massive increase in the number of older adults, the increase in people living with age-related health conditions and disability is expected.

1.1.1 Type 2 diabetes

Type 2 diabetes (hereafter, diabetes) is a chronic metabolic condition with a high prevalence worldwide (5), and aging is a relevant driver of the diabetes epidemic (6). To date, 123 million people aged 65 years or older living with diabetes, making up almost 10% of the population of this age-group in the world. In the coming three decades, the number is expected to rise to 253 million, which is assumed to represent 18% of the world's population of this age-group by then (7).

A variety of complications results from diabetes, including cerebrovascular and cardiovascular disorders (CVDs), peripheral arterial diseases, retinopathy, nephropathy, neuropathy, and oral conditions, leading to reduced functional capacity, institutionalization, and increased mortality (7, 8). Among all age-groups, older adults with diabetes have the worst prognosis in the complications (9), and contribute to more than 60% of deaths attributable to diabetes (7).

1.1.2 Cognitive decline and dementia

A lifelong, gradual, ongoing, yet variable change in cognitive function is one of the hallmarks in the aging process, that is, cognitive aging (10). Despite the inevitable nature, the progression of cognitive aging demonstrates high variability between individuals. Multiple factors, such as lifestyles, CVDs, metabolic and neurodegenerative diseases, can speed up the decrement in cognitive function (11). People with accelerated cognitive decline may experience cognitive impairment, and further develop dementia (12, 13).

Dementia is a multifactorial and heterogeneous clinical syndrome, resulting from a range of neurological disorders and characterized by progressive decline in multiple cognitive functions that lead to dysfunctions in daily living (14). Dementia is one of the most burdensome health conditions, not only to individuals, families, but also to societies. Worldwide, around 50 million people were affected by dementia in 2018, and the number is

projected to multiply in the following decades (15, 16). Alzheimer´s disease (AD) underlies the majority of dementia cases, often in association with cerebrovascular pathology. Considering the current absence of a cure for dementia (17), identification of modifiable risk factors has become a promising strategy to promote prevention against dementia (18). Despite the fact that a bunch of modifiable risk factors for dementia has been recognized, including low educational attainment, CVDs, diabetes mellitus, depression, and sedentary lifestyles, only 30% of the dementia cases can be attributed to them (19). Therefore, research on exploring novel risk factors for dementia is warranted.

1.1.3 Disability

Disability refers to the limitation in independently carrying out daily tasks, which include activities of daily living (ADL) mainly related to personal care (i.e., dressing, bathing, toileting, eating, transferring, and continence), and instrumental activities of daily living (IADL), consisting of activities necessary to reside in the community (i.e., grocery shopping, meal preparation, laundry, housekeeping, managing medication, handling money, using telephone, and taking public transportation) (20). The booming elderly population can result in an enormous demand for help in daily living, either from family members or social services. Independently managing tasks in daily life will facilitate the maintenance of quality of life in elderly people, alleviate burdens on families, and reduce cost to societies (21).

In summary, various chronic conditions often come along with aging, including metabolic, brain vascular and degenerative diseases. These disorders can subsequently lead to functional limitation and disability. The rapid growth of aging population and the amount of people with age-related health outcomes will impose an even greater burden on modern societies around the world in the near future. Therefore, research into identifying modifiable risk factors for age-related health outcomes, aiding the identification of targets to implement preventive strategies or early interventions, is crucial.

1.2 PSYCHOSOCIAL WORKING CONDITIONS

To most people, work is one of the main activities that substantially occupy one’s lifetime. People work not only to make a living, but also to seek self-identity, status, and a sense of purpose (22). Generally, working conditions include physical and psychosocial factors. Physical factors in a work environment refer to hardware, room, light, sound, and equipment; psychosocial factors result from the interaction between psychological and social factors in the work environment, that is, the way how workers perceive and react to their surroundings.

Several concepts of psychosocial working conditions have been proposed, such as stress, time pressure, work overload, job insecurity, social support, job satisfaction, and organizational justice. Subsequently, a few theoretical models of psychosocial work environment have been established (23), for example, the effort-reward imbalance model (24), the demand induced

strain compensation model (25), and the job characteristics model (26). Among all, one of the most frequently applied models is the job demand-control model (27, 28).

1.2.1 The job demand-control model

The job demand-control model (shown in **Figure 1**), developed by Robert Karasek (27), ponders two dimensions: job control and job demands. This model aims to characterize the main psychosocial factors experienced in work environment, and to demonstrate how they can relate to health outcomes. The demand dimension represents psychological demands, time restriction, and mental workload. The control dimension (also called decision latitude) includes two concepts, decision authority and skill discretion, which are mutually reinforcing and usually appear together in the work environment (28). It is believed that having decision latitude to accomplish work tasks can reduce stress and facilitate learning, while a high level of job demands can increase stress and learning at the same time (28). Following these ideas, the strain hypothesis and the active learning hypothesis were generated from the demand-control model, based on the cross-tabulation of job control and demands.

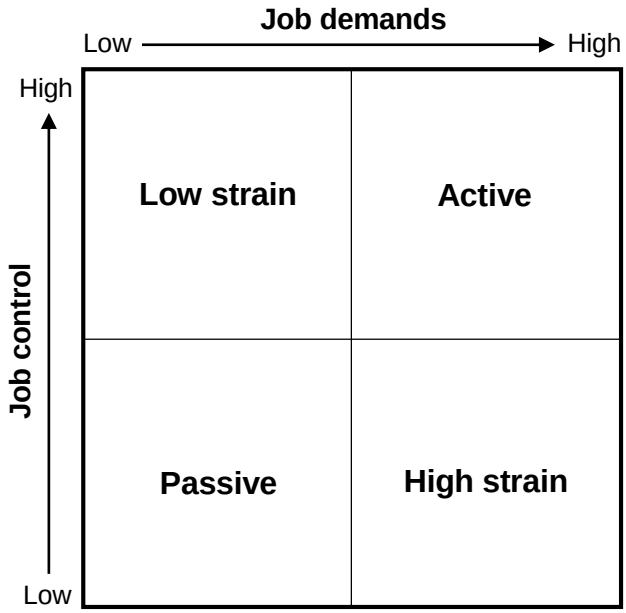

Figure 1. The job demand-control model (28), modified by author.

The strain hypothesis

The lower right-hand quadrant in **Figure 1** represents the combination of high job demands and low job control, forming the high strain scenario that is reckoned to reflect a stressful working condition (27). At the opposite corner appears low job strain (high control incorporated with low demands), a relaxing circumstance at work that seems ideal yet possibly lacks mental stimulation (29). Approximately a decade after the demand-control model was introduced, another component, social support at work, was additionally added to expand the model, resulting in the demand-control-support model (30, 31). It is further

hypothesized that stress level in workers with high job strain may be exacerbated when there is no sufficient social support in the workplace, that is, iso-strain (31).

The active learning hypothesis

The active learning hypothesis was less studied than the strain hypothesis but has drawn increasing attention in the recent years, especially in the literature focusing on cognitive function. Jobs consisting of both high degrees of control and demands are called active jobs because workers with these jobs tend to actively engage in leisure or popular activities outside of work (28). Active jobs are usually professional types of work, with high mental challenges and stimulation that induce motivation rather than psychological strain. According to the active learning hypothesis, difficult situations can be perceived as challenges and opportunities if workers are given decision-making latitude to experiment potential solutions, and to further learn/develop new behavioral patterns. Once the learning process succeeds, stress can be simultaneously reduced. The learning and problem-solving development are optimized when demands are matched by one's capability to handle alternatives and tackle those challenges (28). Passive jobs, on the other side of the spectrum where low control is combined with low demands, can demotivate workers because of underutilization of their abilities and loss of self-efficacy. Restricting renovation of work processing may further atrophy skills and learning capacity. It is also believed that understimulation in a work context can be perceived as a source of stress, similar to overstimulation (32).

1.2.2 View from the life-course perspective

The life-course approach is widely used in all sorts of research investigating long-term effects of exposures occurring across the life course on later health outcomes (33). It proposes a conceptual framework (i.e., life-course principle) to epidemiology that orients researchers to understand how a life course is shaped or structured (34), and how biological, behavioral, and psychosocial exposures operate throughout one's lifetime to impact on health or disease risk (33, 35). Work is related to many other factors in our lives. For example, the occupational choice is a complex and multifactorial process and influenced by multiple factors, such as sex, educational attainment, parental socioeconomic status (SES), health status, culture, or other societal contexts (36-39). Further, these determinants and occupation can interact and affect self-identity, life satisfaction, income, and finally, health (40-42). Therefore, it is important to bear the concepts of life-course approach in mind when studying working conditions and health outcomes.

There are three issues stressed by the life-course approach that can be relevant when studying health in relation to work (**Figure 2**): 1) causal pathway related to time (e.g. chain of risk and risk accumulation); 2) timing of causal actions (e.g. critical/sensitive periods and birth cohorts); and 3) different types of mechanism (e.g. susceptibility, modifying and mediating factors) (33). The chain of risk model asserts a sequence of linked exposures that lead to illness, for example, childhood financial hardship may decrease educational achievement,

limiting occupational opportunities to manual work, thus worsening the severity of low-back pain and subsequently increasing the risk of sick leave (43). In this case, any factor between an exposure and an outcome along the chronological timeline is a mediating factor. The concept of risk accumulation focuses on the number, duration, and severity of exposures during the lifetime, and thus can be thought as an expanded version of chain of risk without the time sequence. By translating this concept to working-life course, the duration of work experience may become one center of focus (44). A critical/sensitive period refers to a time-window in which work exposures have a significantly greater impact on an individual's health than at other time. Modification occurs when the associations between working conditions and the outcome of interest differ across the varied levels of modifying factors. Susceptibility refers to a situation where intrinsic/prior exposures increase the likelihood that another exposure will produce the outcome. Interaction is one way of testing susceptibility which examines the joint effect of work and one or more concurrent exposures on the outcomes (45). The idea of susceptibility has been given greater salience especially in genetic epidemiology where gene-environment interaction is examined. Finally, studies on working conditions and health should be viewed in a historical time/context, considering that people from different birth cohorts react to the environment differently due to societal changes, and the social context also influences labor market substantially (i.e., birth cohort effect).

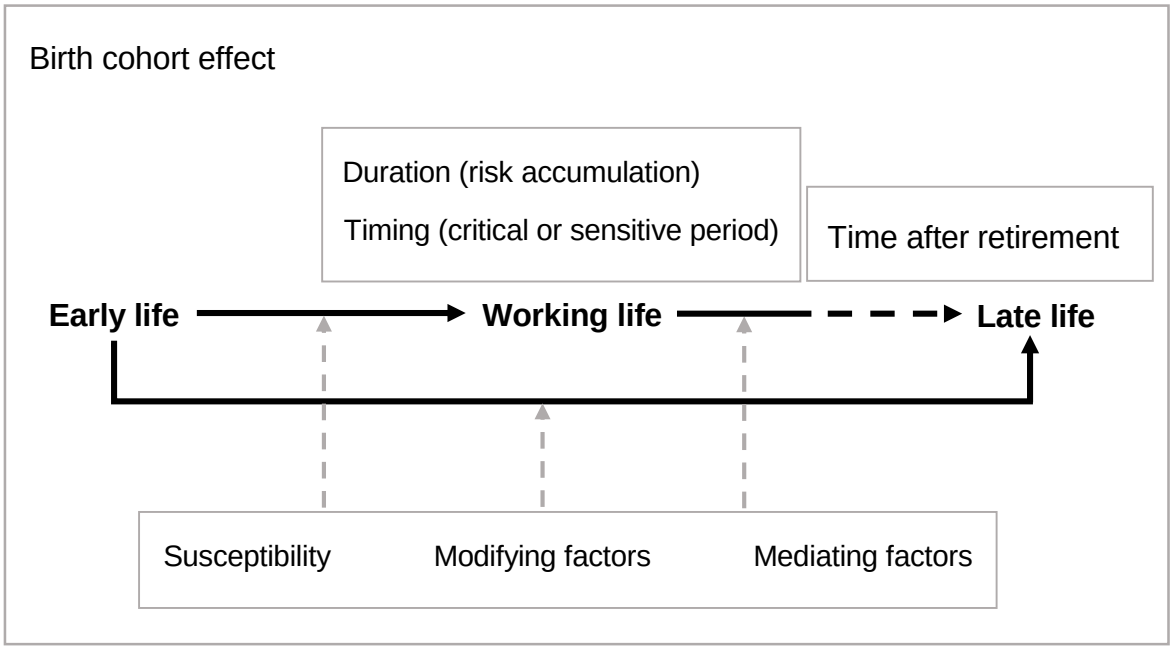

Figure 2. The life-course perspective on working conditions and health in later life (44), modified by author.

Over all, the fundamental purpose of life-course approach is to elucidate the role of time in epidemiological studies (44). When zooming the focus on working-life course and health, one should consider the length of work experience (accumulation of risk), age of workers (critical/sensitive period), as well as the duration after labor market exit (i.e., retirement).

Since most people spend a considerable amount of lifetime on work, it is plausible that work can impact on health not only during working life but also after retirement or even later life. With this concern, associations between working conditions and health in older age have drawn increasing attention in occupational health research during the past decade.

1.3 PSYCHOSOCIAL WORKING CONDITIONS AND HEALTH IN OLDER AGE

There is a growing body of evidence linking working conditions to several health outcomes in later life, including mobility, physical function, musculoskeletal pain, mental health, and survival (46-53). Studies investigating associations between psychosocial work environment and late-life metabolic and cognitive functions, and limitations in activities of daily living (i.e., disability) are relatively scarce.

1.3.1 Psychosocial working conditions and type 2 diabetes

Notwithstanding the consistent findings of increased risk of diabetes in relation to the psychosocial working condition, characterized by high job strain, among the working population, there has been an ongoing debate concerning the possible different vulnerability of men and women. That is, the majority (six out of seven) of longitudinal population-based studies demonstrated the association between high strain and an elevated risk of diabetes only among female workers (54-58), but not among male workers, while one cohort study reported such association in both men and women (59). The discrepancy may be due to different diagnostic criteria to identify subjects with diabetes. Studies reporting the higher diabetes risk only in women diagnosed diabetes through clinical examinations, while the study showing a similar risk in two sexes used self-reported information or hospital records to identify diabetes cases. In addition, one large-scale project based on pooled data from 13 European cohort studies reported the association of high strain with diabetes occurrence in both men and women, despite the fact that only one single study showed the statistically significant association (60). Finally, the latest meta-analysis merging aforementioned studies demonstrated that high strain was related to a higher risk of diabetes only in women, but not in men (61). However, to our knowledge, no study has examined whether work-related strain can impact on diabetes occurrence beyond working life. Moreover, no study applied the life-course approach to explore the role of work duration in the association between job strain and diabetes.

1.3.2 Psychosocial working conditions, cognitive decline, and dementia

Some epidemiological studies have tentatively related psychosocial working conditions to late-life cognition and dementia risk (62, 63), but the evidence is still limited. To date, low job control, by itself or in combination with either high or low job demands (i.e., high job strain or passive job), has been linked to worse cognitive function (64-67). Among these studies, two did not capture the changes in cognitive function over time (66, 67), and the other two studies examining cognitive decline over time focused on various cognitive

domains (64, 65). In addition, one study showed better cognitive performance in several cognitive domains among workers with shorter work experience in high job strain or longer experience in active jobs (68). Similarly, three studies focusing on dementia reported the increased occurrence of dementia among people with low job control (69-71), high strain, or passive jobs (71). One study showed no association between job demands and dementia (72).

In spite of the importance of work duration from the life-course perspective in occupational health research, the majority (four out of five) of the studies that looked into the relation of working conditions to cognitive function only assessed demand-control status at a single point in time. Thus, the role of work duration in the work-cognition association remains unknown. Other studies regarding job demands and control and dementia risk have attempted to take into account work duration, either by assessing the longest-held job (70, 71) or by weighing each occupation in life with its duration (69). Nevertheless, duration of demand-control status in relation to dementia risk is not well characterized. Moreover, it is unclear how long the effect of working conditions on dementia risk can last after withdrawing from work. Furthermore, the apolipoprotein E epsilon 4 (*APOE* ε4), a well-known genetic risk factor for dementia, has been shown to modify the association between lifestyle-related factors and dementia risk (73). However, the joint effect of detrimental working conditions and *APOE* ε4 on dementia is unclear.

1.3.3 Psychosocial working conditions and disability

Previous studies regarding occupational activities and disability in old age have focused on occupational characteristics (74) and physical demands (75), leaving the association between psychosocial work status and late-life disability unclear. To our knowledge, only one study showed that both high job strain and passive jobs were related to more disabilities in ADL and IADL 28 years after the work experience (76). However, this study did not capture the changes in disability over time. In addition, it has been demonstrated that both rapid cognitive decline (77) and chronic disease accumulation (78) accelerated the progression of ADL and IADL disabilities in old age. However, it is unknown whether and to what extent the decrement in cognitive function and increased burden of medical conditions can mediate the association between working conditions and late-life disability.

1.4 CURRENT KNOWLEDGE GAPS

Overall, a great void of understanding remains regarding psychosocial working conditions in relation to late-life metabolic and cognitive health consequences and disability. First, it has been repeatedly shown that work stress increases the risk of diabetes among the working population, in spite of a potential sex difference that women are more vulnerable than men. The understanding of whether work-related stress can impact on diabetes after retirement persists unclear. Second, according to the limited number of studies, both stressful and passive jobs seem to accelerate cognitive decline and increase the risk of dementia. However, the roles of work duration and *APOE* ε4 in these associations are not well explored. Finally, the association of psychosocial work environment with disability progression in older age has been seldom examined, and there is a lack of understanding whether the changes in cognitive function and medical condition can mediate the work-disability association.

1.5 RESEARCH HYPOTHESES

This thesis tested the hypotheses that adverse psychosocial working conditions increase the risk of type 2 diabetes and dementia occurrence and accelerate the rate of cognitive decline and disability progression in older age. In accordance with the concepts of life-course epidemiology, a further assumption in the thesis was that length of work experience, duration after retirement, sex, and genetic factors may modulate the relationships between working conditions and health outcomes. Furthermore, cognitive decline and chronic disease accumulation may mediate the association between psychosocial working conditions and disability progression.

2 AIMS

GENERAL AIM

The overall aim of this doctoral thesis is to better understand the impact of psychosocial working conditions on health consequences in older age.

SPECIFIC AIMS

To achieve the general aim, the specific aims addressed in four studies are listed below:

1. To examine whether work-related stress increases the risk of type 2 diabetes in later life, and to check the potential sex difference and the role of work duration in the association (*Study I*).

2. To investigate the association between psychosocial working conditions and the rate of cognitive decline, and to explore the role of duration of work experience throughout the working life in the association (*Study II*).

3. To evaluate the effect of psychosocial working conditions on the risk of dementia, taking into consideration lengh of work, duration after retirement, and *APOE* ε4 status (*Study III*).

4. To verify the relationship between psychosocial working conditions and trajectories of disability, and to test whether and to what extent this relationship is mediated by cognitive decline and chronic disease accumulation (*Study IV*).

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

The Swedish National Study on Aging and Care in Kungsholmen

This thesis is based on data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). SNAC-K is an ongoing, population-based longitudinal study undertaken in the urban district, Kungsholmen, in Stockholm, Sweden (79). SNAC-K is part of a national multi-center study known as SNAC that includes four longitudinal studies in Sweden. The goal of SNAC-K is to investigate the aging process and improve health of older adults by identifying possible preventive strategies.

Between March 2001 and June 2004, a random sample of 5111 older adults aged 60 years and older living in their homes or in institutions in Kungsholmen was invited to the baseline examination. Of them, 321 were not eligible (4 were deaf, 23 did not speak Swedish, 32 had moved, and 262 were not traceable) and 200 died, leaving 4590 alive and eligible, of which 3363 (73.3%) individuals participated in the baseline examination.

The study population in SNAC-K was stratified into eleven age cohorts, with an interval of six years between the younger age cohorts (60, 66, and 72 years old), and three years between the older ones (78, 81, 84, 87, 90, 93, 96, and 99 years and older). Follow-up examinations were carried out every six years for the younger age cohorts and every three years for the older age cohorts (**Figure 3**).

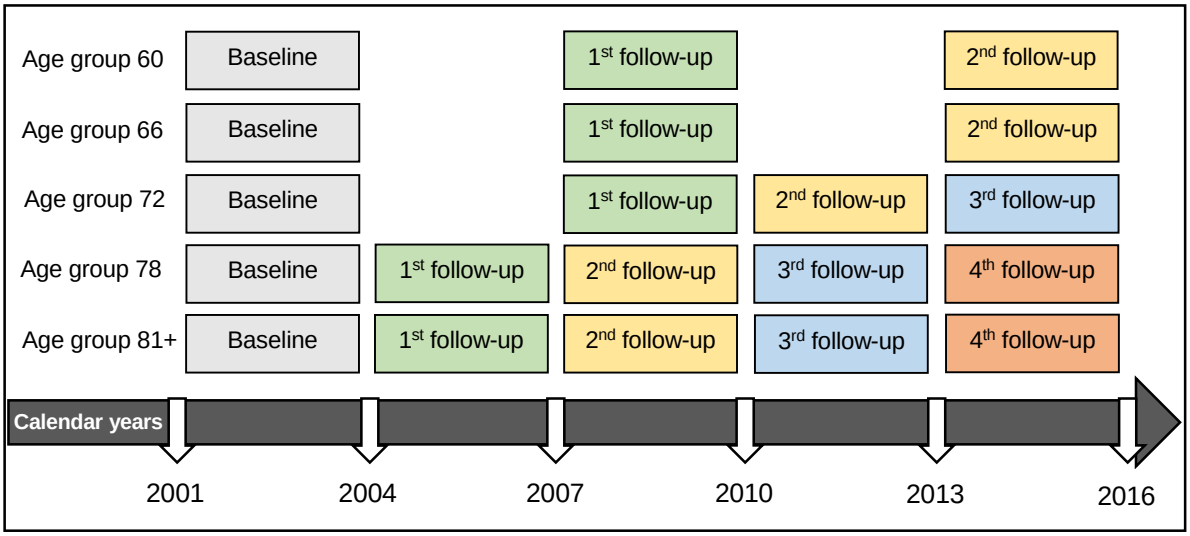

Figure 3. Swedish National Study on Aging and Care in Kungsholmen cohort, 2001-2016.

Figure 4 illustrates a schematic representation of baseline population in each of the studies. The study design in all studies was longitudinal. In Study I, 2719 diabetes-free participants were followed up until year 2010. A group of 2873 cognitively intact participants was followed until year 2013 in Study II. Study III (2969 dementia-free participants) and Study IV (2937 participants with sufficient information) used data up to year 2016.

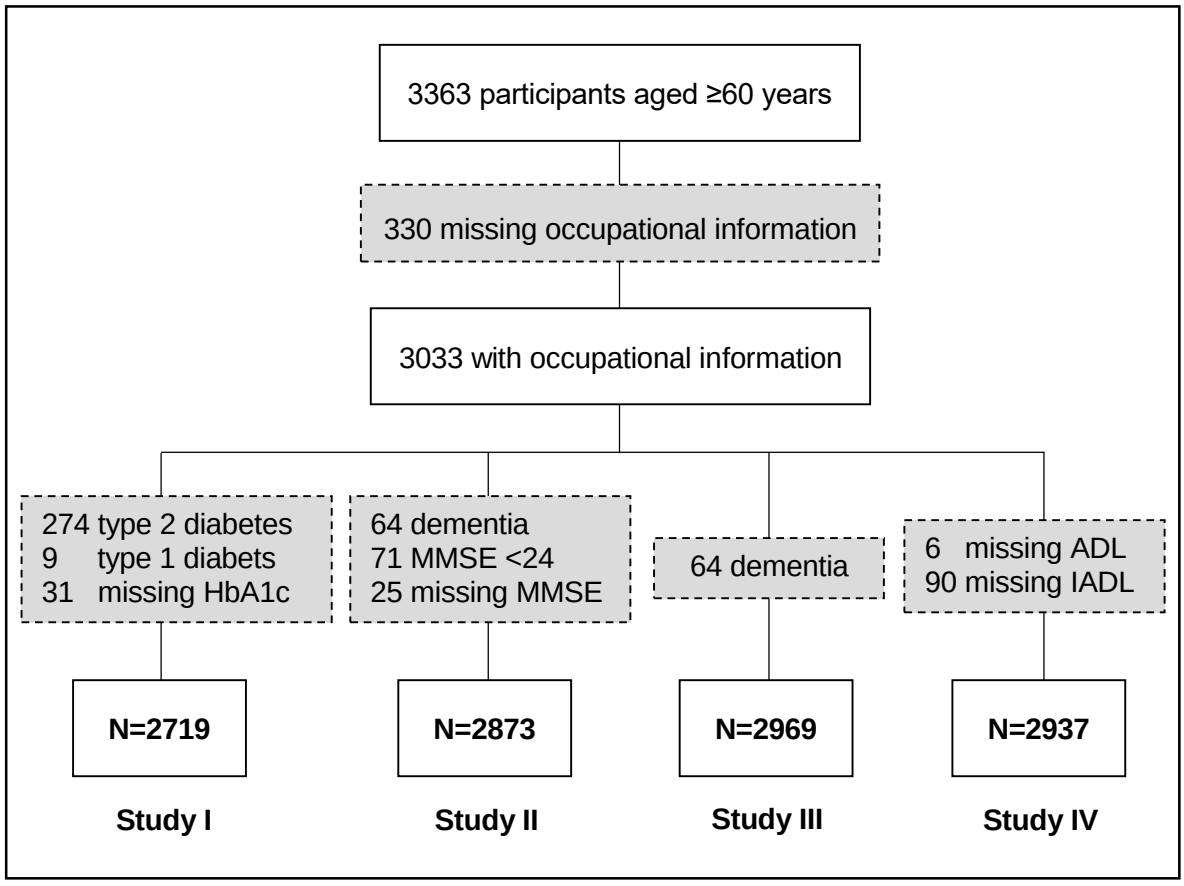

Figure 4. Baseline study population in Studies I to IV. Abbreviations: ADL, activities of daily living; HbA1c, glycated hemoglobin; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

3.2 ETHICAL CONSIDERATIONS

SNAC-K follows the ethical guidelines for medical research involving human subjects described in the World Medical Association's Declaration of Helsinki, and in the Swedish Council for Research in the Humanities and Social Sciences. At first, participants were contacted by letter. They received a personal letter two weeks before the visit which explained the aim, duration, examinations in the study, and the role and relevance of the participants. It was clearly stated that the participation was voluntary and could be terminated by participants at any time without having to give a reason. Next, potential participants were called to confirm the participation and to schedule an appointment. In case of cognitively impaired participants, consent was given from the participants together with a proxy (e.g., close family member or caregiver). The participants were also asked whether they would like

to be informed of results from medical assessments. As part of the informed consent procedure, the participants were further assured that their data would be anonymous and confidential. Both written and oral consent to participate was obtained.

With regards to confidentiality, at the SNAC-K center completed questionnaires were kept in locked drawers. The data were entered into the database system according to the rules for security and privacy. Permission must be received from the principle investigator of SNAC-K prior to utilizing the data and conducting research, and researchers were only given data marked with codes, leaving the name and personal identification of participants anonymous.

The safety and well-being of participants were prioritized during the examinations. Assessments occurred in a friendly and comfortable environment. If anguish or discomfort was expressed at any time during the examination, the interview ended immediately. In the case of disorders or diseases being detected, the examining physicians informed participants' family doctors if the participants previously expressed the wish to be informed of health status.

SNAC-K received ethical approval from the Ethics Committee at Karolinska Institutet and the Region Ethics Review Board in Stockholm for baseline and follow-ups of 3-, 6-, 9-, and 12- years (Dnrs 01-114, 04-929/3, Ö 26-2007, 2010/447-31/2, 2013/828-31/3), as well as for the data from the Swedish National Patient Registry (Dnr: 2009/595-32).

3.3 DATA COLLECTION

Data collection of SNAC-K followed a structured protocol at baseline and all follow-ups (available at http://www.snac-k.se/), which took approximately six hours to perform each time. Physicians conducted clinical examinations; nurses collected information on socio-demographics, occupational experience, lifestyle factors, and functional status in daily living activities, measured anthropometrics and arterial parameters, and took peripheral blood samples from all participants. Cognitive function was evaluated by psychologists. Information on medical conditions was also obtained from the Swedish National Patient Registry. Vital status was received from the Swedish Cause of Death Registry.

3.4 ASSESSMENT OF EXPOSURE: PSYCHOSOCIAL WORKING CONDITIONS

At baseline, nurses asked participants to recall all of the work experience throughout their professional lives. Then, detailed information on the five longest-held jobs, including employers, job titles, tasks, and time spans, was recorded (79). Each occupation was coded in accordance with the three-digit Nordic Occupation Classification Codes (Nordisk yrkesklassificering, NYK) (80). Psychosocial working conditions in this thesis were defined based on the job demand-control-support model (27, 30, 31). Levels of job control, job demands, and social support at work were evaluated by a validated psychosocial job exposure

matrix (81) constructed on the basis of a random sample of 48,894 Swedish workers from the Swedish Work Environment Survey between 1989 and 1997. The items measuring job control, demands, and social support were identified by factor analyses, and the exact wordings of questions for the three job dimensions are listed in **Table 1**. In total, average scores of job control, demands, and social support of 320 occupations were generated for men and women separately. The average score of each job dimension was transformed to vary between 0 and 10. Occupations in this matrix were coded in accordance with the three-digit NYK codes, the same coding scheme used in SNAC-K.

Table 1. Questions used to measure job control, demands, and social support in the psychosocial job exposure matrix

Components	Questions
Job control	Can you organize your work tasks yourself (e.g., what to do, how to do it, or who to work with)?
	Can you decide when to do different tasks?
	Can you decide the pace of work yourself?
	Can you take a short break at any time?
	How long does it take to learn to do tasks in the job?
	Does the job require you to repeat the same tasks?
	Does the job give you opportunity to learn something new or to develop in the profession?
Job demands	Do you sometimes have such stress that you cannot talk about or even think of anything but work?
	Do you sometimes have so much work that you have to work overtime or take the work home?
	Does the work require all of your attention and concentration?
	Do you have difficult work that you need help for? If yes, how often do you have such difficult tasks?
Social support	Do you have the opportunity to get support and encouragement from coworkers when having difficult tasks?
	Do you have the opportunity to get support and encouragement from supervisors when having difficult tasks?
	Do you have the opportunity to get advice or help for difficult tasks?

For the operationalization of demand-control-support status in SNAC-K, job control, demands, and social support in each of the five jobs were dichotomized as high and low using the median values from the job exposure matrix, respectively. Further, occupations were classified into four scenarios based on the demand-control combinations: high job strain (high demands, low control), low job strain (low demands, high control), passive job (low demands, low control), and active job (high demands, high control). Iso-strain was defined as

the combination of high job strain and low social support at work (30). In SNAC-K, occupations classified as high strain were, for example, actor/actress, dentist, pharmacist, telephone operator, taxi driver, tailor, graphic designer, and hair dresser; low strain were librarian, home care assistant, cartographer, and nurse assistant; active jobs were engineer, teacher, journalist, artist, physician, police, and banker; passive jobs were vender, sailor, miner, postman, graphic printer, confectioner, construction worker, assembling worker, locksmith, and cleaner. In all studies, we focused on the longest-held occupation since it is deemed the main contributor to psychosocial working conditions of one's professional life. In Studies I, II, and III, duration of work experience in each of the demand-control categories was calculated based on the time spans of the five occupations.

3.5 ASSESSMENT OF OUTCOMES

3.5.1 Type 2 diabetes

Glycated hemoglobin (HbA1c [%]) was measured using the Swedish Mono-S High Performance Liquid Chromatography and modified by adding 1.1% to the HbA1c value in accordance with the National Glycohemoglobin Standardization Program to meet the international standard (82). Diabetes was ascertained based on the clinical examination, medical history, use of blood glucose-lowering agents, HbA1c ≥6.5% (48 mmol/mol) (83), or medical records from the Swedish National Patient Registry, where diabetes was recorded by the criteria of the 9th and 10th revisions of the International Classification of Diseases (ICD-9 code 250 and ICD-10 codes E11-E14).

3.5.2 Global cognitive function

Global cognitive function was evaluated using a 30-point version of the Mini-Mental State Examination (MMSE) at baseline and each follow-up. MMSE consists of questions on orientation in time and space, attention, memory, numeracy, language, and visual construction (84).

3.5.3 Dementia

Dementia was diagnosed following the criteria of the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition. Following a validated three-step procedure (85), two examining physicians independently made preliminary diagnoses based on interview, clinical examination, and cognitive testing. In case of disagreement, a third opinion from a senior neurologist was sought to reach a concordant diagnosis. AD was diagnosed according to the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (86). For those who died before the subsequent follow-up examination, incident dementia was identified by physicians through an extensive review on medical records, hospital discharge diagnoses, and death certificates.

3.5.4 Disability

The capacity to independently carry out ADL (i.e., dressing, bathing, toileting, eating, transferring, and continence) and IADL (i.e., grocery shopping, meal preparation, laundry, housekeeping, managing medication, handling money, using telephone, and taking public transportation) was reported by participants at baseline and all of the follow-up examinations. Caregivers were also asked to confirm these reports. People living in institutions were assumed to be dependent on others for meal preparation, grocery shopping, housekeeping, and laundry. Level of disability was measured by summing the numbers of ADL and IADL limitations in one scale to enhance range and sensitivity of disability measurement (20).

3.6 COVARIATES

Socio-demographics

Education was recorded as elementary, high school, and university according to the highest degree achieved. Occupation of participants' father was used to assess early-life SES in accordance with three groups: manual, intermediate, and professional (87). Living place was documented as community-dwelling and living in institutions.

Occupational characteristics

In addition to psychosocial working condition, other occupational characteristics, such as occupational type (i.e., blue- and white-collar workers) as well as physical demands at work (i.e., light, moderate, and strenuous) were considered (75).

Lifestyle factors

Smoking status was recorded as never, former and current smoking. Alcohol consumption was assessed based on the frequency and amount consumed and classified as none or occasional, light-to-moderate (1-7 drinks per week for women and 1-14 drinks per week for men), and heavy drinking (>7 drinks per week for women and >14 drinks per week for men) (88). In Study I, physical activity was assessed by the frequency of participation and intensity of physical exercise and classified as fitness-enhancing (moderate-to-intense exercise several times per week or everyday), health-enhancing (light exercise several times per week or everyday) and physically inactive (never or exercise less than 2-3 times per month) (89, 90). In Studies II, III, and IV, global leisure activity was assessed based on the engagement in mental (e.g., reading books, playing chess, listening to music, painting), social (e.g., religious activities, travelling, social meetings, voluntary work) and physical activities (e.g., long bike ride, brisk walking, jogging, intense gym). Engagements in mental and social activities were categorized as low (score 0), moderate (score 1), and high (score 2) according to the variety of activities, respectively. Engagement in physical activities was coded based on the frequency of participation as low (less than once a week; score 0), moderate (at least once a week; score 1), and high (more than once a week; score 2). Scores of engagement in these

three activities were summed (ranged from 0-6) to evaluate the global leisure activity engagement, which was further categorized into three levels as low (score 0-1), moderate (score 2-3), and high (score 4-6) (91, 92).

Medical conditions and biological factors

Chronic medical conditions were ascertained by clinical examination, medication use, medical history, laboratory data, linkage to inpatient and outpatient care data from the Swedish National Patient Registry, and/or through proxy interviews (93). All diagnoses were coded in accordance with ICD-10. Chronic diseases were defined as conditions with prolonged duration and when either 1) residual disability remained or quality of life was worsened, or 2) long-term care, treatment or rehabilitation was required. A total of 918 ICD-10 codes were identified and classified into 60 chronic disease categories (78, 93). At baseline and each follow-up, the total number of chronic diseases was calculated. Specifically, heart diseases included atrial fibrillation, ischemic heart disease, heart failure, cardiac valve disease, bradycardias and conduction diseases. Arterial blood pressure was measured twice with a 5-minute interval and the mean of two values was recorded. Hypertension was defined as systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. As for anthropometric data, height and weight were measured in light clothes without shoes. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meter and classified as underweight (<20), normal (20-24.9), overweight (25-29.9), and obese (≥30). High-density lipoprotein cholesterol and C-reactive protein (CRP) values and genetic polymorphisms were derived from blood samples taken at baseline and determined following standard procedures. *APOE* genotype was dichotomized as ε4 carrier and non-ε4 carrier. CRP indicates overall inflammation level of the body and high CRP was defined as serum level ≥5mg/L (94).

3.7 STATISTICAL ANALYSES

In all studies, analyses were computed using Stata SE 13.0 or 15.0 (StataCorp LP., College Station, Texas, USA). Statistical tests were two-tailed and *p*-values <0.05 were considered statistically significant. Baseline characteristics between participants with different demand-control categories were compared using chi-square (χ^2) for categorical variables or one-way ANOVA followed by pairwise comparison with Bonferroni correction for continuous variables. **Table 2** displays the overview of the studies and methods included in this thesis.

In Study I, logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of the association between high strain and diabetes, as compared to non-high strain jobs (including low strain, passive, and active jobs). Statistical interactions between high strain and age, as well as high strain and sex, with respect to estimating diabetes risk were tested by introducing interaction terms in the model first, followed by stratified analyses by age and sex. To explore the role of duration of work experience in the association between

high job strain and diabetes, duration of high-strain work was categorized into zero years, equal to or less than, and greater than the median duration of work. Models were adjusted for sex, age, education, follow-up time, cholesterol, BMI, smoking, alcohol consumption, physical activity, and early-life SES.

In Study II, linear mixed-effects models were applied to examine the association of job demand-control status with the rate of annual change in global cognitive function, using active jobs as reference. The models included demand-control combinations, linear follow-up time and their interaction term as the fixed effect. The random effect took into account individual differences in cognitive function at baseline (random intercept) and in the rate of cognitive decline (random slope). The procedures to explore the role of work duration in the association of job categories with changes in cognitive function are as follows: people with 0 years of exposure were identified first, followed by categorizing other people into ten groups based on the distribution of years of exposure to each demand-control category. Further, the effect of each decile on cognitive decline was compared, using 0 years of exposure as reference. Cut-off point to dichotomize the years of exposure to each job demand-control category was set when either the direction of effect of estimation changed or a significant magnitude was shown. Age, sex, education, depression, heart disease, hypertension, CRP, BMI, smoking, alcohol consumption, leisure activity engagement and early-life SES were controlled for in the models.

In Study III, Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CIs of dementia in relation to demand-control combinations, using active jobs as reference. Follow-up time was calculated from the date of baseline examination until the date of dementia diagnosis, the date of death, or the date of last examination. The proportional hazard assumption was tested by regressing the Scaled Schoenfeld's residuals against survival time. No violation of proportionality was detected. Statistical interaction between demand-control status and *APOE* genotype with respect to estimating dementia risk was tested by introducing an interaction term in the model. To test the joint effect of occupational status and *APOE* on dementia in the case of a statistically significant interaction detected, we created an eight-category indicator variable by the cross-tabulation of four job categories (i.e., low strain, high strain, active job or passive job) and two *APOE* genotypes (i.e., presence or absence). To explore the role of duration of work experience in the association between demand-control status and dementia, duration of each job category was categorized into zero years, equal to or less than, and greater than the median duration of work. Stratified analyses were conducted in all models by two age cohorts, the younger-old (aged $\leq$72 years) and the older-old (aged $\geq$78 years) to explore the potential time window where effect of work status on dementia risk could last. All the analyses were adjusted for age, sex, education, heart disease, hypertension, depression, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

In Study IV, linear mixed-effects models were used to investigate the association of job demand-control status with the rate of disability progression, using follow-up time in year as

time scale. The models included demand-control status, linear follow-up time and their interaction term as fixed effect. The random effect took into consideration individual differences in total disability at baseline (random intercept) and in the rate of disability progression (random slope). Statistical interaction between high strain and low social support with respect to predicting disability trajectories was tested by introducing a three-way interaction term (i.e., job strain, social support, and time) in the model first, followed by stratified analyses by social support at work. To test and quantify the mediating effects of changes in global cognitive function and chronic disease burden during the follow-up on the association between demand-control status and the rate of disability progression, mediation analyses were performed where the MMSE score and number of chronic diseases were treated as time-varying variables. In all models, age, sex, education, alcohol consumption, smoking, leisure activity engagement, early-life SES, occupational type, and physical demands at work were controlled for.

In sensitivity analyses, we repeated the analyses in all studies using psychosocial work status of the latest job to reduce recall bias. In addition, to address the potential reversed causation, in Studies II and III, incident dementia cases in the first three years of follow-up were excluded. Furthermore, multiple imputation by chained equation was carried out for missing data in covariates in all of the analyses, which helped maintain statistical power.

Table 2. Overview of the studies and methods included in this thesis

Study	Exposure	Outcome / Follow-up time	Potential confounder	Statistical analysis
Study I	High strain vs Non-high strain Work duration in high strain	Type 2 diabetes 6 years of follow-up	Age, sex, education, follow-up time, cholesterol, BMI, smoking, alcohol consumption, physical activity, and early-life SES	Logistic regression
Study II	Active jobs vs Non-active jobs Work duration in each demand-control category	MMSE trajectory 9 years of follow-up	Age, sex, education, heart disease, hypertension, depression, CRP, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES	Mixed-effect models
Study III	Active jobs vs Non-active jobs Work duration in each demand-control category	Dementia 12 years of follow-up	Age, sex, education, heart disease, hypertension, depression, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES	Cox regression
Study IV	Active jobs vs Non-active jobs Effect modifier: social support at work	Disability trajectory Mediator: MMSE, multimorbidity 12 years of follow-up	Age, sex, education, smoking, alcohol consumption, leisure activity engagement, early-life SES, occupational type, and physical demands at work	Mixed-effect models Mediation analysis

Abbreviations: BMI, body mass index; CRP, C-reactive protein; MMSE, Mini-Mental State Examination; SES, socioeconomic status.

4 RESULTS

Below we summarize the main results derived from the four individual studies included in this thesis. For more detailed results, please refer to the published papers and manuscripts.

4.1 PSYCHOSOCIAL WORKING CONDITIONS AND TYPE 2 DIABETES

In Study I, of the 2719 participants at baseline (mean age 72.7±10.7), 1756 (65%) were women. During the 6 years of follow-up, 154 participants developed diabetes. Incident diabetes cases were more likely to be men, obese, and to have cardiovascular disorders.

Association of psychosocial working conditions with diabetes risk

Work-related stress characterized by high job strain was not associated with diabetes occurrence in the total population. Borderline-significant multiplicative interactions were observed between high strain and age and sex (p=0.08 and 0.06, respectively). In the stratified analyses by age and sex, people aged 60 years at baseline who had had high strain in the longest-held job were at an increased risk of diabetes compared to those without such work experience. Further, the association of high strain with diabetes was statistically significant in women, but not in men (**Table 3**).

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of incident diabetes in relation to high strain in the longest-held job, by age and sex

	No. cases	OR (95% CI)	*p*
Whole population	154	1.30 (0.78-2.17)	0.31
Aged 60 years	28	3.13 (1.14-8.59)	<0.05
Male	16	1.27 (0.22-7.25)	0.78
Female	12	8.52 (1.86-39.0)	<0.01
Aged 66+ years	126	1.04 (0.57-1.92)	0.89
Male	51	1.00 (0.96-1.04)	0.93
Female	75	1.37 (0.69-2.72)	0.37

Models were adjusted for age, sex, education, follow-up time, cholesterol, BMI, smoking, alcohol consumption, physical activity, and early-life SES.

Duration of high job strain throughout the working life and diabetes risk

In the study population the median duration spent in high job strain was 14 years, therefore we created a three-category variable regarding the duration of high strain: zero, equal to or less than 14 years, and more than 14 years. Following the same stratified analyses, among women aged 60 years at baseline, in comparison with people with no high strain during the whole working life, those who had 15+ years of experience in high job strain demonstrated an increased risk of diabetes (OR 9.29, 95% CI 2.27-37.95) (**Figure 5**).

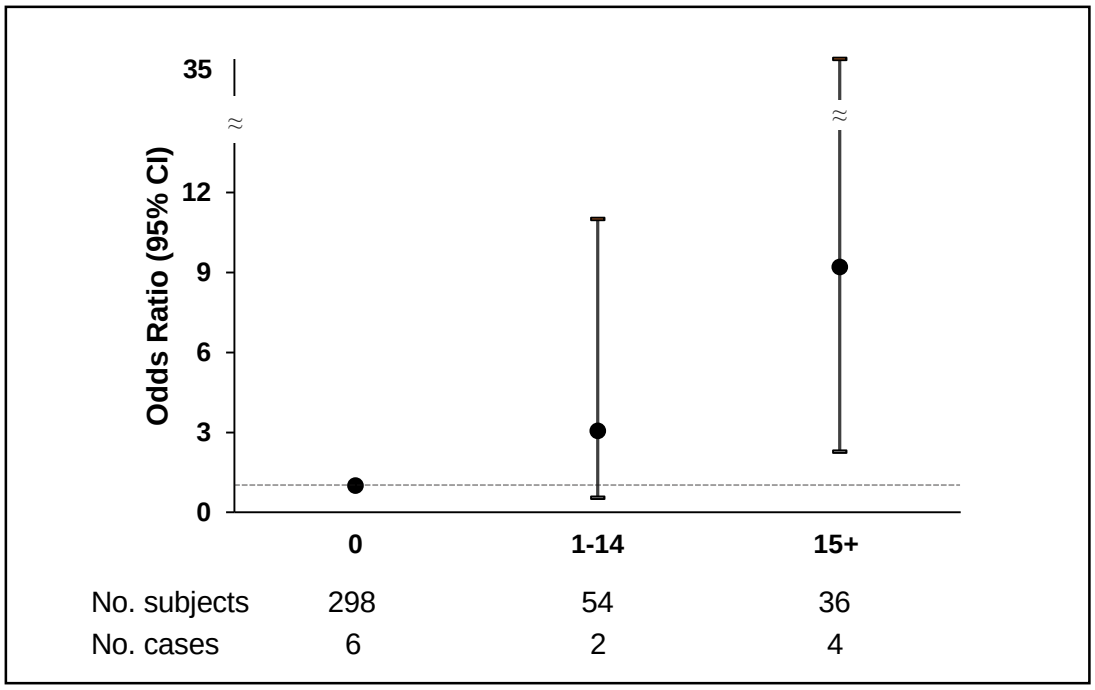

Figure 5. Odds ratios and 95% confidence intervals of incident diabetes in relation to work duration of high strain throughout the working life among women aged 60 years at baseline. Model was adjusted for education, follow-up time, cholesterol, BMI, smoking, alcohol consumption, physical activity, and early-life SES.

4.2 PSYCHOSOCIAL WORKING CONDITIONS AND COGNITIVE DECLINE

In Study II, of the 2873 participants (mean age 72.7±10.2), 1783 (62%) were women. People with active jobs were younger, more likely to be men, to have higher education, to engage in leisure activities, and had higher baseline MMSE score. Those who had had passive jobs were less educated, and more likely to come from a manual worker's family. Compared to participants who at least had two examinations (n=2198), those who did not (n=675, 23.5%) were older, less educated, had lower MMSE score at baseline, more likely to have chronic diseases, less likely to engage in leisure activities and to work in active jobs.

Association of psychosocial working conditions with rate of cognitive decline

Compared to people with active jobs, those with the other three demand-control categories (i.e., high job strain, low job strain, and passive jobs) all demonstrated faster cognitive decline over the follow-up period (β -0.17, 95% CI -0.26, -0.08; β -0.13, 95% CI -0.24, -0.03; β -0.22, 95% CI -0.34, -0.11). In the stratified analyses by age, passive jobs were associated with an accelerated rate of cognitive decline (β -0.10, 95% CI -0.19, -0.01), but not high or low strain, among the younger-old (aged ≤72 years). No statistically significant association was found between demand-control status and the changes in cognitive function among the older-old (aged ≥78 years) (**Figure 6**).

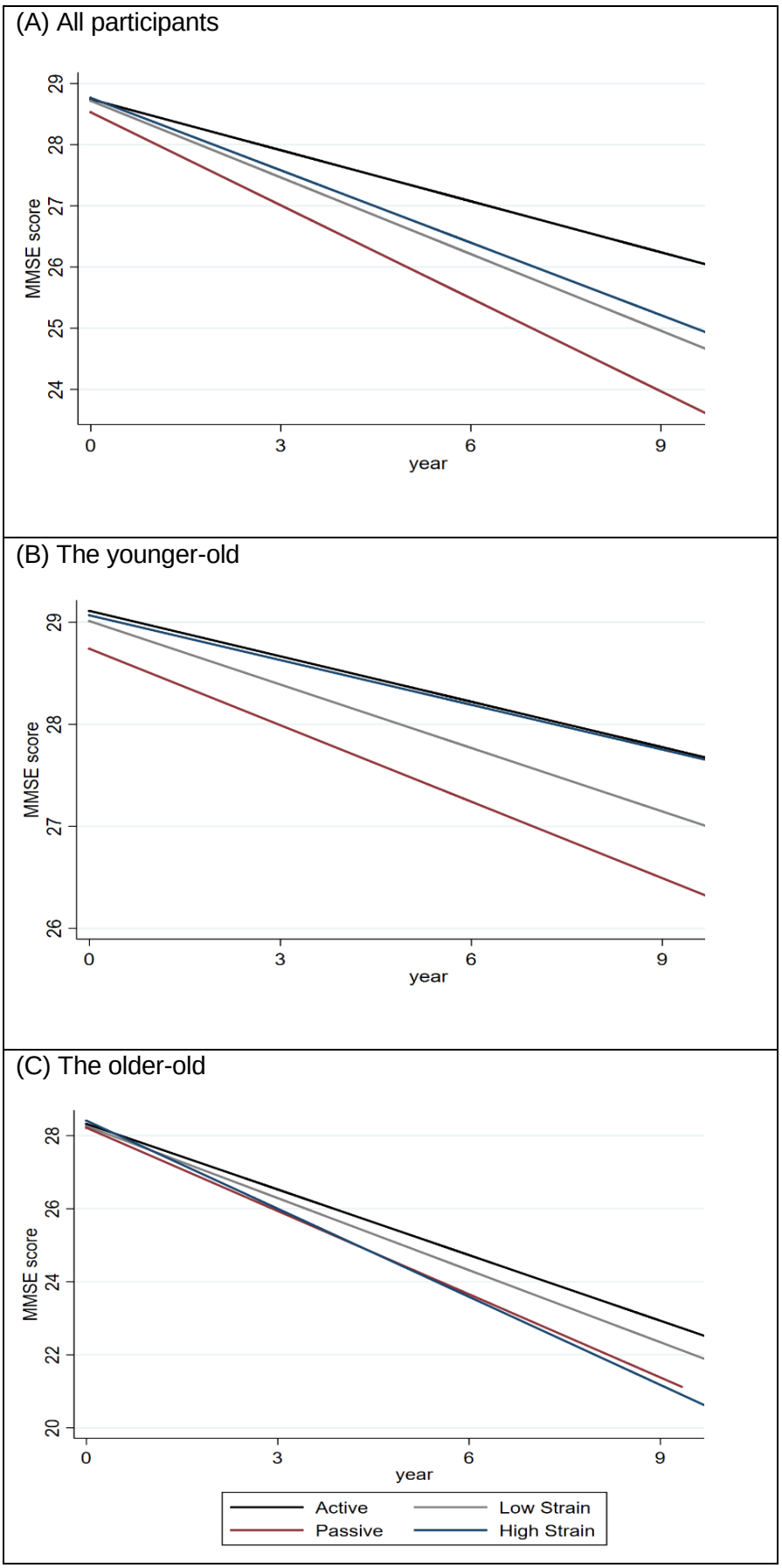

Figure 6. Trajectories of MMSE score by demand-control status among (A) all participants, (B) the younger-old (aged ≤72 years), and (C) the older-old (aged ≥78 years). Models were adjusted for age, sex, education, heart disease, hypertension, depression, CRP, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

Work duration of each psychosocial working condition and cognitive decline

Through the procedure mentioned in the method section we identified a threshold of duration in year for each demand-control category over which the rate of change in cognitive function started to accelerate, that was, 5 years for high job strain, 6 years for low job strain, 3 years for passive jobs, and 1 year for active jobs. Compared to those with shorter work experience, people with more than one year of work in active jobs showed a slower rate of cognitive decline (β 0.24, 95% CI 0.16, 0.32). By contrast, an accelerated rate of cognitive decline was seen among people with longer duration of high job strain (β -0.13, 95% CI -0.21, -0.04), low job strain (β -0.12, 95% CI -0.19, -0.05), or passive jobs (β -0.12, 95% CI -0.20, -0.04), in comparison with those with shorter duration in those jobs (**Figure 7**).

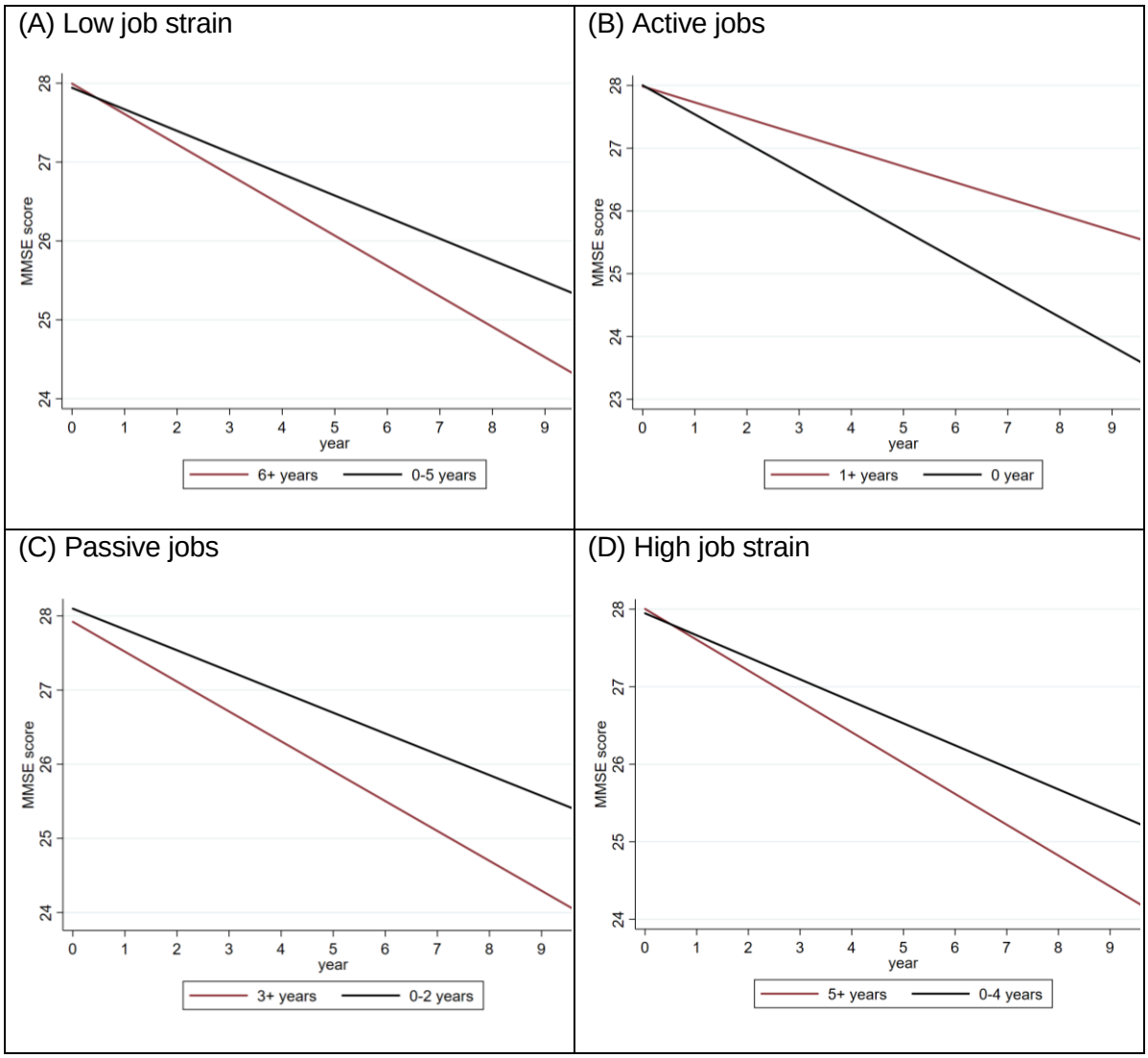

Figure 7. Trajectories of MMSE score by duration of work in (A) low job strain, (B) active jobs, (C) passive jobs, (D) high job strain. Models were adjusted for age, sex, education, heart disease, hypertension, depression, CRP, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

4.3 PSYCHOSOCIAL WORKING CONDITIONS AND DEMENTIA

In Study III, of the 2579 participants in the study sample (mean age 72.7±10.4), 1602 (62%) were women. At baseline, people who had had a passive job were less educated and more likely to have heart diseases. Those who had active jobs were younger, more likely to be men, and had higher baseline MMSE score. A similar pattern was observed when comparing characteristics of participants in the two age cohorts (i.e., the younger-old aged ≤72 years and the older-old aged ≥78 years) separately. During the 12-year follow-up (mean 8.8±3.7 years), 282 participants developed dementia, of which 63 were younger-old and 219 were older-old. In both age groups, incident dementia cases were less educated, more likely to be *APOE* ε4 carriers, and had lower MMSE score at baseline. Among the younger-old, cases were older and more likely to have heart diseases.

Association of psychosocial working conditions with dementia risk

Psychosocial working conditions in the longest-held job, characterized by job control, job demands, or demand-control categories, were not associated with dementia in the entire study population. When stratified by age, using active jobs as reference, passive jobs were associated with an increased risk of dementia among the younger-old (HR 2.43, 95% CI 1.06, 5.55), but not among the older-old individuals (**Table 4**).

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) of incident dementia associated with demand-control categories in the total sample and in two age cohorts

	No. subjects	No. cases	HR (95% CI)	*p*
Whole population				
Active	1611	151	Ref.	
Low strain	421	55	1.08 (0.78-1.51)	0.65
High strain	292	37	1.05 (0.71-1.55)	0.80
Passive	255	39	1.00 (0.68-1.47)	0.98
Aged ≤72				
Active	1064	40	Ref.	
Low strain	196	10	0.77 (0.36-1.66)	0.50
High strain	158	4	0.39 (0.12-1.28)	0.12
Passive	98	9	2.43 (1.06-5.55)	<0.05
Aged ≥78				
Active	547	111	Ref.	
Low strain	225	45	1.08 (0.75-1.58)	0.67
High strain	134	33	1.20 (0.78-1.83)	0.41
Passive	157	30	0.91 (0.59-1.42)	0.68

Models were adjusted for age, sex, education, heart disease, hypertension, depression, BMI, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

The joint effect of passive jobs and *APOE* ε4 on dementia risk

There was a multiplicative interaction between passive jobs and *APOE* ε4 allele with respect to estimating dementia risk among the younger-old (p <0.05), but not among the older-old. In the joint effect analyses, among the younger-old, *APOE* ε4 carriers with passive jobs had a higher risk of dementia compared to *APOE* ε4 non-carriers with active jobs (HR 8.1, 95% CI 2.9, 22.8) (**Figure 8**).

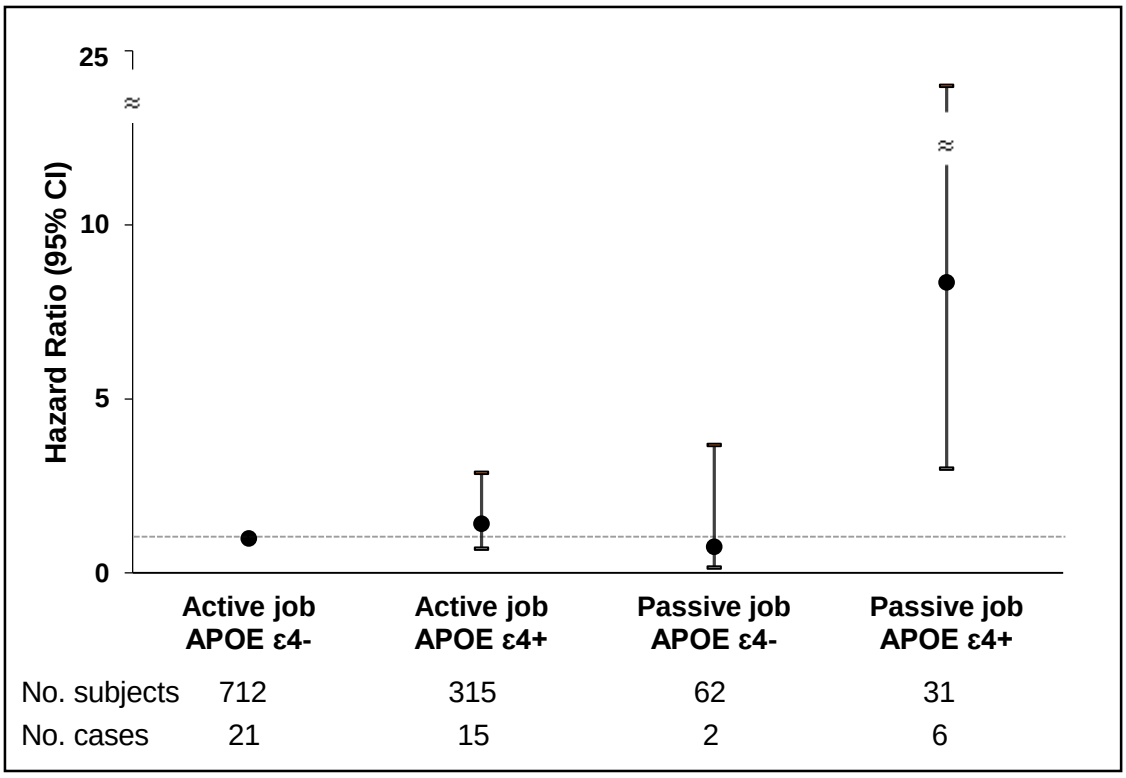

Figure 8. Hazard ratios and 95% confidence intervals (CI) for the association of demand-control categories with incident dementia by *APOE* genotype among adults aged ≤72 years. Model was adjusted for age, sex, education, heart disease, hypertension, BMI, depression, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

Duration of passive jobs throughout the working life and dementia risk

Since passive job was the only demand-control category that emerged to have an effect on dementia risk, we focused on this category in analyses regarding duration of work in relation to dementia incidence. As in this study population the median duration spent in passive jobs was ten years, we created a three-category variable: zero, equal to or less than ten years, and more than ten years. Following the same stratified analyses, among the younger-old, in comparison with people with no passive job at all during the whole working life, those who had worked with passive jobs for more than ten years demonstrated an increased risk of dementia (HR 2.5, 95% CI 1.2, 5.2) (**Figure 9**).

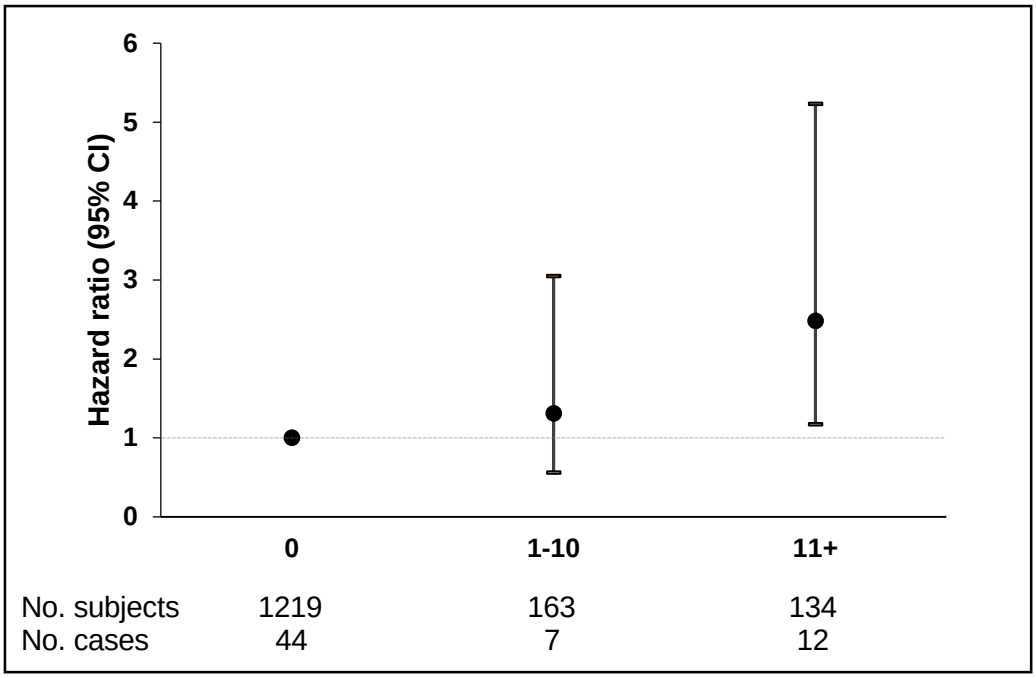

Figure 9. Hazard ratios and 95% confidence intervals (CI) of incident dementia associated with duration of work in passive jobs among adults aged ≤72 years. Model was adjusted for age, sex, education, heart disease, hypertension, BMI, depression, smoking, alcohol consumption, leisure activity engagement, and early-life SES.

4.4 PSYCHOSOCIAL WORKING CONDITIONS AND DISABILITY TRAJECTORY

In Study IV, of the 2202 participants included in the study sample (mean age 71.8±10.1), 1398 (63.5%) were women. At baseline, people who had had a passive job were less educated, more likely to be blue-collar workers, and had more strenuous physical demands at work. Those who had had an active job were younger, more likely to be men and white-collar workers, had higher educational level, lighter physical demands at work, higher MMSE score, less chronic diseases, and less ADL and IADL disabilities at baseline.

Association of psychosocial working conditions with disability progression

Compared to active jobs, high strain (β 0.07, 95% CI 0.02, 0.13), low strain (β 0.10, 95% CI 0.06, 0.15), and passive job (β 0.11, 95% CI 0.05, 0.18) were all associated with an accelerated speed of disability progression during the 12 years of follow-up (**Figure 10**). Further, we detected a multiplicative interaction between high strain and low social support at work with respect to predicting disability trajectories (p <0.05). In the subsequent stratified analyses by social support, we observed that the association between high strain and disability accumulation was only present among workers with low social support, but not among those with high social support (**Table 5**). The association between working conditions and disability progression did not differ between the younger-old and the older-old.

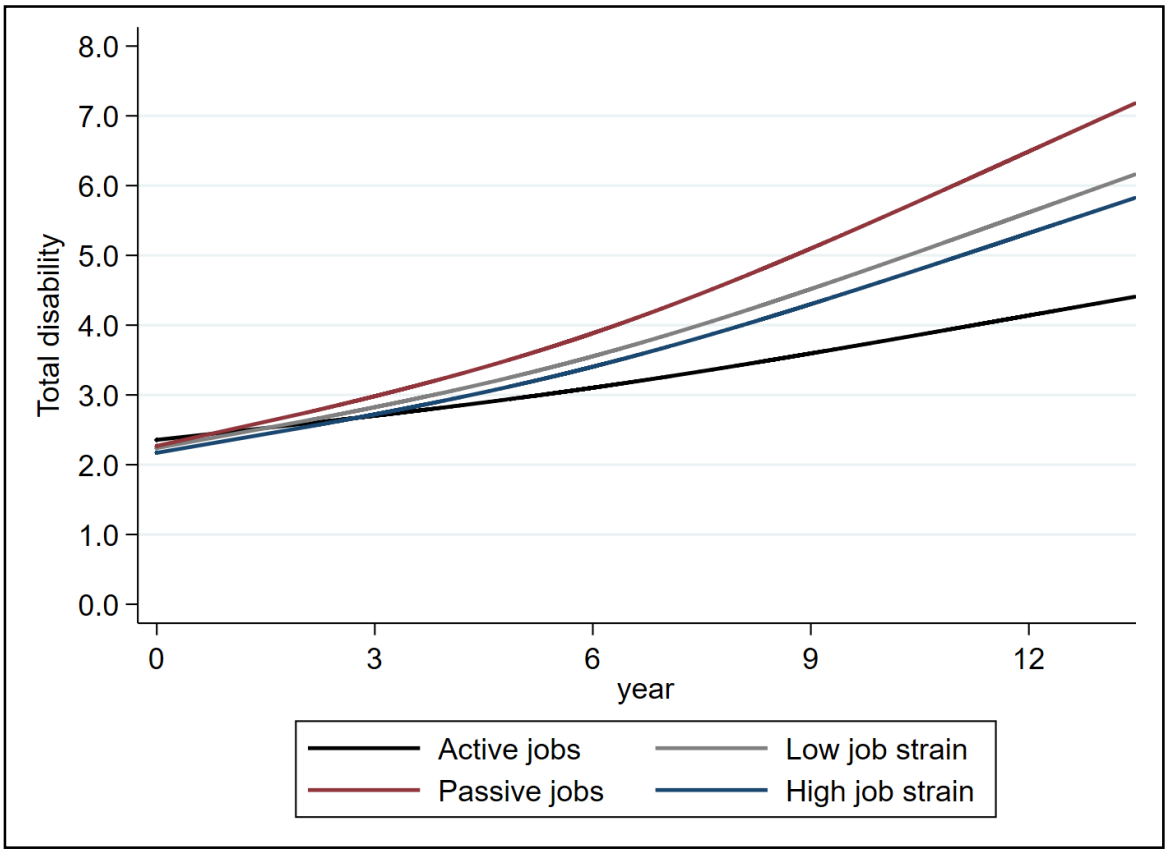

Figure 10. Trajectories of total disability by demand-control status. Model was adjusted for age, sex, education, smoking, alcohol consumption, leisure activity engagement, baseline MMSE score and number of chronic diseases, early-life SES, occupational type, and physical demands at work.

Table 5. β coefficients and 95% confidence intervals (CI) for the association of demand-control status with the annual change in total number of disabilities by level of social support at work

	No. subjects	β (95% CI)	*p*
High social support at work			
Active	697	Ref.	
Low strain	410	0.09 (0.02 to 0.15)	<0.01
High strain	157	0.004 (-0.09 to 0.10)	0.93
Passive	252	0.09 (0.01 to 0.17)	<0.05
Low social support at work			
Active	1110	Ref.	
Low strain	85	0.09 (-0.01 to 0.18)	0.06
High strain	171	0.13 (0.07 to 0.19)	<0.001
Passive	55	0.09 (-0.03 to 0.20)	0.15

Models were adjusted for age, sex, education, smoking, alcohol consumption, leisure activity engagement, baseline MMSE score and number of chronic diseases, early-life SES, occupational type, and physical demands at work.

The mediating role of changes in cognitive function and chronic disease burden in the association of psychosocial working conditions with disability trajectories

In the mediation analyses, demand-control status was treated as an ordinal variable according to the magnitude of the associations between demand-control combinations and the annual change in total disability (i.e., the slopes shown in **Figure 10**), that is, the detrimental effects of demand-control categories followed an order from the lowest to the highest: active jobs, high strain, low strain, and passive jobs. Such dose-response pattern was also seen in the changes in MMSE score (**Figure 6-A**) and number of chronic diseases over time (95) in relation to these job categories. The mediation analyses revealed that 38.5% of the total association between demand-control status and disability trajectories was mediated by the decline in cognitive function, while 18.4% was mediated by the accumulation of medical conditions that occurred during the follow-up period (**Figure 11**).

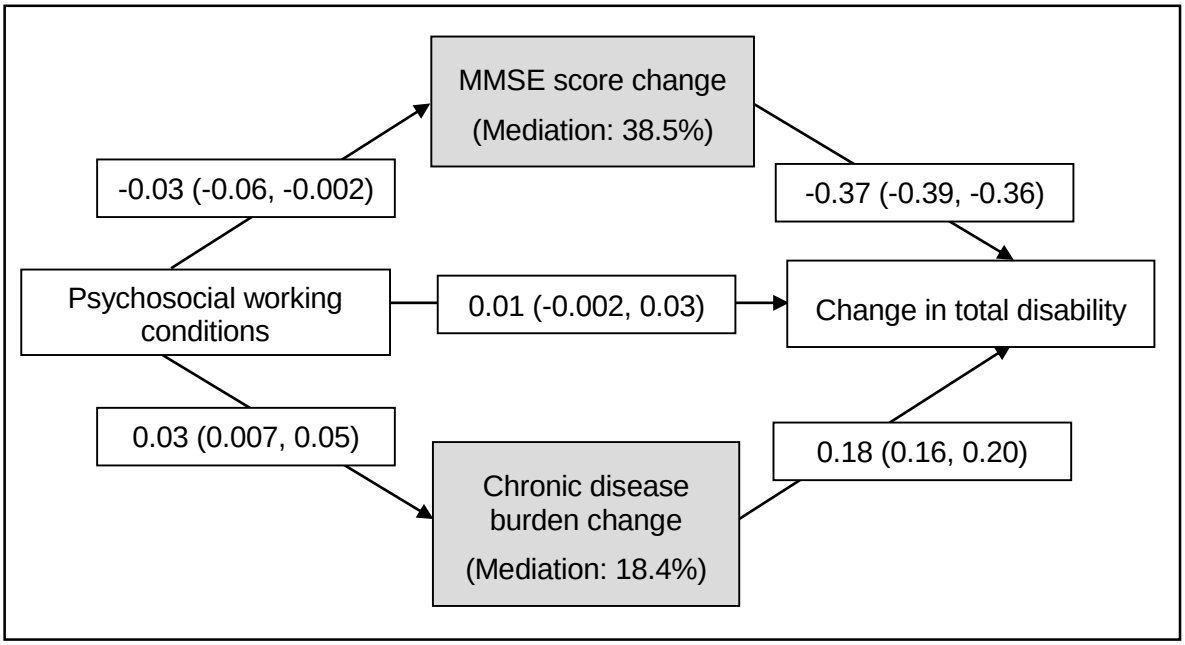

Figure 11. Mediating effects of the changes in MMSE score and number of chronic diseases during the follow-up on the association of psychosocial working conditions with the changes in total disability. Model was adjusted for age, sex, education, smoking, alcohol consumption, leisure activity engagement, early-life SES, occupational type, and physical demands at work.

5 DISCUSSION

5.1 SUMMARY OF THE MAIN FINDINGS

This doctoral thesis examined the associations of psychosocial working conditions, characterized by the demand-control combinations, with negative health outcomes in older age, including diabetes, dementia, cognitive decline and disability progression. Furthermore, several concepts from the life-course epidemiology were adopted to investigate the roles of duration of work experience, time after retirement, susceptibility, and modifying and mediating factors in those associations. The main findings of this thesis are summarized as follows:

1. High job strain was associated with an increased risk of type 2 diabetes among people aged 60 years, especially in women, but not in men. Having more than 14 years of work experience in high job strain increased diabetes risk among women aged 60 years.

2. Low strain, high strain, and passive jobs were all associated with faster cognitive decline, as compared to active jobs. In addition, longer duration of work in low strain (6+ years), high strain (5+ years), or passive jobs (3+ years) throughout the working life was associated with an accelerated rate of cognitive decline, whereas longer duration of active jobs (1+ years) was related to slower cognitive decline.

3. Passive jobs were associated with a higher risk of dementia among the younger-old (aged ≤72 years), but not among the older-old individuals (aged ≥78 years). Having more than ten years of work experience in passive jobs increased dementia risk among the younger-old. *APOE* ε4 amplified the effect of passive jobs on dementia occurrence.

4. Compared to active jobs, low strain, high strain, and passive jobs were all related to an accelerated rate of disability progression. However, the association between high strain and disability was only shown among people with low social support at work, but not among those with high social support. Furthermore, the association between psychosocial working conditions and disability was mediated 38% by cognitive decline and 18% by chronic disease accumulation.

5.2 IMPACT OF DEMAND-CONTROL STATUS ON HEALTH IN OLDER AGE

Work-related stress

High job strain, which was hypothesized as a stressful workplace scenario, was associated with a higher risk of diabetes (Study I) and an accelerated rate of cognitive decline (Study II) and disability progression (Study IV). Nevertheless, we did not observe the association between high strain and dementia (Study III).

Type 2 diabetes

The finding that high-strain work environment increased the risk of diabetes among women aged 60 years, but not in men (Study I), was in line with the majority of previous studies investigating such association in working population (54-58, 61). One may speculate this sex-specific association in several ways. First, it is commonly acknowledged that men and women tend to report health conditions and perceived stress level differently, resulting in a sex-related reporting bias. This may be due to the different patterns of generating stress at work between sexes. In women, both quantitative (e.g., mental work load) and qualitative demands (e.g., role conflict or emotion) determine job strain, while quantitative demands are more dominant in forming stress in men (96). Our study relied on a job-exposure matrix built for men and women separately, and we categorized demand-control status in two sexes too (i.e., jobs grouped as high strain in men were not always the case in women). Thus, the potential bias due to report-differentiation between sexes might have been addressed here. Second, the fact that there is a sex segregation in the labor force is not deniable, meaning that men and women tend to work in different types of occupation, which may also contribute to the sex-restricted results. However, in the supplementary analyses where type of occupation was further adjusted for the results did not change. Third, the divergent role outside of work between sexes may help explain the stronger effect of work stress on diabetes in women than in men. Women tend to take more responsibilities in household and child care, thereby prolonging stress reaction even after work (97-101). Indeed, in Study I, it was also observed that heavy household chores load amplified the effect of high strain on diabetes in women. Finally, there might be a fundamental difference in the biological response to stress between sexes, which has been seen in studies where women generally had a higher level of stress hormone (i.e., cortisol; stress response will be discussed in the later sections) than men when faced with a stressful situation at work (102-104).

Rate of cognitive decline and disability trajectory

The association between high job strain and faster cognitive decline shown in Study II was supported by previous findings (64-67) in spite of the different study design or outcomes of interest in those studies. In addition, the association between high strain and faster late-life disability progression shown in Study IV was in line with the study that reported more ADL and IADL limitations in older adults who used to work in high-strain jobs during their working lives (76). Similarly, high strain was also linked to work disability (105-108) and poor functioning in old age (51, 109, 110). Furthermore, social support at work served as an effect modifier in the associations between high strain and cognitive decline (Study II) and disability trajectories (Study IV). In detail, the associations between high strain and faster cognitive decline and disability progression were only shown among people with low social support, but not among those with high social support. Iso-strain, the combination of high strain and low social support, has been proposed as the most detrimental workplace scenario (30) and has been related to the higher risk of sick leave (111), anxiety, and depression (112). On the other hand, high strain was no longer detrimental when social support at work was

sufficient, which suggests the importance of work-related support especially in a stressful work environment.

Dementia

To our surprise, high job strain was not associated with dementia in Study III. So far, two case-control studies have reported that low job control, a component of high strain, was associated with an increased risk of dementia (69, 70), but none of them tested the effects of job demands and control on dementia using categories in accordance with the demand-control model. One previous work from our group detected an association between high strain and higher risk of dementia and AD within the Kungsholmen Project (KP) – a population-based study carried out during 1987-1994 among people aged 75+ years in the same geographical area of the SNAC-K study (71). It is possible that stress affects brain and cognition through both direct and indirect pathways. The direct mechanism concerns the stress response and inflammation and will be discussed in the following sections. The indirect effect of stress on brain may be related to several major risk factors for dementia (113) that have also been associated with high strain, including vascular risk factors (VRFs) (114, 115), depression (112, 116), and CVDs (117-119). Considering the reduced depressive symptoms (120) and VRFs (121, 122), as well as the improvement in control of CVDs across the past two decades in Sweden, the possible indirect effect of high strain through these factors on dementia might have been attenuated.

There is an apparent contradiction between the findings of an accelerated rate of cognitive decline and disability progression, but no increased dementia risk among people exposed to high job strain. Indeed, the decrements in cognitive function and ADL independency are both considered in dementia diagnosis and closely related to dementia development and progression. In the attempt to explain such contradiction, we looked at the trajectories of MMSE score and number of disabilities. At the end of the follow-up, people with high strain had an average MMSE score of 25, and they developed only one ADL disability over the 12 years. This suggests that the magnitude of cognitive and functional decline related to high strain was not sufficiently large to fulfill the dementia diagnostic criteria.

Biological mechanisms

In general, one of the plausible biological mechanisms that underlie all of the detected associations between high strain and negative health outcomes is related to repeated or chronic stress. The human body has two main self-regulated systems that are activated when faced with a stressful situation, the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. The activation of these systems results in a physiological adaptation, so that the organism can maintain homeostasis, the state of steady internal conditions (123, 124). In response to stress, the SNS – that innervates multiple tissues and works in conjunction with the adrenal medulla which releases adrenaline into the blood – promotes various physical changes, including the elevated heart rate, blood pressure, and blood glucose, and the release of pro-inflammatory cytokines (125). Meanwhile, the HPA

axis controls a cascade of events where the hypothalamus releases corticotropin-releasing factor, which activates the pituitary gland to produce adrenocorticotropic hormone that in turn induces adrenal glands to release glucocorticoid hormones (e.g., cortisol) (126-128). In addition, the innate immune system serves as the body's rapid defense against environmental threats such as infection, injury, or stress (129). The "trouble detectors" such as macrophages and endothelium included in the immune system release pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α (130). These cytokines can stimulate a systematic inflammatory reaction in human body, inducing the production of acute phase proteins such as CRP synthesized in the liver (125). In fact, the nervous and immune systems interact bi-directionally. For example, the elevated blood pressure induced by SNS has a pro-inflammatory effect on endothelium to produce pro-inflammatory cytokines (131), which in turn induces the release of corticotropin-releasing factor from the hypothalamus, and thus, the HPA axis is activated (130).

This dynamic regulatory process, named allostasis, is the key to the maintenance of homeostasis, which, however, can fail to operate within an adaptive limit due to constant stimulation of sustained or repeated stress. In fact, the cost of this chronic energy mobilization, allostatic load, can ultimately lead to the dysregulation of multiple systems in the body, increase vulnerability to diseases, and further contribute to functional limitations (132) (Study IV).

In the context of diabetes (Study I), overabundance of adrenaline and cortisol disrupts glucose allostasis, promoting hepatic glucose output and increasing insulin resistance, while insulin secretion and sensitivity decrease (133, 134). In addition, inflammatory and metabolic pathways are tightly linked and converge at several levels to maintain homeostasis (135). CRP, IL-6 and TNF-α are positively correlated with insulin resistance by interrupting insulin signaling (125, 130). Moreover, oversecretion of cortisol promotes visceral obesity where the increased adipose tissue mass leads to chronic inflammation that further increases insulin resistance over time. (136, 137).

Persistent stress leads to faster cognitive decline (Study II) maybe due to the over-secreted cortisol that interferes with the transcriptional mechanisms in the brain, resulting in the reduced dendritic density (138, 139) and downregulation of brain-derived neurotrophic factor, which is associated with neural plasticity especially in hippocampus (140). Hippocampus is a limbic structure and of crucial importance for memory and learning (141). In AD patients, hippocampus atrophy is commonly seen (142). In addition, IL-6 is often found inside and around β-amyloid plaques in AD patients' brains, suggesting that the inflammatory response plays an important role in the pathogenesis of AD (143). Nevertheless, no association of high job strain with dementia was observed in Study III.

Relaxing yet understimulating jobs

Opposite to high strain, low job strain (high control incorporated with low demands) refers to a relatively relaxing circumstance at work that seems ideal yet possibly lacks mental stimulation (29).

Rate of cognitive decline and disability trajectory

Despite the assumption concerning insufficient mental stimulation in low job strain, it is still surprising that, similar to a stressful work environment, this scenario was also associated with faster cognitive decline (Study II) and disability progression (Study IV), as compared to active jobs. In the demand-control quadrants the difference between low strain and active job is the level of job demands, therefore our findings highlighted the importance of mental stimulation for maintaining cognitive function and independence in later life. Indeed, higher mental demands at work (144-146) and work complexity (147, 148) have been constantly related to better cognitive outcomes. However, low strain did not affect the risk of dementia in Study III. It is possible to speculate that also in this case, like what we have already suggested when discussing high strain and dementia, the magnitude of cognitive decline and disability progression related to low strain was not sufficient to make people meet the criteria of dementia diagnosis.

Biological mechanisms

The concept of cognitive reserve suggests that brain tends to actively cope with brain changes by using preexisting neuronal processing approach or by generating compensatory network to maintain cognitive function (149, 150). The adaptability (i.e., efficiency, capacity, and flexibility) of cognitive processes can be influenced by the interaction of genetic predisposition and life experiences accumulated throughout the life course (149, 150). Previous epidemiological studies have shown that beneficial lifelong factors including early-life cognitive capacity, education, occupation, leisure activity, and social network can boost cognitive reserve (149-151). Thus, the findings of low job strain and accelerated cognitive decline and disability progression might have suggested that deficient mental work load during working life does not provide sufficient cognitive reserve. This in turn fails to help maintain cognitive function in older age, further leading to difficulties in performing daily activities.

Passive jobs

In the active learning hypothesis, passive jobs, the concurrence of low control and low demands, represent demotivating work scenarios where workers are not encouraged to utilize their potential and capacity, which further results in loss of skills and self-efficacy (28).

Rate of cognitive decline and disability trajectory

The greatest magnitude of speed of cognitive decline (Study II) and disability accumulation (Study IV) was shown in passive jobs, among all of the other demand-control categories. These results were in line with previous studies relating passive jobs to worse cognitive function (64-67) and the increased number of ADL and IADL disabilities in later life (76). In addition, it has been reported that unskilled blue-collar workers (74) and physically demanding jobs (152) were related to an increased risk of disability. In fact, passive jobs in SNAC-K were more likely to be manual work. Nevertheless, the finding of passive jobs and disability progression remained after adjusting for occupational type and physical demands at work.

Dementia

Passive job appeared to be the only quadrant in the demand-control model that increased the risk of dementia in Study III, which was consistent with the previous study from our group (71). However, such association was only shown among the younger-old individuals, but not among the older-old, which can be explained in several ways. There may be a limited time window beyond the working life, during which previous exposure to psychosocial working conditions can affect health in later life (44). A similar finding has been reported that constant hurry at work increased dementia risk among the younger-old (mean age 71 years), but not among the older-old (mean age 78 years) (153). In addition, the association between passive jobs and faster cognitive decline was only shown among the younger-old, but not among the older-old (Study II), although no difference was seen in the association of passive jobs with disability progression between two age groups (Study IV). The other possible explanation for this result may be survival bias. Passive jobs have been associated with increased mortality (154), therefore survivors among the older-old with passive jobs may be more resilient and less likely to develop dementia. While dementia cases were also identified from deceased subjects, the survival issue may have been partially addressed. Finally, the higher heterogeneity among older-old dementia cases could result from a more complex combination of risk factors and chronic conditions (155), which may dilute the effect of a single psychosocial factor on dementia.

Nevertheless, the association between passive jobs and dementia was seen in the KP study, which consisted of people aged 75+ years (71). Yet, the discrepancy between results from KP and SNAC-K is not surprising. Education has been shown to be protective against dementia, possibly by inducing cognitive reserve (113). As the educational level of the older-old adults with passive jobs in SNAC-K was higher than that in KP, the adverse effect of passive jobs on dementia may have been attenuated by more education.

Biological mechanisms

The cognitive reserve theory was developed to explain the inter-individual discrepancy between cognitive performance and brain pathology (149, 150). This theory aims to explain

why some individuals can have normal cognitive function despite the presence of brain damage, which can be sufficient to cause cognitive impairment in others. As aforementioned, cognitive reserve is determined by both genetic and environmental factors. *APOE* ε4, a well-known genetic risk factor for dementia/AD, has been related to the accumulation of neurofibrillary tangles and neuritic plaques (156, 157), and might entail an increased neuronal vulnerability to environmental factors. In relation to dementia risk, *APOE* ε4 carriers have been reported to be more vulnerable to the detrimental effects of smoking, heavy alcohol consumption, physical inactivity, and high intake of saturated fats (158). Passive jobs were found to interact with *APOE* ε4 allele with regard to dementia occurrence, suggesting that *APOE* ε4 carriers might have higher vulnerability to the detrimental effect of jobs with low control and low demands, which do not contribute to the building of cognitive reserve.

It is also believed that understimulation in a work context can be perceived as a source of stress, similar to overstimulation (32). Workers in passive jobs might have difficulties in living up to expectations from the social context or finding self-identify, thus leading to chronic stress, anxiety, and depression (159), which in turn compromise homeostasis state, affect multiple systems, and eventually deteriorate function.

5.3 REFLECTION FROM THE LIFE-COURSE PERSPECTIVE

Several core concepts of life-course approach were adopted in the four studies to investigate working-life psychosocial conditions in relation to adverse health outcomes, including causal pathway related to time (i.e., risk accumulation and chain of risk), birth cohort, and different types of mechanism (i.e., susceptibility, modifying, and mediating factors) (33). The risk accumulation was evaluated using the total year of work experience in each of the demand-control categories throughout the working life. We observed a threshold of 15+ years in high-strain jobs that increased the risk of diabetes among women in their early 60s (Study I), as well as 11+ years of passive jobs for a higher dementia risk among the younger-old individuals (Study III). In Study II, longer duration spent in unfavorable working conditions (5+ years in high job strain, 6+ years in low job strain, and 3+ years in passive jobs) accelerated cognitive decline. These results support the hypothesis that negative working conditions become harmful to health especially when the experience is long-lasting or repeated (44). The chain of risk model depicts a sequence in which (dis)advantageous factors influence the following (dis)advantageous consequences. Occupational choices are often made as a result of various factors (160-162). Indeed, in SNAC-K people who worked in active jobs were more likely to have higher education and come from professionals' families, while those with passive jobs had lower education and were more likely to come from manual workers' families. To disentangle the effects of these factors and psychosocial working conditions on the outcomes, we controlled for these factors in all studies.

Cohort effect postulates the differences in responding to social context (e.g., labor market) between people from different birth cohorts (163). In Study III we found the association

between passive jobs and dementia among the younger-old participants in SNAC-K, but not among the older-old (aged 78+ years), which was inconsistent with the result from KP that showed such association among people aged 75+ years. The fact that structure of Swedish labor market had been reformed since 1960s (164) may suggest possible changes in psychosocial working conditions over the past decades. Thus, the discrepant findings between KP (baseline year 1987-1989) and SNAC-K (baseline year 2001-2004) may imply a potential cohort effect on the association between psychosocial working conditions and dementia risk in Swedish population across the twenty years.

Different types of mechanism were examined. With regard to susceptibility, in Study III passive jobs were related to dementia especially among the *APOE* ε4 carriers, and age was a modifying factor in this relationship. In addition, sex and age also served as modifying factors in the association between high strain and diabetes (Study I), while social support at work modified the associations of high strain with cognitive decline (Study II) and disability progression (Study IV). Finally, the association between demand-control combinations and disability trajectories was mediated by both cognitive decline and chronic disease accumulation (Study IV).

5.4 METHODOLOGICAL CONSIDERATIONS

This doctoral thesis includes four observational studies with longitudinal study design, using data from a large population-based cohort study. In epidemiological studies, issues of random and systematic error may occur and consequently introduce bias and affect the internal validity. We designed the studies and chose methods with an intention to reduce potential bias to the minimum. Nevertheless, it is also important to take into consideration external validity when interpreting our findings.

Systematic error

The occurrence of systematic error is related to the way studies were conducted. In general, there are three main issues in systematic error: selection bias, information bias, and confounding (165).

Selection bias

Selection bias can arise when there is a systematic error in selecting sample into a study and/or in retaining participants during the process of study. This can result from not only the procedures of recruiting participants, but also factors associated with subjects (i.e., self-selection), both of which will impact on the magnitude of examined associations because it is conditioned on the drawn sample. In SNAC-K, the procedure of randomization was undertaken when selecting study sample from the general population of older people, which helped reduce such bias related to the recruitment of participants. Nevertheless, self-selection of subjects into SNAC-K was inevitable. The healthy respondent effect denotes the notion

that people who choose to take part in a study are generally healthier than those who decline to participate, both in cognitive and physical functions. Indeed, those 1227 (out of 4590) persons who rejected to participate in the baseline survey of SNAC-K had shorter survival time than those who decided to take part (166).

The other source of selection bias in longitudinal studies is related to the loss of follow-up, including non-response (i.e., dropouts) and attrition (i.e., death). In Study I, 24.4% were non-participants in the follow-up, of which 11.7% dropped out and 12.7% died. Specifically, among women aged 60 years at baseline, 14.4% dropped out and 1.8% died; among men aged 60 years at baseline, 12.4% dropped out and 5.3% died. In both sex groups of 60-year-old people, no difference was found regarding education, smoking, BMI, physical exercise, and work experience in high strain between participants and non-participants. In Study II and Study IV, 23.5% (13.2% dropped out, 10.3 died) and 25% (13.2% dropped out, 11.8 died) did not attend the first follow-up examination, respectively. In both studies, at baseline the non-participants were older, less educated, more likely to be men and to smoke, had lower MMSE score and more chronic diseases, and less likely to engage in leisure activities and to work in active jobs. In Study III, no participants were lost because of attrition since dementia diagnosis was also made among those who died by going through clinical records. The drop-out rate was 11.8% (12.8% among the younger-old and 10.3% among the older-old). In both age cohorts, no difference was observed regarding sex, education, chronic conditions, leisure activity engagement, and work experience between participants and non-participants. Among the older-old, those who dropped out were younger and had higher MMSE score at baseline compared to participants, while no difference regarding age and MMSE score between participants and non-participants was found among the younger-old.

Taken together, considering that the non-participants at baseline and during the follow-up were more likely to have disadvantageous characteristics, the potential selection bias might have resulted in an underestimation of the associations between psychosocial working conditions and the outcomes of the four studies.

Information bias

Information bias can result from measurement error when collecting information from and about the participants (165, 167). In turn, subjects may be assigned to incorrect categories, leading to misclassification. Non-differential misclassification refers to the situation where all subjects have the same possibility to be misclassified, independent of other variables. This type of misclassification often results in a weakened association between the exposure and outcome. Differential misclassification, on the other hand, occurs when the probability of misclassification differs between groups with different characteristics (e.g., exposed and unexposed). Such misclassification can lead to an over- or underestimation of the association. In SNAC-K, to minimize or avoid both types of misclassification, medical professionals underwent training prior to data collection, and the standardized protocol and questionnaires

were used in order to ensure that the same procedure was followed during repeated interviews and examinations.

Ascertainment of exposure: Differential misclassification may have occurred in the categorization of exposure (i.e., demand-control status), since information on job experience throughout the working life was self-reported during the nurse interview at baseline. Participants who were younger, still working, or recently retired may recall more accurately than those who were older or had been retired for a long time. Similarly, in Studies II and III where cognitive function and dementia were the main outcomes, worse cognitive function or pre-clinical dementia can affect the accuracy of recalling work experience. Therefore, to address this issue, in the sensitivity analyses we excluded participants with an MMSE score lower than 27 at baseline and/or incident dementia in the first three years of follow-up in Study II and Study III. In addition, in all studies we repeated the analyses using working conditions of the latest job. These sensitivity analyses produced similar results to those from the main analyses. On the other hand, misclassification of exposure related to the use of job exposure matrix to assess job control, demands, and social support should be non-differential. The occupation-based approach may not take into consideration the variations within professions or perception of workers. However, this approach might have helped reduce report bias. In the case of SNAC-K, instead of self-assessment on these job components, occupation-based approach was more preferable since the majority of participants was no longer in the work position. Moreover, our approach enabled us to capture the accumulation of exposure to different demand-control status throughout the working life.

Ascertainment of outcomes: Potential misclassification of outcomes of the four studies was most likely non-differential. In Studies I and III, diabetes and dementia diagnoses were made using multiple sources for all participants, including medical examinations conducted by physicians as well as the linkage to patient registries. In Study II, global cognitive function was assessed by MMSE, which may lack sensitivity to detect minor cognitive changes (168). Thus, the magnitude of observed associations between demand-control combinations and cognitive decline could have been underestimated. In Study IV, limitations in ADL and IADL were self-reported which might have aroused the concern of false recall, especially among those participants with cognitive impairment. However, a proxy or caregiver was additionally asked to confirm participants' reports.

Confounding

Confounding occurs when a third variable (i.e., confounder) is associated with the exposure and is a cause of the outcome (167). The confounder is not on the causal path between the exposure and outcome, otherwise it is a mediator. It may lead to an under- or overestimation of the observed association if confounders are not accounted for. In epidemiological studies one can never rule out the possibility of unknown or unmeasured confounders, leading to residual confounding. However, a range of major potential confounders was carefully chosen and controlled for in each of the four studies included in this thesis.

Random error

Random error or lack of precision is often related to population sampling or measurement. Sampling variability of the population results from the sample being not representative of the population of interest. One way of reducing random error or increasing precision due to sampling variability is to increase the sample size. In addition, confidence intervals of estimates drawn from the sample can reflect the degree of precision. Generally, narrower confidence intervals represent higher precision or less random error and vice versa. In each of the four studies, the sample size was fairly large. However, in Studies I and III, some of the subgroups in the stratified analyses were fairly small, resulting in the rather wide confidence intervals of the estimates. Thus, we acknowledge the possible error due to sampling variability in these studies. On the other hand, random error can also arise from mismeasurement, including the limited precision of tools, devices, or methods used to assess exposures, outcomes, and covariates. Random error due to mismeasurement can be reduced by collecting or averaging several measurements of the same variable.

Generalizability

Generalizability, also termed external validity, refers to the transferability of results from one population to other populations in order to make unbiased inferences. Yet, no study population could be completely representative of all other populations because each population has unique characteristics. SNAC-K is comprised of older people living in Kungsholmen, a central area in Stockholm. In general, residents in this neighborhood are characterized as having a higher level of education and mainly working in white-collar jobs. We can therefore expect our study population to have a lower figure of negative health conditions and disability compared to the national average. Overall, caution is warranted when generalizing our results to other older populations living in rural areas, having lower education or SES, or outside the Western societies. Notwithstanding, this may have, if anything, resulted in an underestimation in the magnitude of associations between detrimental psychosocial working conditions and health outcomes investigated in this thesis.

6 CONCLUSIONS

On the basis of the four studies, the main conclusions of this doctoral thesis are presented below.

1. High strain is related to an increased risk of diabetes among women aged 60 years. Having long work experience of more than 14 years in high strain increases diabetes risk among women in their early 60s.

2. High strain, low strain, and passive jobs are all associated with a faster rate of cognitive decline, whereas active jobs may decelerate cognitve decline. Duration of work seems to play a role in these associations. Longer duration of work in low strain (6+ years), high strain (5+ years), or passive jobs (3+ years) throughout the working life accelerates the rate of cognitive decline, whereas longer duration of active jobs (1+ years) is related to slower cognitive decline.

3. Passive jobs are related to an elevated risk of dementia among the younger-old adults (aged ≤72 years). Having more than ten years of work experience in passive jobs increases dementia risk among the younger-old. Genetic predisposition may amplify the effect of passive jobs on dementia risk.

4. High strain, low strain, and passive jobs are associated with an accelerated rate of disability progression in later life, and cognitive decline seems to play a more relevant role in this association than chronic disease accumulation. Notably, high social support at work may buffer the detrimental effect of high strain on disability progression.

7 RELEVANCE AND IMPLICATIONS

Diabetes and dementia are among the most common chronic disorders in older adults, and both of them can subsequently lead to functional limitation and disability. With the increasing aging population, the number of people with these negative health outcomes is expected to keep growing. Consequently, an even greater burden will be posed on individuals, families, and societies in the future. Work is one of the life activities that take up a great deal of time in one's adult life, which possibly makes it an important determinant of health in later life. As retirement age is gradually increasing, the impact of working conditions on health later in life will most likely become even stronger.

This doctoral project is highly relevant from the public health perspective and has clinical implications in identifying workplace scenarios that are detrimental to late-life metabolic and cognitive health and disability, in order to implement preventive strategies or early interventions. In detail, health care professionals may pay more attention to people who have been working in a stressful work environment since it may increase the risk of developing diabetes (especially in younger women) and accelerate cognitive decline and disability progression. Clinicians may consider early interventions for genetically susceptible individuals who have had long-term work experience in passive jobs to postpone the occurrence of dementia. Moreover, for future clinical trials with regard to diabetes, dementia, and disability, our findings may help provide additional criteria to select participants at risk.

The findings of this project also have implications in promoting occupational health. In general, we underscore the notion that not only stressful workplace scenarios but also understimulating or passive jobs can adversely impact on health and function in older age. Social support at work is particularly important in a stressful work environment considering that it has the potential to buffer the detrimental effect of high job strain on cognitive function and disability. Therefore, on the organizational level, regulations aiming to reduce stress in workers can put emphasis on reinforcing workers' control over decision-making and skill development, restricting work load to a reasonable quantity, and providing sufficient social support in a work environment. Moreover, individuals should be encouraged to utilize skills to deal with difficult work tasks, especially in the case of insufficient mental challenges at work.

8 FUTURE DIRECTIONS

In this doctoral project, a further comprehension was obtained regarding the associations of psychosocial working conditions throughout the working life with metabolic and cognitive health and disability in older age. To gain an advanced insight into the biological pathways that underlie the observed associations, long-term longitudinal studies with data on lifelong occupational information, serum biomarkers (e.g., markers of lipid and glucose metabolism or inflammatory cytokines), biomarkers from saliva (e.g., stress hormone), or neuroimaging (e.g., brain volume or lesions) are needed. Further studies are also required to explore other factors that potentially mediate the association between psychosocial working conditions and disability trajectories.

With regard to the measurement on work-related stress, considering that there are pros and cons in both self-reported and occupation-based measures, it will be beneficial to implement both approaches at the same time. Similarly, in addition to demand-control status, future studies may consider to include multiple aspects of psychosocial working conditions (e.g., effort-reward imbalance, organizational injustice, or job satisfaction) and stress outside work place (e.g., from family or life event) in order to achieve a more comprehensive measurement on stress level.

Moreover, studies on occupational exposures and health mostly rely on observational data since it is theoretically impossible to conduct a randomized controlled trial where people are assigned to different occupations. Thus, the causation of the results is always limited. To address this issue, future longitudinal studies with register data on occupation may analyze observational data as a "non-randomized pseudo-trial" (169) where the onset of work exposure (e.g., high strain) is treated as the study entry to ensure temporal order of the exposures and outcomes.

Furthermore, a large-scale population-based study that covers several geographical regions (e.g., both urban and suburban areas) and includes participants of different birth cohorts will be useful to investigate the roles of social context and cohort effect in the associations between psychosocial working conditions and health in older age.

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11 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991–2019

1991

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

1992

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

1993

Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.
Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.
Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

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

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

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

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease.
Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
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