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HOW CAN OLDER ADULTS COMBAT DIABETES TO ACHIEVE A LONGER AND HEALTHIER LIFE?

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How Can Older Adults Combat Diabetes to Achieve A Longer and Healthier Life?
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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致我深爱的奶奶

To my beloved grandma

"…afraid,

yes,

but among you again

crying yes risk joy

in the raw wind of the new world."

Louise Glück

ABSTRACT

Type 2 diabetes (hereafter, diabetes) and prediabetes are very common in older adults and constitute a great health concern for this population. The objective of this project is to investigate the impact of prediabetes and diabetes on health and survival among older adults, and to identify modifiable factors that may attenuate the risk of diabetes on disability and mortality to prolong survival with independence. Data used in this project were derived from the ongoing population-based Swedish National study on Aging and Care in Kungsholmen (SNAC-K).

Study I described the natural history of prediabetes and identified prognostic factors related to different outcomes of prediabetes. We found that among 918 participants with prediabetes at baseline, 204 (22%) reverted back to normoglycemia, 119 (13%) developed diabetes, and 215 (23%) died during the 12-year follow-up. Lower systolic blood pressure, and weight loss, and the absence of heart diseases were associated with the reversion of prediabetes to normoglycemia, whereas obesity was related to its progression to diabetes.

Study II examined the association of prediabetes and diabetes with the risk of stroke and subsequent dementia. Among 2,655 dementia-free participants at baseline, a stroke-free cohort and a prevalent stroke cohort were identified based on prevalent stroke. In the stroke-free cohort, 236 participants developed ischemic stroke and 47 developed post-stroke dementia. Diabetes was associated with a higher risk of ischemic stroke and post-stroke dementia. In the prevalent stroke cohort, diabetes was also related to dementia risk. We did not find a significant association between prediabetes and stroke or post-stroke dementia.

Study III assessed the association of prediabetes and diabetes with physical function decline and disability progression and explored whether cardiovascular diseases (CVDs) mediate these associations. During a 12-year follow-up, prediabetes accelerated the deterioration in chair stand performance, walking speed, and disability progression, independent of the future development of diabetes. Diabetes led to a faster decline than prediabetes, especially among those with uncontrolled diabetes. CVDs mediated 7.1%, 7.8%, and 20.9% of the associations between prediabetes and chair stand performance, walking speed, and disability progression, respectively.

Study IV examined the association of prediabetes and diabetes on a composite outcome of disability or death and further identified modifiable factors that may prolong disability-free survival. Diabetes, but not prediabetes, was associated with a higher risk of disability or death. Compared to diabetes-free participants with a favorable lifestyle profile including the presence of at least one of the healthy behaviours, active leisure activities, or moderate-to-rich social network, those with diabetes and an unfavorable

profile had 2.46 times higher risk of the outcomes. However, among participants with diabetes, the risk of the outcome was attenuated (HR 1.19, 95% CI 0.93 to 1.53) in those with a favorable profile, which prolonged disability-free survival by 3 years compared to those with an unfavorable profile.

Conclusions. In addition to its associations with stroke and cardiovascular diseases, diabetes could increase the risk of dementia secondary to stroke and accelerate decline in physical function. This decline in physical function might start already during prediabetes. Yet, one out of five older adults with prediabetes could revert back to normoglycemia with lifestyle modifications such as weight management. Diabetes is related to the risk of disability or death among older adults, but a healthy and socially active lifestyle may attenuate this risk and prolong disability-free survival.

Keywords. Prediabetes, Type 2 diabetes, Stroke, Dementia, Cardiovascular diseases, Physical function, Disability, Modifiable factors, Population-based cohort study

SAMMANFATTNING

Typ 2-diabetes (hädanefter diabetes) och prediabetes är mycket vanliga hos äldre vuxna, vilket gör det till ett stort bekymmer för den äldre populationen. Syftet med denna avhandling är att bidra till förståelsen av effekterna av prediabetes och diabetes på hälsa och överlevnad hos äldre vuxna, och att identifiera modifierbara faktorer som kan minska risken för diabetes och förlänga livet utanfunktionshinder. Data som används i detta projekt härrör från den pågående befolkningsbaserade svenska nationella studien om åldrande och vård i Kungsholmen (SNAC-K).

Studie I beskrev prediabetes naturliga kurs och identifierade prognostiska faktorer relaterade till olika utfall av prediabetes. Vi fann att bland 918 deltagare med prediabetes vid baseline, återgick 204 (22%) till normoglykemi, 119 (13%) utvecklade diabetes, och 215 (23%) dog under den 12-åriga uppföljningen. Sänkning av det systoliska blodtrycket, viktminskning, och frånvaron av hjärtsjukdomar var associerat med att prediabetes återgick till normoglykemi, medan fetma var relaterat till dess utveckling till diabetes.

Studie II undersökte sambandet mellan prediabetes och diabetes med stroke och efterföljande demens. En stroke-fri kohort och en stroke kohort identifierades, baserat på förekomst av stroke vid baseline. I den strokefria kohorten utvecklade 236 deltagare ischemisk stroke och 47 utvecklade demens efter stroke. Diabetes var associerad med en högre risk för ischemisk stroke och demens efter stroke. I strokekohorten var diabetes också relaterad till demensrisk. Vi hittade inte ett signifikant samband mellan prediabetes och stroke eller demens efter stroke.

Studie III utvärderade sambandet mellan prediabetes och diabetes med försämrad fysisk funktion och funktionsnedsättning, samt undersökte om hjärt-kärlsjukdomar (CVDs) medierar dessa samband. Prediabetes påskyndade försämringen av chair stand testet, gånghastighet och utveckling av funktionshinder, oberoende av framtida utveckling av diabetes. Diabetes ledde till en snabbare nedgång än prediabetes, särskilt bland deltagare med okontrollerad diabetes. CVDs medierade 7,1%, 7,8% och 20,9% av sambandet mellan prediabetes och prestation på chair stand testet, gånghastighet, och utveckling av funktionshinder.

Studie IV undersökte sambandet mellan prediabetes och diabetes på den sammansatta slutpunkten för funktionshinder och dödsfall, och identifierade modifierbara faktorer som kan förlänga funktionshindringsfri överlevnad. Diabetes, men inte prediabetes, var associerad med en högre risk för den sammansatta slutpunkten. Jämfört med diabetesfria deltagare med gynnsam profil inklusive minst en närvaro av hälsosamt beteende, aktiva fritidsaktiviteter eller måttligt till rikt socialt nätverk, hade de med diabetes och ogynnsam profil 2,46 gånger högre risk för utfallen. Bland deltagare med diabetes, var en gynnsam profil associerad med en mindre ökad risk för den

sammansatta slutpunkten (HR 1,19, 95% KI 0,93 till 1,53) och förlängd funktionshinderfri överlevnad med 3 år än de med ogynnsam profil.

Slutsatser. Förutom associeringarna med stroke och hjärt-kärlsjukdomar kan diabetes öka risken av demens sekundärt till stroke, och accelerera nedgång i fysisk funktion. Nedgångi fysisk funktion kan börja redan under prediabetes fasen. Men en av fem äldre vuxna med prediabetes kan återgå till normoglykemi med livsstilsförändringar som till exempel viktkontroll. Diabetes är relaterad till funktionshinder eller dödsfall, men en hälsosam och socialt aktiv livsstil kan minska risken för diabetes och förlänga funktionshindringsfri överlevnad bland äldre vuxna med diabetes.

Nyckelord. Prediabetes, Typ 2-diabetes, Stroke, Demens, Hjärt-kärlsjukdomar, Fysisk funktion, Funktionshinder, Modifierbara faktorer, Befolkningsbaserad kohortstudie

中文摘要

二型糖尿病（以下称糖尿病）和前驱糖尿病在老年人中较为常见，因此在老年人中倍受关注。本博士论文旨在阐明前驱糖尿病和糖尿病对老年人健康和生存的影响，并探讨可修饰因素在减轻糖尿病的预后风险以及其对于延长无残疾生存年限的作用。本论文涉及四项独立研究，其所使用的数据均来源于瑞典斯德哥尔摩 Kungsholmen 地区进行的老龄化与护理前瞻性研究（SNAC-K）。

研究一描述了前驱糖尿病的自然病史，并探讨了影响前驱糖尿病转归的因素。对 918 位前驱糖尿病者随访 12 年，其中 204 人（22%）逆转为正常血糖，119 人（13%）发展为糖尿病，215 人（23%）死亡。未患心脏病，较低的收缩压和减轻体重与前驱糖尿病逆转为正常血糖相关，而肥胖则与前驱糖尿病发展为糖尿病有关。

研究二纳入 2655 名基线无痴呆症者并对其随访 12 年，分析了前驱糖尿病和糖尿病与中风以及中风后痴呆症的关系。根据参与者在基线是否患有中风的情况，我们进一步分成了无中风组和中风组。在无中风组中， 236 例为新发缺血性脑卒中，其中，47 人发展为痴呆症。糖尿病可增加脑卒中及卒中后痴呆症的风险。在基线患中风人群中，糖尿病增加了痴呆症的风险。前驱糖尿病与卒中或卒中后痴呆的关联无统计学显著性。

研究三阐明了前驱糖尿病和糖尿病与身体机能下降和失能之间的关联，并探讨了心血管疾病在上述关联中的中介作用。经十二年随访结果显示，与正常血糖相比，前驱糖尿病与座椅站立时间的增加，步行速度的减缓，以及独立生活能力的加速退化有关，该关联独立于前驱糖尿病发展为糖尿病的作用。与前驱糖尿病患者相比，糖尿病患者身体机能和独立生活能力的下降更加快速，尤其在血糖控制较差的患者中较为明显。另外，心血管疾病的中介效应可以部分解释上述关联。

研究四评价了前驱糖尿病和糖尿病对残疾和死亡为一合并终点结局的影响，并探讨了健康的生活方式是否能够延长糖尿病患者的能够独立生存的年限。结果显示，与正常血糖相比，糖尿病与结局的风险显著相关，但前驱糖尿病与该结局的关联无统计学显著性。患有糖尿病且无健康生活方式以及社交生活贫乏的参与者发生复合终点的风险是无糖尿病且有健康生活方式或者有足够的社交生活的参与者的 2.46 倍。然而，在糖尿病患者中，具有健康生活方式或者有足够的社交生活的参与者发生复合终点的风险较低，且这些生活方式能够延长三年无残疾生存时间。

结论:除显著增加中风和心血管疾病风险外，糖尿病还会影响功能性结局，包括继发于中风后的痴呆症和身体机能下降。身体机能的下降可能已经在糖尿病前期开始。但是，五分之一患有前驱糖尿病的老年人仍然可以通过改善生活方式（包括体重控制）恢复到正常血糖。糖尿病与残疾和死亡有关，但是健康的生活方式以及积极的社交可以降低糖尿病的负担，并延长老年糖尿病患者的无残疾生存时间。

关键字:前驱糖尿病，二型糖尿病，中风，心血管疾病，老年痴呆，身体机能，失能，可修饰因素，基于人群的队列研究

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IV. **Shang Y**, Wu W, Dove A, Guo J, Welmer AK, Rizzuto D, Fratiglioni L, Xu W. Healthy behaviours, leisure activities, and social network prolong disability-free survival in older adults with diabetes. *Manuscript*

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CONTENTS

LIST OF ABBREVIATIONS

2h-PG	2h plasma glucose
ADL	Activities of daily living
ARIC	Atherosclerosis Risk in Communities Study
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CIF	Cumulative incidence function
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DBP	Diastolic blood pressure
DPP	Diabetes Prevention Program
eGFR	Estimated glomerular filtration rate
HbA1c	Glycated hemoglobin A1c
HR	Hazard ratio
IADL	Instrumental activities of daily living
ICD	International Classification of Diseases
IGT	Impaired glucose tolerance
IFG	Impaired fasting glucose
MMSE	Mini-mental state examination
NPR	National patient register
OGTT	Oral glucose tolerance test
OR	Odds ratio
PSD	Post-stroke dementia
SBP	Systolic blood pressure
SNAC-K	The Swedish National Study on Aging and Care in Kungsholmen
WHO	World Health Organization

1 INTRODUCTION

1.1. Pre/diabetes in older adults

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to the insufficient insulin secretion from the beta cells of the pancreatic islet or/and declined response to insulin (i.e., insulin resistance) in the target tissues (muscle, liver, or adipose tissue). Together, the three major types of diabetes – type 1, type 2, and gestational diabetes – had a prevalence of 9% in Europe in 2019 (1). Type 1 diabetes results from an autoimmune response that triggers T-cell mediated destruction of beta cells. It involves a genetic predisposition and often manifests in childhood or adolescence. Type 2 diabetes begins with insulin resistance and eventually progresses to impaired insulin secretion due to the failure of beta cells to keep up with increasing demand for insulin production. Finally, gestational diabetes occurs when pregnant women without a history of diabetes develop hyperglycemia. Type 2 diabetes is by far the most common form of diabetes. It accounts for 90% of diabetes cases and is mostly seen in older adults (1). Hereafter, "diabetes" refers to type 2 diabetes, which is the focus of this thesis.

Age is a major risk factor for diabetes (2). Older adults have the highest prevalence of diabetes. In Europe, among adults aged 65-99, 20% were living with diabetes in 2019 (1). Men have a slightly higher prevalence of diabetes than women (1). According to criteria from the *American Diabetes Association* (3), diabetes is diagnosed by having any of the following:

- fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L);
- 2-h plasma glucose (2h-PG) ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT);
- glycated hemoglobin A1C (HbA1c) ≥ 6.5% (48 mmol/mol);
- random plasma glucose ≥ 200 mg (11.1 mmol/L) in the presence of symptoms of hyperglycemia

Because diabetes can be asymptomatic in the early stages, the exact onset of diabetes is often difficult to determine. It is estimated that approximately half of the older adults with diabetes in the U.S. are underdiagnosed (4). Additionally, nearly 47% of older adults aged ≥65 have prediabetes (5), an intermediate state where blood glucose is higher than normal but below the threshold for the onset of diabetes. Prediabetes is a high-risk state preceding diabetes. Annually, approximately 2% of prediabetes cases progress to overt diabetes, translating to 20% diabetes incidence among people with prediabetes within 10 years (6). Prediabetes is a highly heterogeneous metabolic state with different phenotypes including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. Furthermore, prediabetes can be defined based on HbA1c value according to the *American Diabetes Association* (3). Depending on which

measures of hyperglycemia are used, a diagnosis of prediabetes requires any one of the following criteria among people without a history of diabetes:

- FPG between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) (IFG);
- 2-h PG during OGTT between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) (IGT);
- HbA1c between 5.7% and 6.4% (39-47 mmol/mol)

The numbers of prediabetes and diabetes in older adults are projected to grow dramatically as a result of the burgeon of the aging population, so too do the health concerns and costs of providing care. The health status of older adults with diabetes is heterogeneous and therefore clinically complex, ranging from robust and otherwise healthy individuals to those with geriatric syndromes and multimorbidity (7). Older adults with diabetes may either have diabetes onset at an older age or live with diabetes that was first diagnosed earlier in life. This might lead to differences in pathophysiological abnormalities, susceptibility to diabetic complications, or responses to treatment. Furthermore, metabolic syndrome, a cluster of several cardiovascular risk factors including insulin resistance, is very common in older adults, representing an abnormal homeostatic function that increases cardiovascular risk much more dramatically than each of them alone (8). All of these yield a challenge concerning the impact of prediabetes and diabetes on health and the management of diabetes in older adults.

1.2 The impact of pre/diabetes on health

Chronic hyperglycemia can cause nerve and blood vessel damage, which in turn leads to diabetic complications such as macro- and microvascular disease (9,10). Individuals with prediabetes also run an increased risk of future development of cerebrovascular disease, cardiovascular disease, retinopathy, and nephropathy (11). In addition to these classical complications, older adults with diabetes are at a higher risk of geriatric syndromes such as falls (12), incontinence (13), frailty (14), and cognitive impairment and dementia (15). Insulin sensitivity also appears to decline with age (2). Superimposed with the aging process, these factors may interact to further increase the biological vulnerability of people with diabetes to physiological stressors (16). Over time, these adverse health outcomes will progressively lead to cognitive and physical impairments and ultimately disability, profoundly affecting the quality of life in older people with diabetes.

In spite of the decline in the incidence of microvascular complications in the general population, the incidence of macrovascular complications including stroke and coronary heart disease continues to be highest among older adults (17). In this thesis, we address a chain of events that possibly share the pathophysiological profiles directly

linked to prediabetes and diabetes: from diabetes occurrence, through the development of major complications, and to subsequent functional outcomes and mortality in the end.

1.2.1 Natural history of prediabetes

Although diabetes is a chronic disease with no available cure, hope is not lost. Delaying diabetes progression is important, but more attention should be dedicated to the prevention of diabetes onset. Prediabetes represents a narrow window of opportunity to prevent a lifetime battle with diabetes. Indeed, the diagnosis of prediabetes does not guarantee the development future diabetes, and prediabetes can even revert back to normoglycemia. According to previous reports, up to one-third of middle-aged adults with prediabetes revert to normoglycemia over a decade (18,19). However, most studies looking at the reversion and progression of prediabetes only include middle-aged adults.

So far, only three population-based studies have examined the rates of progression and reversion of prediabetes among older people, and with mixed results. One study showed a reversion rate of 16.3% after 7 years of follow-up (20), another reported a rate of 27.3% and a 9.2% based on HbA1c and 2-h PG after 6 years follow-up (21), and yet the other study reported that around 34% of prediabetes cases progressed to diabetes (22). Reversion to normoglycemia is beneficial not only from the perspective of diabetes prevention; it also shows a protective effect for cardiovascular health. A study using data from Germany found that reversion to normoglycemia was associated with a 5.6% reduction in 10-year cardiovascular risk in older adults (21). Indeed, age-related insulin resistance is associated with changes in body composition and physical inactivity (23), where modifiable factors promoting weight loss appear to improve insulin sensitivity (21). Therefore, the identification of individuals who are likely to revert to normoglycemia or are at risk of developing diabetes is an important step toward understanding possible mechanisms underlying the natural course of prediabetes, as well as to inform health care practitioners, to plan clinical services, and to design interventional trials to decrease the future burden of diabetes.

1.2.2 Pre/diabetes, stroke, and post-stroke dementia

Pre/diabetes and stroke

As one of the most devastating complications of diabetes, stroke is an acute medical condition that occurs when the blood flow to an area of the brain is cut off by a clot or burst. When a stroke occurs, the brain is deprived of oxygen, and brain cells start to die. The affecting area by stroke in the brain might affect the corresponding cognitive and physical function. As a leading cause of long-term disability in the aging population (24), stroke – especially ischemic stroke – is very common among people with diabetes.

Previous studies showed that a diabetes-attributable risk of stroke is around 12%, given a population-wide prevalence of diabetes of around 10% (25). Age and sex seem to modulate the risk of stroke in people with diabetes. Older age is one of the strongest predictors for stroke. However, stroke incidence in younger adults seems to be on the rise, with the mean age at stroke falling from 71.2 years in 1993/1994 to 68.2 years in 2005 in the U.S (26). Female sex may increase the risk of stroke among those with diabetes, independent of other major cardiovascular risk factors. Furthermore, other determinants such as a previous history of stroke also increase the risk of a new stroke event (27), and diabetes has been shown to be an independent risk factor for recurrent stroke assessed at 1 year and at 3 years post-discharge (28,29). However, diabetes does not appear to confer risk for recurrent stroke over the short-term (e.g., 90 days) (30).

Though people with prediabetes harboring the same vascular risk factors (e.g., insulin insensitivity, hypertension, obesity) as people with diabetes, thereby placing them at a higher risk of macrovascular complications, studies have shown conflicting results regarding the relationship between prediabetes and stroke. A meta-analysis reported that a modest risk of stroke was observed among people with prediabetes using a stringent definition of fasting glucose of 110-125 mg/dL (RR 1.21, 95% 1.02-1.44), or impaired glucose tolerance (RR 1.26, 95% CI 1.10-1.43), although these results might be overestimated by unmeasured confounders (31). Another meta-analysis, however, demonstrated that prediabetes defined by HbA1c of 5.7%-6.4% was not associated with the risk of stroke (32). This literature suggests that the definition of prediabetes seems important in evaluating the risk of stroke associated with prediabetes. OGTT seems to be the strongest predictor for macrovascular complications amongst other definitions (31,33).

The relationship between hyperglycemia and ischemic stroke appears to be bidirectional. As mentioned above, people with diabetes carry more than double the risk of ischemic stroke than those without diabetes (34). Meanwhile, an acute stroke may result in disturbance of glucose metabolism (35). Hyperglycemia arises in around 40% of patients after experiencing acute ischemic stroke (36). By increasing the risk of impaired recanalization (including impaired coagulation and fibrinolysis) and reperfusion injury (34,37), hyperglycemia might further deteriorate the outcomes after acute stroke, leading to disability, cognitive decline and dementia. Based on the current evidence, the *American Heart Association/American Stroke Association* guidelines for the early management of stroke patients recommend maintaining serum glucose concentration in the range of 7.8-10 mmol/L during the first 24 hours after acute ischemic stroke (38). Although it is important to actively control hyperglycemia, great concern should be placed on overtreatment, which could lead to hypoglycemia. Severe or prolonged hypoglycemia might lead to permanent brain damage (39). Therefore, a reasonably tight, yet therapeutic glycemic treatment goal should be prioritized for

optimized physical and cognitive outcomes in patients with diabetes after an acute stroke.

Diabetes and post-stroke dementia

Stroke is associated with an increased risk of dementia, and one in three stroke patients will eventually develop dementia (40). Among individuals in the first year after the first-ever stroke, the risk of incident dementia is 9-fold higher than those without stroke. A systematic review showed that the pooled estimates of prevalent post-stroke dementia within 1 year of a stroke varied from 7.4% to 41.3%, due to different study designs (population-based vs. hospital-based), exclusion criteria (e.g., pre-stroke dementia patients), and study populations (e.g., recurrent-stroke cases) (41). Nonetheless, the cumulative incidence of post-stroke dementia rises to 23% within ten years of a stroke due to the improvement of survival after stroke (42).

A prospective longitudinal study found that the presence of more than three vascular risk factors (including diabetes) is associated with 4-fold increased dementia risk in stroke survivors (43). Contrary to this, a meta-analysis indicated that recurrent stroke explained more dementia risk among stroke patients than other cardiovascular risk factors (41). Stroke characteristics including location, lesion size, multiple infarcts, and severity are also determinants of post-stroke dementia (44). Some recent studies have reported that early-onset post-stroke dementia (<1 year) mainly results from the interplay between dementia-prone stroke lesions (such as large infarcts or strategic stroke) and brain resilience including cognitive reserve or brain reserve. On the other hand, delayed-onset post-stroke dementia (≥ 1 year) is triggered mainly by small vessel diseases and "secondary insults" including hypoperfusion (45). These vascular profiles appear relatively more important to delay-onset post-stroke dementia.

Given that diabetes is one of the major cardiovascular risk factors for both stroke and dementia, it has been proposed to be linked with ischemic damage to the brain, which is manifested as small vessel disease or infarcts, further exacerbating the progression from stroke to dementia (15). However, the association between diabetes and post-stroke dementia remains unclear. Among 13 prospective cohort studies, eight showed a non-significant association between diabetes and post-stroke dementia and only five reported an increased risk of post-stroke dementia in people with diabetes (**Table 1**). These inconsistencies may be due to differences in study design, diagnostic criteria, study populations, and duration of follow-up. It is noteworthy that most studies were conducted in clinical settings, where pre-stroke dementia might not be reliably excluded and referral bias might be introduced, giving rise to an overestimation of the association. In addition, in some studies, dementia cases were identified from registers, which might render misclassifications that therefore underestimate the association. Additionally, most studies that have investigated the association between diabetes and dementia treated stroke as a confounder rather than a mediator (46,47). Whether the

higher risk of dementia in diabetes patients can be explained by the occurrence of stroke is less clear, although previous studies suggest that diabetes-related dementia is most of vascular origin (46,48).

Taking all these together, it is important to delineate the role of diabetes in stroke and post-stroke dementia, using a population-based design with a relatively longer follow-up. This will help establish strategies for diabetes management in order to prevent both stroke and dementia.

Table 1. A summary of 13 prospective cohort studies that examined the association between diabetes and stroke and post-stroke dementia (PSD)

Study, year, country	Country/ region, participants	Settings	No. of participants	Follow-up	Effect size
Allan, 2011 (43)	UK, mean age 80	Hospital-based	335	8 years	1.5 (0.7–3.2)
Mok, 2016 (49)	Hong Kong, mean age 67	Hospital-based	919	5 years	2.0 (1.1–3.9)
Desmond, 2000 (50)	US, age ≥ 60	Hospital-based	453	3 months	1.8 (1.1-3.0)
Henon, 2001 (51)	France, age ≥40	Hospital-based	169	3 years	2.7 (1.1-6.2)
Portegies, 2016 (52)	Netherlands, age >45	Population-based	6,165	12 years	1.2 (0.8–1.9)
Cheng, 2012(53)	Taiwan, mean age 60	Population-based	40,887	7 years	1.5 (0.9–2.2)
Luchsinger, 2001 (54)	US, mean age 76	Population-based	1,262	4.3 years	3.4 (1.7-6.9)
Ivan, 2004 (55)	Netherland, mean age 79	Population-based	1,272	10 years	2.2 (0.8-6.6)
Klimikowicz, 2006 (56)	Poland, mean age 68	Hospital-based	220	3 months	3.3 (1.2-9.0)
Srikanth, 2006 (57)	Australia, mean age 70	Population-based	99	2 years	NS for PSD
Altieri, 2004 (58)	Italy, mean age 71	Hospital-based	191	2 years	NS for PSD
Reitz, 2008 (59)	Netherland, mean age 69	Population-based	6,274	15 years	NS for PSD
Bejot, 2011 (60)	France, mean age 73	Population-based	3,948	24 years	1.3 (0.9-1.6)

1.2.3 Pre/diabetes, cardiovascular diseases, and physical function

Cardiovascular diseases

Individuals with diabetes are at a high risk of developing CVD and this risk increases with age (61). Patients with diabetes predominately suffer from coronary heart disease (CHD), and the accelerated atherosclerotic process in the coronary vasculature is suggested to be the underlying mechanism linking diabetes to CHD (61). Regarding heart failure, which is one of the major CVDs, a bidirectional association has been proposed such that diabetes is related to a 2- to 4-fold increased risk of heart failure and a significantly higher incidence rate of diabetes was observed among people with vs. without heart failure (62). However, some epidemiological studies suggest that diabetes might be protective against other vascular disorders such as hemorrhagic events (63). Of note is that a sex difference has been reported in the risk of CVD and CVD mortality among people with diabetes (64). Women with diabetes appear to have a higher risk of CVD and CVD mortality than men with diabetes (65,66). Diabetes increases the risk of CVD about 4-fold in women compared to 2-fold in men. Though female sex is related to approximately 50% reduced risk of CVD and an approximately 10-year delay in the first occurrence of CVD, the presence of diabetes seems to cancel out this protective effect (67). The reasons for a higher CVD risk for women compared to men with diabetes is not well understood. Possible explanations might include hormonal imbalances, higher risk factor burden, lower medication use, and atypical occlusive symptoms such as silent ischemia (64). Furthermore, women seem to be more affected by psychological stress. The typical example being takotsubo disease, a particular form of acute heart failure almost exclusively occurs in women (68).

CVD risk is also modestly elevated among individuals with prediabetes, defined either by OGTT, fasting plasma, or HbA1c (69). The risk for heart failure and CHD appears to be higher among people with prediabetes by any definition, and the elevated risk in women occurs at an even lower glucose level than in men. OGTT-defined pre/diabetes seems to be the strongest predictor for CVD, independent of fasting plasma glucose (69). The duration of diabetes seems to play a major role in the diabetes-CVD association, as diagnosis of diabetes at age 60-79 is not associated with a higher risk of CHD (65,70). This suggests the development of diabetes in older age may be a reflection of the natural aging process of the cardiovascular system rather than an insult that causes future pathophysiological changes.

Physical function

Decline in physical functioning and loss of independence may be more concerning and of greater damage to quality of life than the clinical diagnosis of complications in older adults. Physical function impairment, defined by poor physical performance, is a prodromal stage of disability (14). It can be measured with objective, validated physical performance tests (e.g., walking speed, chair stand, balance), which are subject to only minor influences from culture and education (71). These tests are widely used in

clinical setting as a part of geriatric assessments owing to their ease of administration and high sensitivity. Apart from identifying those with low physical function, these tests have been shown to discriminate even between high functioning individuals (72). Furthermore, objective low physical performance is related to a higher risk of dementia, multimorbidity, hospitalization, and mortality (73–75). Among these tests, walking speed has been investigated most widely in relation to health status. Indeed, walking speed alone has the strongest prognostic value for disability compared to a full battery of tests including chair stands and a balance test (73). A plausible bidirectional relationship between walking speed and cardiovascular health has been demonstrated, suggesting that slow walking speed may be both a consequence of and a factor driving the prognosis of cardiovascular multimorbidity (75,76). However, other physical functional tests have been less studied, although they measure different physical constructs and domains which may provide distinct information on different aspects of physical function. For example, the chair stand test is often used to measure lower muscle strength and is strongly correlated with sarcopenia. The balance test measures postural stability, and the deterioration of balance is suggested to occur prior to walking speed decline (77).

Epidemiological studies demonstrate that people with diabetes to have 50%-90% increased risk of physical limitations (78,79). Despite many studies suggesting that diabetes is related to poorer physical performance, the association may vary by sex and age. Diabetes-related physical function impairment is more common in women than in men, and there is no significant association between diabetes and slow walking speed among those aged ≥65 (80,81). In six studies examining the impact of prediabetes on physical function (7,82–86), two found significant associations between prediabetes HbA1c and mobility and lower extremities (85,86). As physical function and disability represent different phases of the disabling progress, investigating the rate of physical function decline as a proxy for biological aging is of greater clinical interest, as it can capture the subtle changes in functionality that occur among older adults over time before reaching the clinical manifestation of impaired mobility.

The potential role of CVD in pre/diabetes and physical function

Accumulating evidence indicates that baseline CVD may explain the excess odds of functional decline with diabetes (79,87). A study from our group also suggests that cardiovascular multimorbidity could drive the decline of walking speed over time (75). Therefore, it is conceivable that CVD accumulation could mediate such an association; however, there is little empirical data on this topic. With physical disability being one of the most adverse consequences of diabetes, other complications have also been suggested as biological mechanisms underlying poor physical function and disability related to diabetes (88–90). Yet, the increased risk of physical decline and disability cannot be fully explained by these comorbid conditions. Factors that precede diabetes

diagnosis as part of the hyperglycemia pathogenesis – including obesity, hyperinsulinemia, insulin resistance, and elevated inflammatory markers – could also account for the higher risk of disability in diabetes (84). Rapid loss of skeletal muscles and strength due to poor glycemic control may also contribute to physical function limitations and eventually disability (89). Therefore, assessing the mediating effect of such complications might help us understand the pathophysiological pathways linking diabetes to functional outcomes, which are of particular important among older adults. In this thesis, we focus on the role of CVDs in the pre/diabetes-physical function association, given that over half of the diabetes population will develop CVDs over a lifetime (91).

1.2.4 Pre/diabetes, disability, and mortality

When it comes to long-term outcomes secondary to diabetic complications, disability and premature death are the least sequelae a patient with diabetes wish they would experience. Disability is a useful measure to evaluate one's capacity to maintain engagement in the activities of daily life. Disability refers to limitations in an individual's ability to independently carry out daily tasks, consisting of the activities of daily living (ADL) and instrumental activities of daily living (IADL) (92). ADL is often used to measure the basic functions of living, and it is currently used by health professionals in older adults (93). IADLs, on the other hand, are not essential for fundamental functioning but refer to one's capacity to live independently in the society. Physical disability has often been observed in the older population, with prevalence ranging from 10% to 20% among people aged 65-74 and 22% to 38% among people aged ≥75 years (94). Of the various diseases that occur with increasing age, some can lead to disability and premature death.

To date, there are no consistent findings regarding the relationship between diabetes and disability. Results from previous studies range from no association to a doubling of the risk (95) (**Table 2**). As aging is a continuous process, disability can accumulate if effective management is not in place (96). However, the evidence regarding the association between diabetes and disability progression is scant. One of the major reasons for studying disability trajectories is that more than 46% of older adults aged 60 years and above already have at least one disability, and more than 250 million of them experience moderate to severe disability (97).

Prediabetes, on the other hand, is usually neglected or grouped together with normoglycemia when it comes to studying functional outcomes. The few studies that have assessed the association between prediabetes and disability are cross-sectional and have reported mixed results (7,86,98). Given that disability might already occur even before the manifestation of full-blown diabetes, the risk of disability might increase in a graded manner from prediabetes to diabetes. However, this hypothesis has not been verified.

Unlike disability, the association between diabetes and mortality is well-established (99). Since the discovery of insulin 100 years ago, the main cause of death among people with diabetes has shifted from diabetic coma to microvascular complications, to cardiovascular complications. Almost 70% of overall mortality in people with diabetes is of cardiovascular origin, with ischemic heart disease and heart failure as the leading causes of death (100). Nevertheless, the relationship between prediabetes and mortality is less clear, especially in old age. A meta-analysis showed that prediabetes confers 1.1 to 1.3 relative risk of all-cause mortality, depending on the diagnostic criteria (101). While a recent meta-analysis and a nationwide register-based study in Sweden both emphasized that the effect of age at diabetes diagnosis on CVD and mortality varies, increasing age at diabetes diagnosis is associated with lower risk of CVD, CVD mortality, and premature death, and no increased risk is conferred from being diagnosed with diabetes at the age of 80 (70). Whether prediabetes is associated with a higher mortality and whether the diagnosis of diabetes in old age could place individuals at a higher risk of premature death is of paramount interest to better evaluate the effectiveness of long-term treatment of pre/diabetes in older adults.

Table 2. Studies investigating the link between prediabetes/diabetes and disability

Study	Country/region, participants	Number of participants	Follow-up (year)	Outcome	Effect size
Diabetes (Longitudinal)					
Woo, 1998 (102)	Hong Kong, adults age ≥70 years	1334	1.5	ADL	1.6 (0.7-2.3)
Volpato, 2003 (103)	U.S, women age ≥65 years	729	3	ADL	1.6 (1.2-2.1)
Reynolds, 2003 (104)	U.S, adults age ≥70 years	4,228	5	IADL ADL	1.4 (1.1-1.7) 1.5 (1.1-2.0)
Spiers, 2005 (105)	U.K, adults age ≥65 years	10,528	2	IADL	1.7 (1.2-2.4)
Al Snih, 2005 (106)	Hispanic, age ≥65 years	1,834	7	ADL	2.1 (1.6-2.7)
Gregg, 2002 (107)	U.S, women age ≥65 years	6,971	9	IADL	1.6 (1.4-1.8)
Prediabetes (Cross-sectional)*					
Lee, 2013 (86)	U.S, adults age ≥65 years	5,991	NA	ADL IADL	1.2 (0.9-1.6) 1.1 (0.8-1.5)
Hiltunen, 1996 (98)	Finland, adults age ≥70 years	483	NA	ADL IADL	1.4 (0.8-2.3) 0.9 (0.5-1.7)
Godino, 2016 (7)	U.S, adults with mean age of 75	5,035	NA	ADL+IADL	1.0 (0.9-1.1)

*no longitudinal study assessing prediabetes and disability in older adults.

1.3. Healthy aging with prediabetes and diabetes

Healthy aging-theoretical perspectives

The framework of "healthy aging" has been endorsed by the World Health Organization (WHO) in 2015. This replaced the previous framework focused on "active aging" that was developed in 2002 (108). WHO defines healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing in older age" (108). Functional ability includes but is not limited to the intrinsic capacity of daily living that is influenced by the presence of diseases, and the environmental factors that are supported or implemented by community and society. The interaction between intrinsic capacity and environmental factors on aging is regarded as imperative to maintaining a good functional capacity. The ability to live in the environment that preserves and fortifies the intrinsic capacity is key to healthy aging.

Over recent decades, increasing attention has been given to the relationship between environmental factors and maintaining functional capacity. Behavioural factors, leisure activities, social support, living condition, and subjective psychosocial well-being in old age have shown a reversed association with different health outcomes, such as disability (96,109), depression (110), dementia (46), and mortality (111). However, one should consider the regional difference, cultural preferences, tradition, and infrastructure when studying the impact of environmental factors on health outcomes.

As people get old, they need to cope with and adapt to challenges related to their own aging. There are several theories of aging that explain how behaviours change in old age and how behaviours influence health. The "**activity theory**" states that the continuation and maintenance of high activity levels is necessary to mitigate the negative effects caused by old age (112). This theory emphasizes the importance of ongoing social activity and posits that an individual's self-concept is related to the role they hold in society. Older adults may experience a decreased social role as a result of retirement or the loss of a partner and can adjust to this by maintaining an active lifestyle as middle age. "**Successful aging**" theory is built on the concept that aging is plastic, and the trajectories of aging can be modified by changes in attitudes, coping strategies, and lifestyle behaviours. The three components of successful aging – namely, avoiding disease, engagement with life, and maintaining high physical and mental function – can be achieved by remaining socially and cognitively active through a close social network, and having high life satisfaction (113).

As life expectancy increases and better treatments emerge, people with diabetes are living longer than ever before (94). As individuals with diabetes enter old age, maintaining independence is one of their most important priorities (beyond longer survival) (94). Therefore, it is imperative to identify the environmental factors that may modify the risk of diabetes and prolong healthy life without disability.

Modifiable factors

Modifiable factors are the factors that can be changed through behaviours. Contrary to modifiable factors, non-modifiable factors (i.e., age, family history, ethnic background), as the name implies, are factors that cannot be changed. However, many non-modifiable factors can be controlled, and their risk decreased by modifying lifestyle behaviours. In public health practice, modifiable factors are often integrated into different stages of prevention, be it primary, secondary, and tertiary prevention (114). Having modifiable factors in place at different stages of diabetes prevention would be a promising strategy to improve general health, since many of these factors have lasting benefits for macro/microvascular health beyond glycemic control. A recent study identified 14 potentially modifiable factors including behavioural factors (e.g., tobacco use, alcohol consumption, physical activity) and sociodemographic factors (e.g., education) and revealed that around 70% of CVD events and deaths were attributed to modifiable risk factors (115). Hence, given the high prevalence of prediabetes and diabetes among older adults, investigating modifiable factors in the different phases of pre/diabetes is highly relevant to public health.

Role of modifiable factors in prediabetes

Most evidence on the modifiable factors for prediabetes is based on the studies in middle-aged adults. Three intervention studies including middle-aged adults with prediabetes and without comorbidities, reported a 40% to 60% reduction in diabetes risk after a modest amount of weight loss through dietary changes and increased physical exercise (116–118). Treatment with metformin, often a first-line therapy for diabetes, also reduced the risk of future diabetes, but to a lesser extent than lifestyle modification (119). An observational study found that for every one unit decrease in BMI, the probability of prediabetes reverting to normoglycemia increased by 40% (20). Given that the reversion from prediabetes to normoglycemia could be transient, frequent glucose monitoring is needed to assess whether the effects of weight loss on prediabetes reversion persist over the long term (120). Moreover, weight loss has been associated with increased mortality in older adults. Questions remain regarding which factors are related to the reversion from prediabetes to normoglycemia, independent of higher mortality among older population.

Role of modifiable factors in diabetes

Knowing that diabetes imposes great risks of adverse health outcomes and excess mortality, many randomized control trials in diabetes have been initiated. The results from several landmark diabetes trials have shown the encouraging results that glucose lowering (by lifestyle interventions and/or pharmacological treatments) can reduce diabetes complications. For example, the *Diabetes Prevention Program* (DPP), which aimed to bring participants with prediabetes and overweight/obesity to a healthy

weight through diet and physical activity, showed that the intervention delayed diabetes onset, improved cardiovascular risk factors, and lowered the risk of microvascular complications after 15-year follow-up (121). In addition, the ADVANCE trial demonstrated reduced incidence of microvascular events, especially diabetic nephropathy, among people with diabetes who were brought to an intensive HbA1c target of 6.5% with metformin and sulfonylurea, compared to the comparison group with a standard HbA1c target of around 7% (122). However, none of these aforementioned trials found a significant benefit for cardiovascular events in the intervention group. One possible explanation might be that all these trials mostly included middle-aged individuals rather than older adults, who are at the highest risk of CVDs. Unlike lifestyle modification, some antidiabetic medications have been associated with cardiovascular benefits, reduced microvascular events, and reduced mortality. Treatment with metformin has been shown to decelerate the progression of diabetes, but to a lesser extent compared to lifestyle modification (121). However, this evidence comes mainly from middle-aged individuals with diabetes. In fact, there are essentially no direct data from clinical trials designed for older adults on the impact of intensive glucose control, let alone evidence addressing the modifiable factors for long-term outcomes such as disability related to diabetes. Though older adults experience the highest burden of the pre/diabetes across all age groups, they are underrepresented in most clinical trials.

On the other hand, observational studies possibly fill these gaps and provide insights on lifestyle factors that can potentially modify the course of diabetes, particularly among older adults. **Intentional weight loss** through physical activity results in improved glycemic control, lower diabetes and CVD risk, and improved mobility among older adults with overweight or obesity (123,124). **Regular physical activity** has also shown a protective effect against accelerated muscle loss and reduced muscle strength, which in turn decreases the risk of sarcopenia and frailty among older adults with diabetes (125,126). Apart from these, observational studies provide convincing evidence on the benefits of behavioural changes such as **smoking cessation** and **no-to-moderate alcohol consumption** on the development and the prognosis of diabetes (127,128). Although these studies were not designed for individuals with advancing age, it is conceivable that the benefits of smoking cessation and moderate alcohol consumption could persist across the lifespan. **Leisure activities** involving mental stimulation or social engagement have been proposed to provide additional advantages to cognitive health and physical function beyond glycemic control in older adults with or without diabetes (46,109). Few studies have investigated the impact of multiple modifiable factors in combination on general health in older adults with diabetes. As healthy behaviours are mutually associated and often cluster together in individual's daily life, it is plausible that these factors have a synergic effect on health.

In addition to the aforementioned factors, social well-being (including social, environmental, and emotional factors) may have an influence on clinical outcomes among people with diabetes. This is particularly important for integrating diabetes care into daily life (129). Findings on the associations between **social network** and various health outcomes are inconsistent; this may be due to the chosen construct of social well-being or the investigated outcomes (130). For example, social support has been found to be protective against myocardial infarcts while the relationship between social integration and all-cause mortality was not significant among older adults with heart failure (131). Requiring help from others in order to perform daily tasks is heavily related to the availability of social support. Social isolation or reduced support from family or health facilities have been shown to disrupt an individual's diabetes self-management and ability to cope with diabetes distress, and could therefore potentially compromise health status (129). On the other hand, a rich network has been shown to improve health by facilitating lifestyle changes and adherence to medication (132–135). However, the impact of social network on health has not been widely studied in older adults, despite the fact that social support and connection are perhaps most sorely needed in this group – especially among those with diabetes, due to a higher risk of cognitive impairment or disability.

1.4 Knowledge gaps

First, although numerous studies have addressed the progression and reversion of prediabetes, these studies focused only on middle-age adults. The paucity of evidence in older adults limits us to grasp the natural history of prediabetes in old age, and begs the question of whether the predictors for different prognosis of prediabetes among middle-aged adults still apply to people in old age. Second, for older adults living with diabetes, further evidence is warranted concerning whether pre/diabetes is independently associated with a sequela of events secondary to major complications – namely post-stroke dementia, functional decline, and disability, which are of particular importance to older adults. Finally, given the higher risk of the aforementioned adverse outcomes associated with diabetes, identifying modifiable factors that can potentially attenuate the risk of diabetes and prolong disability-free survival is essential. Such knowledge will contribute to planning potential preventative strategies to support healthy aging with diabetes.

2 AIMS

The overarching aim of this thesis is to understand the impact of prediabetes and diabetes on health and survival among older adults, and to identify the modifiable factors that can attenuate the impact of prediabetes/diabetes on adverse health outcomes and prolong disability-free survival.

Specifically, we aimed to:

1) Describe the natural history of prediabetes and identify the predictors of prediabetes progression over a 12-year follow-up (*Study I*).

2) Examine the association of prediabetes and diabetes with stroke and subsequent dementia and assess whether and to what extent diabetes may accelerate the progression from stroke to dementia (*Study II*).

3) Examine and compare the impact of prediabetes and diabetes on trajectories of physical function and disability, and to explore whether cardiovascular diseases mediate these associations (*Study III*).

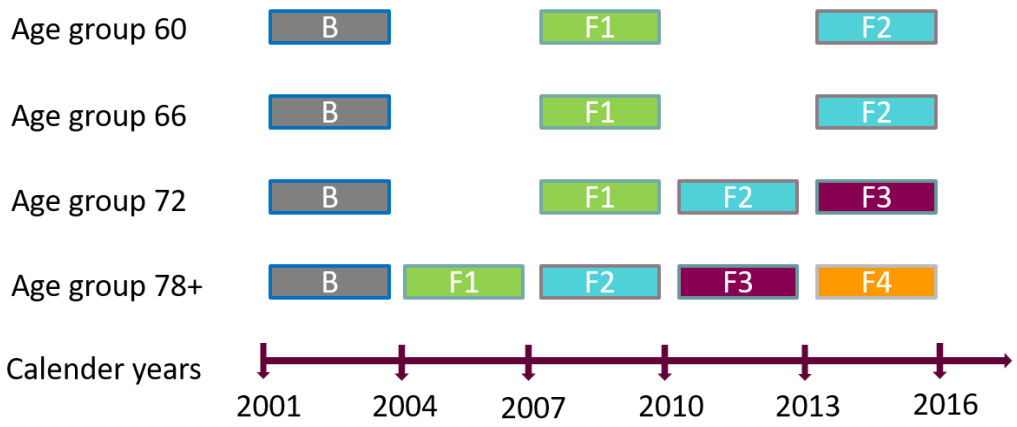
4) Assess the extent to which diabetes shortens disability-free survival and identify the modifiable factors that may prolong disability-free survival among older adults with diabetes (*Study IV*).

3 MATERIALS AND METHODS

3.1 Study population

The Swedish National Study on Aging and Care in Kungsholmen

This thesis is based on the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), an ongoing, population-based longitudinal study consisting of older adults aged ≥60 years living at home or in institutions in the central area of Kungsholmen, Stockholm, Sweden. The general target population was stratified into 11 age cohorts with a 6-year follow-up interval in the younger cohorts (60, 66, 72 years) and a 3-year follow-up interval in the older cohorts (78, 81, 84, 87, 90, 93, 96, and 99+ years). Random samples were drawn from each age cohort, resulting in a total of 5,111 individuals who were initially invited to participate in the SNAC-K baseline examination (2001- 2004). Of them, 200 died before the start of the study, 262 were not able to be contacted, and 59 were deaf, non-Swedish speakers, or had moved away. Of the remaining 4590 individuals who were alive and eligible, 3363 (response rate 73.3%) took part in the baseline examination. Participants were invited to follow-up examinations every 6 years for the younger cohorts and every 3 years for the older cohorts, given higher attrition rates and more rapid changes in health among older adults. **Figure 1** shows the study population of the SNAC-K project.



B=baseline, F1=first, F2=second, F3=third, F4=fourth

Figure 1. Data collection timeline for SNAC-K over the age cohorts.

In *Study I*, 2,575 diabetes-free participants were included in the analysis. *Study II* consisted of two sub-samples of 2,510 participants free of stroke and dementia, and 145 stroke patients without dementia. *Study III* included 2,013 participants at baseline, and *Study IV* was composed of 2,216 disability-free participants at baseline. All four individual studies were longitudinal and used the data from baseline up until 2016.

3.2 Data collection and assessments

Data collection in SNAC-K followed a structured protocol at each wave in accordance with a standard protocol (available at http://www.snac-k.se/). Information on socio-demographics, living situation, and lifestyle factors was collected through interviews by trained nurses. Nurses measured physical functional status and anthropometrics and collected peripheral blood samples. Data on medical history were collected and clinical examinations were conducted by physicians. In addition, participants were asked to bring their medication containers during study visits, and information on medication use was collected through visual inspection and recorded by a physician in accordance with the Anatomical Therapeutic Chemical Classification System. A comprehensive neuropsychological testing battery was administrated by psychologists. Information on social well-being was collected from a self-administrated questionnaire. SNAC-K is also linked to the Swedish National Patient Register (NPR) and the Swedish Cause of Death Register.

3.2.1 Assessment of prediabetes and diabetes

In all studies, diabetes status (prediabetes, diabetes, controlled diabetes, and uncontrolled diabetes) was assessed at baseline and at each follow-up.

Until December 2010, HbA1c was assessed with Swedish Mono-S filament High Performance Liquide Chromatography, and 1.1% was added to each value in order to harmonize to the international values according to National Glycohemoglobin Standardization Program (NGSP, HbA1c in %) (136). Since January 2011, HbA1c has been measured in accordance with the International Federation of Clinical Chemistry (IFCC, HbA1c in mmol/mol) reference method. A standard equation (NGSP = [0.09148 * IFCC] + 2.152; available at www.ngsp.org/ifccngsp.asp) was applied to convert IFCC HbA1c (mmol/mol) to the NGSP value (%) in order to render HbA1c comparable at all waves (137).

Diabetes was ascertained by combining information from clinical examinations, antidiabetic medication use, medical records from the National Patient Register (NPR) (ICD-9: code 250; ICD-10: code E11), or HbA1c ≥6.5% (3). Prediabetes was identified as HbA1c of 5.7% to 6.4% in diabetes-free participants. In *Study I*, diabetes was additionally ascertained from the Swedish Cause of Death Register (ICD-10: code E11). In *Studies III and IV*, diabetes was further categorized as controlled (HbA1c <7.5%) or uncontrolled (HbA1c ≥7.5%), based on the recommended glycemic targets for older adults (3).

3.2.2 Assessment of outcomes

Stroke and post-stroke dementia

Stroke was identified based on the stroke diagnosis from the NPR and Cause of Death register. The diagnosis of stroke and its subtypes was made based on patients' clinical manifestation and neuroimaging (138), and only clinical overt stroke with symptomatology was included in the study. The NPR has been shown to be highly reliable, with a validity of 95% for stroke diagnosis (139). The ICD-8 was used by the Swedish Register systems from 1969 to1986, the ICD-9 was used from 1987 to 1996, and the ICD-10 has been employed since 1997. Discharge diagnoses from the ICD-8, ICD-9, and ICD-10 were used to identify stroke from the first recorded date (December 1974) until the last available date (December 2016). The ICD codes were applied to identify hemorrhagic stroke (ICD-8 and ICD-9: 430-432; ICD-10: I60-I62), and ischemic stroke (ICD-8 and ICD-9: 433-432; ICD-10: I63-I64).

In SNAC-K, medical records on stroke were retrieved and reviewed by physicians, and the ICD codes from the registers were recorded in the physician questionnaires. Prevalent stroke was defined as the diagnosis of stroke before the baseline examination (until 2003). Incident stroke was defined as the first-ever stroke occurring during the follow-up period (from 2003 to 2016) among participants who were stroke-free at baseline.

For **dementia**, all participants were examined by neurologists, and the diagnosis was made according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria, with a validated three-step procedure (140). Two physicians made an independent diagnosis of dementia based on cognitive tests, and neurological examinations, and participants' cognitive status from the clinical interview (step one and two). In the case of disagreement between the two diagnoses, a neurologist was consulted to reach a concordant diagnosis (step three). For participants who died before a follow-up assessment without having received a diagnosis of dementia, dementia was ascertained through death certificates and clinical charts.

Post-stroke dementia was defined as having dementia following an index stroke, and dementia without stroke was defined as dementia without any stroke occurrence.

Physical function and disability

The measures of physical function used in this thesis included performance on a walking speed test and a five-time sit-to-stand chair stand test, both of which were assessed by nurses at baseline and follow-ups. Walking speed and chair stand tests are considered highly reliable and are able to discriminate functionality even in high-functioning older adults (72). Information on disability including basic activities of daily living (ADL) and instrumental

activities of daily living (IADL) was collected through interview by nurses at baseline and follow-ups.

Walking speed was assessed by asking participants to walk at their normal pace for 2.44 meters or 6 meters depending on the participant's self-rated usual speed. Self-rated fast or normal walkers completed the 6 meters test, while self-rated slow walkers performed the 2.44 meters walk test. Shorter walking tests were also performed during home visits because of limited space. Walking speed is the time in which the 2.44 or 6 meter distance is walked and is presented in meter per second (m/s) (141).

Chair stand performance was measured as the time in which participants could move from a sitting to standing position give times consecutively, with their arms folded across the chest. The time required for chair stand is measured in seconds (s). Participants who were unable to perform the test received the worst possible score; that is, 0 m/s for walking speed, or 75 s for chair stand time, which were defined as walking speed limitation or chair stand limitation (141).

Disability was evaluated by asking participants their dependence in ADL (bathing, dressing, toileting, eating, transferring, and continence) and IADL (meal preparing, grocery shopping, housekeeping, using the telephone, taking transportation, doing laundry, handling money, and managing medications). Disability was defined as the inability to undertake one or more ADLs or IADLs. The severity of disability was measured by summing the numbers of ADL and IADL limitations, which ranged from 0 to 14. The combination of ADL and IADL is considered to be more sensitive to discriminate functional disability as opposed to the use of solely ADL or IADL (92).

Cardiovascular diseases

Information on cardiovascular diseases (CVDs) was collected through several sources. Participants were interviewed on their medical history, and physicians reviewed medical charts and current medication use. Moreover, assessments from clinical examinations and laboratory parameters, together with the data from the NPR, were used to define disease. The diagnosis of CVDs was coded in accordance with the ICD-10 and further classified into seven CVD groups based on the clinically-driven methodology developed in our group (142): ischemic heart disease, heart failure, atrial fibrillation, bradycardias and conductive disorders, cardiac valve diseases, peripheral artery diseases, and other cardiovascular diseases (i.e. aortic aneurysm and dissection). The number of CVDs was summed as a measure of CVD burden at baseline and each follow-up.

Disability-free survival

Disability-free survival was defined as the survival time free from disability. A composite endpoint was derived reflecting the first occurrence of disability or death. As mentioned earlier, disability was defined as the inability to carry out one or more ADLs or IADLs. Participants' vital status and date of death were derived from Swedish Cause of Death Register.

3.2.3 Assessment of lifestyle factors and social network

Behavioural factors

Information on behaviours were collected in interviews conducted by nurses at baseline. **Smoking status** was classified as never, former, or current smoker. **Alcohol consumption** was defined as the number of standard drinks (roughly 12 grams of alcohol) per week. Alcohol consumption was further categorized as heavy (>14 standard drinks per week for men or >7 standard drinks per week for women), light-to-moderate (1–14 standard drinks per week for men or 1-7 standard drinks per week for women), or no/occasional drinking (143).

Behaviour was assessed based on current smoking and heavy drinking and categorized as healthy neither of these behaviours were present and unhealthy when any of them were present. **Physical activity** was assessed based on the activity intensity and frequency in a self-administered questionnaire (144): 1) "Do you regularly engage in light exercise? (Walking on roads or in parks, walking in the woods, short bicycle rides, light aerobics, golf)" and 2) "Do you regularly engage in more intense exercise? (Jogging, brisk long walks, heavy-duty gardening, long bicycle rides, high-intensity aerobics, long distance ice skating, skiing, swimming, ball sports or other similar activity)." For both questions the answer alternatives were: "In the last 12 months: every day, several times/week, 2-3 times/month, less, never." A dichotomous variable of physical activity (active vs. inactive) was created based on the answers from these two questions with reference to the WHO recommendations on the frequency of physical activity for older adults (145). Participants were considered physically active if they were engaged in light and/or intense exercise every day or several times per week and inactive if they chose the other response options.

Leisure activities

Leisure activities consisted of three components including mental activities, physical activities, and social activities, all of which were assessed from self-administrated questionnaires. At baseline, participants were asked about their participation in a predefined list of 26 activities over the past 12 months (46). **Mental activities** included 6 items that primarily required cognitive stimulation and little or no social engagement – namely reading books, playing a musical instrument, listening to music,

using the Internet or playing computer games, playing cards/chess, and painting/drawing/working with clay. The number of activities was summed and the level of engagement in mental activities was coded as low (0-1 activity; score 0), moderate (2-3 activities; score 1), or high (≥4 activities; score 2). **Physical activities** were those that predominately involved physical exercise, regardless of mental or social engagement. Participants were considered to have a high level of engagement in physical activities (score 2) if they engaged in any intense exercises (i.e., jogging, long power walks, heavy-duty gardening, long bicycles rides, high-intensity aerobic, long distance ice skating, swimming, ball sports) ≥ 2 times/week. Participants were considered to have a moderate level of engagement in physical activities (score 1) if moderate exercises (i.e., walking along roads or in parks, walking in the woods, short bicycle rides, light aerobics, golf) were performed 1 time/week or other leisure physical activity was performed (i.e., gardening, picking mushrooms/berries, hunting/fishing, home repairs, car repair). Finally, participants were considered to have a low level of engagement in physical activities (score 0) if any kind of physical exercise was performed < 1 time/week and/or no leisure physical activity were performed. **Social activities** were those primarily involving social interactions – namely going to sports events, cinema/theatre/concerts/, restaurants/bar/cafes, museum/art gallery, dancing, bingo, travelling, attending church/revival meeting, study circle or courses, volunteering, and other social meetings. Engagement in social activities was scored as 0 if no activities were reported, 1 if one activity was reported, and 2 if two or more activities were reported. A final leisure activity index was created by summing up the scores of mental, physical, and social activities with the range from 0 to 6. The level of engagement in leisure activities was coded as low (score 0-1), moderate (score 2-3), or high (score 4-6).

Social network

Social network was assessed based on participants' level of social connection and social support from a questionnaire self-administered at baseline (109). **Social connection** was measured by collecting data on participants' marital status, cohabitation status, parenthood, friendships, and frequency of direct or remote contacts to children, relatives, friends, son/daughter-in-law, siblings, parents, or neighbours. **Social support** was measured by assessing participants' satisfaction with these aforementioned contacts, perceived material and psychological support, sense of affinity with their association members, relatives, and residence area, and feeling of being part of a group of friends. The raw scores of social connection and support were standardized into z-scores based on the baseline means and standard deviations, and a social network index was computed by averaging these two measures. Social network index was then divided into tertiles based on its distribution and interpreted as low (≤ -0.14), moderate (-0.13 to 0.30), or rich (>0.30).

3.2.4 Assessment of covariates

Sociodemographic factors

Information on age, education, and living situation were collected through nurse interviews. Number of years of formal schooling was gathered and categorized as elementary school, high school, or university or above based on the highest level of formal education attained. Living arrangement was dichotomized as living alone vs. living with someone by asking the participants if they lived alone in their household.

Metabolic factors

Seated arterial blood pressure was measured on the left upper arm with a sphygmomanometer when participants were resting in a quiet room. It was measured twice with a 5-minute interval and the average of the two readings was used to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as having SBP ≥140 mmHg or DBP ≥90 mmHg, or taking antihypertensive medication (146).

High total cholesterol was defined as a non-fasting cholesterol level ≥6.22 mmol/L or current use of cholesterol lowering medications (146). Height and weight of the participants were measured with light clothes and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m) and categorized as underweight (<20), normal weight (20-24.9), overweight (25-29.9), and obese (≥30 kg/m^2).

In *Study I*, weight change was calculated as the weight when the glycemic status was transited minus the baseline weight. In case of developing diabetes, weight change was calculated as the weight at the follow-up prior to diabetes occurrence minus the baseline weight. We divided the weight change into tertiles based on the distribution and categorized them as “loss” (-33 to -5 kg), “stable” (-4 to 0 kg), and “gain” (1 to 17 kg).

Diabetes-related conditions

Diabetes-related chronic conditions were collected from the physician interview, laboratory tests, and from the NPR. This has been described in detail elsewhere (142). The chronic conditions included depression and mood disorders (e.g., depressive episode), peripheral neuropathy (e.g., nerve root and plexus disorder), and cerebrovascular diseases (e.g., stroke, transit ischemic attack), and further dichotomized as presence vs. absence of the disease. Furthermore, serum creatinine level was measured and estimated glomerular filtration rate (eGFR) was calculated (in mL/min/1.73 m^2) based on the Chronic Kidney Disease Epidemiology Collaboration equation (147). The eGFR describes the

flow rate of filtered fluid through the kidney, which is considered a measure of renal function.

Global cognitive function and genetic factors

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE) at baseline and follow-ups. The MMSE has a maximum score of 30 points, and a score ≤24 is generally indicative of a cognitive impairment (148).

DNA was extracted from peripheral blood samples and genotyping was performed following standard procedures. The APOE gene was analysed and dichotomized as carriers vs. non-carriers of the ε4 allele.

3.3 Statistical analysis

In this thesis, Poisson regression, multinomial logistic regression, flexible parametric multistate modelling, linear mixed-effects model, structural equation modelling (path analysis), Cox proportional hazard regression model, and Laplace regression models were used, depending on the research question. An overview of the exposures, outcomes, potentials confounders and statistical methods used in all four studies is presented in **Table 3**.

In general, because glycemic status is the main exposure of interest in this thesis, the baseline characteristics of the study sample by glycemic status were compared with Chi-square tests for categorical variables and one-way ANOVA tests for continuous variables. Bonferroni corrections were applied in order to minimize the chance of type 1 error derived from multiple comparisons between the groups. The statistical significance level was set at two-tailed test $p<0.05$. Point estimates with 95% confidence intervals (CIs) were presented. Odds ratios (ORs) were calculated in *Study I*, and hazard ratios (HRs) were presented in *Study II* & *Study IV*. In *Study III*, beta coefficients were calculated, and bootstrapping was used to calculate standard errors and construct CIs in mediation analysis. When assessing statistical interactions, p-values <0.10 were considered statistically significant.

3.3.1 Survival analysis

Survival analysis is used to model time-to-event. It includes but is not limited to the well-known Cox proportional hazards regression model. Poisson regression and flexible parametric survival models also belong to the family of survival analyses and were used in this thesis.

Poisson regression

Poisson regression is a member of the generalized linear model family, which can be used to model count data or to calculate incidence rate over a period of

time. It assumes: 1) the response variable (*y*) follows a Poisson distribution, 2) the logarithm of y can be modelled with a linear combination of the explanatory variables (e.g., *x1, x2*), and 3) the variance is equal to the mean. Poisson regression is known as a log-linear model, which is interpreted as the effect per unit of *x*, the change in the logarithm of *y*. By using Poisson regression, the absolute risk (e.g., adjusted-incidence rate) or relative risk (e.g., incidence rate ratio) across the groups can be estimated. Within the survival analysis framework, Poisson regression estimates the overall rate as a constant rate over time or piece-wise rate over a period of time. When time is the confounder, Poisson regression can model the incidence rate by splitting the time bands. It models the baseline rate and allows the rate to differ between the time bands, estimating different baseline rates within each time band. Since estimating the adjusted-absolute risk and effect of time is of interest in *Study I*, we used Poisson regression to calculate the sex-adjusted incidence rates for each age groups and to estimate incidence rate ratios between the first and second 6-year follow-ups.

Cox proportional hazards regression model

Since the rate at which an outcome occurs may change rapidly with time, splitting time into very narrow bands requires a lot of estimates from the Poisson regression. The Cox proportional hazards regression model is an alternative to Poisson regression model. By splitting the time into infinitesimal width, Cox regression does not make any assumption on the shape of the baseline hazard (which is constant for Poisson regression), and allows the baseline rate (hazard) to vary freely. Cox regression is a semi-parametric model because the baseline hazard is not estimated but the hazard ratios across the groups are modelled parametrically, following a proportional hazard assumption. Therefore, the relative rates (i.e., hazard ratios) for different levels of covariates within infinitesimal width of time are estimated. This technique for handling time as an important confounder in Cox regression model is very efficient, since it adjusts for time in very small intervals through the adjustment of underlying time scale. The timescale is integrated into the shape of the baseline hazard so it cannot be estimated directly. As the comparison is made at each time *t*, the hazard ratio is adjusted for each time *t* automatically, which is the underlying time scale. In *Study IV*, because age is a very strong confounder, and because we were not interested in estimating the effect of age, we used age as the underlying time scale. The interpretation of hazard ratios is the probability of an individual having an event at a particular given time point given that this individual survived to that particular time point without having the event.

Flexible parametric multistate model

In contrast to the Cox regression, flexible parametric survival analysis models the baseline hazard, where the absolute risk can be obtained and time-dependent effects can be more easily modelled (149). Although in Poisson regression, the baseline hazard can also be obtained, it is usually not biologically plausible as the shape of it is a stepwise function. Flexible parametric survival models are flexible to capture the shape of the baseline hazard by assuming a certain distribution (e.g., Weibull) or by applying restricted cubic splines. The splines are jointed with knots, where the number of knots is known as the degree of freedom to model the baseline hazard function and time-dependent effect to relax the assumption of proportional hazard. In *Study II*, the baseline hazard function was modelled with three degrees of freedom, guided by the Akaike Information Criteria (150). As the models do not violate the proportional hazard assumption, no modelling of the time-dependent effect of the covariates was applied.

The impact of the exposure on the outcome might vary with the occurrence of other diseases as the individual progresses through the course of the disease. For example, an intermediate event, such as stroke, might change the natural history of the dementia progression, so the effect of diabetes on dementia might not be the same after the development of stroke (i.e., the baseline hazard changes after stroke occurrence). By using a multistate model between disease states, accounting for the competing risk of death at each state, we can gain insight into the disease trajectory as well as how the risk factors affect over the disease pathway (150). The multistate model allows for the inclusion of intermediate events and competing events in the framework of survival analysis (151). For example, one multi-state model is the cause-specific multi-state model, which includes alive (initial state), death from one cause (absorbing state 1), and competing death from the other cause (absorbing state 2), as illustrated in **Figure 2**. More states can be added to the multistate model, such as intermediate states, with the arrow indicating the direction of the possible transitions. In *Study II*, we studied the association between diabetes and stroke and subsequent dementia by including stroke as an intermediate state and death as an absorbing state (**Figure 3**). We did not allow for the transition from dementia to stroke due to the small number of cases in which this occurred.

The multistate models used in this thesis are Markov models, with the underlying assumption that the probability of transition from one state to the next is only dependent on the current state and time since origin, but not on the previous history of transitions (151). However, the Markovian assumption does not hold when the time spent in the current state affects the probability of entering the next state (e.g., the time spent in the state of stroke impacts the probability of entering the state of dementia). For situations of this kind, a semi-Markov model

with a clock-rest approach has been proposed. This can be tested by additionally adjusting for time spent in the current state. If the assumption is violated, this can be handled by resetting the underlying time scale as time since entry into the last state, as was done in *Study II*, where we used time since stroke diagnosis as the underlying time scale for the transition from stroke to dementia.

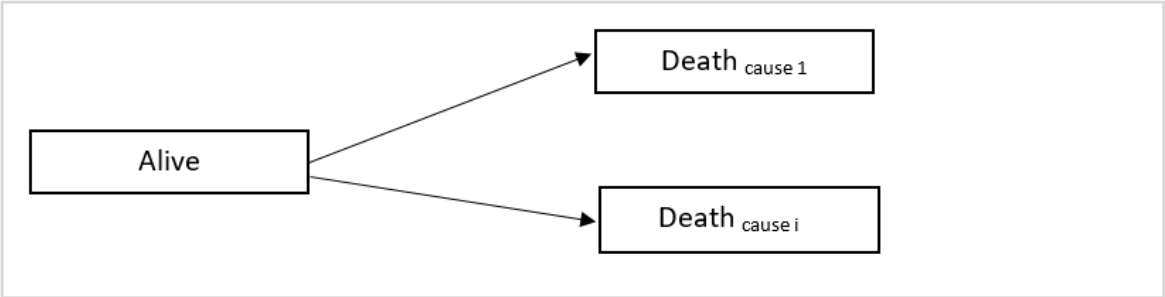


Figure 2. Cause-specific multi-state model

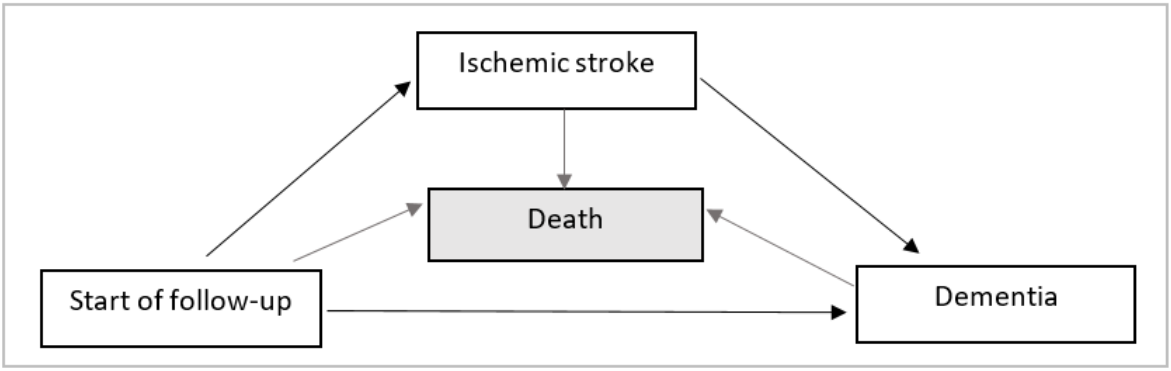


Figure 3. Multistate model in *Study II*

The multistate model can be modeled non-parametrically or parametrically. In *Study II*, we used parametric multistate survival models. There are a number of distinct advantages to this, including prediction and quantification of relative or absolute risks with covariates adjusted through a parametric approach. A transition matrix was defined, where the transition probabilities and the state occupancy probabilities were estimated by the Aalen-Johansen estimator, with the time since diagnosis as the time scale. Because we fitted a flexible parametric model for each transition state, covariate-adjusted and standardized transition probabilities were obtained. In the competing risk framework, transition probabilities are the same as cumulative incidence function (CIF). These can be interpreted as the probability of experiencing an event over time, considering that the competing event can impede the occurrence of the event. In *Study II*, we calculated standardized CIF of dementia by glycemic status, taking the competing risk of death into account. Other measures of clinical interest that can be obtained from flexible parametric multistate model are the probability of ever visiting a

state (by simulation), and the mean amount of time spent in a state between two time points (by integration), with or without a specific covariate pattern.

3.3.2 Multinomial logistic regression

Multinomial logistic regression is commonly used to model nominal outcomes that could have more than two levels. The outcomes were modelled with log odds as a linear combination of predictive variables. Multinomial logistic regression assumes the independence of irrelevance alternatives, meaning that the choice of membership in one category is not related to the choice of the membership in another category. This assumption can be tested with the Hausman-McFadden test. Furthermore, multinomial logistic regression assumes non-perfect separation. If a predictor can perfectly separate the groups of the outcome, the estimates of coefficients will be biased and the effect sizes will be greatly overestimated. We fitted a multinomial regression model in *Study I*, where a set of modifiable variables were used to predict different prognosis of prediabetes (reversion to normoglycemia, progression to diabetes, or death).

3.3.3 Linear mixed-effects modelling

Linear mixed-effects model is an extension of linear regression, with the added benefit of modelling longitudinal data with repeated measurements and clustered data where there is non-independence in the data. It can be used to estimate the change in an outcome per unit of time, taking into account the individual differences at baseline (random intercept) and rate of change over the follow-up (random slope). Linear mixed-effects modelling handles missing data with maximum likelihood estimation. The assumptions for linear mixed-effects modelling are similar to those for linear regression, which are linearity, homoscedasticity, and normality. In *Study III*, we used the linear mixed-effects model to test the effect of pre/diabetes on physical function decline and disability progression over 12 years. Each linear mixed-effects model included glycemic status, follow-up time, and an interaction term between glycemic status and follow-up time. The estimates of the glycemic reflect differences in outcome at baseline, the estimate of follow-up time reflects the annual change in the outcome, and the estimates of interaction term reflects the additional annual change in the outcome for participants with prediabetes or diabetes, relative to those with normoglycemia.

3.3.4 Mediation analysis by path analysis

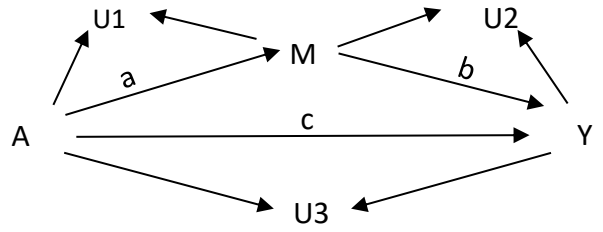


Figure 4. Causal DAG for the Mediation analysis where A=prediabetes or diabetes, M=CVDs accumulation; Y is annual change of chair stand or walking speed or disability progression. U1, U2, U3 are confounding factors.

Mediation analysis aims to identify and explain the mechanism that underlies an observed association between exposure and outcome by including a mediator (or mediators) in the pathway. It is inherently a causal notion, therefore a causal relationship between the exposure, the mediator, and the outcome is assumed. Path analysis was performed for mediation analysis in *Study III*, under the assumption of a causal directed acyclic graph (DAG) illustrated in **Figure 4**. We performed six mediation analyses in total, with prediabetes and diabetes as the exposures, and chair stand, walking speed, and disability progression as the outcomes, separately. Take the mediation analysis with prediabetes and chair stand as an example: The exposure is prediabetes, dichotomized as having prediabetes or normoglycemia (A); the mediator is CVD accumulation (M); the outcome is chair stand (Y); confounders (U1, U2, U3) are denoted.

The chain approach was used to decompose the total effect of prediabetes on chair stand performance into the direct effect (A->Y) and the indirect effect through the accumulation of CVDs (A->M->Y). The estimates from each path are noted as *a, b*, and *c*. The estimate of *a* is obtained by regressing CVD accumulation on prediabetes, and *b* and *c* are obtained simultaneously by regressing chair stand on prediabetes condition and on CVD accumulation. Therefore, the direct effect is *c*, the indirect effect is *a*b*, and the total effect is *c+a*b*. Of note, mediation analysis follows several assumptions (152). where in *Study IV* we assumed: 1) no unmeasured exposure-outcome confounders given U1; 2) no unmeasured mediator-outcome confounders given U2; 3) no unmeasured exposure-outcome confounders given U3; and 4) no mediator-outcome confounder U2 affected by exposure A. Other issues such as moderated mediation are also taken into account by modelling the person-specific annual rate of CVD accumulation adjusted for CVDs at baseline.

Many statistical methods have been developed for mediation analysis, one of which is the path analysis that we performed in *Study III*. Within the structural equation modelling framework, path analysis is used to describe the directed dependencies among a set of variables (153). Only the single indicator is employed for each of the variables in path analysis, without inferring latent constructs. Unlike the measurement models (such as confirmatory factor analysis), path analysis is a structural model. Each arrow of the path analysis

represents a hypothesis. We integrated the linear mixed-effect models into the path analysis (154) to estimate the mediating effect (indirect effect) of CVD accumulation on the association between prediabetes and chair stand performance.

3.3.5 Laplace regression

Laplace regression modeling belongs to the family of quantile regressions, which represent an alternative to Cox regression (155). Laplace regression makes inferences on percentiles (i.e., median) of survival time conditional on a set of covariates and accounting for censoring. The benefits of using Laplace regression are to estimate percentiles of survival time and to allow comparisons across groups while adjusting for confounders. In the context of survival analysis, instead of using Kaplan Meier curves to determine the proportion of subjects who are still alive at the end of follow-up, the Laplace regression estimates describe how much time it takes before a specific percentile of participants (i.e., 50%) die. In other words, Cox regression model estimates the risk of experiencing an event while Laplace regression estimates the absolute survival difference, and these two estimates can be used to complement one another in interpreting results. To this end, in *Study IV*, in addition to Cox regression, we used Laplace regression with attained age as the timescale to estimate the median age of disability-free survival across the groups of participants with different diabetes status and lifestyle profiles.

Table 3. Overview of the studies and main methods included in this thesis

Study	Title	Exposures	Outcomes and follow-up time	Potential confounders	Statistical analysis
Study I	Natural history of prediabetes in older adults from a population-based longitudinal study	Prediabetes	Normoglycemia, diabetes, and death during 12-year follow-up	age, sex, education, follow-up time, alcohol consumption, physical activity, BMI, weight change, SBP, heart diseases, MMSE score, total medication use.	Poisson regression, Multinomial logistic regressions
Study II	Association of diabetes with stroke and post-stroke dementia: A population-based cohort study	Diabetes, prediabetes	Stroke, dementia, and post-stroke dementia during 12-year follow-up	age, sex, education, physical activity, body mass index, SBP, and heart disease. The HRs of transition to dementia were also adjusted for *APOE ε4*	Flexible parametric multistate modelling, using follow-up time as time scale
Study III	Not only diabetes but also prediabetes leads to functional decline and disability in older adults	Prediabetes, diabetes, controlled diabetes, uncontrolled diabetes	Walking speed, chair stand, and disability scores during 12-year follow-up	age, sex, education, BMI, physical activity, alcohol consumption, smoking status, SBP, high total cholesterol, eGFR, depression and mood disorders, cerebrovascular disease, and peripheral neuropathy.	Linear mixed-effects models with random intercepts and slopes, using follow-up time as timescale; Path analysis
Study IV	Healthy behaviours, leisure activities, and social network prolong disability-free survival in older adults with diabetes	Prediabetes, diabetes, lifestyle behaviours, leisure activities, social network	A composite outcome of disability or death. Disability-free survival during 15-year follow-up	age, sex, education, living alone, BMI, heart diseases, cerebrovascular diseases, depression, and hypertension	Cox regressions and Laplace regressions, using age as timescale

3.4 Ethical considerations

All phases of data collection in SNAC-K, as well as the use of data from the National Patient Register and the death register have been approved by the Ethics Committee at KI and the Regional Ethical Review Board in Stockholm. The serial numbers for each phase are 01-114 (baseline), 04-929/3 (first follow-up), Ö26-2007 (second follow-up), 2010/447-31/2 (third follow-up), 2013/828-31/3 (fourth follow-up), 2016/730-31/1) (fifth follow-up), and 2009/595-32 (register data).

Written informed consent was obtained from each participant at the beginning of the study. If the person could not answer, a proxy (usually a next of kin) was asked for consent. All participants were informed about the purpose and context of the study, and were informed that they could choose to drop out the study at any point and for any reason. The information is only used until last examination prior to the dropout date. If a participant chose to remove her/himself from the study, all information would be deleted from the database.

When entering the study, an artificial personal identification number called LopNr was given to each participant. All names and personal identification numbers were then removed from the dataset to ensure anonymity. All original questionnaires and lab results that contained names or personal identification numbers are locked in the safe areas.

During the examination process, participants were asked if they are willing and able to take part in each test before it begins. The physicians and nurses also evaluated whether it is safe for the participants to conduct each test. If a participant expressed any anguish or discomfort, the examination or interview was stopped. Furthermore, when taking physical function tests, a nurse was always standing nearby in order to assist participants if they lost their balance. For any diseases or conditions that were detected during the medical examination, participants are asked whether they wanted to be informed of the results. Most participants wanted to know the results, but there were some exceptions. If participants opted in, a letter with their results was sent to their homes with recommendations on referral to a family doctor or other physician if the newly-discovered condition required medical attention.

In addition, the participants were informed of the results from research conducted using SNAC-K data via booklets, magazines, and regular seminars. All researchers working with the SNAC-K dataset respect and follow the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences and the Ethical Principles for Medical Involving Human Subjects expressed in the Declaration of Helsinki.

4 RESULTS

Brief summaries of the four individual studies included in the thesis are presented below. For more details on each study, please refer to the corresponding published articles and manuscript at the end of the thesis.

4.1 Natural history of prediabetes (Study I)

The analytical sample included 2,575 diabetes-free participants (919 men, 35.7%) with a mean age of 74 (±SD 11.3) years at the baseline. Of them, 918 (36%) had prediabetes. People with prediabetes were more likely to be older and overweight/obese, consume less alcohol, have a higher MMSE score and heart disease, and take more medication than those with normoglycemia at baseline.

Of the 918 participants with prediabetes, 204 (22.2%) reverted to normoglycemia, 119 (11.0%) progressed to diabetes, and 214 (23.4%) died over the 12-year follow-up. More than one-third of those remained in the prediabetes state (**Figure 5**). We observed that the reversion rate increased with older age (*p* for trend < 0.001), while the progression rate was stable across the age groups (**Table 4**). The highest mortality rate was observed arguably among those ≥90 years. There were no sex differences in the rates of reversion, progression, or death. No significant difference was observed for the rates of reversion, progression and mortality in the first and second 6-year follow-up.

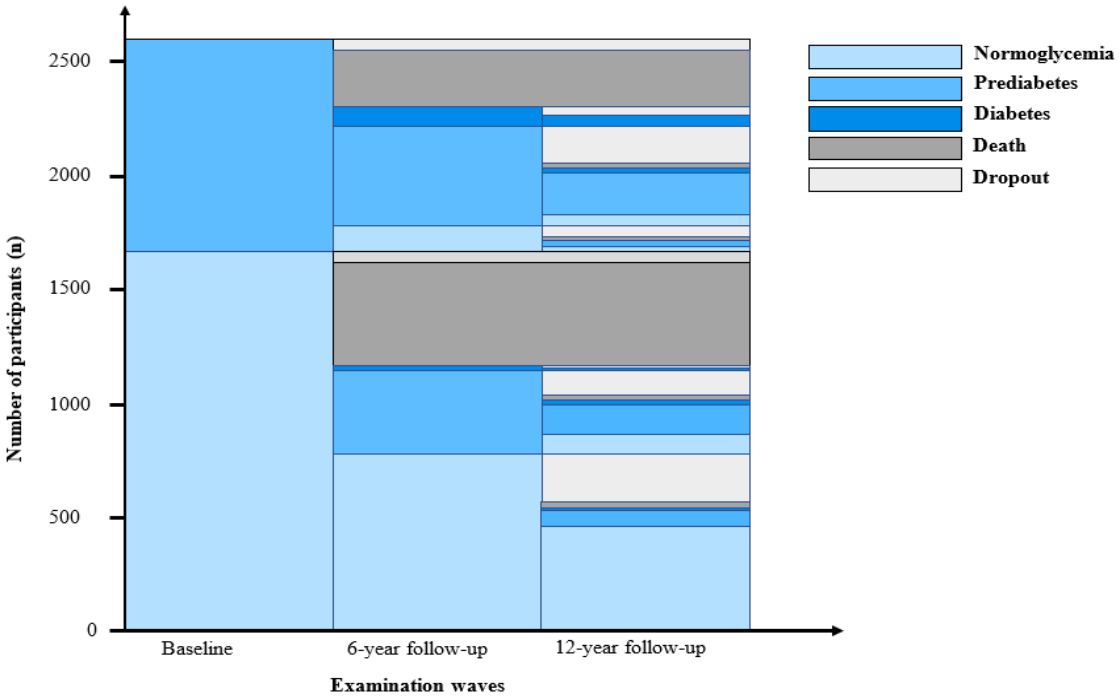


Figure 5. Transition of glycemic status and death over the follow-up period.

Table 4. Reversion, progression, and mortality rates (100 person-years, [95% confidence interval]) by age group during 12 years among people with prediabetes.

Age group	**Prediabetes** (n)	**Reversion rate** (95% CI)	**Progression rate** (95% CI)	**Mortality** (95% CI)
60/66	305	2.8 (2.3-3.6)	2.0 (1.5-2.6)	13.7 (9.8-19.2)
72/78	276	3.3 (2.5-4.3)	2.2 (1.6-3.0)	12.0 (0.3-15.6)
81-87	198	4.6 (3.4-6.2)	2.7 (1.9-4.1)	8.9 (6.7-11.9)
90+	139	8.9 (6.1-13.3)	2.7 (1.3-5.6)	18.9 (15.1-23.8)
Total	918	3.4 (3.1-4.1)	2.3 (1.9-2.7)	13.0 (11.4-14.9)

Multi-adjusted multinomial logistic regression showed that participants who experienced weight loss over the follow-up had a significantly higher probability of reverting to normoglycemia (OR=2.0, 95% CI 1.1-3.2) compared to those who had stable weight. This probability was significantly higher for those who were overweight or obese (OR=2.9, 95% CI 1.4-6.2) at baseline. However, higher SBP (OR=0.9, 95% CI 0.8-0.9) and the presence of heart disease (OR=0.5, 95% CI 0.3-0.9) were inversely associated with the reversion to normoglycemia. On the other hand, obesity (OR=2.8, 95% CI 1.3-6.0) was significantly related to the progression to diabetes. We did not find any factors that were significantly associated with prediabetes-related death.

4.2 The impact of pre/diabetes on stroke and post-stroke dementia (Study II)

At baseline, of the 2,655 dementia-free participants, 2,510 were stroke-free and 145 had prevalent stroke, constituting a stroke-free cohort and prevalent stroke cohort, respectively. In the stroke-free cohort, 835 (33.3%) had prediabetes and 231 (8.4%) had diabetes. Participants with prediabetes or diabetes were more likely to be older, male, less educated, consume less alcohol, be physically inactive, have comorbid hypertension, heart disease, and have lower MMSE scores than those with normoglycemia. In the prevalent stroke cohort, 120 participants had a history of ischemic stroke (82.6%) and 25 had haemorrhagic stroke. Among them, 53 (36.6%) had prediabetes and 25 (17.2%) had diabetes. A higher proportion of participants with pre/diabetes had hypertension and ischemic stroke compared to those with normoglycemia.

In the stroke-free cohort, 254 (10.1%) participants developed ischemic stroke (including 236 with ischemic stroke without dementia and 18 with ischemic stroke after dementia diagnosis) and 50 (1.9%) had hemorrhagic stroke during the 12-year follow-up. Among the 236 ischemic stroke cases, 47 developed subsequent dementia. Of the stroke-free participants, 250 (10%) developed dementia without prior ischemic stroke (**Figure 6**). Diabetes was associated with a higher risk of ischemic stroke (HR=1.76, 95% CI 1.16-2.67) and post-stroke dementia (HR=2.56, 95% CI 1.04-6.25), but not with dementia

without a prior stroke (HR=1.14, 95% CI 0.88-2.40). Prediabetes was not related to either the risk of stroke or post-stroke dementia.

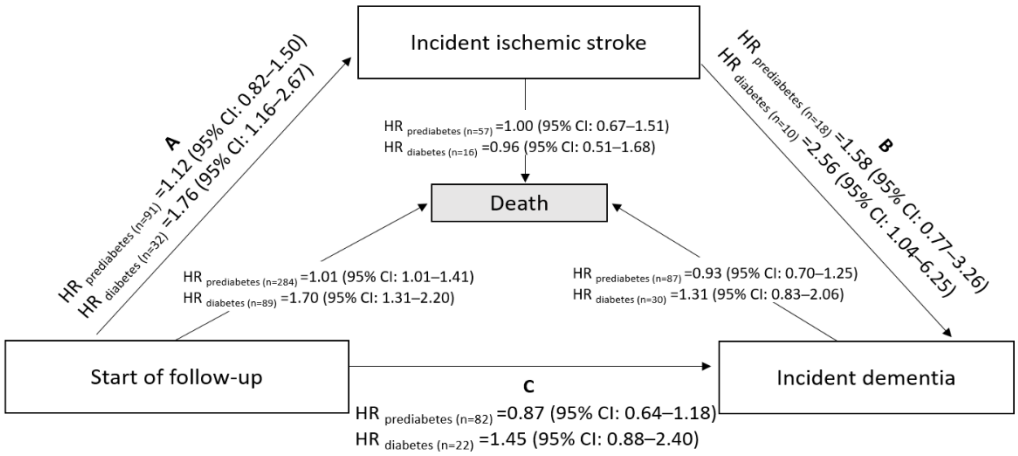


Figure 6: Multi-state model examining the role of prediabetes and diabetes on the risk of ischemic stroke and dementia in the stroke-free cohort.
Start of follow-up is a state where participants were stroke- and dementia-free. Hazard ratios (HR) due to prediabetes and diabetes on the risk of transition from: (A) stroke and dementia-free to incident ischemic stroke; (B) ischemic stroke to incident dementia; (C) stroke and dementia-free to incident dementia. The reference group is people with normoglycemia. N represents the number of prediabetes or diabetes transit to a specific state. All HRs adjusted for age, sex, education, physical activity, body mass index, systolic blood pressure, and heart disease. The HRs of transition to dementia were also adjusted for *APOE* ε4.

In the prevalent stroke cohort, 35 patients developed dementia. A higher risk of post-stroke dementia (HR=3.82, 95% CI 1.40-9.89) was observed only among participants with diabetes.

We further estimated the cumulative incidence of dementia after stroke diagnosis according to glycemic status. We found that patients with diabetes had the highest probability of developing dementia compared to those with prediabetes or normoglycemia (**Figure 7**). For example, 6 years after ischemic stroke diagnosis, the probability of developing dementia was 34.8%, 24.9% and 22.8% for participants with diabetes, prediabetes, or normoglycemia, respectively (**Panel A**). In other words, 20% of people with diabetes were diagnosed with dementia within 2.3 years of incident ischemic stroke, compared to 4.3 years in people with normoglycemia. This demonstrates that diabetes could accelerate the progression from ischemic stroke to dementia by 2 years. **Panel B** illustrates that, among those with stroke at baseline, 21.1%, 10.9%, and 10.0% of participants with diabetes, prediabetes, or normoglycemia were respectively diagnosed with dementia after 6 years of follow-up.

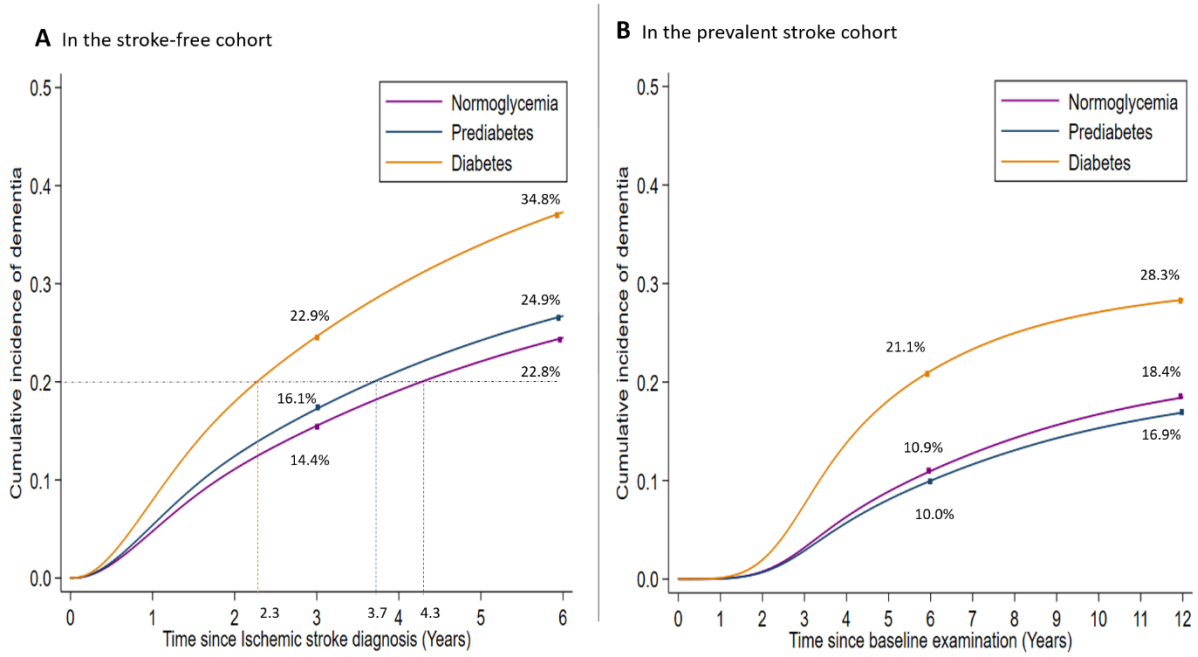


Figure 7: Adjusted cumulative incidence of dementia by glycemic status in stroke-free cohort (A) and prevalent stroke cohort (B).
Cumulative incidence function of dementia by normoglycemia, prediabetes and diabetes, over time since ischemic stroke diagnosis in stroke-free cohort (A), or over time since baseline examination in prevalent stroke cohort (B). The cumulative incidence function was derived from flexible parametric competing risk models adjusted for age, sex, education, physical activity, body mass index, systolic blood pressure, heart disease in both cohorts (A&B). The model was additionally adjusted for APOE ε4 in stroke-free cohort (A). In stroke-free cohort (A), cumulative incidence of dementia by glycemic status after 3 and 6 years since diagnosis of ischemic stroke was calculated. The time (years) for 20% of participants diagnosed with dementia (long dash dotted line) by normoglycemia, prediabetes, and diabetes was also noted. In prevalent stroke cohort (B), cumulative incidence of dementia by glycemic status after 6 and 12 years since baseline examination was noted.

4.3 Trajectories of physical function and disability in pre/diabetes (Study III)

Out of 2,013 participants at baseline, 650 (32.3%) participants had prediabetes and 151 had diabetes (7.5%). Individuals with prediabetes or diabetes were older, had a higher BMI, and were more likely to have hypertension, chronic diseases, a lower eGFR, and be less physically active than those with normoglycemia. In addition, individuals with prediabetes and diabetes had a longer chair stand time, slower gait speed, and lower disability score than those with normoglycemia.

Over the follow-up, prediabetes was related to an increased chair stand time (β=0.33, 95% CI 0.05 to 0.61), a decreased walking speed (β=-0.006, -0.010 to -0.002), and an accelerated disability progression (β=0.05, 95% CI 0.01 to 0.08) annually, independent of demographic factors, diabetes chronic conditions, and future development of diabetes (**Figure 8**). Diabetes led to faster functional decline than prediabetes, and these deteriorations were more evident among those with uncontrolled diabetes.

Since both prediabetes and diabetes were significantly associated with CVD accumulation over time, a mediation analysis was conducted to estimate the extent to which CVD accumulation can explain the faster decline in physical function associated with prediabetes and diabetes. The mediation analyses showed the CVDs mediated 7.1%, 7.8%, and 20.9% of the associations between prediabetes and chair stand, walking speed, and disability progression, respectively. The corresponding proportions of the diabetes-functionality associations mediated by CVDs were 13.3%, 22.9%, and 14.4% (**Table 5**).

Table 5. Mediation analysis of changes in CVDs during the follow-up on the associations of baseline prediabetes and diabetes with chair stand, walking speed, and disability scores**.**

	β coefficient (95% CI)			
	Total effect	**Direct effect**	**Indirect effect**	**Mediation (%) by CVDs**
Prediabetes to functional decline and disability				
Annual chair stand change	0.72* (0.25 to 1.18)	0.67* (0.21 to 1.12)	0.05* (0.00 to 0.10)	7.1%
Annual walking speed change	-0.011* (-0.015 to -0.003)	-0.01** (-0.01 to -0.00)	-0.001* (-0.001 to -0.000)	7.8%
Annual disability score change	0.026¤¤ (-0.003 to 0.06)	0.02 (-0.00 to 0.06)	0.006* (0.001 to 0.012)	20.9%
Diabetes to functional decline and disability				
Annual chair stand change	1.40* (0.47 to 2.32)	1.21* (0.27 to 2.16)	0.19* (0.01 to 0.37)	13.3%
Annual walking speed change	-0.011* (-0.022 to -0.000)	-0.008¤ (-0.018 to 0.001)	-0.002* (-0.004 to -0.000)	22.9%
Annual disability score change	0.13* (0.06 to 0.18)	0.11* (0.02 to 0.20)	0.02* (0.00 to 0.04)	14.4%

The estimates are given as standardized coefficients, with P values and 95% confidence intervals derived from bootstrapping in path analysis adjusted for baseline age, sex, education, BMI, physical activity, alcohol consumption, smoking status, SBP, eGFR, high total cholesterol, depression and mood disorders, cerebrovascular diseases, and peripheral neuropathy. The results also show the proportion mediated by the CVDs accumulation in each association. CVD = Cardiovascular disease **p< 0.01 *p< 0.05 ¤p=0.075 ¤¤p=0.09

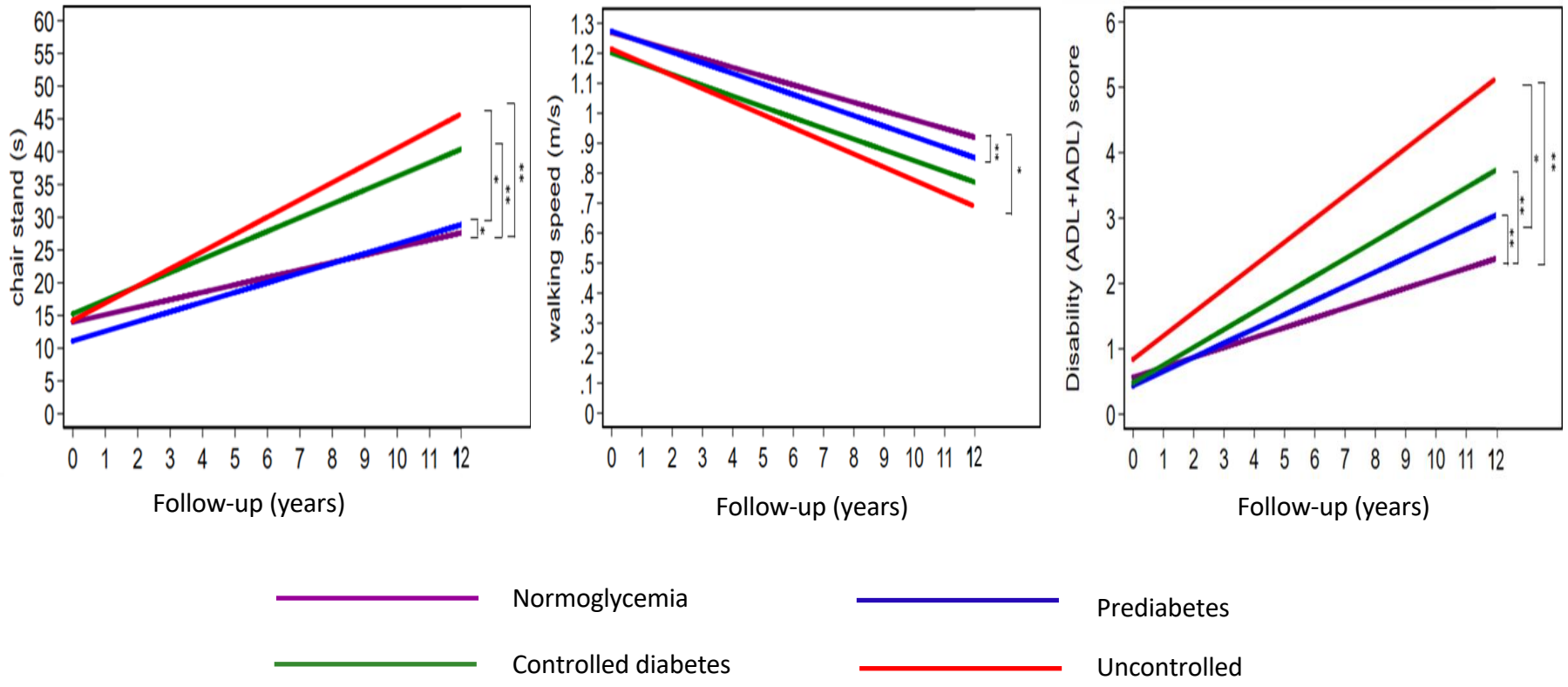


Figure 8. Predicted trajectories of chair stand, walking speed, and disability score (ADL+IADL) over 12-year follow-up by glycemic status. Purple line=individuals with normoglycemia; Blue line= individuals with prediabetes; Green line= individuals with controlled diabetes; Red line= individuals with uncontrolled diabetes. Lines represent β coefficients from linear mixed-effects model adjusted for age, sex, education, body mass index, physical activity, alcohol consumption, smoking status, systolic blood pressure, estimated glomerular filtration rate, high total cholesterol, depression and mood disorders, cerebrovascular diseases, and peripheral neuropathy, with normoglycemia or prediabetes as reference group. **p<0.01 *p<0.05

4.4 The impact of behaviours, leisure activities, and social network on disability-free survival in people with diabetes (Study IV)

A total of 2,216 disability-free participants were identified at baseline, of whom 176 (7.9%) had diabetes. During the follow-up, 1,347 participants developed a composite outcome of disability or death. Participants with diabetes had a 29% (HR=1.29, 95% CI 1.06-1.57) increased risk of developing the outcome compared to those with normoglycemia after adjustment for potential covariates. The median age at the development of disability or death was 2.2 years younger among those with diabetes relative to normoglycemia. However, healthy behaviours (no current smoking and no heavy drinking), active leisure activities, and moderate-to-rich social network were associated with a lower risk of the composite endpoint of disability or death compared to those with unhealthy behaviours, inactive leisure activities, or poor social network (**Table 6**).

Table 6. Hazard ratios (HR), 95% confidence interval, and difference in median age at developing disability or death, according to glycemic status and modifiable factors.

Modifiable factors	No. of events	**Cox regression**[a] HR (95% CI)	**Laplace regression**[a] Difference in median age (95% CI)
Glycemic status			
Normoglycemia	723	Reference	Reference
Prediabetes	489	1.00 (0.89, 1.13)	0.20 (-0.64, 1.04)
Diabetes	133	1.29 (1.06, 1.57)	-2.15 (-3.27, -1.02)
Controlled (<7.5%)	102	1.27 (1.02, 1.58)	-1.60 (-3.21, 0.00)
Uncontrolled (≥7.5%)	30	1.34 (0.89, 2.00)	-2.53 (-4.82, -0.24)
Behaviours[b]			
Unhealthy	387	Reference	Reference
Healthy	941	0.68 (0.61, 0.78)	2.38 (1.53, 3.22)
Leisure activities index			
Inactive	378	Reference	Reference
Active	812	0.78 (0.67, 0.90)	1.91 (0.85, 2.97)
Moderate	560	0.87 (0.76. 1.00)[c]	0.89 (-0.01, 1.81)
High	252	0.71 (0.60, 0.85)	2.50 (1.32, 3.68)
Social network			
Poor	402	Reference	Reference
Moderate to rich	877	0.75 (0.66, 0.86)	1.36 (0.50, 2.22)
Moderate	448	0.76 (0.66, 0.87)	1.16 (0.31, 2.02)
Rich	429	0.75 (0.64, 0.87)	1.57 (0.45, 2.69)

[a] The composite endpoint was the first occurrence of disability or death from any cause.

[b] Healthy lifestyle behaviours include both no current smoking and no heavy drinking, and unhealthy lifestyle include any of the aforementioned behaviours. Models are adjusted for baseline age, sex, education, living alone, BMI, cardiovascular diseases, cerebrovascular diseases, depression, hypertension [c] p=0.07

Among participants with a favourable profile, defined as the presence of at least one of the healthy lifestyle, active engagement in leisure activities, and moderate-to-rich social network, having diabetes appears not to significantly increase the risk of the composite endpoint (HR=1.19, 95% CI 0.93-1.56) compared to being diabetes-free (**Figure 9**). Furthermore, among participants with diabetes, having a favourable profile was significantly related to a lower risk of developing the composite endpoint compared to those with an unfavourable profile (i.e., having none of the aforementioned variables) (p for difference=0.037).

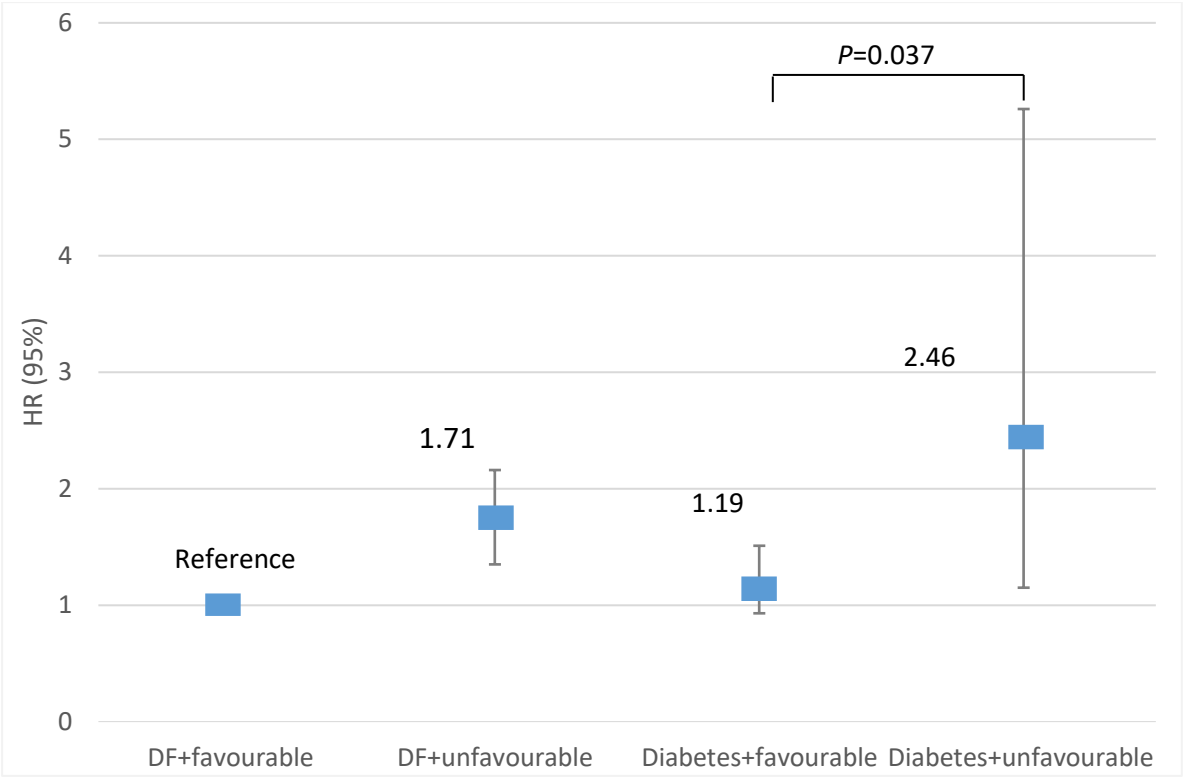


Figure 9. Joint associations between diabetes and the combination of healthy lifestyle, active leisure activities, or social network and on the risk of composite endpoint of disability or death. HR (95% CI) of composite endpoint from Cox regression models adjusted for baseline age, sex, education, living status, BMI, cardiovascular diseases, cerebrovascular diseases, depression and hypertension. "Favourable profile" refers to the presence of at least one of the factors including healthy behaviours, active engagement in leisure activities, or moderate-to-rich social network. "Unfavourable profile" refers to having none of the factors including healthy lifestyle, active leisure activities, or moderate-to-rich social network. DF: diabetes-free; HR: hazard ratios; CI: confidence interval. P = 0.037 refers to the significance level of the risk difference for the composite endpoint between "diabetes + favourable" group and "diabetes + unfavourable" group.

In addition, among participants with diabetes, median age of developing disability/death was 79.6 (95% CI 74.6 –84.5) years in the favourable profile group, and 76.3 years (95% CI 70.4–82.2) in the unfavourable profile group, suggesting that participants with a favourable profile could have 3.26 years (95% CI 2.33 – 4.18) longer disability-free survival than those without (**Figure 10**).

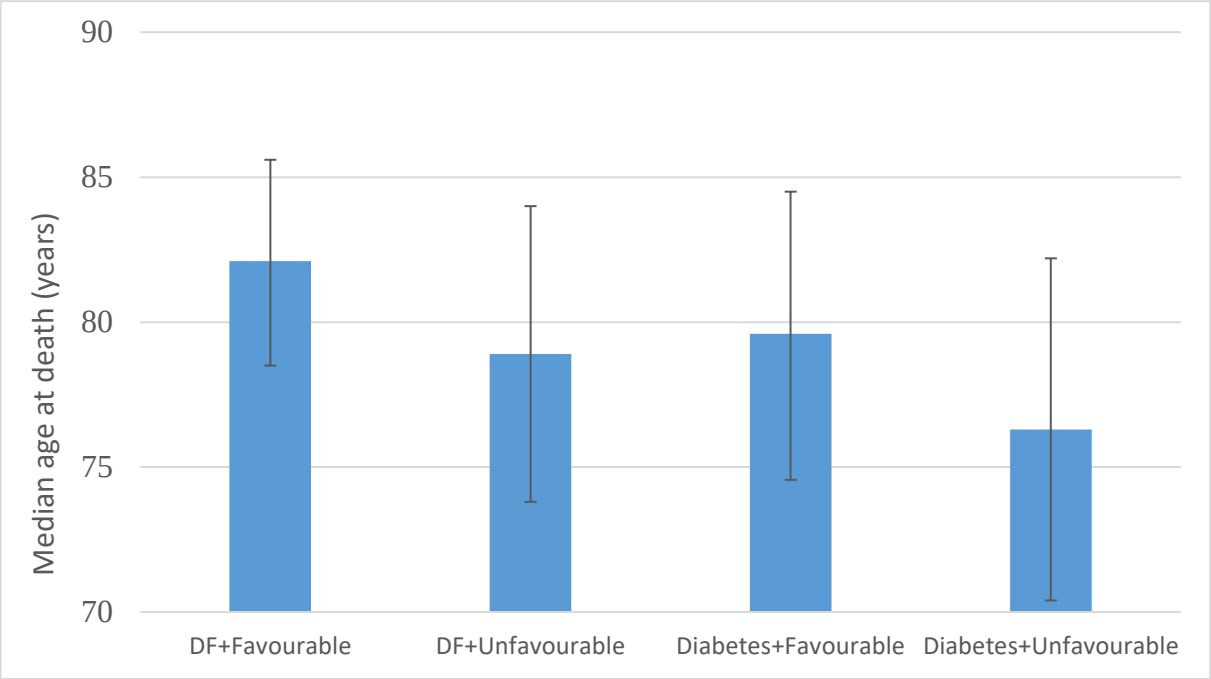


Figure 10. Median age at disability or death according to status of diabetes and favourable profile. Estimates were obtained by fitting multivariable Laplace regression model adjusted for baseline age groups, sex, education, living status, body mass index, cardiovascular diseases, cerebrovascular diseases, depression, and hypertension. "Favourable profile" refers to having the presence of at least one of the healthy behaviours, active engagement in leisure activities, or moderate-to-rich social network. "Unfavourable profile" refers to having none of the factors including healthy lifestyle, active leisure activities, or moderate-to-rich social network. DF: diabetes-free.

5 DISCUSSION

5.1 Summary of the main findings

This doctoral thesis investigated the impact of pre/diabetes on health and survival in older adults and identified the modifiable factors that may attenuate the risk of diabetes to achieve a longer survival with independence. The main findings are summarized as follows:

1) Most older adults with prediabetes remain stable or revert to normoglycemia, whereas only one-third develop diabetes or die during 12-year follow-up. Weight management, preventing heart diseases, and lowering systolic blood pressure may help individuals with prediabetes prevent the progression to diabetes or even return to normoglycemia (*Study I*).
2) Diabetes, but not prediabetes, is associated with an increased risk of ischemic stroke and subsequent dementia, and further accelerates the development of dementia in patients with stroke (*Study II*).
3) Not only diabetes but also prediabetes is related to physical function decline and disability progression over time. These associations can be in part explained by the accumulation of cardiovascular diseases (*Study III*).
4) Diabetes, but not prediabetes, is associated with a higher risk of disability or death. However, a favourable profile including healthy lifestyle behaviours, active engagement in leisure activities, or moderate-to-high social network may attenuate this risk and prolong disability-free survival among older adults with diabetes (*Study IV*).

5.2 Interpretation of the main findings

5.2.1 Reversion and progression of prediabetes

Most studies on reversion and progression of prediabetes have been mainly based on middle-aged populations. A Swedish study of middle-aged adults showed a reversion rate of 36% over 8-10 years (156). In the KORA S4/F4 study, a longitudinal study on adults aged between 55 and 74 years, the reversion rate was 16.3% among those with IGT over 7 years follow-up (20). One recent study from a sub-cohort of KORA S4/F4 (KORA F4/FF4) showed that 27.3% of people with HbA1c-defined prediabetes and 9.2% with glucose-based prediabetes reverted back to normoglycemia over 7 years follow-up (21). In *Study I*, we provided the first evidence describing the prognosis of prediabetes simultaneously in

older population aged ≥60 years. Using HbA1c-defined prediabetes, the reversion rate of 16% in our study was lower compared to the KORA F4/FF4 study. This could be explained by the age difference between the two study populations. Apart from this, the discrepancy in reversion rate among other studies could also be explained by different ascertainment of prediabetes. The incidence rate of diabetes (2.0/100 person-years) from our study was slightly higher than the results from the PAQIUD Epidemiological Survey carried out in the other regions of Europe, which reported an incidence of diabetes ranging from 0.7 to 1.2/100 person-years in people of the same age range with normoglycemia or prediabetes (157). In addition, a higher incidence of diabetes defined either by IGT (5.8/100 person-year) or by IFG (5.2/100 person-year) was reported from the Hoorn Study of a Dutch population aged 55 to 75 years (22). With regard to mortality, we found that 23% of older adults with prediabetes died over the 12-year follow-up. This result was slightly higher than the results reported in two previous studies based on younger populations in Japan (158) and Denmark (159), but is very similar to the 23% mortality rate reported in the Atherosclerosis Risk in Communities (ARIC) Study, which involved older adults aged 66-90 years in the U.S with a median follow-up of 6 years (160). We speculate that older age, higher HbA1c levels, and more comorbidities at baseline in the ARIC and SNAC-K populations could explain the higher mortality rate compared to the other two studies, which enrolled a younger and relatively healthier population.

5.2.2 Pre/diabetes, stroke, and cardiovascular diseases

A large body of evidence demonstrated a higher risk of stroke, in particular ischemic stroke, among people with diabetes (25,115). However, the association between prediabetes and stroke is less clear. In *Study II & III*, we found that diabetes was associated with increased risk of ischemic stroke and a faster accumulation of cardiovascular disease over time. However, we did not observe any significant association between prediabetes and ischemic stroke. The discrepancy might largely lie in the measurement of prediabetes, the inclusion of confounders, and the age differences among study populations. A meta-analysis of 15 prospective cohort studies including 760,925 participants with prediabetes showed apparent conflicting results on the association of prediabetes with stroke when examining different definitions of prediabetes. The authors reported that participants with IGT or combined IGT and IFG were at an increased risk of stroke after adjustment for established cardiovascular risk factors, whereas FPG above the threshold for prediabetes alone did not confer an independent risk for stroke (31). Of note is that a higher IFG cut-off (110-125 mg/dl instead of the conventional 100-125 mg/dl) led to a risk ratio of 1.21 (95% CI 1.02 to 1.44) for stroke. Yet, regardless of definition, IGT is consistently associated with stroke risk. This suggests that stroke risk increases progressively from IFG to IGT and to diabetes, and hyperglycemia per se is related to a continuous, but not proportionally higher risk of stroke. On the other hand, the

relationship between stroke and HbA1c-defined prediabetes has been studied less extensively. In a study within the European Prospective Investigation Into Cancer (EPIC)-Norfolk project including 10,489 diabetes-free adults aged 40-79 years, the RR for stroke was 0.7, 0.8, and 2.8 for those with an HbA1c of 5% to 5.4%, 5.5% to 6.9%, and ≥7%, compared to those with HbA1c< 5% (161), respectively. Meanwhile, Hjalmarsson et al. reported that having an HbA1c >6% was correlated with greater stroke severity (162). Taken together, this evidence suggests that, in the absence of diabetes, there might be a threshold glycemic level at which the risk of stroke is increased.

Given the well-established risk of CVD related to diabetes, we took a different approach to assessing the relation of diabetes to CVD accumulation in *Study III*. We found that both prediabetes and diabetes accelerated the speed of CVD accumulation over time, an issue that had not been previously addressed. Multimorbidity is a common clinical presentation often observed in older adults. Patients with diabetes and comorbid CVD are very likely to progress to greater or more severe comorbidities if effective treatments for CVD are lacking. Interestingly, we also found that prediabetes was related to a faster progression of CVDs over time, suggesting that cardiovascular atherogenesis and inflammation might start at the early stage of insulin resistance before the development of overt diabetes. Future studies are warranted to investigate the association between hyperglycemia and speed of CVD accumulation.

5.2.3 Pre/diabetes, dementia, and physical function

The association between diabetes and dementia has been well-established (15,46,47,163). Most previous studies have examined the independent effect of diabetes on dementia by adjusting for prevalent stroke or investing the combined effect of stroke and diabetes on dementia (46,47). However, scarce evidence on the role of incident stroke in this pathway from diabetes to dementia. Neuroimaging studies have also shown a higher risk of vascular lacunar infarcts in individuals with diabetes. Therefore, a higher risk of vascular dementia after vascular insults associated with diabetes could be expected (164,165). Furthermore, patients with diabetes without cerebrovascular diseases have poorer performance on cognitive tests than their nondiabetic counterparts (166). To the contrary, a previous study showed that diabetes was not associated with cognitive decline after stroke (54). These results suggest both a direct and indirect effect of diabetes on dementia through stroke occurrence. In *Study II*, we found that diabetes was associated with a higher risk of dementia with stroke, but not dementia without prior stroke, indicating that stroke plays an important role in the diabetes-dementia association. This finding is supported by some studies (49,51,167,168), but not by others (52,60). The inconsistent results are possibly due to methodological differences. Most previous studies are hospital-based, where prevalent dementia cases were not reliably excluded. In addition, the definition of post-stroke dementia differs depending on the duration elapsed

from stroke, and different studies focused on early-onset vs. late-onset of dementia. No association of diabetes with post-stroke dementia was observed in early-onset dementia, perhaps due to the compensatory effect of cognitive reserve, or the fact that cognitive function is still recovering (45). In *Study II*, we further excluded participants who developed dementia within 6 months after stroke, and the results were similar. We also confirmed our findings by using the prevalent stroke cohort, where the temporality of stroke and dementia is clear. However, we did not detect a significant association of prediabetes with post-stroke dementia, and this is in agreement with the results from the STROKEOG Collaboration Study among adults with mean age of 66 years, where non-significant differences between IFG and normoglycemia in cognitive domains were shown (169).

To the best of our knowledge, *Study III* was the first to demonstrate that prediabetes was independently associated with a steeper decline in physical function and a faster progression of disability. Existing evidence on the relationship was derived from cross-sectional design, using different measures of physical function, with mixed results (7,85,86). On the other hand, the risk of physical impairment in people with diabetes is well-established (78,95), and data show that older adults with diabetes lose 33% more muscle mass per year than their non-diabetic counterparts (170). In *Study III*, we provided new evidence that both prediabetes and diabetes could accelerate the deterioration of physical function over time. Prediabetes may be related to physical function impairment through a threshold relationship. We reported that prediabetes and diabetes were associated with a faster speed of disability progression. This result is in tandem with others mainly considering diabetes as the exposure (95).

The mediation analysis in *Study III* further showed that CVDs could partially mediate the association between hyperglycemia and physical function decline and disability progression, which is not surprising. The relation between hyperglycemia and physical function impairment might be multifactorial. In addition to the indirect effect of CVDs, hyperglycemia per se might have a distinct direct effect on physical function decline, as was shown in this study. Other medical conditions may also be involved in the pathway linking hyperglycemia and physical function (80). For instance, motor neuropathy (171) and sarcopenia (172) resulting from insulin resistance have been suggested to reduce physical function. Importantly, cognitive impairment resulting from hyperglycemia may interfere with routine diabetic self-management, and impacts daily functionality and dependency (8). Following the result from *Study II*, hyperglycemia could accelerate cognitive decline in the aftermath of cerebrovascular insults, (e.g., stroke), which is also strongly related to physical function decline and disability.

Results from *Study IV* showed that diabetes was associated with a shorter disability-free survival. These results are comparable to several studies investigating disability-free life

expectancy related to diabetes using data from Australia (173), Canada (174) and the United States (17). Furthermore, diabetes-related disability or death might start as early as the prediabetic stage (101). Our results, however, did not support the link between prediabetes and disability or death. Again, this discrepancy might be due to the distinct age distribution of the study population, and different methods of prediabetes ascertainment. Indeed, several studies showed no associations between all-cause death and prediabetes defined solely by HbA1c (101).

5.2.4 Reducing the burden of diabetes

Modifiable factors for prediabetes

In *Study I*, we identified that weight loss, lower systolic blood pressure, and the absence of heart diseases were associated with the normalization of prediabetes. This is consistent with previous findings mostly derived from middle-aged adults (20,175,176). The only past observational study to include older adults, the KORA S4/F4 study, showed that weight loss, but not initial BMI, promoted reversion from prediabetes to normoglycemia (20), and weight loss could contribute to the maintenance of normoglycemia (21). In addition, we found that the association between weight loss and the reversion to normoglycemia was present only among individuals who with overweight/obesity at baseline. This suggests that in addition to bringing benefits to middle aged-adults, lifestyle modification can improve the insulin resistance even among older adults with adiposity (177). Since cardiometabolic syndrome including high blood pressure and hyperglycemia is often observed in older adults, one starts to ponder the possible shared mechanisms underlying this group of disorders. Indeed, hypertension is crucial in the etiology of insulin resistance, and lowering blood pressure is related to improved insulin sensitivity (175), as shown in *Study I*. Current guidelines for the management of diabetes emphasize the importance of managing blood pressure through lowering SBP, based on the evidence from the SPRINT and ACCORD trials (178). It is therefore reasonable to believe that lower SBP can also improve glucose control even at the prediabetic stage. Moreover, insulin resistance is worsened by oxidative stress and vascular endothelial dysfunction induced by atherosclerosis, which is often manifested in the presence of heart disease (179). Hence, the absence of heart disease reflects a low inflammatory environment that could be related to an improved insulin sensitivity over time.

Obesity is associated with the progression to diabetes, and weight gain may also increase the risk of such progression according to results from *Study I*. This is in tandem with prior results from the DPP showing that weight loss was exceptionally effective in preventing diabetes in older adults aged 60-85 years, even more so than treatment with metformin (119). Our results demonstrating an association between physical activity and reduced mortality in prediabetes are consistent with previous findings using pooled data (180).

This protective effect was reduced after additionally adjusting for weight loss during follow-up, suggesting that weight loss in part accounts for the benefit of physical activity.

Taken together, weight management seems to benefit adults with prediabetes, especially for those who with overweight or obesity. Effective weight management is not only related to improved insulin sensitivity, but also reduces long-term risk of mortality. Yet, for individuals with prediabetes and normal weight, impaired insulin secretion might be the main reason for hyperglycemia, and this group usually converts from normoglycemia to diabetes directly, passing through the transient stage of prediabetes very quickly (181). Except for higher prevalence of insulin secretion failure, the prevalence of the other phenotypes, such as insulin resistance, are very low in people with normal weight and prediabetes. Therefore, lifestyle modifications for these people should be tailored according to their clinical profiles, because this feature may represent a different pathophysiology that has not been widely explored. As the prevalence of diabetes is still on the rise, characterizing different phenotypes of prediabetes with respect to its pathogenesis and prediction of disease is necessary for planning prevention efforts to stem the tide of diabetes.

Role of modifiable factors in the diabetes-physical function/disability-survival association

In *Study III*, diabetes-related factors (i.e., high HbA1c, development of CVDs) contributed to the faster decline in functionality and increase in disability severity. In *Study IV*, lifestyle factors (i.e., healthy lifestyle behaviours, active leisure activities, and moderate-to-rich social network) could attenuate the harmfulness of diabetes on disability and survival.

Results from *Study III* fall well within the published measures of the greater risk of physical impairment and disability associated with an elevated HbA1c among patients with diabetes (83,182,183). Kalyani et al. reported that poor glycemic control (HbA1c ≥8%) was related to reduced performance in the walking speed test general physical activities including chair stand, ADL and IADL disability (182). Further adjustment for comorbidities including cardiovascular diseases, could explain up to 85% of the excess odds of physical impairment with diabetes. Our findings confirmed the mediating role of CVDs, but to a lesser extent. One reason for the discrepancy is that Kalyani et al. included additional comorbidities beyond CVD, including diabetic complications such as peripheral neuropathy, visual impairment, chronic kidney diseases, and arthritis, which conceivably would explain more associations between diabetes and physical impairment. Another reason is that we defined uncontrolled diabetes with a cut-off of 7.5% due to better levels of glycemic control in the SNAC-K population (mean HbA1c of 6.9% in SNAC-K vs. 7.1% in the U.S. study; HbA1c of 7.9% for users of oral agents plus insulin in SNAC-K vs. 13.8% in the U.S study). Therefore, our study population had a lower burden of CVD compared to others (40.4% CVD in SNAC-K vs. >71% CVD in the U.S study). The small sample of people

with HbA1c ≥8.0% in SNAC-K limits our ability to further investigate the de facto relationship of HbA1c with functionality, as a U-shape relationship was proposed with no association of functional decline with HbA1c over 9% (183). HbA1c levels that are either too low or too high show more harm than benefit in older adults, and a stable level of glycemic control within the range of 6-8% may be more beneficial than intensive glycemic control (184). Besides, we found that uncontrolled diabetes was related to a faster accumulation of CVD over time, suggesting that controlling diabetes might slow down the CVD development. In addition, clinical trials demonstrating cardiovascular benefits for antidiabetic medication such as SGLT-2 inhibitors and GLP-1 receptor agonists on reducing risk of CVD in patients with diabetes and established CVD or multiple CVD risk factors (185,186). These intriguing results underscore that beyond lowering glucose level, SGLT-2 inhibitors and GLP-1 receptors agonists may have additional cardiovascular benefits for people with diabetes.

Diabetic complications can be delayed or prevented by managing the risk factors which are strongly related to blood vessel impairment. In addition to glucose management, effective treatment for hypertension and hypercholesterolemia with statins at the same time are also important to consider for future CVD risk. Lifestyle modifications such as smoking cessation and becoming more physically active also add to the benefits to CVD health.

Indeed, numerous studies have consistently observed a protective effect of lifestyle factors including smoking cessation, moderate alcohol consumption, and physical activity (individually or collectively) on major chronic diseases (187), dementia (46), disability (188), and mortality (189,190). Our findings from *Study IV* indicated a protective effect of lifestyle factors in combination on the composite endpoint of disability and mortality, and this is in line with previous population studies conducted in Japan (188) and Sweden (111). In particular, we demonstrated the beneficial effect of a moderate-to-rich social network on disability-free survival among people with diabetes, meaning that a socially integrated life is important in old age for people with diabetes. The long-term health outcomes associated with social network have not been fully addressed in the diabetes population. A few epidemiological studies have examined the association of social support with excess mortality and diabetes-related complications, with mixed results (132–135). These inconsistent results might be related to the choice of social well-being constructs (e.g., network size, type of support), cultural differences, or the investigated outcomes. A large discrepancy between perceived and received social support has been found in mortality prediction (191). In our study, we operationalized more refined domains that discriminate between the type of social support received and an individual's subjective perceptions of social connection. As individuals with rich social networks tend to have healthy behaviours and more frequent participation in leisure activities, we observed a

greater effect of these factors in combination on prolonged disability-free survival among diabetes patients in *Study IV*. However, interventional studies on disability or mortality among people with diabetes mostly focus on physical activity, neglecting the social components. Given that both lifestyle and social network are modifiable and amenable to interventions, our study highlights the need for integrating social components in lifestyle modifications when designing future interventions for people with diabetes.

5.2.5 Variations by sex and age

Sex appears to have an impact on the occurrence and prognosis of diabetes. In SNAC-K, there were more men than women with diabetes at baseline. This was on par with the national-wide estimates of a sex difference in diabetes prevalence in 2013 in Swedish adult populations born between 1937-1979 (5.2% in men vs. 3.2% in women) (192). This study also reported a higher incidence of diabetes in men than in women, as observed in our study (*Study I*). Regarding macrovascular complications, we found that women had a lower risk of stroke (*Study II*) and slower accumulation of cardiovascular diseases (*Study III*) than men, which falls well within the range of published evidence (193,194). Compared to men, women suffering from ischemic heart disease are older, and this may result from the protection of endogenous estrogens prior to the onset of menopause (195). However, the occurrence of diabetes may negate this beneficial biology in women. In *Study II* and *Study III*, we found that the risks of stroke and CVDs did not significantly differ between women with diabetes and men with diabetes. This is supported by a systematic review demonstrating that women with diabetes had a higher risk of stroke than men with diabetes (193), and women with diabetes have an especially higher risk of cardiovascular complications (64). A similar pattern was observed for adverse outcomes that come after complications, where women with diabetes experienced a higher risk of post-stroke dementia. However, these estimates were not statistically significant due to limited sample size. It is noteworthy that while women have a lower mortality rate than men, diabetes appears to offset this benefit, as no difference in mortality was observed for women and men with diabetes (*Study IV*). Taken together, it seems that relative to men, women have fewer cases of diabetes but once the disease is established, it predisposes women to a greater risk of complications and a worse prognosis.

The underlying mechanisms may involve both biological and social components in terms of cardiovascular risk burden, hormonal imbalance, adoption of lifestyle modification, and utilization of treatments. Marjan et al. provided possible explanations for the sex variations in diabetes, arguing that primary prevention strategies with lifestyle modification targeting cardiovascular burden were more frequent in women than in men, leading to a lower prevalence and incidence of diabetes in women (196). But the contrary is seen in secondary preventive strategies including diseases investigation and treatments. Women are more likely to have undertreated diabetes and are less likely to

manage their HbA1c to a target level (197). There is also a sex difference in the response to treatment, such that women are less likely than men to receive evidence-based treatment for ischemic heart disease (198) or acute myocardial infarction (199,200). Women with diabetes are more likely to adopt healthy behaviours that are beneficial for survival, but in the meantime they are more likely to have worse prognosis of diabetes. Therefore, the overall risk of mortality did not differ between men and in women in *Study IV*.

It is important to appreciate that diabetes in late life can span four decades, ranging from robust individuals still participating in the workforce to frail people living in nursing homes. The impact of diabetes on physical function and disability can be heterogeneous by age groups. We observed that the association of prediabetes or diabetes with physical decline and disability progression was stronger in younger age groups (60-78 years), but not in older age groups (≥78 years), as was the case in many studies (83,107). This might be due to the survival bias, as those who survive beyond 78 years old at baseline are otherwise healthier. Furthermore, the "adaption" theory might also provide an explanation for this age variation (201). As an individual ages, blood supply is tailored to compensate by distal autoregulatory dilation (201). While younger old adults are still going through the adaption process, older adults are already adapted to limited blood supply therefore physical function is not much affected.

Another point we want to raise is that age at diabetes diagnosis appears to play an important role in the prognosis of diabetes. In SNAC-K, among all diabetes cases (n=411) during the study period, 71% (n=292) had been diagnosed with diabetes prior to the baseline examination. In *Study II & Study IV*, indeed the stronger association of stroke, post-stroke dementia, and higher mortality was observed in individuals with diabetes diagnosed before or at baseline, rather than in those who developed diabetes during follow-up. This is on par with a nationwide study in Sweden showing that age at diabetes diagnosis is prognostically important for survival and CVD risk. The risk for CVD and mortality attenuated progressively with each increasing decade at diagnostic age, whereas diagnosing diabetes at age >80 was not associated with overall mortality, CVD mortality, and non-CVD mortality (70). Our results, together with the findings from the ARIC study, suggest that when considering hyperglycemic status in older age, only adults with a long duration of diabetes have a significantly elevated risk of mortality.

5.3 Biological mechanisms

Several mechanisms may explain the associations between hyperglycemia with macrovascular diseases including stroke and CVDs. Chronic hyperglycemia induced by insulin resistance produces excessive advanced glycation end products (AGEs), which promotes oxidative stress and inflammation, damaging endothelial function (202).

Endothelial dysfunction is an early marker of atherosclerosis, which predisposes for cerebral or myocardial infarcts and manifests as ischemic stroke or cardiovascular diseases. The accumulation of AGEs can increase arterial stiffness and permeability, which accelerate the aging of the cardiovascular system. In the brain, stroke could further exacerbate these adverse effects by increasing the brain's susceptibility to neurological insults via hypoperfusion and/or disruption of the blood-brain-barrier (15). Alongside the vascular lesions caused by the atherogeneric process, excessive glucose is suggested to have a direct toxic effect on functional and structural abnormalities in the brain with atrophy and white-matter changes (168). What's more, the alteration in insulin receptors in the brain and glucose homeostasis by AGEs could also affect amyloid deposition. All these might contribute to the mechanisms linking diabetes, stroke, and dementia.

Apart from the atherosclerosis pathway, hyperglycemia can damage the heart through cardiomyopathy and/or cardiovascular autonomic neuropathy. Due to impaired glucose utilization, the heart accordingly relies on free fatty acids for energy. Excessive free fatty acid oxidation might lead to energy abnormalities that give rises to systolic and diastolic dysfunction and changes in coronary heart flow, manifesting as contractile dysfunction and eventually cardiomyocyte apoptosis (61). Chronic hyperglycemia can damage autonomic nerves that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics including tachycardia (203). In addition to large blood vessels, chronic hyperglycemia contributes to small bloods vessel damage (e.g., retinopathy) and nerve damage in other part of body (e.g., neuropathy). The diminished heart capacity and concomitant decrease in peripheral insulin sensitivity associated with aging are also believed underlie the deterioration in physical function in older age. Lower cardiovascular fitness impacts the oxygen supply to several tissues (e.g., muscle) (204). Furthermore, hyperglycemia damages muscle tissue and is associated with sarcopenia (205). Peripheral neuropathy impairs skeletal muscles and gives rise to muscle atrophy, leading to physical function decline over time (206).

The mechanism underlying the benefits of a healthy lifestyle and rich social network are not completely understood. Healthy lifestyle and better social support have been linked to improvements in cardiovascular, immune, endocrine, and pulmonary function, possibly through reduced inflammation and higher serum antioxidant levels (207). The benefits of these combined factors might lead to a reduction in cardiovascular diseases, and sarcopenia that play a major role in the pathology of disability.

5.4 Methodological considerations

The overall goal of an epidemiological study is to obtain a valid and precise estimate of the frequency and distribution of a disease in the source of population (208). It can be viewed as an exercise of measurement, where accuracy is of vital importance. Errors in estimation

can be classified as random and systematic errors, the latter of which is often referred as bias. The opposite of random error and systematic error are referred as precision and validity, which are the components of accuracy. Validity is usually separated into two parts: internal validity and external validity. Inference of internal validity pertains to the members of source population while external validity pertains to people outside the source population.

5.4.1 Random error

Random error includes sampling and measurements errors. Sampling error occurs when the sample does not represent the population, and leads to large standard error and therefore low-precision estimates. Sampling error can be reduced by a random sampling strategy and by increasing the sample size to mirror the wider population as much as possible. Measurement error arises from variation in measurements and can be minimized by repeating the measurements and averaging the estimates. Random error can lead to systematic error in the final estimates.

5.4.2 Interval validity (Systematic error)

Internal validity can be classified in three general categories: selection bias, confounding, and information bias.

Selection bias

Selection bias occurs when the procedure to select participation is influenced by the exposure and the outcome. The relation between exposure and outcome is different for those who take part in the study and for all those who should have been eligible for the study. Selection bias is conditional on participation, therefore the inference drawn from the participants reflects the forces that determine the participation, rather than from the population of interest. Selection bias can occur before subjects are identified for the study (e.g., healthy-worker effect) and during the follow-up period (e.g., attrition).

In SNAC-K, out of 4590 eligible individuals, 1227 (participation rate 73%) declined to participate in the baseline examination. Even though we did not know the reasons for the refusal, these individuals were more likely to die within the 2 years than the people who agreed to participate in the study (209). This meaning that those who were healthier were more willing to participate to the study, a phenomenon known as the “healthy-worker effect.” The self-selection of participants due to health status might have led to an underestimation of the effect of exposure on the outcomes.

Selection bias can also come from the missing values, which are related to a problem of differential loss to follow-up due to non-response (dropouts) and/or death. In this thesis, the influence of dropouts or attrition on the estimates varied between studies. For example, in *Study I*, those who completed the follow-ups were generally younger and more educated, and less likely to have vascular diseases than those lost to follow-up. However, the probability of participating in the follow-up examination was not associated

with HbA1c level. Hence, selection bias might not have substantially affect the estimates of prediabetes reversion or progression. However, selection bias might have influenced the estimates of prognostic factors, as those who participated in the study were less likely to have vascular risk factors. This may have led to an underestimation of the association.

We used multiple imputation to understand how dropout would have affected our estimates in *Study I & IV*, and the results were similar to those from the initial analysis. When it comes to death, we found that individuals who survived until the end of follow-up were otherwise healthy compared to those who died during follow-up. This could have led to an underestimation of the association. In *Studies I and IV*, death was an outcome of interest. In *Study II*, we accounted for death by using flexible parametric models accounting for the competing risk of death and provided the cumulative incidence function for the outcomes together with mortality data. In *Study III*, missing data points were managed in the mixed models. However, these models assumed that data was missing at random, which may not have been the case. In order to assess how attrition influenced the results, we conducted a sensitivity analysis that included only participants who completed all follow-ups. This analysis showed slightly weaker associations than those from the initial analysis, as would be expected.

Confounding

Confounding is the confusion or the mixture of extraneous effects with the effect of the exposure. For a variable to be a confounder, three criteria should be fulfilled: 1) a confounder should be a risk factor for the outcome; 2) a confounder should be associated with the exposure under the population at risk from which the outcomes were derived; and 3) a confounder must not be an intermediate step in the causal pathway between the exposure and outcome. Confounding could mask a true association or falsely indicate that an association exists between the exposure and outcome. Confounding can never be completely ruled out (residual confounding) in observational studies, but confounding can be minimized by collecting adequate information from study participants and using stratification, adjustment, or matching in data analysis. Through our studies, we addressed major known confounders by multi-adjustment (e.g., demographic, vascular risk factors).

In *Study III,* we performed mediation analysis to explore whether the faster decline in physical function associated with prediabetes and diabetes can be explained by CVD accumulation. As mentioned in **Figure 4**, four assumptions need to be fulfilled in order to calculate a direct or indirect effect: 1) no unmeasured exposure-mediator confounders given U1; 2) no unmeasured mediator-outcome confounders given U2; 3) no unmeasured exposure-outcome confounders given U3; and 4) no mediator-outcome confounder U2 affected by exposure A. Assumptions 1 and 3 are likely to hold because we adjusted for a range of baseline variables including sociodemographic factors, lifestyle factors, and comorbidities. Assumption 2 is also likely to hold since we attempted to include most suggested confounders in the association between CVDs and physical function decline

(e.g., peripheral neuropathy, living alone, cerebrovascular diseases, and depression and mood disorders). It is assumed that no mediator-outcome is influenced by the exposure (Assumption 4), but it is difficult to assess whether this assumption is violated.

Information bias

Information bias can result from either imprecise definition of variables of interest or flawed data collection (210). These errors lead to misclassification of exposures, outcomes, or covariates, where the misclassification can either be non-differential or differential. Non-differential misclassification occurs when the variables of interest have the same probability of being misclassified and are not related to other variables. In most scenarios, non-differential misclassification will produce bias towards the null. On the other hand, differential misclassification occurs when the variables of interest have a different probability of being misclassified depending on other variables (e.g., health status), which can either exaggerate or underestimate an effect. For example, recall bias is a form of differential misclassification that is heavily reliant on social preferences and subjects' memories. In *Study IV*, people with diabetes may have been more likely to exaggerate their desirable lifestyle behaviours than those who did not have diabetes, therefore giving rise to an underestimation of the association between lifestyle and diabetes.

Ascertainment of exposure. In SNAC-K, normoglycemia and prediabetes are defined by HbA1c. Non-differential misclassification could have occurred due to the diagnostic capacity of HbA1c. The overlap between HbA1c, OGTT, and FPG is limited, as these entities represent different phenotypes of prediabetes with respect to its pathogenesis and prediction of the disease (181), thereby arriving at somewhat discrepant results regarding the prognosis of prediabetes. IFG appears to be driven by insulin secretion and an increase in hepatic glucose production, whereas IGT seems to be more related to postprandial whole-body insulin sensitivity and the later stages of impaired insulin secretion. Although IFG and IGT, together with higher HbA1c, are characterized as hyperglycemia, HbA1c does not capture this diversity in pathogenesis (181). Most studies comparing the diagnostic capacity of HbA1c testing with OGTT have demonstrated that HbA1c less sensitive in detecting prediabetes and diabetes. It follows that in our study, we did not find any significant association between prediabetes and stroke. This may have been because some cases of prediabetes were misclassified as normoglycemia. However, one might question the use of OGTT the gold standard for pre/diabetes diagnosis on the grounds that the DETECT-2 collaboration pooled data across several ethnicities and age ranges and demonstrated that HbA1c in fact more sensitive than OGTT for the detection of retinopathy (211). HbA1c has several advantages over OGTT and FPG tests that make it a more pragmatic and feasible option for use at a mass scale (such as for screening). HbA1c has a far higher reproducibility than OGTT, a better pre-analytical stability, and, because it

reflects average glycemic level over the past 3 months, is relatively unaffected by acute perturbations such as stress or recent illness. Notably, the HbA1c test has no fasting requirement and can be taken at any time of day, making it very feasible for the older population. Despite these advantages, it is important to note that HbA1c is influenced not only by glycemia but also some other factors that influence erythrocyte turnover rates (e.g., malaria, hemoglobinpathy, anemia) (212). Therefore, HbA1c values can be misleading among individuals with such conditions. We repeated the analysis after excluding people with anemia, and the results remained largely unchanged. It is worth mentioning that in addition to HbA1c, the diagnosis of diabetes in SNAC-K was complemented by information on antidiabetic medication use, medical records, and medication examinations, which reduced the possibility of misclassification to a large extent.

Ascertainment of outcome. The potential misclassification of the outcomes in this doctoral thesis is more likely to be non-differential, given that a standardized procedure and multiple sources were used to identify the outcomes (e.g., stroke, dementia, CVD, physical function). Some cases of CVD (e.g., atrial fibrillation) that were asymptomatic were partially identified from the medication containers that participants brought to the study visits. Differential misclassification might arise if participants with cognitive impairment forgot to bring their medications, as those with hyperglycemia were more likely to have cognitive impairment. This is also the case with respect to self-reported disability, as those who were not cognitively intact may have reported inaccurate information on their level of disability, potentially leading a distortion of the association between diabetes and disability. In order to minimize information bias, a proxy of cognitive impaired participants was always consulted and physicians and nurses reviewed the medical charts carefully. Moreover, in *Studies III & IV,* where the potential differential misclassification might incur, we repeated the analyses after excluding those with MMSE ≤24 (in *Study III)* and MMSE≤ 27 (in *Study IV*) or those who developed dementia at first follow-up, and the results were not materially changed compared to those in the initial analyses.

Ascertainment of confounding. Confounding could be misclassified, which might hamper the ability to control confounding in the analysis. This problem can be viewed as an issue of residual confounding. If the degree of residual confounding left within strata differs across strata, the association might be biased toward the null hypothesis.

5.4.3 External validity (Generalizability)

External validity evaluates whether the conclusions of a study can be extended outside the source population. The SNAC-K population is derived from a central urban area in Stockholm, Sweden, where residents are generally healthier and wealthier than the national average. Thus, caution is needed when comparing the results to other

populations with lower socio-economic status or countries with different healthcare systems. However, the investigation of an association between an exposure and outcome should be driven by the biological plausibility instead of relying on the representativeness of a study sample. Even though the observed estimates from the SNAC-K population might be underestimated compared to other populations with a higher burden of risk factors or lower socio-economic status, this does not detract from the biological plausibility of the findings. Therefore, beyond the representativeness of the sample, it is also important to consider the plausibility of the biological mechanisms and the proper handling of bias when considering the generalizability of these findings to other populations.

6 CONCLUSIONS

Based on the findings from the four studies, the following conclusions can be drawn from this doctoral thesis:

1) Older adults with prediabetes can revert to normoglycemia, and weight change is a prognostic factor associated with both reversion and progression of prediabetes in older adults. Other vascular factors including lower blood pressure and the absence of heart disease also promote reversion to normoglycemia.

2) Diabetes, but not prediabetes, is related to an increased risk of stroke. Diabetes can accelerate the development of dementia after stroke occurrence.

3) Not only diabetes but prediabetes is associated with physical functional decline and disability progression over time, and these associations can be partly mediated by the development of cardiovascular diseases.

4) Diabetes, but not prediabetes, is associated with a higher risk of disability and death. Healthy behaviours, active participation in leisure activities, and/or moderate-to-rich social network attenuates the risk of diabetes on disability and death and prolongs disability-free survival among people with diabetes by 3 years.

7 IMPLICATIONS

Reducing the burden of diabetes has largely relied on the classical three stages of prevention in epidemiology (primary, secondary, and tertiary). Identifying factors that can lessen the burden of diabetes on health and carefully implement effective strategies in each stage is imperative. Primary prevention aims to intervene before the occurrence of diabetes, through alterations in behaviours known to be associated with hyperglycemia (213). Secondary prevention seeks to identify individuals with a higher risk of diabetes through screening, before the onset of symptoms of diabetes (214). Finally, tertiary prevention focuses on diabetes management to slow or arrest the development of diabetes-related complications (e.g., cardiovascular and renal disease) and consequences (e.g., disability, premature death), through treatments or behaviour modifications (215). In this thesis, we touched upon all three stages of prevention and provide evidence on preventative strategies, with the hope of reducing the burden of diabetes in older age.

The first study detailing the natural history of prediabetes helped us understand different stages of prediabetes. By investigating the prognostic factors related to each stage, we revealed different components regarding pathological process and provided knowledge that supports early interventions to change the course of prediabetes and prevent its progression to overt diabetes.

Beyond studying the evolution of prediabetes, we investigated the impact of pre/diabetes on diabetes-related complications and distal outcomes in older adults. We concluded that prediabetes may not trigger the onset of macrovascular disease per se, it appears to facilitate its progression once CVD is already established, further worsening functionality over time. As older adults often present complex health patterns and multimorbidity, these findings underscore the need for regular check-ups for cardiovascular health and monitoring of functionality for older adults with prediabetes. In addition, diabetes accelerates the progression to morbidity and mobility secondary to complications; this is especially pronounced among participants with uncontrolled diabetes. These results suggest that diabetes could have an impact on cognitive and physical function in the aftermath of the occurrence of complications. Maintaining appropriate glucose control is therefore essential for people with diabetes as they reach old age.

Finally, we concluded that maintaining a healthy lifestyle, active participation in leisure activities, and/or having moderate-to-rich social network are important components of diabetes care in older age, as in the earlier phases of life. Together with the findings from *Study I*, our findings provide evidence on the important role of behavioural and social components in the process of successful aging related to hyperglycemia, which might be useful for targeted interventions that promote the adoptions of healthy choices in order to reduce diabetes burden among older adults.

8 FUTURE PERSPECTIVE

Despite the existing strategies to prevent diabetes, this disease is still on the rise. One begins to query whether the identification and treatment of diabetes is sufficient to stem the diabetes tide. Recent studies have proposed different phenotypes of prediabetes and subgroups of diabetes (181,216), with the hope of identifying individuals with different pathologies and tailoring early treatment to patients who would benefit most. People with atypical phenotypes, such as "metabolically healthy obesity" or "lean diabetes", are quite common, and they may benefit less from lifestyle modifications aimed at weight loss. Changes in body composition, a marked decrease in insulin resistance and β cell function, and negative effects of glucose intolerance induced by comorbid diseases associated with aging add complexity to the issue of preventing diabetes in older adults. Therefore, age-specific criteria for the diagnosis of prediabetes and diabetes and the identification of clinical subgroups among older adults might be helpful to guide treatment decisions and implement effective preventative strategies.

This thesis does not broadly touch upon the management of hypertension and dyslipidemia in older adults with diabetes. These three conditions often cluster together and pose a substantial risk of cardiovascular disease. Further investigation is warranted to identify optimal treatment regimens for older adults falling into different metabolic profiles. Indeed, it is not straightforward to manage diabetes in older adults given that they commonly have multiple coexisting medical conditions that complicate the management of diabetes. Lack of evidence makes it somewhat difficult to provide concrete guidelines for clinicians. Older adults with diabetes require an individualized approach to care, but so far we do not have a reliable classification to identify subgroups that are clinically distinct. The type and severity of comorbidities are likely to matter more than an overall count. Common geriatric syndromes including frailty and sarcopenia should be considered when classifying patients. Beyond improving patient classification, further studies are needed to investigate the appropriate glycemic targets and optimal selection of drugs for each class of patients. First-level evidence from clinical trials of older adults with diabetes with/without comorbidities investigating functional outcomes such as disability, cognitive function, frailty, and quality of life are warranted.

We notice that there might be distinct pathology and clinical manifestations for individuals who have lived with diabetes since early age and those newly diagnosed in old age. The negative effect of chronic hyperglycemia could accumulate over time, posing a greater health burden for those with a longer diabetes duration. It is therefore important to prevent diabetes and its complications in younger age. Work-related stress such as bullying at work is an important area to explore further with regard to the progression of diabetes and the development of diabetes-related complications. Moreover, in this thesis we did not investigate the effectiveness of diabetic medications on health in general. It is

still unclear how the effectiveness of different treatment modalities may differ by age and health profiles, wherein hypoglycemic episode resulting from overtreatment could theoretically pose a huge impact on health. A life course approach with granular data may help to untangle these aspects.

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11 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2020

1991

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

1992

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

1993

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

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

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

1994

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

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

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

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

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

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

1996

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

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

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

1997

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

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

1998

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

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

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

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

1999

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

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

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

2000

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

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

2001

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

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

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

2002

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

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

2003

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

2004

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

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

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

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

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

2005

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

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

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

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

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

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

2006

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

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

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

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

2007

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

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

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

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

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

2008

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

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

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

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

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

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

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

2009

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

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

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

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

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

2010

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

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

2011

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

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

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

2012

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

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

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

2013

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

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

2014

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

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

2015

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

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

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

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

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

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

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

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

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

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

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.

Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

Morin Lucas. Too much, too late? Drug prescribing for older people near the end of life.

de Boer Lieke. Dopamine, decision-making, and aging: Neural and behavioural correlates.

Ek Stina. Predictors and consequences of injurious falls among older adults: A holistic Approach.

Ding Mozhu. The role of atrial fibrillation in cognitive aging: a population-based study

2020

Dintica Cristina Silvia. Oral health & olfactory function: what can they tell us about cognitive ageing?

Payton Nicola Maria. Understanding preclinical dementia: early detection of dementia through cognitive and biological markers.

Li Xin. The relation among aging, dopamine-regulating genes, and neurocognition.

Grande Giulia. Development of dementia in older adults: the body-mind connection.