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DIABETES MELLITUS AND THE RISK OF DEMENTIA

A Population-based Study

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To my parents

ABSTRACT

ENGLISH

This doctoral thesis investigated the complex relationship between diabetes and the risk of dementia, Alzheimer's disease (AD) and vascular dementia (VaD), and examined the effect of borderline diabetes on the risk of dementia and AD. The data of this thesis were derived from the Kungsholmen Project (*Studies I, II, and III*) and from the HARMONY Study (*Study IV*). The Kungsholmen Project is a community-based prospective study on aging and dementia in people aged ≥ 75 years in Stockholm, Sweden. The HARMONY Study is a study on dementia in a population-based Swedish twin cohort aged ≥ 65 years. The major findings are summarized below.

Study I. The relationship between diabetes and dementia, AD and VaD was investigated using 6-year follow-up data. Diabetes was associated with hazard ratios (HRs) of 1.5 (95% CI, 1.0-2.1) for dementia, 2.6 (95% CI, 1.2-6.1) for VaD, and 1.3 (95% CI, 0.9-2.1) for AD after adjustment for vascular disease and other potential confounders. There were joint effects of diabetes and severe systolic hypertension (SBP ≥ 180 mm Hg) on AD and VaD, and of diabetes and heart disease on VaD.

Study II. The hypothesis that borderline diabetes may increase the risk of dementia and AD was verified using 9-year follow-up data. Borderline diabetes (random blood glucose: 7.8-11.0 mmol/l) was associated with an increased risk of dementia (HR 1.7; 95% CI, 1.0-2.7) and AD (HR 1.8; 95% CI, 1.1-2.9); the risk effect was independent of vascular disease and future development of diabetes. Borderline diabetes may interact with severe systolic hypertension to multiply the risk of AD.

Study III. The relation of diabetes to AD was clarified by examining the role of glycemic control and vascular comorbidities. Diabetes in general was only related to VaD (HR 3.2; 95% CI, 1.2-8.6), but undiagnosed diabetes led to HRs of 3.4 (95% CI, 1.5-7.7) for dementia, and 3.3 (95% CI, 1.2-9.0) for AD. Borderline and undiagnosed diabetes were further related to pure AD. Diabetic patients with random blood glucose level < 11.0 mmol/l showed no increased dementia risk.

Study IV. The association between diabetes and an increased risk of dementia, AD and VaD was confirmed in twins. Diabetes was associated with adjusted ORs (odds ratios) of 1.9 (95% CI, 1.5-2.4) for dementia, 1.7 (95% CI, 1.2-2.4) for AD, and 2.2 (95% CI, 1.4-3.5) for VaD. The risk effect was stronger in patients with diabetes onset at midlife than in patients with diabetes onset in late life. Paired analysis showed that genetic and environmental factors in early life might account for the association between late life diabetes and dementia, but could not explain the midlife diabetes-dementia association.

Conclusions. Diabetes increases the risk of dementia, AD and VaD in the elderly. The risk of dementia is very high when diabetes occurs together with severe systolic hypertension and heart disease. Even borderline diabetes is associated with an increased risk of dementia and AD. The risk of dementia is stronger when diabetes occurs in midlife rather than late life. However, good control of blood glucose may reduce the risk of dementia due to diabetes. These findings support the growing evidence of a link between glucose dysregulation and vascular damage and neurodegenerative changes in the brain. Finally, genetic and early life environmental factors, and adulthood environments may be implicated in the development of the diabetes-dementia association.

Key words: diabetes, borderline diabetes, dementia, Alzheimer's disease, vascular dementia, blood glucose, vascular comorbidities, prospective study, population-based twin study

SAMMANFATTNING

SVENSKA

Denna avhandling studerade det komplexa sambandet mellan diabetes och risken för demens, Alzheimers sjukdom (AS) och vaskulär demens (VD). Dessutom undersöktes effekten av "borderline" diabetes för risken att drabbas av demens och AS. Data från två olika studiepopulationer användes: Kungsholmsprojektet (*Studie I, II och III*) och HARMONY (*Studie IV*). Kungsholmsprojektet är en longitudinell befolkningsbaserad studie om åldrande och demens hos personer ≥ 75 år och boende i Stockholm. HARMONY är en svensk populationsbaserad studie av tvillingar, 65+ år. De huvudsakliga resultaten sammanfattas nedan.

Studie I. Sambandet mellan diabetes och demens, AS och VD undersöktes med data insamlat med 6 års intervall. Diabetes ökade risken (hazard ratios, HRs) för demens med 1,5 (95% KI 1,0-2,1), för AS med 1,3 (95% KI 0,9-2,1) och för VD med 2,6 (95% KI 1,2-6,1). Diabetes och svår systolisk hypertoni (SBT ≥ 180 mm Hg) uppvisade en additiv effekt för AS och VD, medan Diabetes och hjärtsjukdom uppvisade en additiv effekt för VD.

Studie II. Under en nio års uppföljning bekräftades hypotesen att borderline diabetes kan öka risken för demens och AS. Borderline diabetes (blodsocker vid stickprov: 7,8-11,0 mmol/l) var kopplat till en ökad risk för demens (HR 1,7; 95% KI 1,0-2,7) och AS (HR 1,8; 95% KI 1,1-2,9). Den förhöjda risken var oberoende av vaskulära faktorer och presumtiv insjuknande i diabetes.

Studie III. Relationen mellan borderline diabetes och diabetes med AS klargjordes genom att undersöka vikten av blodsockerkontroll och vaskulär samsjuklighet. Generellt var diabetes enbart relaterat till VD (HR 3,2; 1,2-8,6) medan odiagnostiserad diabetes gav ett HR på 3,4 (95% KI 1,5-7,7) för demens och 3,3 (95% KI 1,2-9,0) för AS. Vidare var borderline och odiagnostiserad diabetes relaterade till äkta AS. Diabetespatienter med ett icke fastande blodsockervärde på $< 11,0$ mmol/l visade ingen förhöjd risk för demens.

Studie IV. Sambandet mellan diabetes och en ökad risk för demens, AS och VD bekräftades hos tvillingar. Diabetes var korrelerat till demens, justerad oddskvot (aOR) 1,9 (95% KI 1,5-2,4); till AS med aOR 1,7 (95% KI 1,2-2,4); och till VD med aOR 2,2 (95% KI 1,4-3,5). Risken var högre för patienter med diabetes som debuterat i medelåldern jämfört med patienter med diabetesdebut sent i livet. Analys av tvillingparen visade att miljöfaktorer i barndomen kan ha samband med åldersdiabetes och demens, men det kunde inte förklara sambandet mellan diabetesdebut i medelåldern och demens.

Slutsatser. Diabetes ökar risken för demens, AS och VD hos äldre personer. Risken för demens är mycket hög då diabetes förekommer tillsammans med svår systolisk hypertoni och hjärtsjukdom. Det finns även ett samband mellan borderline diabetes och ökad risk för demens och AS. Risken för demens är större om diabetes debuterar i medelåldern jämfört med debut sent i livet. En effektiv kontroll av blodsockret kan dock minska risken för demens pga diabetes. Våra resultat stöder det ökande antalet studier som visar på ett samband mellan nedsatt funktion av glukosreglering och vaskulär skada och neurodegenerativa förändringar i hjärnan. Slutligen, genetiska faktorer, miljöfaktorer i unga år och miljön under vuxenlivet är faktorer som kan behöva inkluderas i arbetet med att förstå sambandet mellan diabetes och demens.

Nyckel ord: diabetes, borderline diabetes, demens, Alzheimers sjukdom, vaskulär demens, blodsocker, vaskulär samsjuklighet, longitudinell studie, populationsbaserad, tvillingstudie

“糖尿病与老年痴呆的关系：一项以人群为基础的研究” – 该博士论文探讨了糖尿病和临界糖尿病与老年痴呆、阿尔茨海默病 (AD) 以及血管性痴呆 (VaD) 之间的关系。该论文的数据来自于瑞典的 Kungsholmen 研究项目 (研究 I、II、III) 和 HARMONY 研究 (研究 IV)。前者是在瑞典斯德哥尔摩市中心地区进行的一项社区人群老年痴呆的前瞻性研究 (年龄 ≥ 75 岁)；后者是在瑞典全国双生子人群中进行的关于老年痴呆的研究 (年龄 ≥ 65 岁)。这一系列研究的主要发现和结论概括如下：

研究 I：研究了糖尿病与老年痴呆、AD 以及与 VaD 之间的关系。研究发现在控制了血管性疾病和可能的混杂因素后，糖尿病与老年痴呆、AD 及 VaD 关系的相对危险度 (HR) 分别是 1.5 (95% CI, 1.0-2.1)；1.3 (95% CI, 0.9-2.1)；和 2.6 (95% CI, 1.2-6.1)。结果还显示，糖尿病与严重的收缩性高血压 (SBP ≥ 180 mm Hg) 或与心脏病对老年痴呆、AD 和 VaD 发病的危险性具有联合作用。

研究 II：验证了临界糖尿病 (随机血糖水平介于 7.8-11.0 mmol/l 之间) 可增加老年痴呆和 AD 发病危险性这一假设。结果显示，临界糖尿病可增加老年痴呆 (HR 1.7; 95% CI, 1.0-2.7) 和 AD (HR 1.8; 95% CI, 1.1-2.9) 的发病危险性；该危险效应独立于血管性疾病和临界糖尿病随后发展为糖尿病的作用，临界糖尿病与严重的收缩性高血压对 AD 的发病危险性具有交互作用。

研究 III：通过按血糖水平和血管性疾病的分层分析，进一步澄清了糖尿病和临界糖尿病与 AD 发病危险性的关系。结果显示，未按血糖水平和治疗情况分层的糖尿病仅与 VaD 的发病危险性有关 (HR 3.2; 95% CI, 1.2-8.6)，但分层分析结果显示，未确诊的糖尿病可增加老年痴呆 (HR 3.4; 95% CI, 1.5-7.7)、以及 AD (HR 3.3; 95% CI, 1.2-9.0) 的发病危险性。临界糖尿病和未确诊的糖尿病还与纯 AD (未伴发任何血管性疾病的 AD) 的发病危险性有关。在糖尿病患者中有效地控制血糖可降低糖尿病对老年痴呆发病的危险作用。

研究 IV：在双生子中证实了糖尿病与老年痴呆的关系。在双生子人群中，成组病例对照分析结果显示，控制了可能的混杂因素后，糖尿病与老年痴呆关系的比值比 (OR) 是 1.9 (95% CI, 1.5-2.4)；与 AD 关系的 OR 是 1.7 (95% CI 1.2-2.4)；与 VaD 关系的 OR 是 2.2 (95% CI, 1.4-3.5)。同时发现，发生于中年的糖尿病 (OR 2.8; 95% CI, 2.0-3.9) 对老年痴呆的危险作用强于发生在老年的糖尿病 (OR 1.6; 95% CI, 1.2-2.2)。在双生子对子中的配比病例对照研究分析结果显示，遗传和早期环境因素可能参与了发生于老年的糖尿病与老年痴呆的关系，但不能解释发生于中年的糖尿病与老年痴呆的关系。

结论：糖尿病可增加老年痴呆、AD 和 VaD 的危险性，其危险作用独立于心脑血管疾病。当糖尿病与严重高血压或心脏病伴发时，其危险作用会明显增加。临界糖尿病亦可增加老年痴呆、AD 和纯 AD 的发病危险性，该危险效应独立于其随后发展为糖尿病的作用。在糖尿病患者中，有效地控制血糖可降低糖尿病对老年痴呆的危险作用。这些发现支持血糖调节紊乱可导致脑血管损害和神经退行性病变这一观点。研究进一步发现，发生于中年的糖尿病对老年痴呆的危险作用强于发生在老年时期的糖尿病。发生于老年的糖尿病与老年痴呆的关系可能归因于遗传和早期环境因素，但发生于中年时期的糖尿病与老年痴呆的关系可能取决于成年时期环境因素的作用。

关键词：糖尿病，临界糖尿病，老年痴呆，阿尔茨海默病，血管性痴呆，血糖水平，血管性疾病，前瞻性研究，人群为基础的双生子研究

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ANOVA	Analysis of Variance
APOE	Apolipoprotein E gene
ATC	Anatomical Therapeutic Chemical (classification system)
A β	Amyloid- β
BDRS	Blessed Dementia Rating Scale
BMI	Body Mass Index
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CDR	Clinical Dementia Rating Scale (Washington University)
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DSM-III-R (DSM-IV)	Diagnostic and Statistical Manual of Mental Disorder, Revised Third Edition (Fourth Edition)
DZ	Dizygosity
EM	Expectation Maximization
GEE	Generalized Estimating Equation
HARMONY	Swedish words for "health" (Hälsa), "genes" (Arv), "environment" (Miljö), "and" (och), and "new" (NY)
HR	Hazard Ratio
ICD-8 (ICD-9)	International Classification of Diseases and Related Health Problems, Eighth Revision (Ninth Revision)
IDE	Insulin Degrading Enzyme
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IR	Incidence Rate
MCAR	Missing Completely at Random
MMSE	Mini-Mental State Examination
MZ	Monozygosity
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences
OR	Odds Ratio
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMR	Standardized Mortality Ratio
VaD	Vascular Dementia

LIST OF PUBLICATIONS

This doctoral thesis is based on the following original papers, referred to in the text by their Roman numerals:

- I. Xu WL, Qiu CX, Wahlin Å, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen Project: a 6-year follow-up study. *Neurology* 2004;63:1181-1186.
- II. Xu WL, Qiu CX, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. *Diabetes* 2007;56:211-216.
- III. Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L. The relation of diabetes to Alzheimer's disease: the role of glycemic control and vascular comorbidities. *Submitted.*
- IV. Xu WL, Qiu CX, Gatz M, Pedersen NL, Fratiglioni L. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. *Submitted.*

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1 INTRODUCTION

1.1 GLOBAL AGING

The aging of populations has become a worldwide phenomenon.¹ In 1990, 26 nations had more than two million elderly citizens aged 65 years and older, and the projections indicate that an additional 34 countries will join the list by 2030. In 2000, the number of old people (65+ years) in the world was estimated to be 420 million and it is projected to be nearly one billion by 2030, with the proportion of old people increasing from 7 to 12%. The largest increase in absolute numbers of old people will occur in developing countries; it will almost triple from 249 million in 2000 to an estimated 690 million in 2030. The developing regions' share of the worldwide aging population will increase from 59 to 71%.² Developed countries, which have already shown a dramatic increase in people over 65 years of age, will experience a progressive aging of the elderly population. Underlying global population aging is a process known as the “demographic transition” in which mortality and then fertility decline.³ Decreasing fertility and lengthening life expectancy have together reshaped the age structure of the population in most regions of the planet by shifting relative weight from younger to older groups. By 2050, the distribution is expected to become closer to a rectangle (Figure 1). Life expectancy at birth ranges from 76 to 80 years in developed countries, and has also increased in developing countries.²

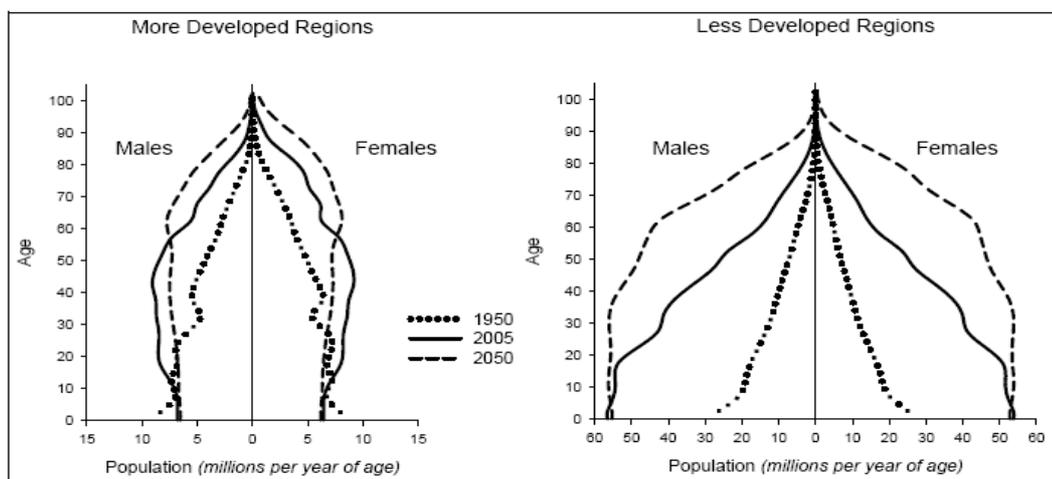


Figure 1. Age and sex distribution of the population, more developed and less developed regions, 1950, 2005 and 2050 (World Population Prospects, United Nations, 2005).

Consequently, both developed and developing countries will face the challenge of coping with a high frequency of chronic conditions, such as dementia, which is characteristic of aging societies. These conditions impair the ability of older persons to function optimally in the community and reduce well-being among affected individuals and their families. Further, these conditions are associated with significant health care costs that must be sustained by the society at large. Thus, the global trend in the phenomenon of population aging has a dramatic impact on public health, healthcare financing and delivery systems throughout the world.⁴ Due to the aging of the population, dementia has become a major challenge to elderly care and public health.

1.2 EPIDEMIOLOGY OF DEMENTIA AND MAJOR SUBTYPES

1.2.1 Definitions

In the last two decades, the dementia field has registered a tremendous scientific progression in many research areas, including aetiology, pathogenesis, clinical aspects, treatment and prevention. These advances have opened new perspectives, especially concerning definitions and diagnostic criteria, which have a relevant impact on epidemiological research. Dementia is defined as a clinical syndrome characterized by the development of multiple cognitive deficits that are severe enough to interfere with daily functioning, including social and professional functioning. The cognitive deficits include memory impairment and at least one of the other cognitive domains, such as aphasia, apraxia, agnosia or disturbances in executive functioning.^{5,6} Alzheimer's disease (AD) is the most common cause of dementia in the elderly, accounting for 60-70% of all demented cases.⁷ AD is strictly a neuropathological diagnosis determined by the presence of neurofibrillary tangles and senile plaques in the brain of a patient with dementia. The disease frequently starts with memory impairment, but is invariably followed by a progressive global cognitive impairment.⁸ Vascular dementia (VaD) is the second most common cause of dementia in the elderly after AD. VaD is defined as loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology. Diagnosis of VaD requires cognitive impairment; vascular brain lesions, often predominantly subcortical, as demonstrated by imaging; a temporal link between stroke and dementia; and exclusion of other causes of dementia.⁹ The combination of AD and

VaD pathological changes in the brain of older people is extremely common, making mixed dementia probably the most common type of dementia.¹⁰

1.2.2 Prevalence and incidence

In all countries, both the prevalence and incidence of dementia rise with increasing age.^{11,12} Despite different inclusion criteria, several meta-analyses have resulted in strikingly similar estimates of dementia prevalence.¹³ The age specific prevalence of dementia almost doubles every five years, from approximately 1.5% in persons aged 60-69 years to 40% in nonagenarians. The global dementia prevalence in people aged over 60 is 3.9%, with the regional prevalence varying from 1.6% in Africa, 3.9% in Eastern Europe, 4.0% in China, 4.6% in Latin America, 5.4% in western Europe, and 6.4% in North America.¹⁴ There is a similar pattern in the distribution of dementia subtypes across the world, with the two most common forms of dementia, AD and VaD, accounting for 60-79% and 15-25% of all dementia cases, respectively.¹⁵ In Europe, the age-adjusted prevalence is 6.4% for dementia in general, 4.4% for AD, and 1.6% for VaD among people 65 years and older.^{16,17} Even dementia incidence does not show great geographical variation in the world.¹³ The global annual incidence of dementia is around 7.5 per 1,000 population.¹⁴ The incidence rate of dementia increases exponentially with age, from approximately one per 1,000 person-years in people aged 60-64 years to more than 70 per 1,000 person-years in 90+ year-olds. The incidence rates of dementia across regions are quite similar in the younger-old (<75 years), but greater variations are seen among the older ages.¹⁵ Slightly lower rates have been detected in the USA in comparison with Europe and Asia, and this is possibly due to differences in the study designs and the case ascertainment procedures.

Based on the available epidemiological data, a group of experts estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year (one new case every 7 seconds). The number of people affected will double every 20 years to 81.1 million by 2040.¹⁴ Similar estimates have been reported previously.¹⁸ Most people with dementia live in developing countries. China and its western Pacific neighbors have the highest number of people with dementia (6 million), followed by the European Union (5.0 million), USA (2.9 million), and India (1.5 million). The rates of increase in the number of dementia cases are not uniform across the world; numbers

in developed countries are forecasted to increase by 100% between 2001 and 2040, but to increase by more than 300% in India, China, and other south Asian and western Pacific countries.¹⁴

1.2.3 Prognosis and impact

The prognosis of dementia is dramatic. In three years, more than 50% of the dementia cases reach the severe stage. In the Kungsholmen Project, the proportion of severe dementia among prevalent cases increased from 19% at baseline to 48% after three years, and to 78% after seven years. This progression is due to both cognitive and functional decline.¹⁹ Dementia is strongly associated with disability as it has been found to be the major determinant of developing dependence and functional decline over three years. Approximately half of the persons who developed functional dependence in a three year period can attribute this disability to dementia.²⁰ In industrialised countries, mental disease and cognitive impairment are the most prevalent disorders among older adults living in nursing homes or other institutions. However, institutionalisation of dementia patients varies depending on age structure, urban or rural residence, and other cultural aspects. In a 75+ year old population, 70% of incident dementia cases die during the five years following the diagnosis, accounting for a mortality rate specific for dementia of 2.4 per 100 person-years. Dementia triples the risk of death.²¹ The demands of healthcare and social service of the huge and rapidly growing numbers of dementia patients have a major economic impact at the societal levels.²² The worldwide direct costs for dementia in 2003 are estimated at 156 billion USD in the main scenario of a worldwide prevalence of 27.7 million demented persons. It is obvious that due to these costs and the expected increase in the number of elderly people in developing countries, the dementing conditions will present a great challenge.²³

1.2.4 Risk and protective factors

Our current knowledge on risk factors of the dementias is derived mostly from population-based prospective studies carried out in the last 15 years. AD is a multifactorial disease, in which both genetic and environmental factors are involved.²⁴ VaD has been linked to most vascular risk factors and disorders such as hypertension, cerebral vascular disease, heart disease and diabetes.^{17,25}

1.2.4.1 Genetic factors

The *APOE* ϵ 4 allele is the only established susceptibility gene for both early- and late-onset AD. The risk effect of the *APOE* ϵ 4 allele decreases with increasing age, and after age 75, 15–20% of AD cases are attributable to *APOE* genotype.²⁶ Several other genes have been examined as possible candidates, but the reports are sporadic or the results are inconsistent.²⁷

1.2.4.2 Biological risk factors

Increasing age is a well-established risk factor for AD and VaD. The incidence of AD and VaD almost doubles with every 5 years of age.^{17,24} Female sex is often associated with an increased risk of AD, especially at the oldest-old age.¹⁵ Men seem to be at greater risk for VaD than women.²⁸

1.2.4.3 Vascular risk factors and disorders

Increasing evidence supports the involvement of vascular risk factors and vascular disorders in dementia, even in AD.

Blood pressure. Several studies have consistently reported an association between midlife high blood pressure and increased risk of dementia and AD.^{29,30} Hypertension has been linked to neurodegenerative markers in the brain, suggesting that long-term high blood pressure may play a causal role in the neurodegenerative process itself or by causing brain atrophy. In very old people, the deleterious effect of high blood pressure is less evident, whereas low blood pressure seems to be predictive of dementia and AD. As dementia has a long latent period, low blood pressure may be a sign of impending illness,³¹ which was confirmed by the longitudinal data from the Kungsholmen Project, suggesting the involvement of late life low blood pressure and cerebral hypoperfusion in the development of dementia and AD.³² All these findings suggest that the relation of blood pressure to dementia may be age-dependent.¹⁵

Heart disease. Cardiovascular disease was found to be associated with increased risk of dementia and AD, especially in people with peripheral arterial disease,³³ suggesting that extensive peripheral atherosclerosis is a risk factor for AD. In addition, heart failure and atrial fibrillation may be independently related to increased risk of dementia.

In the Kungsholmen Project, heart failure was associated with a more than 80% increased risk of dementia and AD.³⁴

Cerebrovascular disease. Multiple cerebral infarcts, recurrent and strategic strokes are main risk factors for post-stroke dementia. Silent stroke and white matter lesions detected on neuroimaging are associated with increased risk of dementia and cognitive decline. Spontaneous cerebral emboli were related to both AD and VaD. Some studies reported an association of stroke with AD and cognitive decline.³⁵ Cerebral vascular lesions may interact with neurodegenerative lesions to produce a dementia syndrome in individuals not having sufficient neurodegenerative damages to express dementia.¹⁵

Obesity. Similar to hypertension, recent studies suggested a lifespan-dependent relation of obesity with dementia.^{36,37} A higher body mass index (BMI) at middle age was related to increased risk of dementia in late life.³⁸ A greater decline in BMI approximately 10 years prior to dementia onset was detected, which is in line with the other studies suggesting an association of accelerated BMI decline with AD.^{39,40} Low BMI in late life and weight loss may be related to high risk of dementia and AD,⁴¹ but low BMI and weight loss can be interpreted as markers of preclinical AD, especially when measured less than 10 years prior to clinical diagnosis.¹⁵

Hyperlipidemia. An association of elevated cholesterol at middle life with increased risk of late-life AD was reported in some studies.³⁰ Controversial findings have also been reported on the relation of cholesterol in late life to dementia risk. Some cohort studies found no association or even an inverse association of total cholesterol with dementia risk.⁴² A study showed a decline in total cholesterol at least 15 years before dementia onset.⁴³ Recently, a bidirectional cholesterol-cognition relationship has been reported. High midlife cholesterol was associated with poorer late-life cognition, but decreasing cholesterol after midlife may reflect poorer cognitive status.⁴⁴

The metabolic syndrome. A clustering of interrelated metabolic risk factors such as diabetes, obesity, hypertension and dyslipidemia has received increasing attention in the past few years. Several components of the metabolic syndrome have been individually related to cognitive outcomes. A prospective study found that the metabolic syndrome contributed to cognitive decline.⁴⁵ But this finding was not confirmed in a population of the oldest old. The concept of the metabolic syndrome

may be less valid in this age group.⁴⁶ Finally, a cross-sectional study showed that metabolic syndrome was associated with an increased risk of AD.⁴⁷

Inflammation. Inflammation is known to be involved in the atherosclerotic process. Thus, serum inflammatory makers may be associated with dementia. Some cohort studies found such an association, and C-reactive protein may be the most promising in predicting dementia risk.⁴⁸ In addition, long-term use of non-steroidal anti-inflammatory drugs was suggested to be associated with a lower risk of AD.¹⁵

Fat intake. Several population-based studies suggested that moderate to high intake of unsaturated fats at midlife is protective, whereas a moderate intake of saturated fats may increase the risk of dementia and AD,^{49,50} especially among *APOE* $\epsilon 4$ carriers.^{51,52} Fatty acids may affect dementia through various mechanisms such as atherosclerosis and inflammation.

1.2.4.4 Environmental factors

Socioeconomic status. A number of studies have found that higher socioeconomic status (SES) is associated with reduced risk of developing AD.⁵³⁻⁵⁵ In most of these studies, SES was assessed based on occupational attainment, current income to reflect socioeconomic level in adulthood, or educational attainment. Findings from a prospective study, however, suggested that early life socioeconomic status assessed at the household or community level was related to level of cognition in late life but not to rate of cognitive decline or risk of AD.⁵⁶

Occupation. Occupation and occupational exposures (e.g., electromagnetic fields and heavy metals) may play a role in dementia and AD.^{57,58} Data from the Kungsholmen Project showed that manual work involving goods production was associated with an increased risk of dementia and AD,⁵⁸ and specifically a risk effect was detected with electromagnetic exposure.⁵⁷

Alcohol consumption. Excessive alcohol intake can cause alcoholic dementia and may increase the risk of VaD. Heavier alcohol intake at middle age was associated with increased risk of late-life dementia.⁵⁹ By contrast, increasing evidence suggests that light to moderate alcohol consumption may be associated with a reduced risk of

dementia and cognitive decline,⁶⁰ a similar effect as observed for cardiovascular disease.¹⁵

Cigarette smoking. Some prospective studies have found an increased risk of AD associated with smoking.⁶¹ The previously reported association of cigarette smoking with low prevalence of dementia was probably due to survival bias. In the Kungsholmen Project, smoking affected survival in AD cases more than in non-demented subjects, and the protective effect of smoking on the AD was no longer present when incident AD cases were studied.⁷

Head trauma. For many years, head trauma has been suggested as a possible risk factor for AD, and it has been extensively investigated in several studies, but this possible association still remains controversial.²⁴

1.2.4.5 Protective factors

High education. Low dementia prevalence among highly educated persons has been reported by numerous surveys. Educational attainment and lifespan mental activity associated with childhood education may reduce the risk of dementia.¹⁵

Social network. Data from longitudinal studies have suggested that a poor social network is related to cognitive decline and dementia. The risk of dementia is decreased in old people with social integration and frequent contacts with relatives and friends, suggesting that a socially integrated lifestyle in late life might protect against dementia.⁶²

Leisure activities. Leisure activities with a high mental component have been repeatedly associated with a reduced risk of dementia.⁶³ However, complex leisure activities with physical, mental and social components seem to have the most beneficial effect,⁶⁴ as shown by a study from the Kungsholmen Project.⁶⁵

Physical activity. The relevance of physical activity itself remains in debate, as most physical activities also include social and mental components. Regular exercise, even low-intensity activity such as walking, is associated with reduced risk of dementia and cognitive decline.⁶⁶ The possible benefits of a short-term physical training program on cognition remain equivocal.

Diet. High or supplementary intake of vitamins C, E, B6, B12, and folate has been related to a decreased risk of AD.⁶⁷ Adherence to ‘Mediterranean diet’ (higher intake of fish, fruits, and vegetables rich in antioxidants) was associated with a reduced risk of AD independent of vascular pathways.⁶⁸ Indeed, low levels of B12 and folate were found to be related to an increased risk of AD in a study from the Kungsholmen Project.⁶⁹

1.3 DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders with the common manifestation of hyperglycemia caused by defective insulin secretion, defective insulin action, or both. The World Health Organization recognizes three main forms of diabetes: type 1, type 2 and gestational diabetes. Type 1 diabetes is usually due to the autoimmune destruction of the pancreatic β -cells and accounts for 5-10% of diabetes in the population. The prevalence of type 1 diabetes is higher in younger than in older age groups. Type 2 diabetes is characterized by insulin resistance in target tissues, and accounts for 90-95% of all diabetes cases in the population. Gestational diabetes is similar to type 2 diabetes occurring during pregnancy.⁷⁰ In the present study, type 1 and type 2 diabetes are not distinguished, but in view of the age of the study populations involved, most participants probably have type 2 diabetes. In the following text, diabetes will be referred to type 2 diabetes mellitus.

Type 2 diabetes is frequently undiagnosed for many years because the hyperglycemia is often not severe enough to provoke noticeable symptoms of diabetes. Approximately one-third of all people with diabetes may be undiagnosed.⁷¹ Nevertheless, such patients are at increased risk of developing micro- and macro-vascular complications, and related disorders. In addition, type 2 diabetes is a slow onset disease, and onset is preceded by impaired glucose regulation (impaired fasting glucose and impaired glucose tolerance), which refers to a metabolic state intermediate between normal glucose homeostasis and diabetes. Recently, impaired glucose regulation has been termed “pre-diabetes”, or “borderline diabetes”. Borderline diabetes often progresses to full-blown diabetes and increases the risk of cardiovascular disease.⁷¹

1.3.1 Diagnosis of diabetes and borderline diabetes

Diabetes is diagnosed by demonstrating any one of the following:⁷²

- Fasting plasma glucose level at or above 126 mg/dL (7.0 mmol/l).
- Plasma glucose at or above 200 mg/dL (11.1 mmol/l) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Random plasma glucose at or above 200 mg/dL (11.1 mmol/l).

Borderline diabetes, pre-diabetes, or impaired glucose regulation is defined as two pre-diabetic states:⁷²

- Impaired fasting glycemia (IFG): fasting glucose levels between 100 and 125 mg/dL (6.1 and 7.0 mmol/l).
- Impaired glucose tolerance (IGT): random plasma or two hours after a 75 g oral glucose load, glucose levels between 140 mg/dL (7.8 mmol/l) and 200 mg/dL (11.1 mmol/l).

1.3.2 Global diabetes epidemic

The number of people with diabetes is increasing due to population growth, aging, urbanization and the increasing prevalence of obesity and physical inactivity. The prevalence of diabetes for all age groups worldwide is estimated to be 2.8% in 2000 and predicted to be 4.4% in 2030. Diabetes occurs throughout the world, but is more common (especially type 2) in the more developed countries than in developing nations (Figure 2). The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Currently, type 2 diabetes affects 250 million people worldwide, with 6 million new cases each year. The prevalence of diabetes is higher in men than in women, but there are more women with diabetes than men due to their longer survival after age over 65.⁷³ According to the American Diabetes Association, approximately 18.3% (8.6 million) of Americans aged 60 and older have diabetes. Diabetes prevalence increases with age, and the number of older persons with diabetes is expected to grow as the size of the elderly population increases. The Third National Health and Nutrition Examination Survey in the USA has demonstrated that in the population over 65 years old 18% to 20% have diabetes, and 40% have either diabetes or its precursor form of impaired glucose tolerance.⁷⁴ The incidence of diabetes increases with age. The annual incidence rates are 0.3-0.5% in

people aged 50-60 years, 0.5-1.0% for 60-70 years, and 1% above 70 years.⁷⁵ In addition to diabetes, prediabetes also constitutes a major public health problem. In 2003, around 314 million people worldwide, or 8.2%, in the age group 20-79 years had impaired glucose tolerance (Figure 3); by 2025 the number is projected to increase to 472 million, or 9.0% in the adult population.⁷⁶ The prevalence of impaired glucose tolerance is more than twice that of diabetes in the African and South-East Asian regions, whereas in the Eastern Mediterranean and Middle East, and North American Regions, the prevalence of impaired glucose tolerance is slightly lower than that of diabetes (Figure 4).

1.3.3 Complications

Diabetes is ranked among the leading causes of blindness, renal failure and lower limb amputation, and 70-80% of people with diabetes die of cardiovascular disease. In fact, diabetes is one of the leading causes of death through its effects on the cardiovascular system. From a public health perspective the diabetes complications have a huge impact both as major determinants of human suffering and disability and also through the elevated socio-economic costs due to premature morbidity and mortality.

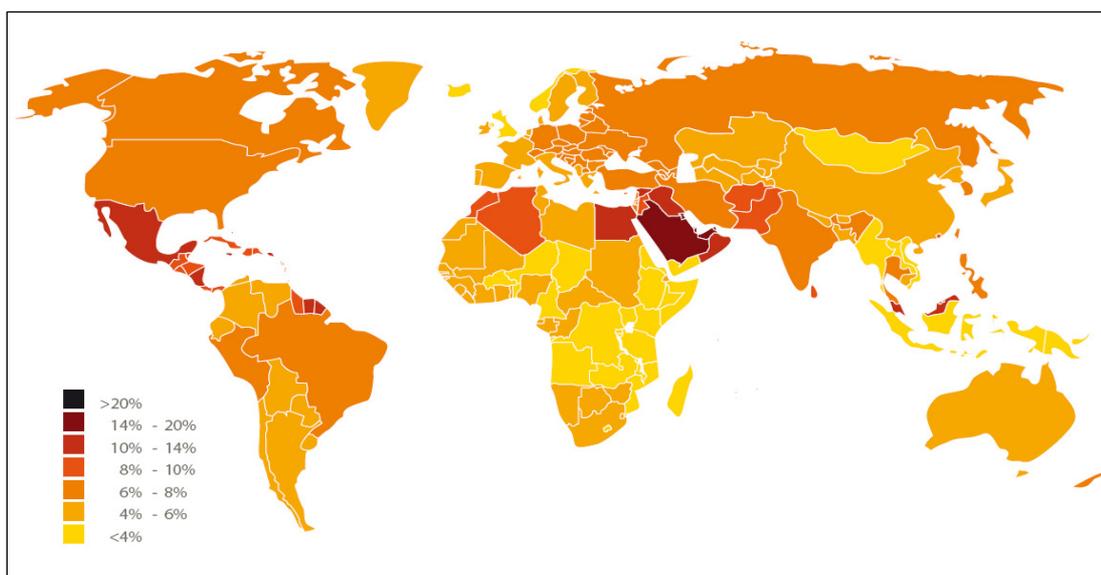


Figure 2. Estimated prevalence of diabetes in 2007 (Diabetes Atlas Third Edition, International Diabetes Federation, 2006)

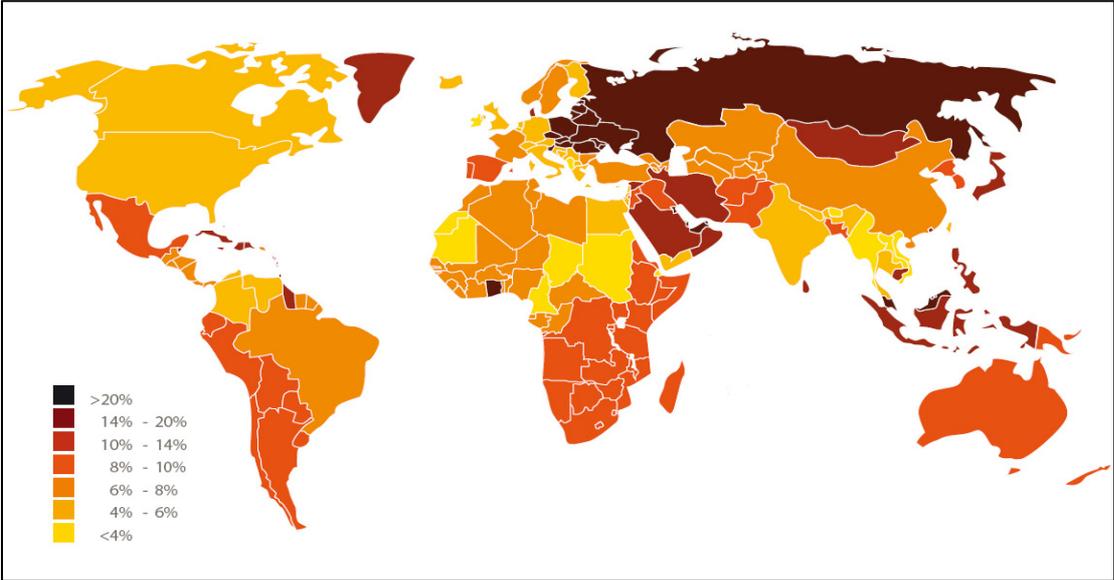


Figure 3. Estimated prevalence of impaired glucose tolerance in 2007 (Diabetes Atlas, Third Edition, International Diabetes Federation, 2006)

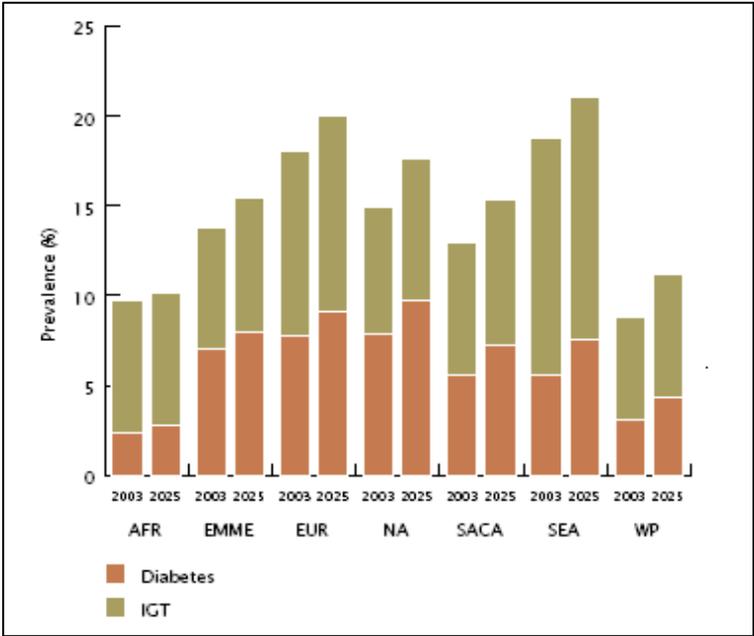


Figure 4. Estimated prevalence of diabetes and impaired glucose tolerance by region (20-79 age group, Diabetes Atlas, Second Edition, International Diabetes Federation, 2003).

AFR: Africa, EMME: Eastern Mediterranean and Middle East, EUR: Europe, NA: North America, SACA: South and Central America, SEA: South-East Asia, WP: Western Pacific
 IGT=impaired glucose tolerance

Chronic elevation of blood glucose, even when no symptoms are present to alert the individual to the presence of diabetes, will eventually lead to tissue damage, with consequent, and often serious, disease.⁷⁷ Whilst evidence of tissue damage can be found in many organ systems, it is the kidneys, eyes, peripheral nerves and vascular tree that manifest the most significant, and sometimes fatal, diabetic complications due to micro- and macro-vascular damage.^{78,79} The mechanism by which diabetes leads to these complications is complex, and not yet fully understood, but involves the direct toxic effects of high glucose levels, along with the impact of elevated blood pressure, abnormal lipid levels and both functional and structural abnormalities of small blood vessels.⁷⁸ Diabetes and old age come together to increase the frequency and severity of vascular disease.⁸⁰ In the last decade it has become increasingly evident that diabetes may also affect the central nervous system, a complication referred to as “diabetic encephalopathy”.⁸¹ This complication is reflected in impaired cognitive functioning, and it is also associated with an increased risk of dementia.

1.4 THE RELATIONSHIP BETWEEN DIABETES AND DEMENTIA

A potential link between diabetes and cognitive impairment was first reported more than 80 years ago. The association of diabetes with these cognitive changes is now well established.⁸² There is substantial evidence suggesting that type 2 diabetes is associated with cognitive impairment involving both memory and executive function.⁸³⁻⁸⁵ Several large longitudinal population-based studies have also shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes.⁸⁶ With regard to more profound degrees of cognitive impairment, namely dementia, both cross-sectional and prospective studies suggest that diabetes is associated with an increased risk of dementia, but the issue whether this concerns only VaD or also AD is debated. Since diabetes is strongly related to vascular disease, the association between diabetes and VaD is expected.

1.4.1 Cross-sectional studies

As early as 1984, a case-control study was performed to determine the role of prior illness, including diabetes, in the development of AD. The results showed a non-significant association of diabetes with AD. This was followed by several studies,

which have yielded conflicting results about the association of diabetes with VaD and AD. Table 1 summarizes 20 cross-sectional studies that have investigated this issue.⁸⁷⁻¹⁰⁶ The Rotterdam study is the first population-based cross-sectional study to have used ‘dementia’ as a variable in association with diabetes, and it found an association of diabetes with VaD, and with AD only in subjects treated with insulin.⁸⁸ Most studies have instead examined subjects with either AD or VaD and compared them with each other or with control subjects. A major problem with these first reports is that the most commonly used diagnostic criteria for AD emphasized the exclusion of underlying disorders, particularly cerebrovascular disease. It is not surprising therefore that these studies have tended to report an excess of cerebrovascular risk factors, including diabetes, in VaD group compared to non-demented control or AD groups. Another problem is that cases have been drawn from secondary or tertiary dementia referral centers, which may have introduced some selection bias. In addition, cross-sectional investigation of the association of diabetes with prevalent dementia cases will generally underestimate or even detect an inverse association due to the raised mortality in later life related to diabetes, probably higher in combination with dementia.

1.4.2 Prospective studies

Population-based longitudinal studies that compared the incidence of dementia between patients with and without diabetes provide more reliable risk estimates than studies on patients with prevalent dementia. Over the last decade, many population-based longitudinal studies have revealed a relationship between diabetes and an increased risk of dementia and VaD, although the results concerning the association of diabetes with the Alzheimer type of dementia are inconsistent. In fact, some prospective studies showed the association between diabetes and an increased risk of AD, or observed such an association only in specific subgroups, and others did not. Nineteen population-based longitudinal studies have examined the relation of diabetes and dementia (Table 2).^{30,55,107-123} The incidence of any dementia was approximately two- to three-fold higher in people with diabetes than in those without diabetes in seven of the ten studies reporting this aggregate outcome. This high risk included both AD (eight of fifteen studies including two studies that showed the association of diabetes with AD only in *APOE* $\epsilon 4$ non-carriers) and VaD (five of seven studies). The limitation of clinical diagnostic criteria in the classification of dementia by pathological subtypes should be

considered, especially in a complex disorder such as diabetes. Among these studies, detailed data on modulating or mediating effects of glycemic control, microvascular complications, and comorbidities were generally absent.

1.4.3 Post-stroke dementia studies

The risk of dementia increases after stroke.¹²⁴ Diabetes is a major risk factor for cerebrovascular disease. It is likely that the association between diabetes and dementia is mediated or modulated by cerebrovascular disease. Little progress has been made in understanding the role of diabetes in the development of dementia in stroke patients. Studies which have examined the role of diabetes in the development of dementia after stroke have produced conflicting results. Among the ten studies, six showed that diabetes was related to post-stroke dementia (Table 3).¹²⁵⁻¹³⁴ It has been suggested that if diabetes has an effect on dementia after stroke, it may accelerate the dementia onset rather than increase the longer term risk of the disorder. Another consideration is that the raised mortality associated with stroke in the presence of diabetes may mask the association of diabetes with post-stroke dementia.¹³⁵

1.4.4 Borderline diabetes and cognitive impairment

The hypothesis that impaired glucose regulation is related to decrements in cognitive performance is verified by several studies that evaluated the neuropsychological performance in prediabetic adults. In 1995, the relationship between impaired glucose tolerance and reduced Mini-Mental State Examination (MMSE) score was first reported.¹³⁶ To date, there are few studies that have examined the impact of impaired glucose regulation on cognitive functions. Collectively, five studies have demonstrated the presence of mild cognitive deficits in people with prediabetes (Table 4).¹³⁶⁻¹⁴⁰ To the best of our knowledge, no studies have so far investigated the effect of early stage diabetes on the risk of dementia and its major subtypes.

1.4.5 Methodological considerations

Before drawing any conclusions from this short review of the literature concerning the association of diabetes with dementia, some points need to be taken into account. First, the characteristics of the study populations are different from study to study, especially

regarding age and gender. Mortality risk is elevated in diabetes and diabetes-associated diseases. In a higher age range, selected survival might result in milder forms of diabetes being examined with respect to potential dementia. Therefore, it should be emphasized that these results from elderly populations cannot be generalized to younger persons. Second, different methods of assessment have been used in different studies to identify diabetic patients. A number of studies defined diabetes only based on the information from self-reports, medical records, or the use of antidiabetic medications, and they did not assess blood glucose concentration. As diabetes is often undiagnosed among elderly people, in these studies, a substantial proportion of people with diabetes might have been erroneously assigned to the non-diabetic group, which might have led to an underestimation of the disease risk attributable to diabetes. In addition, the diabetes-related cognitive deterioration may be attenuated by effective glycemic control,^{141,142} but studies that addressed the relation of diabetes to dementia generally did not take into account the effect of glycemic control and diabetes duration. Third, different criteria used in the diagnosis of dementia and its subtypes can have a large impact on the frequency of dementia. Most of the longitudinal studies have used similar criteria for dementia and AD. Yet the criteria for VaD differed among the studies. These criteria are not interchangeable, with the California criteria being more sensitive but less specific than the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.¹⁴³ Within individual studies the reliability of these diagnostic criteria will be affected by the nature of the diagnostic work-up. The diagnosis of VaD is difficult in epidemiological studies, and the boundaries between AD and VaD remain controversial.¹⁴⁴ Fourth, an in-depth analysis of the modulating effect of comorbid disorders was generally not provided. Stroke, cardiovascular disease, and hypertension are known risk factors for dementia, and they should be taken into account when the relation between diabetes and dementia is examined.

In summary, there is an increasing interest in the scientific world towards the suggested diabetes-dementia association due to the high relevance of the topic, not only from a public health perspective, but also from a scientific point of view. In fact, exploring this association may help in clarifying some new pathways leading to neurodegeneration. For all these reasons, some years ago we started this project that now is summarized in this thesis.

Table 1. Major epidemiological studies concerning the association between diabetes and dementia: Cross-sectional and retrospective studies. The odds ratios (OR) refer to dementia, when not otherwise specified.

Author, year	Country and sample	Age (y)	Diabetes: Ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Stella et al, ⁸⁷ 2007	Brazil, 78 outpatients	60+	Medical records	VaD (78) ICD-10 Neuroimaging	23.1% diabetes in VaD cases	Not reported
Valcour et al, ⁸⁹ 2005	USA, 203 HIV-1 infected patients	20-76	Self-report, Fasting blood glucose	Dementia (39) Neuropsychological tests and neurological examination	OR 5.4 (1.66-17.70)	Age, education, and vascular factors
Beeri et al, ⁹⁰ 2005	USA, 385 specimen from autopsies, 15.8% diabetics, and 66% female	84	Medical records	CERAD neuropathological categories	Diabetics had fewer neuritic plaques ($p=0.008$) and NFTs ($p=0.047$)	Age, dementia severity, and <i>APOE</i> $\epsilon 4$
Haan et al, ⁹¹ 2003	USA, 1789 Latinos	60+	Self-report, Antidiabetic drugs Fasting blood glucose	Dementia (69) AD (31), NINCDS-ADRDA VaD (14), California criteria	43% of dementia risk was attributable to diabetes	Not reported
Bowirrat et al, ⁹² 2002	Israel, 823 Arabs	60+	Medical records	AD (168) DSM-IV VaD (49)	OR 1.1 (0.6-1.7) OR 1.8 (0.9-3.5)	Univariate analysis
Tariot et al, ⁹³ 1999	USA, 467 long-term care residents	74.8	Medical records	AD (85) NINCDS-ADRDA VaD (84) Clinical diagnosis	Diabetes was 6.1% in AD, and 47.4% in VaD	Age, sex, and race
Boston et al, ⁹⁴ 1999	UK, 438 community-based sample	75+	Self-report	AD (222) VaD (34) CAMDEX	A greater proportion of diabetes in VaD ($p=0.002$)	Age and sex

Brayne et al, ⁹⁵ 1998	UK, a nested case-control study, 36 case and 340 controls	75+	Self-report Diabetes 6% in controls, 16% in cases	Dementia (36) ICD-10 AD (18) CAMDEX Autopsy	OR 2.6 (0.9-7.8) OR 1.4 (1.1-17.0)	Age and sex
Kuusisto et al, ⁹⁶ 1997	Finland, 980 subjects	69-78	Fasting blood glucose	AD (46), NINCDS-ADRDA	OR 1.1 (0.9-2.4)	Age, sex, and education
Heitner et al, ⁹⁷ 1997	USA, a matched case-control study, 49 diabetics and 52 controls	69.4	Medical records	AD, autopsy neuropathologic diagnoses	Diabetes was not associated with AD pathology	Age and sex
Lindsay et al, ⁹⁸ 1997	Canada, a matched case-control study, 129 VaD cases and 535 controls	Not shown	Medical records	VaD, DSM-III-R clinical grounds	OR 1.7 (0.9-3.1)	Age, sex, and education
Nielson et al, ⁹⁹ 1996	USA, an observational survey, 265 dementia cases	74	Medical records	AD (123) NINCDS-ADRDA VaD (51) California criteria Mixed (57)	Diabetes was 0.8% in AD, 11.8% in VaD, and 8.8% in mixed dementia	Not reported
Ott et al, ⁸⁸ 1996	The Netherlands, a population-based study, 6330 subjects	55-99	Antidiabetic drugs, Random blood glucose OGTT	Dementia (265) DSM-III-R AD (194) NINCDS-ADRDA VaD (44) NINDS-AIREN	OR 1.3 (1.0-1.9) OR 1.3 (0.9-1.9) OR 2.1 (1.1-4.0)	Age, sex, education, vascular disease
Gorelick et al, ¹⁰⁰ 1993	USA, a case-control study, 61 multi-infarcts disease	60+	Medical records	Multi-infarct dementia, DSM-III-R	Diabetes was not related to multi-infarct dementia	Not reported
Landin et al, ¹⁰¹ 1993	Sweden, a retrospective study, 38 AD, 14 VaD and 19 other dementia	Not shown	Medical records	AD (38) NINCDS-ADRDA VaD (14) DSM-III-R Other dementia (19)	AD cases had lower blood glucose compared with other dementia and VaD	Not reported
Kokmen et al, ¹⁰² 1991	USA, a case-control study, 415 cases and 415 controls	Not shown	Medical records	AD (415), Consensus criteria, similar to DSM-III-R	OR 1.2 (0.8-1.8)	Not reported

Broe et al, ¹⁰³ 1990	Australia, a matched case-control study, 170 AD, and 170 controls	52-96	Self-report	AD (170), NINCDS-ADRDA	OR 0.6 (0.2-1.6)	Univariate analysis
Wolf-Klein et al, ¹⁰⁴ 1988	USA, 348 subjects, 173 men and 165 women	62-98	Medical records	AD (75), NINCDS-ADRDA	Less diabetes in AD cases	Not reported
Amaducci et al, ¹⁰⁵ 1986	Italy, case-control study, 119 cases, 116 hospital and 97 population controls	41-80	Self- or informant-report	AD (119), NINCDS-ADRDA	OR 0.7 ($p=0.54$) for hospital controls; 1.0 ($p=1.0$) for hospital controls	Not reported
Heyman et al, ¹⁰⁶ 1984	USA, a matched case-control study, 40 AD cases, 80 controls	51-71	Self- or informant-report	Duke University Hospital Uniform criteria for diagnosis of AD	Diabetes was 7.5% in AD, and 8.8 % in controls ($p=0.84$)	Not reported

Table 2. Major population-based prospective studies concerning the association of diabetes with dementia. The relative risk (RR), hazard ratios (HR), odds ratios (OR), or standard mortality rate (SMR) refer to dementia, when not otherwise specified.

Author, year	Country and study population	Age (y)	Follow-up (y)	Diabetes: Ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Irie et al, ¹⁰⁷ 2008	USA, The Cardiovascular Health Study Cognition Study, 2547 dementia-free subjects	74.4	5.4	Antidiabetic drugs Fasting blood glucose 320 (12.6%) diabetes	Dementia (411) MRI AD (207) NINCDS-ADRDA Mixed AD (132) VaD (58) NINDS-AIREN California criteria	HR 1.4 (1.0-2.0) HR 1.6 (0.98-2.67) HR 1.8 (1.0-3.0) HR 0.8 (0.3-2.1)	Age, race, education, depression, and vascular factors
Akomolafe et al, ¹⁰⁸ 2006	USA, The Framingham Study, 2210 community-based subjects, 1325 (60%) women	70±7.0	12.7	Medical records Antidiabetic drugs Random blood glucose 202 (9.1%) diabetes	AD (237) DSM-IV NINCDS-ADRDA NINDS-AIREN	RR 3.0 (1.1-8.4) in subjects without <i>APOE</i> ε4 or elevated plasma homocysteine levels	Age, sex, education, and vascular factors
Hayden et al, ¹⁰⁹ 2006	USA, community-based 3264 subjects, 58.2% women	65+	3.2	Medical records Self-report 343 (10.5%) diabetes	Dementia (185) DSM-III-R AD (104) NINCDS-ADRDA VaD (37) NINDS-AIREN	HR 1.6 (0.9-2.6) HR 0.9 (0.3-2.2) HR 3.3 (1.0-9.8) in women	Age, education, <i>APOE</i> ε4, BMI, and vascular disease
Luchsinger et al, ¹¹⁰ 2005	USA, 1138 Medicare recipients, 69.8% women	65+	5.5	Self-report Antidiabetic drugs 20.3% diabetes	AD (176) NINCDS-ADRDA Dementia (270) Clinical diagnosis	HR 4.8 (1.9-11.6)	Age, sex, race, education, and <i>APOE</i> ε4
Borenstein et al, ⁵⁵ 2005	USA, The Kame Project, 1859 Japanese Americans, 55.9% women	65+	6	Self-report Antidiabetic drugs 17.2% diabetes	AD DSM-IV NINCDS-ADRDA	HR 3.3 (1.4-8.1) in ε4 noncarriers	Age, gender, low income, and TIA

Whitmer et al, ³⁰ 2005	USA, a retrospective cohort study, 8845 participants, 53.7% women	40-44	30	Self-report Antidiabetic drugs Fasting or random blood glucose, 11.3% diabetes	Dementia (721) ICD-9	HR 1.5 (1.2-1.8)	Age, sex, race, and education
Schnaider-Beeri et al, ¹¹¹ 2004	USA, a retrospective cohort study, 1892 Jewish men	40-65	35	Medical records Antidiabetic drugs OGTT 2.5% diabetes	Dementia (309) DSM-IV Hachinski's ischemic scale	OR 2.8 (1.4-5.7)	Age, sex, education, and cardiovascular disease
Xu et al, ¹¹² 2004	Sweden, The Kungsholmen Project, 1301 community-based dementia-free individuals, 75% women	75+	6	Medical records Antidiabetic drugs Random blood glucose 8.8% diabetes	Dementia (350) DMS-III-R AD (260) NINCDS-ADRDA VaD (49) NINDS-AIREN Hachinski's ischemic scale	HR 1.5 (1.0-2.1) HR 1.3 (0.9-2.1) HR 2.6 (1.2-6.1)	Age, sex, MMSE, education, and vascular factors
Luchsinger et al, ¹¹³ 2004	USA, a random sample of 683 Medicare recipients, 70.5% women	65+	5.4	Self-report Antidiabetic drugs 22.3% diabetes	Dementia (137) DSM-IV AD (137) NINCDS-ADRDA	HR 2.2 (1.5- 3.1) HR 2.2 (1.6-3.2)	Age, sex, and education
Arvanitakis et al, ¹¹⁴ 2004	USA, 824 Catholic nuns, priests and brothers, 68.8% women	55+	9	Medical records Antidiabetic drugs 127 (15.4%) diabetes	AD (151) Clinical diagnosis	HR 1.6 (1.1-2.5)	Age, sex, and education
Yamada et al, ¹¹⁵ 2003	Japan, a prospective study, 1774 subjects	43+	30	Medical records (n of diabetes not shown)	Dementia (114) DSM-III-R AD (51) DSM-IV VaD (38)	OR 4.4 ($p=0.007$) OR 1.3 ($p=0.06$)	Age, sex, and education No significance after multi-adjustment
Macknight et al, ¹¹⁶ 2002	Canada, The Canadian Study of Health and Aging, community-based cohort, 5574 subjects, 61% women	65+	5	Self-report Antidiabetic drugs Random blood glucose 503 (9.0%) diabetes	Dementia (467) CAMDEX AD (267) NINCDS-ADRDA VaD (89) NINDS-AIREN	RR 1.3 (0.9-1.8) RR 1.3 (0.8-2.0) RR 2.0 (1.2-3.6)	Age, sex, education, and vascular disease

Peila et al, ¹¹⁷ 2002	USA, The Honolulu Asia Aging Study, 2574 men (216 autopsy)	72-91	3	Self-report Antidiabetic drugs Fasting or OGTT 35% diabetes	Dementia (128) DSM-II-R AD (68) NINCDS-ADRDA VaD (34) California criteria	RR 1.5 (1.0-2.2) RR 1.8 (1.1-2.9) RR 2.3 (1.1-5.0)	Age, education, APOE ε4, survival status, and vascular factors and disease
Hassing et al, ¹¹⁸ 2002	Sweden, a population-based cohort, 702 individual twins (351 pairs), 70% women	80+	8	Medical records Self-report 18.5% diabetes	Dementia (187) DSM-III-R AD (105) NINCDS-ADRDA VaD (50) NINDS-AIREN	RR 1.2 (0.8-1.7) RR 0.8 (0.5-1.5) RR 2.5 (1.4-4.8)	Age, sex, education, and vascular disease
Ott et al, ¹¹⁹ 1999	The Netherlands, The Rotterdam Study, 6370 elderly, 60% women	55+	2.1	Anti-diabetic drugs Random glucose or OGTT 10.9% diabetes	Dementia (126) DSM-III-R AD (89) NINCDS-ADRDA VaD (18) NINDS-AIREN	RR 1.9 (1.3-2.8) RR 1.9 (1.2-3.1) RR 2.0 (0.7-5.6)	Age and sex
Curb et al, ¹²⁰ 1999	USA, The Honolulu Asia Aging Study, a historical prospective study, 3774 men	45-68	25	OGTT (n of diabetes not shown)	Dementia DSM-III-R AD NINCDS-ADRDA VaD California criteria	RR 1.0 (0.5-2.0) RR 1.5 (0.8-2.8)	Age and education (No number of cases shown)
Leibson et al, ¹²¹ 1997	USA, a population-based historical cohort study, 1455 subjects with diabetes	20+	15	Fasting blood glucose OGTT 100% diabetes	Dementia (101) DSM-III-R AD (77) Autopsy	SMR 1.6 (1.3-2.1) SMR 1.6 (1.3-2.0)	Age and sex
Yoshitake et al, ¹²² 1995	Japan, 826 community-based residents, 59.7% women	65+	7	Self-report 8.4% diabetes	AD (42) NINCDS-ADRDA VaD (50) NINDS-AIREN	RR 2.18 (0.97-4.90) RR 2.8 (2.6-3.0)	Age (no significant effect after multi-adjustment)
Kazman, et al, ¹²³ 1989	USA, 488 volunteer cohort, 64% women	75-85	3.7	Medical records Antidiabetic drugs	AD (32) Neuroimaging VaD (15) Consensus committee	OR 0.5 (0.1-2.3)	Not reported

Table 3. Major epidemiological studies concerning the association between diabetes and post-stroke dementia. The relative risk (RR), or odds ratios (OR) refer to dementia, when not otherwise specified.

Author, year	Country and sample	Age (y)	Diabetes: Ascertainment of cases	Dementia: N of cases and diagnostic criteria	Results	Covariates
Klimkomkiewicz et al, ¹²⁵ 2006	Poland, 220 hospital-based stroke patients	67.5	Medical records, Antidiabetic drugs 14.5% diabetes	Dementia (44) DSM-IV	OR 3.3 (1.2-9.0)	Not reported
Ivan et al, ¹²⁶ 2004	USA, a nested case-control study, 212 stroke subjects, and 1060 controls	79.2 & 78.6	Medical records Antidiabetic drugs Random blood glucose 14.2% diabetes	Dementia (158) DSM-IV NINCDS-ADRDA NINDS-AIREN	25% in cases, 13% in controls ($p < 0.001$)	Not reported
Luchsinger et al, ¹²⁷ 2001	USA, a cohort study, 1262 dementia-free subjects followed for 4.3 years, 68.9% women	75.6±5.9	Medical records Antidiabetic drugs 20% diabetes	Post-stroke dementia (36) DSM-IV AD (157) NINCDS-ADRDA	RR 3.4 (1.7-6.9) RR 1.3 (0.8-1.9)	Sex, education, race, <i>APOE</i> $\epsilon 4$ and vascular disease
Desmond et al, ¹²⁸ 2000	USA, 453 stroke patients followed for 3 months	60+	Medical records Informant-report 34.4% diabetes	Dementia (119) DSM-III-R NINDS-AIREN	OR 1.8 (1.1-3.0)	Age, sex, education, race, and stroke location
Inzitari et al, ¹²⁹ 1998	Italy, 339 stroke patients followed for 1 year	70-76	Antidiabetic drugs Fasting blood glucose 19.6% diabetes	Post-stroke dementia (57) ICD-10 NINCDS-ADRDA	OR 1.4 (0.7-2.5)	Univariate analysis
Pohjasvaara et al, ¹³⁰ 1998	Finland, 337 stroke patients, followed for 3 months	55-85	Inpatient register 23.7% diabetes	Dementia (107) DSM-III	22.4% and 24.4% in demented and nondemented groups, $p=0.70$	Not reported
Censori et al, ¹³¹ 1996	Italy, 104 stroke patients, followed for 3 months	40-79	Antidiabetic drugs Fasting blood glucose 26.9% diabetes	Dementia (15), NINDS-AIREN	OR 59.4 (4.3-82.1)	Age, cognition, and infarctions

Kokmen et al, ¹³² 1996	USA, 971 stroke patients, followed for 6728 person-years	50+	Medical records (n of diabetes not shown)	Dementia (196) Clinical evidence Neuroimaging or autopsy	No significant differences	Not reported
Tatemichi et al, ¹³³ 1993	USA, 251 stroke patients, followed for 3 months	60+	Self-report 35.1% diabetes	Dementia (66) DSM-III-R	OR 2.6 (1.3-5.3)	Age, education, race, and stroke history
Loeb et al, ¹³⁴ 1992	Italy, 108 stroke patients, 17.6% women, followed for 4 years	65.1	Self-report (n of diabetes not shown)	Dementia (25) DSM-III-R	No significant differences	Not reported

Table 4. Major population-based prospective studies concerning the association of prediabetes with cognitive impairment. The odds ratios (OR) refer to cognitive decline or cognitive impairment, when not otherwise specified.

Author, year	Study population	Age (y)	Prediabetes: Ascertainment of cases	Cognitive tests	Results	Covariates
Cross-sectional studies						
Lindeman et al, ¹³⁷ 2001	USA, random sample of 883 Medicare recipients	65+	OGTT or fasting blood glucose 175 (19.5%) prediabetes	MMSE and 9 cognitive tests	Nonsignificant difference between prediabetic and normal groups	Age, sex, education, race, and depression
Vanhanen et al, ¹³⁸ 1997	Finland, 22 fasting blood glucose 5.9-11 mmol/l, 26 controls	65+	Fasting blood glucose 5.9-11 mmol/l (median)	Memory, attention, visuomotor speed, verbal fluency	Subjects with glucose 5.9-11.0 mmol/l developed more associated cognitive deficits than controls	Not reported
Kalmijin et al, ¹³⁶ 1995	The Netherlands, 462 men	69-89	OGTT 47 (9.8%) prediabetes	MMSE <26	OR 1.2 (1.0-1.4)	Age, occupation, and smoking
Longitudinal studies						
Yaffe et al, ¹³⁹ 2006	USA, 7027 postmenopause women, followed 4 years	66	Fasting blood glucose 297(4.6%) prediabetes	5 standard cognition tests (Z scores change <0)	OR 1.6 (1.0-2.6) for cognitive decline	Age
Vanhanen et al, ¹⁴⁰ 1998	Finland, 1300 subjects, followed 3.5 years	73	OGTT and fasting blood glucose 80 (6.2%) prediabetes	MMSE and 6 cognitive tests	Prediabetes was associated with mild impaired cognitive function	Age and education

In Table 1-4:

AD = Alzheimer's Disease

ADDTC Criteria = California Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment

APOE = Apolipoprotein E gene

BMI = Body Mass Index

CAMDEX = Cambridge Mental Disorders of the Elderly Examination

CERAD = Consortium to Establish a Registry for Alzheimer's disease

DSM-III-R (DSM-IV) = Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (Fourth Edition)

HIV = Human Immunodeficiency Virus

HR = Hazard Ratio

ICD = International Classification of Diseases

MMSE = Mini-Mental State Examination

MRI = Magnetic Resonance Imaging

NFTs = Neurofibrillary tangles

NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria

NINDS-AIREN = National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria

OGTT = Oral Glucose Tolerance Test

OR = Odds Ratio

RR = Relative Risk

SMR = Standardized Mortality Rate

TIA = Transient Ischemic Attack

VaD = Vascular Dementia

2 AIMS

2.1 GENERAL AIMS

The general aims of this thesis are to investigate and understand the relationship between diabetes and the occurrence of dementia and its major subtypes in the elderly population.

2.2 SPECIFIC AIMS

The specific aims addressed in four different studies are summarized below.

1. To examine the longitudinal association between diabetes and the risk of incident dementia and its major subtypes (i.e. AD and VaD), and to evaluate the joint effect of diabetes and vascular disease on dementia risk (*Study I*).
2. To investigate the effect of borderline diabetes on the risk of dementia and AD, and to explore the combined effect when borderline diabetes occurs together with two other components of the metabolic syndrome (i.e. high blood pressure and obesity) (*Study II*).
3. To further investigate the association between diabetes and the risk of AD by examining the role of glycemic control and vascular comorbidities as modifiers or mediators of this association (*Study III*).
4. To verify the association between diabetes and risk of dementia, AD and VaD in Swedish twins, and to explore to what extent genetic and early life environmental factors contribute to this association (*Study IV*).

3 METHODS

The data used in this thesis are derived from two projects: The Kungsholmen Project and The HARMONY Study.

3.1 THE KUNGSHOLMEN PROJECT (*Studies I, II, and III*)



3.1.1 Study population

The Kungsholmen Project is a community-based cohort study on aging and dementia. All registered inhabitants ($n=2,368$) who were living in the Kungsholmen district of Stockholm, Sweden, and were 75 years and older on October 1st, 1987 were initially invited to the project, and 1,810 (76.4%) agreed to participate in the baseline survey.^{145,146}

Baseline survey. At baseline (1987-1989), a two-phase survey consisting of a screening phase and a clinical phase was carried out. The screening phase included a health interview and the administration of the MMSE¹⁴⁷ for all 1,810 participants. In the clinical phase, all subjects who screened positive ($MMSE \leq 23$) and an age- and sex-stratified random sample of subjects who screened negative ($MMSE > 23$) were invited to undertake a comprehensive physical, neurological, and psychiatric assessment, similar to the examination usually performed in clinical practice. During the clinical phase, 110 subjects refused to participate and 225 persons were diagnosed as having dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria (DSM-III-R).⁵ Thus, 1,475 of 1,810 baseline participants were identified as being free of dementia. Of them, two subjects had mental disorders and 172 refused to participate in the first follow-up examination (1991-1993) or had moved, leaving 1,301 dementia-free subjects.

Follow-up examination. After the baseline survey, the Kungsholmen population experienced four waves of follow-up examination, each with an average three years interval. At every follow-up occasion, all surviving subjects underwent a structured interview performed by nurses, a clinical examination by physicians, and neuropsychological assessments by psychologists. If the subject was not able to answer, an informant, usually a next-of-kin was interviewed. For those subjects who had died

before the follow-up examination, information regarding their health status was obtained from the computerized inpatient register system, which is a register of discharge diagnoses from all hospitals in Stockholm since 1969. The individual hospital records, discharge diagnoses, and the death certificates were examined. The populations for *Studies I, II, and III* consisted primarily of the baseline dementia-free participants. Data used for this thesis were derived from the baseline survey (Phases I & II, 1987-1989), the first follow-up (Phase III, 1991-1993), the second follow-up (Phase IV, 1994-1996), and the third follow-up (Phase V, 1997-1998) examinations of the Kungsholmen population. Figure 5 shows the flowchart of the study population in the Kungsholmen Project and the numbers of participants in *Studies I, II, and III*.

3.1.2 Data collection

During the screening phase of the baseline survey (Phase I), a health interview was carried out to collect data on demographics, medical history, and cognitive function. The clinical phase (Phase II) of the baseline survey consisted of a dementia work-up including a structured interview, a comprehensive clinical examination, and psychological tests implemented following the standardized protocols.^{145,146,148}

Sociodemographic characteristics. Data on demographic variables (e.g., age, sex, and education) were collected from the subjects at the baseline interview. Education level was measured by the maximum years of formal schooling and was divided into <8 years vs. ≥ 8 years according to a previous study within the Kungsholmen Project.⁵³

Cognitive function. Global cognitive functioning was assessed with the MMSE at baseline (screening phase) for all participants and at each follow-up examination for surviving subjects.

Medical drug use. Data on medical drug use for the two weeks prior to the baseline interview were collected from the subjects and verified by inspecting drug prescriptions and containers. Medical drugs were coded following the *Anatomical Therapeutic and Chemical* (ATC) classification system.¹⁴⁹ Antidiabetic drugs were considered as medications used to control blood glucose levels (hypoglycemic medications or insulin injection, ATC code A10). Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ATC codes C02, C03, and C07).

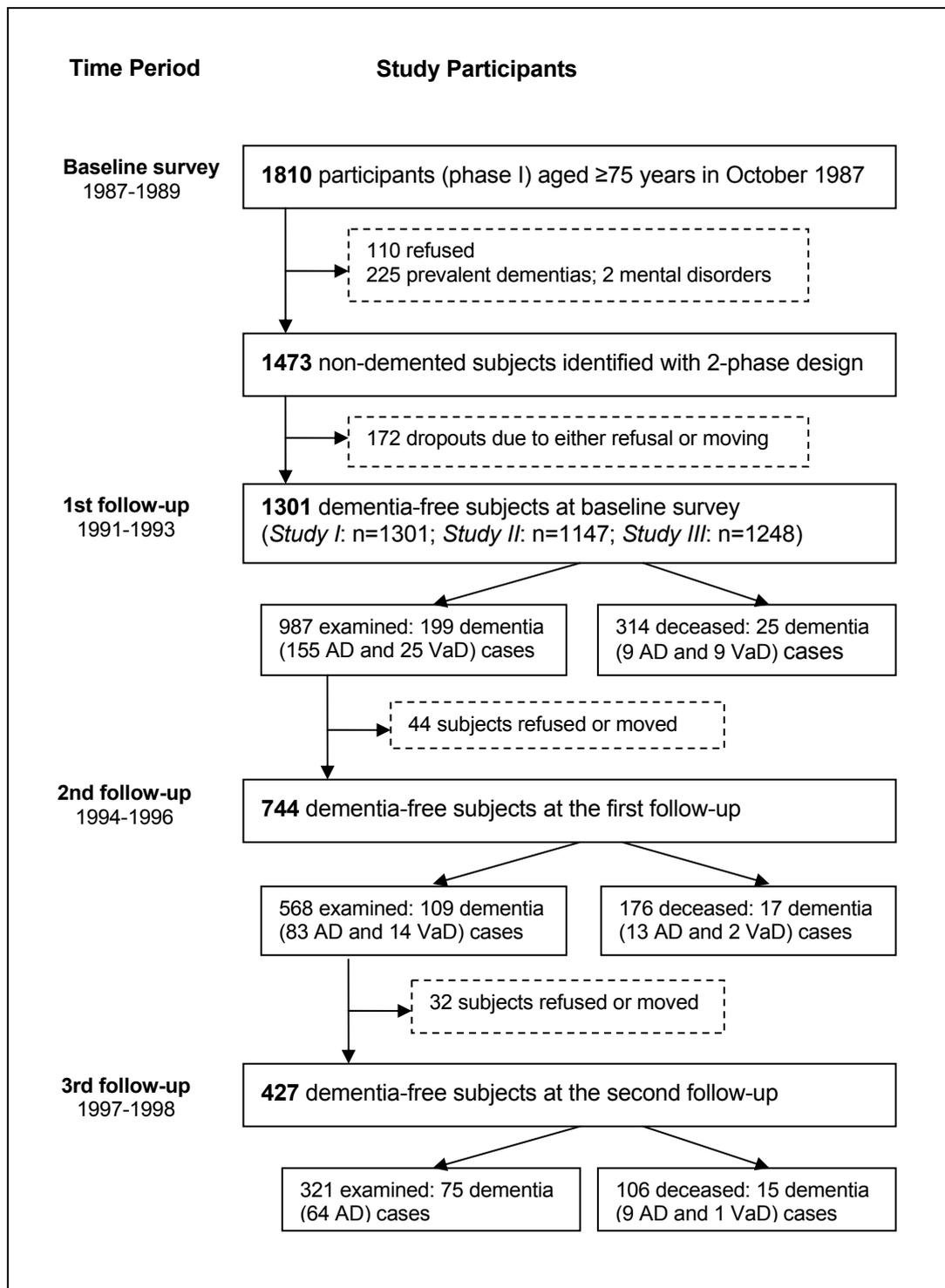


Figure 5. Flowchart of the study population in The Kungsholmen Project, 1987-1998
AD = Alzheimer’s disease, VaD = vascular dementia

Comorbidities. Data on medical history or comorbidities at baseline and during the entire follow-up period were obtained from the computerized inpatient register system, which recorded up to six different diagnosed disorders during each hospital admission. The International Classification of Disease, Eighth revision (ICD-8) was used by the register system until 1986. Since 1987 the ICD Ninth Revision (ICD-9) has been employed. Disease and medical conditions that were considered in various studies included diabetes (ICD-8 and ICD-9 code 250), heart disease (ICD-8 and ICD-9 codes 410–414, 427, and 428), and stroke (ICD-8 and ICD-9 codes 430–438).

Blood glucose measures. Blood samples were taken at baseline and at each follow-up examination. Blood glucose level was measured using a glucose oxidase procedure.¹⁵⁰ Data on blood glucose were available for 95.9% (n=1,248) of the dementia-free subjects at baseline.

Other baseline covariates. Weight and height were measured with a standard scale in light clothing and no shoes.⁴¹ BMI was calculated as weight in kilograms divided by squared height in meters. Arterial blood pressure (i.e., systolic Korotkoff phase I and diastolic phase V) was measured by nurses with the subjects in a sitting position after at least a five minute rest. Genomic DNA was prepared from peripheral blood samples that were taken at baseline, and *APOE* allelic status was determined following a standard procedure.²⁶ Data on *APOE* genotype were available for 75.7% (n = 985) of the dementia-free subjects at baseline (n=1,301).

3.1.3 Assessment of diabetes and borderline diabetes

Diabetes at baseline is considered to be present if the subject was either registered as having diabetes (ICD-8 and ICD-9 code 250), or the subject was taking antidiabetic drugs (ATC code A10), or the blood glucose level was higher than 11.0 mmol/l.^{72,151} The last criterion included all cases of “undiagnosed diabetes” when the random blood glucose level was ≥ 11.0 mmol/l and when there was neither a history of diabetes nor antidiabetic drug use.¹⁵² Borderline diabetes is defined as a random plasma glucose level ≥ 7.8 but < 11.0 mmol/l in diabetes-free subjects.^{72,151}

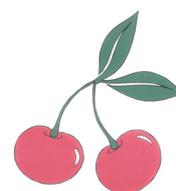
3.1.4 Diagnosis of dementia, AD and VaD

At each follow-up, all participants underwent a comprehensive clinical examination and cognitive tests. Dementia was diagnosed on the basis of clinical judgment following the DSM-III-R criteria, in which a validated 3-step diagnostic procedure was used.^{145,146} In brief, two examining physicians independently made a preliminary diagnosis, and in the case of disagreement, a third opinion from a specialist was sought to reach a concordant diagnosis. The diagnosis of AD required gradual onset, progressive deterioration, and the lack of any other specific causes of dementia. The diagnosis of VaD required abrupt onset, stepwise deterioration, history of stroke, or focal deficits. Hachinski's ischemic scale¹⁴³ was used to support the differential diagnosis between AD and VaD. The diagnostic criteria used for AD and VaD were equivalent to "probable AD" according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria¹⁵³ and to "possible VaD" according to the NINDS-AIREN criteria,¹⁴³ respectively. For subjects who died during each follow-up period, two physicians made a diagnosis of dementia or subtypes by thoroughly reviewing medical records and death certificates. For *Study III*, the AD diagnoses were further subdivided into two groups: AD cases with history of stroke (but not temporally related to dementia onset), and pure AD cases in the absence of any current or past vascular diseases (hypertension, cerebrovascular disease, ischemic heart diseases, heart failure, and atrial fibrillation) and diagnosed diabetes.¹⁵⁴

3.2 THE HARMONY STUDY (*Study IV*)

3.2.1 Study population

Participants were members of the population-based Swedish Twin Registry that was established in the 1960s, when all twins in Sweden had been identified.¹⁵⁵ In 1998-2001, all living twins in the registry who were born in 1935 and earlier (aged ≥ 65 years), both same- and unlike-sex twins, were invited to participate in a study concerning dementia known as HARMONY, which is taken from the Swedish words for "health" (Hälsa), "genes" (Arv), "environment" (Miljö), "and" (och), and "new" (NY).¹⁵⁶ In brief, a total number of 20,206 individuals in the Swedish Twin Registry were eligible for screening. Of them, 5,771 were not reached by telephone, 712 could



be reached but were not able to undertake the interview, and 30 failed to complete the cognitive screening test, leading to 13,693 subjects available for the analysis in *Study IV* (Figure 6). The telephone screening identified 1,569 (11.5%) participants with cognitive dysfunction. A total number of 1,939 individuals were invited to participate in the clinical phase, including: 1) all twins who were screened positive; 2) those who were not able to be screened by telephone if the informant gave an indication that the reason was dementia; 3) twin partners to those index twins who were diagnosed with dementia; and 4) normal controls. Clinical diagnoses were available for 1,357 individuals. The participation rates were 71.4% for the screening phase, and 70.0 % for the clinical phase. The prevalence of dementia in this Swedish twin cohort was comparable with several major epidemiological studies of dementia prevalence in Europe and the USA.¹⁵⁶

3.2.2 Data collection

For all 13,693 individuals who participated in the screening phase, information concerning demographic factors, education, health status, behavior, common diseases, use of medications, height and weight was obtained during the telephone interview. In addition, for subjects who participated in the clinical phase, information about medical and lifestyle factors, including the use of medications, vascular risk factors, and educational level, was collected during the examination and from informants. Finally, information on history of vascular disorders was derived from the inpatient registry system. Each record in the system included discharge diagnoses according to the ICD, seventh revision (ICD-7) through 1968. Medical conditions derived from the inpatient register database included hypertension (ICD-7 codes 444-447; ICD-8 codes 400-404; ICD-9 codes 401-405), ischemic heart disease (ICD-7 codes 420-421; ICD-8, 9 codes 410-414), cardiac dysrhythmia, heart failure or other myocardial insufficiency (ICD-7 codes 433 and 434; ICD-8, 9 codes 427 and 428), and stroke (ICD-7 codes 330-334; ICD-8, 9 codes 430-438). Information on survival status from the screening phase to October 2004 was obtained from the Cause of Death Register.

3.2.3 Ascertainment of diabetes

Diabetes was detected by integrating information from the inpatient registry (ICD-7 code 260; ICD-8, 9 code 250), and self- and informant-reported history of diabetes. The age of diabetes onset was estimated according to the earliest recorded date of diabetes either in the inpatient registry or the date of diabetes onset reported by probands or informants.

3.2.4 Diagnosis of dementia, AD and VaD

A two-step procedure was utilized in the diagnosis of dementia. The first step was cognitive screening through a telephone interview using the validated TELE questionnaire for twins themselves^{157,158} and the Blessed Dementia Rating Scale (BDRS) for informants.¹⁵⁹ The second step was a full dementia workup. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria⁶ were used to define dementia cases. The assessment team made an initial diagnosis based on the workup and review of medical records. These preliminary diagnoses were reviewed by a diagnostic team. Differential diagnoses were made according to the NINCDS-ADRDA criteria for AD¹⁵³ and the NINDS-AIREN criteria for VaD.¹⁴³ The cases completely fulfilling the DSM-IV criteria were diagnosed as “dementia”, in contrast with a category of “questionable dementia”, which was used for individuals who did not fulfill one of the first three DSM-IV diagnostic criteria, but did exhibit either cognitive impairment or functional disability. Participants were first classified as demented, questionable, or non-demented, and then given a differential diagnosis for dementia subtype for demented subjects. Details of the clinical examination and diagnostic procedure have been reported elsewhere.¹⁵⁶

The age of dementia onset was estimated by the assessment team based on information that was obtained from a detailed informant interview including questions such as when various symptoms first occurred and how they interfered with the twin’s life, and from review of medical records for mentioning any problems with memory or thinking or a formal dementia diagnosis. Age at onset was defined as the age when definite and enduring symptoms of dementia first appeared.¹⁶⁰

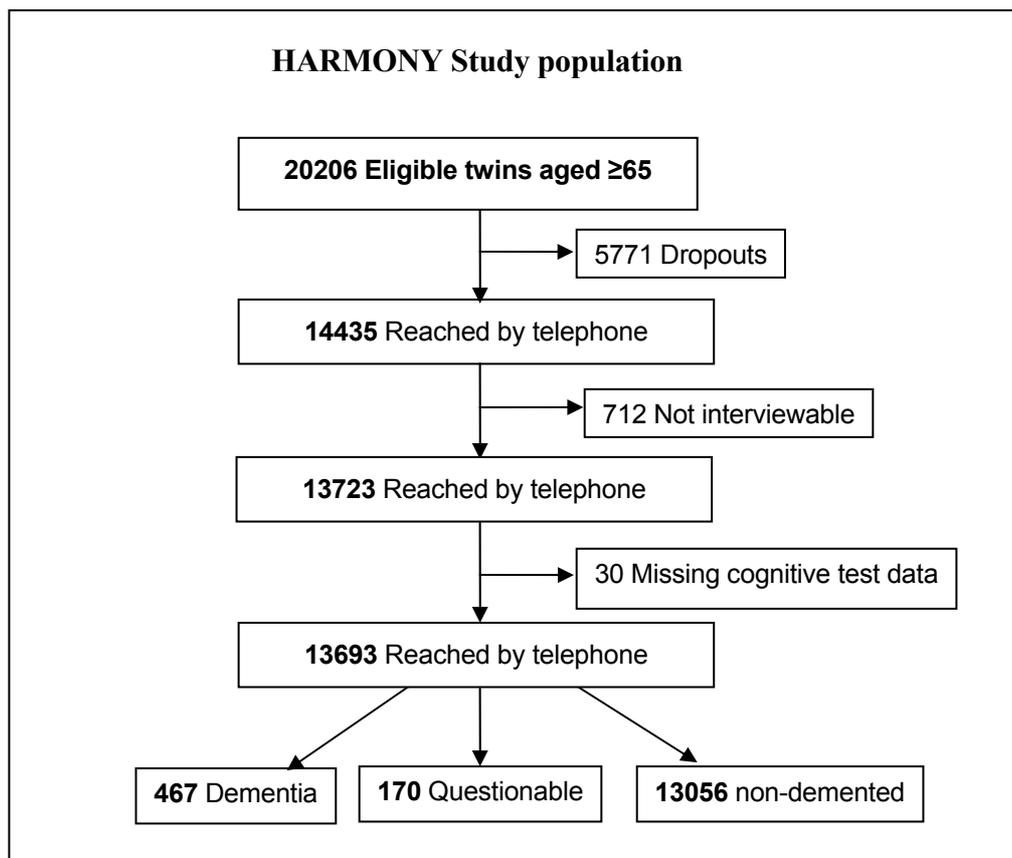


Figure 6. Flowchart of the study population in the HARMONY Study

3.3 STATISTICAL ANALYSIS

All data analyses were completed with the SPSS statistical package (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA), the SAS statistical software version 9.1 for Windows (SAS Institute, Inc., Cary, NC, USA), and the Stata version 9.0 for Windows (Stata-Corp, College Station, Texas). Table 5 summarizes the outcome variables and the determinants for each study.

Statistical tests. The main associations examined in this thesis were between diabetes or borderline diabetes and dementia status. Throughout the four studies a range of statistical tests were employed. Chi-square test and Student's t-test or analysis of variance were performed to assess the statistical differences of proportions and means between groups. The Mann-Whitney test was used to test for differences in the medians between groups for continuous variables with non-normal distribution.

Specific analyses for each study. All types of dementia, AD, and VaD were analyzed as separate outcome variables in all studies, except for in *Study III*, in which AD with stroke, and pure AD were used as additional outcomes. Various possible confounding factors were taken into account in the different studies. The statistical methods that were performed in the various studies are described as below.

In *Studies I, II, and III*,

- 1) The incidence rates were calculated as the number of events divided by follow-up time (i.e., person-years at risk). For the non-demented subjects, the follow-up time was calculated as the time interval between the date of baseline survey and the date of last follow-up contact or death. For demented subjects, half of this time was assumed due to the insidious nature of dementia onset.¹⁴⁶
- 2) Multiple Cox proportional-hazards models were used to estimate the hazard ratios (HRs, or relative risk RRs) and 95% confidence intervals (CIs) of occurrence of dementia and its major subtypes associated with exposure factors (diabetes or borderline diabetes), in which a number of potential confounders were taken into account. The follow-up time was used as time scale in all Cox regression analyses. The proportional hazards assumption was confirmed by graphs and tests based on Schoenfeld residuals. The combined effect of two factors was assessed by creating dummy variables based on the joint exposures to both factors. The statistical interactions were examined by incorporating the independent variables and cross-product terms in the same models.
- 3) Kaplan-Meier survival analysis was used to compare the cumulative survival probability of subjects among different groups.

In *Study IV*, education was missing in 155 subjects. The expectation maximization (EM) imputation method was used to replace the missing information based on Little's test for missing completely at random (MCAR). Multinomial logistic regression was used to estimate the odds ratios (OR) and 95% CI of dementia and questionable dementia separately in relation to diabetes to verify whether the association between diabetes and dementia status differed depending on diagnostic certainty. In the subsequent analyses, a combination of dementia and questionable dementia was considered as an outcome. Two analytical strategies were then applied:

- 1) Unmatched case-control analyses using generalized estimating equations (GEE) models, which are conceptually equivalent to the analysis of classical case-control design, except with control for the clustering of twins within a pair;
- 2) Dementia-discordant co-twin matched case-control analyses using conditional logistic regression models. The latter strategy is more informative than using unrelated case-control samples, as it allows matching for unmeasured familial factors, which could be related to genetic background or early life environment. If the association found in GEE analyses becomes attenuated in co-twin matched case-control analyses, genetic factors or familial environments or both are likely to play a role in the association. If strength of the association further decreases when only monozygotic (MZ) twin pairs are analyzed, genetic confounding can be suspected. In contrast, if a significant association remains when using co-twin matched pairs, the influences of genetic or early environmental factors on the association are likely to be marginal (Figure 7). Logistic regression was also used to test the difference in ORs from GEE and conditional logistic models by examining the difference of diabetes among unmatched versus co-twin controls.

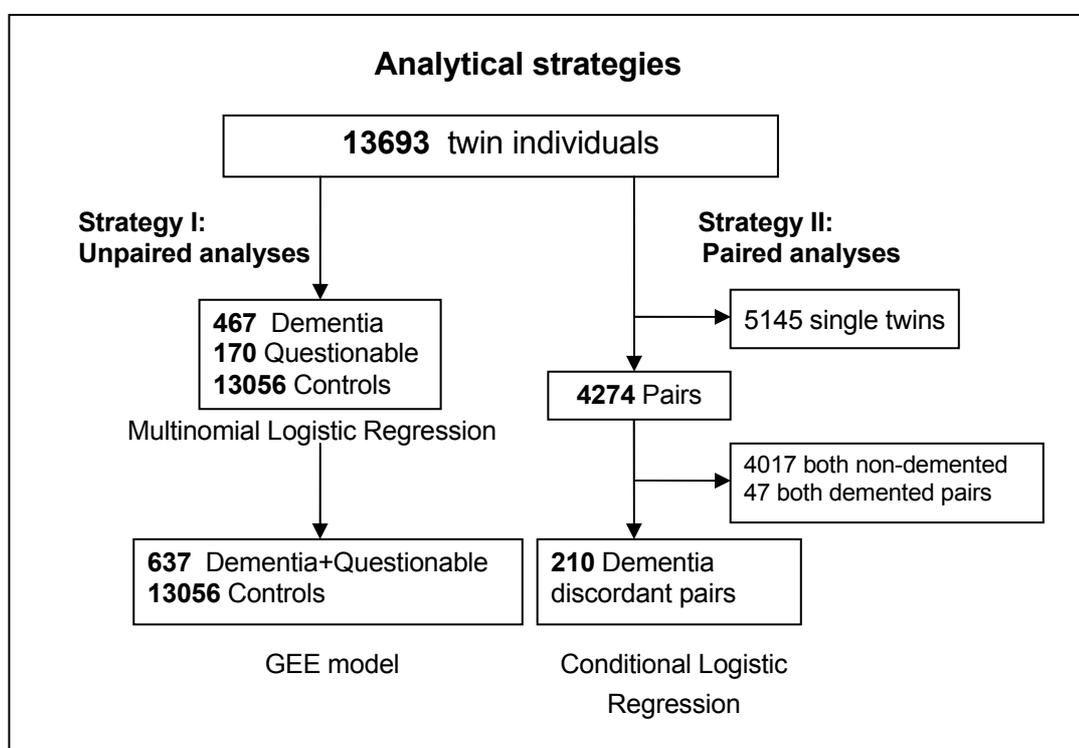


Figure 7. Two analytical strategies for the HARMONY Study (*Study IV*)

GEE = Generalized estimating equation

Table 5. Statistical models used in various studies of this thesis

Studies	Model	Exposure	Outcome	Covariates	Procedure
<i>Study I</i>	Cox proportional hazards model	Diabetes	Dementia AD VaD	Age, sex, education, blood pressure, vascular disease, BMI and antihypertensive drug use	1st, diabetes 2nd, adding age, sex, and education 3rd, adding BMI and vascular disease 4th, interaction of diabetes with heart disease or hypertension, <i>APOE</i> ε4
<i>Study II</i>	Cox proportional hazards model	Borderline diabetes	Dementia AD	Age, sex, education, blood pressure, vascular disease, BMI, development of diabetes, survival status, and antihypertensive drug use	1st, borderline diabetes 2nd, adding age, sex, and education 3rd, adding BMI and vascular disease 4th, adding survival status and development of diabetes 5th, interaction between borderline diabetes, hypertension, obesity and <i>APOE</i> ε4
<i>Study III</i>	Cox proportional hazards model	Diabetes Borderline diabetes	Dementia AD VaD AD with stroke Pure AD	Age, sex, education, blood pressure, vascular disease, BMI, survival status, <i>APOE</i> genotype, development of diabetes, and antihypertensive drug use	1st, diabetes and/or borderline diabetes 2nd, adding age, sex, and education 3rd, adding BMI, <i>APOE</i> genotype, and survival status 4th, adding vascular disease
<i>Study IV</i>	Multinomial logistic regression	Diabetes Diabetes onset age <65 and ≥65	Dementia	Age, sex, education, blood pressure, vascular disease, zygotic status and BMI	1st, diabetes to dementia and to questionable dementia separately
	Generalized estimating equation		Questionable dementia		2nd, diabetes onset age <65 and ≥65 to all dementia in whole twin cohort
	Conditional logistic regression		AD		3rd, adding age, sex, and education
	Logistic regression		VaD		4th, adding BMI and vascular disease 5th, diabetes onset age <65 and ≥65 to dementia in twin pairs 6th, compare estimates from whole twin cohort and twin pairs

AD = Alzheimer’s disease; VaD = vascular dementia

Vascular disease: ischemic heart disease, heart failure, cardiac dysrhythmia, stroke and hypertension

4 ETHICAL CONSIDERATIONS

4.1 THE KUNGSHOLMEN PROJECT

All people living in the Kungsholmen district who were aged ≥ 75 years, and eligible for the study at baseline, were sent a personal letter, which explained the nature of the project and the importance of participation, yet which emphasized that involvement was voluntary. Thereafter, all participants were contacted by phone to check their availability, and to book a date for their first visit. At the screening evaluation, informed consents were obtained directly from the subject, after explaining the aims of the project and clarifying that all information would be kept strictly confidential. If there was any indication that the subject had severe cognitive impairment, consent was taken from a proxy, usually a next-of-kin or close relative. However, the examination or interview was to be interrupted if the participant, in any way, expressed anguish or discomfort, regardless of whether the informed consent had been given by the subjects themselves or by a proxy. All phases of the Kungsholmen Project received approval from the Ethics Committee at the Karolinska Institutet, Stockholm, Sweden.

The first three studies included in this thesis used the data collected from Phase I to Phase V of the project as well as data from medical records, death certificates and inpatient register database. For each phase data collection, approval from the Ethics Committee at the Karolinska Institutet was obtained:

- Phases I & II (baseline survey): Dnr. 87:148; Dnr. 87:234
- Phase III (the first follow-up examination): Dnr. 90:251
- Phase IV (the second follow-up evaluation): Dnr. 94:122
- Phase V (the third follow-up examination): Dnr. 99:308
- Death certificate and Inpatient register data: Dnr. 99:025; Dnr. 01:020

All staff working with the Kungsholmen Project database follow the guidelines of the Swedish Council for Research in the Humanities and Social Sciences: the principles of autonomy and integrity, the rule of consent, and the demand for research.¹⁶¹

4.2 THE HARMONY STUDY

Informed consent was required from each participant during the telephone interview and again during the clinical phase. The data collection procedures were reviewed and approved by the Swedish Data Inspection Board, Stockholm, Sweden, the Regional Ethics Committee at Karolinska Institutet, Stockholm, and the Institutional Review Board of the University of Southern California. For the HARMONY survey, the approval from the Ethics Committee of the Karolinska Institutet was obtained (Dnr: 97:051).

5 RESULTS

5.1 THE KUNGSHOLMEN PROJECT (*Studies I, II, and III*)

5.1.1 Characteristics of the study population at baseline

Of the 1,473 individuals that were initially identified as being free of dementia at baseline, 172 subjects were lost to the first follow-up. The remaining 1,301 non-demented subjects constituted the basic population of the first three studies in this thesis. Compared to participants, dropouts were younger, but the two groups had no significant difference in other demographic features. Multiple logistic regression analysis showed that being a dropout was associated with ORs of 0.94 (95% CI, 0.91-0.98) for old age, 1.26 (95% CI, 0.84-1.87) for female sex, 1.24 (95% CI, 0.89-1.73) for low education (<8 vs. ≥8 years), 1.02 (95% CI, 0.94-1.09) for a lower score on MMSE (<24 vs. ≥24), 0.35 (95% CI, 0.28-1.06) for diabetes, 0.69 (95% CI, 0.47-1.09) for heart disease, and 0.66 (95% CI, 0.45-1.08) for stroke.

Table 6. Characteristics of the initial dementia-free cohort (n=1473) at baseline by participation

Characteristics	Participants (n=1301)	Dropouts (n=172)	p-value
Age (years), mean (SD)	81.5 (5.0)	80.4 (3.9)	0.004
Female sex, n (%)	976 (75.0)	136 (79.1)	0.246
Educational level <8 years, n (%)	760 (58.6)	106 (62.4)	0.355
MMSE score <24, n (%)	89 (6.8)	7 (4.1)	0.166
Stroke, n (%)	94 (7.2)	6 (3.5)	0.067
Heart disease, n (%)	217 (16.7)	21 (12.2)	0.134
Diabetes, n (%)	46 (3.5)	2 (1.2)	0.112
SBP [†] , mm Hg, mean (SD)	157.5 (46.2)	157.4 (22.8)	0.977
DBP [†] , mm Hg, mean (SD)	83.2 (45.8)	82.5 (11.6)	0.862
BMI, mean (SD)	23.7 (3.5)	23.4 (3.3)	0.275
Antihypertensive drug use, n (%)	584 (44.9)	72 (41.9)	0.453

[†]Number of subjects with missing values were 7 for education (2 dropouts), 35 for blood pressure (4 dropouts), and 77 for BMI (6 dropouts).

5.1.2 Relation of diabetes to dementia

At baseline, 114 (8.8%) of the 1,301 participants were identified as having diabetes. Of them, 42 (36.8%) used oral antidiabetic medications, and 6 (5.3%) were treated with insulin. During the 6-year follow-up, 350 subjects developed dementia, including 260 AD and 49 VaD cases. As shown in Table 7, diabetes was significantly related to an increased risk of dementia and VaD independently of vascular disease. In a separate analysis, diabetic patients that used oral antidiabetic medications were at a substantially higher risk for dementia and VaD.

A higher blood glucose level (>11.0 mmol/l) was specifically related to an increased risk of VaD. When the blood glucose level was entered as a continuous variable, the adjusted HR per 1-mmol/l increment was 1.30 (95% CI, 1.11-1.52). Diabetes in combination with severe systolic hypertension significantly increased the risk of dementia, AD and VaD. The adjusted HRs related to the interaction term of severe systolic hypertension-by-diabetes were 3.02 (95% CI, 1.42-6.43) for dementia, 2.60 (95% CI, 1.01-6.82, $p=0.05$) for AD, and 11.33 (95% CI, 1.50-88.31) for VaD. Diabetes and heart disease had a synergistic effect on VaD. The adjusted HR of VaD related to the term of heart disease-by-diabetes was 7.8 (95% CI, 1.12-62.61). There was no statistical interaction of diabetes with *APOE* $\epsilon 4$ allele on the risk of AD (HR 1.02; 95% CI, 0.32-2.93).

5.1.3 Borderline diabetes, dementia and AD

Of the 1,301 dementia-free subjects, 128 subjects were excluded due to having diabetes at baseline (i.e., history of diabetes, use of anti-diabetic medications, or a random blood glucose level ≥ 11.0 mmol/l)¹⁶² or missing baseline blood glucose data, leaving 1,173 subjects for the analysis. At baseline, 47 (4.0%) of the 1,173 dementia- and diabetes-free subjects were identified as having borderline diabetes. The prevalence of borderline diabetes was 4.2% in women, and 3.4% in men ($\chi^2=0.34$, $p>0.50$).

During the 9-year period, 397 subjects were diagnosed with dementia, including 307 with AD. As shown in Table 7, subjects with borderline diabetes had a higher incidence rate of dementia and AD. The borderline diabetes-associated HRs were 1.61 (95% CI, 1.02-2.58) for dementia and 1.68 (95% CI, 1.03-2.86) for AD after controlling for age,

sex and education. Further, Cox regression analyses suggested that the association between borderline diabetes and the elevated risk of dementia and AD was present independently of multiple potential confounders. We repeated the analyses among subjects who survived until the time when dementia status was determined (n=653, 348 dementia and 281 AD). Similar results were obtained after controlling for potential confounders; the borderline diabetes-associated HRs were 2.02 (95% CI, 1.23-3.34) for dementia and 2.23 (95% CI, 1.32-3.67) for AD.

5.1.4 Diabetes and AD

Of the 1,301 dementia-free subjects at baseline, 53 were excluded due to missing blood glucose values. Among the remaining 1,248 dementia-free participants, 75 (6.2%) and 47 (4.0%) were identified as having diabetes and borderline diabetes, respectively. Of the 75 patients with diabetes, 44 (58.7%) were recorded as having diabetes in the inpatient registry, which covered 25 of the 45 (60.0%) who reported use of antidiabetic drugs, and an additional 11 (14.7%) were detected to have undiagnosed diabetes. The modality of detection, treatment and blood glucose levels in subjects with diabetes and borderline diabetes is reported in Table 7.

During the 9-year follow-up period, 420 subjects were diagnosed with dementia, including 320 with AD and 47 with VaD. Among the 320 AD cases, 78 had previous, temporally unrelated stroke, and 137 were reclassified as pure AD. As Table 7 shows, diabetes in general was associated with an increased risk of VaD, and borderline diabetes was related to increased risk of dementia and AD after controlling for possible confounders and for vascular disease. Further, we performed stratified analysis by subgrouping patients with diabetes according to levels of blood glucose and diagnostic status. Compared with the reference group, subjects with undiagnosed diabetes had substantially increased risk of developing dementia, AD and VaD after controlling for vascular disease and other possible confounders. However, diabetic patients with random blood glucose levels <11.0 mmol/l showed no increased risk of developing dementia. In contrast, borderline and undiagnosed diabetes were further related to increased incidence of pure AD. The multi-adjusted HRs of pure AD in relation to borderline diabetes and diabetes were 2.85 (95% CI, 1.29-6.30) and 4.74 (95% CI,

1.28-18.46), respectively (Figure 8). Diagnosed diabetes was marginally related to an elevated risk of AD with stroke (HR 2.37; 95% CI, 0.96-5.85, $p=0.06$).

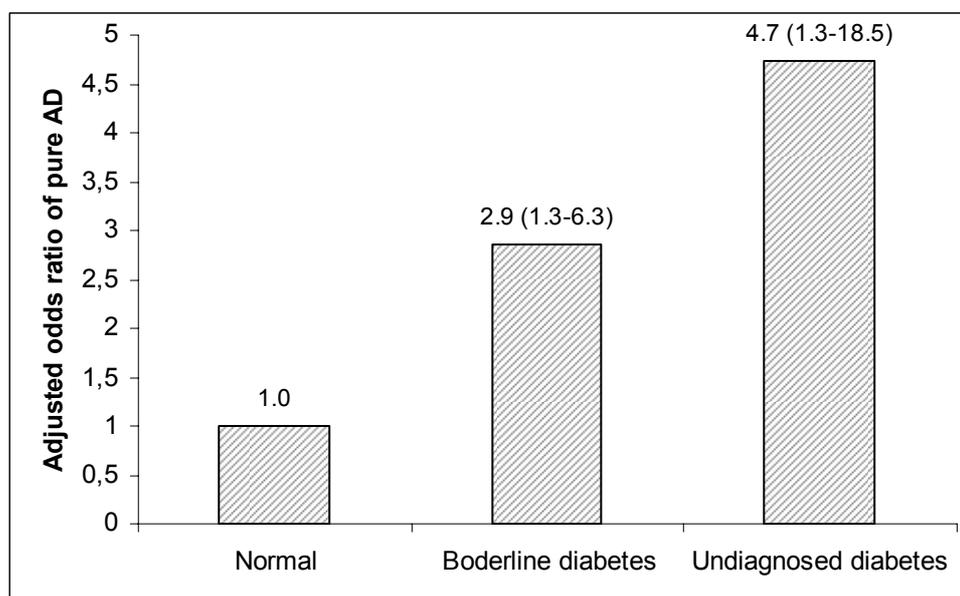


Figure 8. Multi-adjusted hazard ratios of pure Alzheimer's disease in relation to borderline and undiagnosed diabetes

5.2 THE HARMONY STUDY (*Study IV*)

5.2.1 Study participants

A total number of 20,206 twin individuals in the Swedish Twin Registry were eligible for screening. Of them, 5,771 were not reached by telephone, 712 could be reached but were not able to undertake the interview, and 30 failed to complete the cognitive screening test, resulting in 13,693 subjects available for analysis in *Study IV*. Compared to participants, dropouts were older, more likely to be women, and less educated. But the two groups did not differ significantly in the proportion of registered diabetes and vascular disease in the inpatient registry.

Multiple logistic regression analysis showed that being a dropout was associated with ORs of 1.05 (95% CI, 1.02-1.06) for old age, 1.06 (95% CI, 0.86-1.30) for female gender, 0.77 (95% CI, 0.72-0.81) for education (per 1-year increase), 1.05 (95% CI, 0.81-1.35) for stroke, 0.95 (95% CI, 0.72-1.27) for diabetes, 0.79 (95% CI, 0.63-1.03) for heart disease, and 0.98 (95% CI, 0.74-1.29) for hypertension. Dropout rates were

not significantly different for MZ twins compared to DZ twins. The participation rates for the clinical phase were 70.2% for twins who screened positive and 77.2 % for twin partners. Men had a higher participation rate than women (75.1% versus 66.7%, $p<0.01$). Logistic regression analysis showed that refusals were younger than the participants (OR 0.62; 95% CI, 0.51-0.76). The participation rate did not differ significantly according to zygosity.

5.2.2 Diabetes and dementia in twins

The 13,693 participants included 4,274 twin pairs and 5,145 single twins. Of all participants, 467 (3.4%) received a diagnosis of dementia including 292 AD and 105 VaD cases, and an additional 170 (1.4%) were diagnosed with questionable dementia. The prevalence of dementia was 3.9% in women and 2.7% in men ($\chi^2=17.5$, $p<0.001$). Out of the 13,693 participants, 1,288 were self-reported, and 99 were informant-reported as having diabetes at the screening phase, which covered 276 (88.2%) of the 313 recorded as having diabetes in the inpatient registry. In total, diabetes was identified in 1,424 subjects (10.4%) including 28 patients with type 1 diabetes (1.9% of all diabetics). The prevalence of diabetes was 9.8% in women, and 11.2% in men ($\chi^2=6.83$, $p=0.009$).

In the multinomial logistic analysis that included all the study participants, diabetes was significantly associated with an increased risk of both dementia (multi-adjusted OR 1.99; 95% CI, 1.55-2.57) and questionable dementia (multi-adjusted OR 1.72; 95% CI, 1.15-2.59). As the diabetes-related ORs were similar for dementia and questionable dementia, these two categories were combined in subsequent analyses. In the GEE models, diabetes was significantly related to increased risk of dementia (OR 1.89; 95% CI, 1.51-2.38), AD (OR 1.69; 95% CI, 1.16-2.36) and VaD (OR 2.17; 95% CI, 1.36-3.47). The risk tended to be stronger for VaD than for AD. Patients with diabetes onset before age 65 had multi-adjusted ORs of 2.76 (95% CI, 1.97-3.87) for dementia, 2.25 (95% CI, 1.29-2.74) for AD, and 3.94 (95% CI, 1.90-8.15) for VaD, whereas patients with diabetes onset after age 65 had ORs of 1.63 (95% CI, 1.23-2.16) for dementia, 1.56 (95% CI, 1.05-2.32) for AD, and 1.62 (95% CI, 0.92-2.80) for VaD (Figure 9). Patients with diabetes onset at age <65 appeared to be at a higher risk. The effect of

midlife diabetes on dementia risk remained statistically significant even after additional adjustment for diabetes duration (OR 2.1; 95% CI, 1.12-3.68).

Among the 4,274 twin pairs, 4,071 pairs were both non-demented, and 47 pairs were both demented, leaving 210 complete twin pairs discordant for dementia status. In the co-twin matched case-control analyses including both MZ and DZ pairs, the association between midlife diabetes and risk of dementia remained significant (OR 2.41; 95% CI, 1.05-5.51) after adjustment for sex, education, stroke, heart disease, hypertension and BMI at age <65, but the significant association with late-life diabetes disappeared (OR 0.68; 95% CI, 0.30-1.53).

The comparison of the results from unmatched case-control analyses using GEE models and co-twin matched analyses of conditional logistic models for both MZ and DZ twin pairs is graphed in Figure 10. In GEE models, diabetes with onset age before and after age 65 were significantly associated with 176% and 63% increased risk for dementia, respectively. In the conditional logistic regression analyses, the point estimate of OR for dementia related to diabetes starting before 65 years dropped only slightly and was still significant, but the OR related to late-life debut diabetes was largely attenuated and no longer statistically significant. The ORs from GEE models based on all participants and those from conditional logistic models based on dementia-discordant pairs for the association of dementia with late-life diabetes were statistically significantly different (OR 1.76; 95% CI, 1.08-2.88, $p=0.02$), but no difference was detected for midlife diabetes (OR 1.04; 95% CI, 0.55-1.99, $p=0.89$).

Table 7. Adjusted incidence rates (IR, per 1,000 person-years) and multi-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of dementia, Alzheimer's disease, and vascular dementia related to baseline diabetes and borderline diabetes in *Studies I, II and III*.

Studies	Exposure status	No. of Subjects	All dementia			Alzheimer's disease			Vascular dementia		
			No.	IR*	HR (95% CI) [†]	No.	IR*	HR (95% CI) [†]	No.	IR*	HR (95% CI) [†]
<i>I</i> (n=1301)	Diabetes										
	No	1187	313	61.8	1.00 (Ref.)	237	47.8	1.00 (Ref.)	42	8.8	1.00 (Ref.)
	Yes	114	37	89.9	1.53 (1.01-2.11)	23	64.4	1.30 (0.94-2.11)	7	22.8	2.60 (1.23-6.10)
<i>II</i> (n=1173)	B-diabetes [‡]										
	No	1126	378	64.5	1.00 (Ref.)	291	53.0	1.00 (Ref.)	41	9.1	1.00 (Ref.)
	Yes	47	19	91.6	1.77 (1.10-2.84)	16	82.1	1.87 (1.11-3.14)	0	--	--
<i>III</i> (n=1248)	Diabetes and B-diabetes										
	No	1126	378	64.5	1.00 (Ref.)	291	53.0	1.00 (Ref.)	41	9.1	1.00 (Ref.)
	B-diabetes	47	19	91.6	1.77 (1.10-2.84)	16	82.1	1.87 (1.11-3.14)	0	--	--
	Diabetes	75	23	91.1	1.37 (0.88-2.12)	13	55.7	1.19 (0.68-2.12)	6	31.6	3.21 (1.20-8.63)
	Diagnosed	64	17	67.1	1.12 (0.68-1.86)	9	34.9	0.91 (0.46-1.82)	4	39.8	2.25 (0.72-7.08)
	<11.0 mmol/l	33	9	79.3	0.87 (0.54-2.66)	5	50.4	0.78 (0.31-2.69)	1	28.6	3.03 (0.79-11.67)
	≥11.0 mmol/l	31	8	67.1	1.43 (0.70-2.94)	4	34.9	1.08 (0.40-2.95)	3	31.7	3.61 (1.01-12.89)
Undiagnosed	11	6	181.2	3.37 (1.48-7.68)	4	133.1	3.29 (1.20-9.01)	2	87.6	17.21 (3.33-88.85)	

*Adjusted for age, sex, and education.

[†]Adjusted for age, sex, education, baseline MMSE score, *APOE* genotype, follow-up survival status, body mass index, heart disease, systolic blood pressure, diastolic blood pressure, and antihypertensive drug use.

[‡]B-diabetes = borderline diabetes

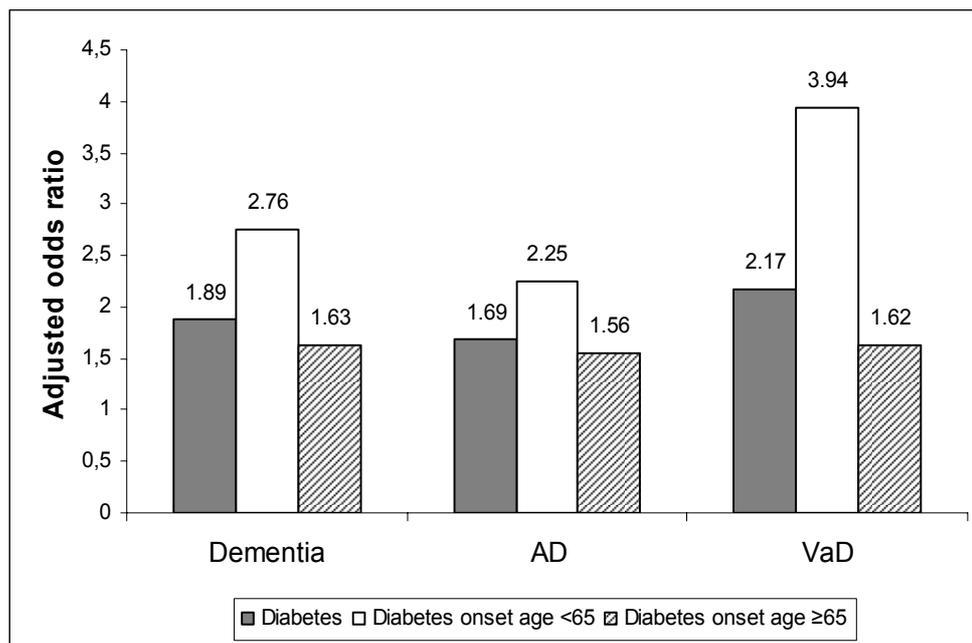


Figure 9. Multi-adjusted odds ratios of dementia, Alzheimer’s disease (AD) and vascular dementia (VaD) in relation to diabetes according to diabetes onset age (<65 and ≥65) from generalized estimating equations.

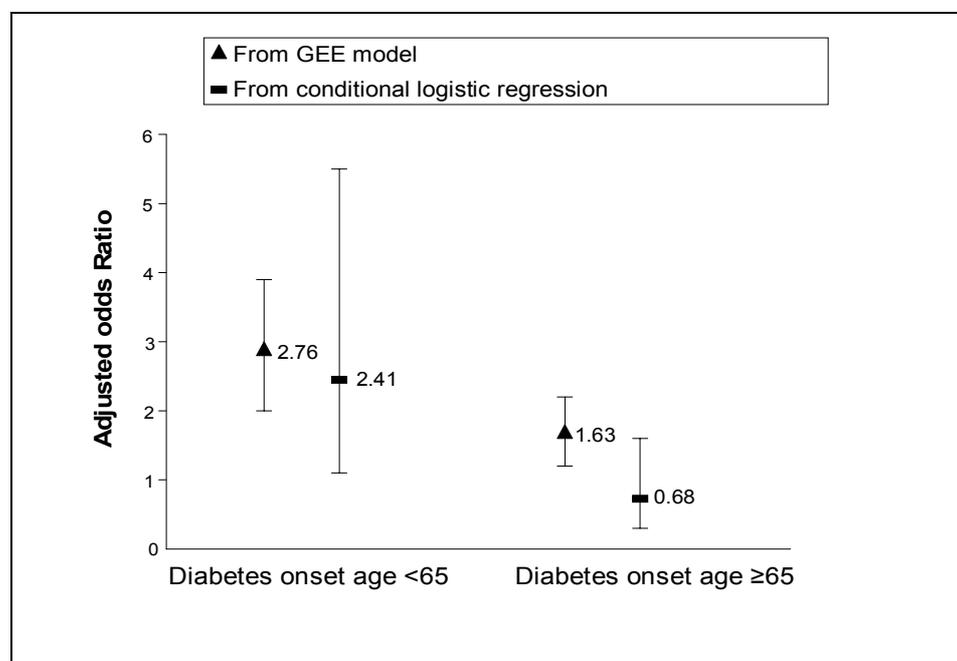


Figure 10. Adjusted odds ratios with 95% confidence intervals for the association of diabetes with dementia from generalized estimating equations (GEE; conventional case-control design), and from conditional logistic regression (dementia-discordant co-twin matched case-control design). Diabetes is analyzed separately according to onset age (<65 and ≥65).

6 DISCUSSION

This thesis explores the relation of diabetes and borderline diabetes with dementia and its major subtypes by analyzing the longitudinal data from a community-based cohort aged ≥ 75 years and from a Swedish twin cohort aged ≥ 65 years. We could also investigate the role of glycemic control, vascular comorbidities, and genetic as well as early-life environmental factors, in the diabetes-dementia association.

6.1 METHODOLOGICAL ISSUES

The four studies in this thesis use the methods of analytical epidemiology, which involves the analysis of the determinants of disease occurrence. In epidemiology, the strength of the relationship between an exposure and a disease is usually measured by the relative risk. In order to evaluate the validity of estimated associations, both systematic and random errors need to be taken into account. The systematic errors include bias and confounding. It is possible to reduce the sources of error, both systematic and random, with appropriate study design and analytical strategies. The reduction of systematic error improves the validity of the measurements, whereas the reduction of random error improves their precision.¹⁶²

6.1.1 Study design

Epidemiological research encompasses several types of study design consisting of both experimental and observational studies. When the aim of research is to detect a risk factor for a disease, most epidemiological research is conducted using an observational design, as experimental studies are usually infeasible. Two principal types of studies exist for the observational design: prospective and retrospective case-control. These two approaches may complement each other.

Studies I, II, and III are prospective cohort studies, in which the assessments of exposures and potential confounders were made at baseline, and the detection of incident outcomes was made during follow-ups. *Study IV* is a cross-sectional case-control study in which the ascertainment of exposures and potential confounders and the identification of prevalent outcomes were made at the same time. Since prevalence

reflects both incidence and disease duration, the use of prevalent cases may have introduced some bias due to differential survival among cases. In the elderly, the simultaneous occurrence of diabetes and dementia can have an additive effect on mortality, which would bias the results concerning the relation of diabetes to dementia toward the null hypothesis or negative association.¹⁶³ A second important aspect in cross-sectional case-control studies is the temporality of the events, as exposures and outcomes are measured at the same time. In the HARMONY Study, the date (age) of diabetes onset is available, and the age of dementia onset was estimated. Temporality of the association between diabetes and dementia could be verified.

6.1.2 Internal validity

A systematic error in the design or conduction of a study is denominated bias. The distinction among different biases is occasionally difficult, but three general types of bias can be identified: selection bias, information bias, and confounding.

6.1.2.1 Selection bias

Selection biases are distortions that result from procedures used to select subjects and from factors that influence study participation.¹⁶² The common element of such biases is that the relation between exposure and disease is different for those who actually participate and those who should be theoretically eligible for the study, but do not participate.

The Kungsholmen Project is a prospective study of a community-based cohort of very old ages (≥ 75 years), which was drawn from a geographically defined area. The dropout rate in the screening phase of the project was 23.6% (558/2368), mainly due to death (32%), refusal (52%), and moving from the area (15%).¹⁴⁵ Compared to those who participated in the screening phase, the dropouts due to death were older and more likely to be men. However, refusals and those who moved did not differ from participants in terms of the major demographic features. In the clinical phase (Phase II) of the baseline survey, 110 subjects dropped out due to similar reasons in Phase I. Of the 1,473 non-demented subjects identified at baseline, 172 (11.7%) were lost to the first follow-up because of refusal or moving. At this phase, dropouts and participants

were similar on most baseline features (Table 6). Among the 788 dementia-free subjects at the second follow-up, 44 (5.6%) refused to undertake the examination. Only 32 (7.5%) of the 427 dementia-free subjects remained at the third follow-up refused to undergo the examination. In fact, after excluding those who died, the rate of participation at each phase was pretty high, varying between 85% and 94%.

The HARMONY Study is a study on dementia in Swedish twins, which was based on a national sample from the twin registry covering the whole country of Sweden. Therefore, the assumption that cases and controls are derived from the same population is respected. The dropout rate in the screening phase of the study was 32.2% (6513/20206) due to refusal (74.8%), and to death (4.6%); 20.6% of the dropouts were unreachable. Compared to those who participated in the screening phase, the dropouts were 1.3 years older ($t=-13.1$, $p<0.001$), 1.3 years less educated ($t=22.6$, $p<0.001$), and more likely to be women ($\chi^2=58.6$, $p<0.001$). The participation rates in the clinical phase were 70.2% for twins who screened positive, and 77.2% for twin partners. The dropouts were younger, and more likely to be women (75.1% versus 66.7%, $p<0.01$). However, dropouts did not differ from participants in terms of vascular disorders that were recorded in the inpatient registry. As old age and low education are well-established risk factors for dementia, and female sex is often associated with an increased risk of AD,¹⁵ possible selection bias could arise if the prevalence of dementia in this twin cohort differs from that in the general population. However, the age-specific prevalence of dementia in this Swedish twin cohort was comparable with several major epidemiological studies of dementia prevalence in Europe and the USA,^{148,164-166} as described in detail elsewhere.¹⁵⁶ The significant mean differences in participation were likely due to the large sample size rather than to meaningful significance.

6.1.2.2 *Information bias*

Information bias can occur whenever there are errors in the measurement of exposures and outcomes. The measurement error is usually called classification error or misclassification, which could be either differential or non-differential, depending on whether the measurement error depends on the outcome or exposure.¹⁶²

The designs of the Kungsholmen Project and the HARMONY Study essentially preclude differential misclassification of exposure among outcome categories. It is unlikely that misclassification in diagnosis of dementia would be related to any of the exposures of interest, whereas non-differential misclassification is a major concern.

Diagnosis of dementia, AD and VaD. In the Kungsholmen Project, the dementia-free cohort was defined with a two-phase design at baseline, a screening phase for all participants, and a clinical phase for those who screened positive and a random sample of those who screened negative.¹⁴⁵ As a result, some very mild dementia cases might have been missed at baseline and been included in the initial “dementia-free” cohort. However, we were able to confirm the initial findings by restricting the analysis to the dementia-free cohort identified at the first follow-up, in which a one-phase procedure (dementia workup for all participants) was implemented. The diagnosis of dementia was given after consensus among three independent physicians. The diagnostic procedure has been validated, with a relatively high overall agreement on diagnosis ($\kappa=0.70$).¹⁶⁷

In the HARMONY Study, the screening phase was conducted by telephone. In epidemiological studies with large community-based samples, it is rare that all participants undergo medical examination due to time and costs restraints. The TELE questionnaire was used for telephone cognitive screening. The TELE has been demonstrated to have a sensitivity of 0.95, and a specificity of 0.52,¹⁵⁸ which are relatively good results in comparison with other telephone screening protocols.¹⁶⁸ The clinical phase entailed complete in-person diagnostic evaluations for dementia for those who screened positive, their co-twins, and a sample of twins who screened negatively. The diagnosis of dementia and its subtypes was made by an assessment team after consensus among independent physicians. The diagnostic procedure has been evaluated with a high agreement on diagnosis ($\kappa=0.86$).¹⁶⁹ In addition, data from longitudinal follow-ups conducted for twins who were diagnosed as having questionable dementia showed that over half of them developed dementia in three years.

In both the Kungsholmen Project and the HARMONY Study, the major subtypes of dementia, AD and VaD were diagnosed basically according to NINCDS-ADRDA and NINDS-AIREN criteria, respectively. The former criteria for AD have a sensitivity of

49-100% and a specificity of 47-100%, the latter criteria for VaD have a sensitivity of 93-98% and specificity of 20-43%.¹⁷⁰ The diagnoses of dementia in both projects were made on a clinical basis without support of neuroimaging. Even if neuroimaging data were available to detect vascular lesions in the brain, they should not have helped in determining the significance of these lesions and the temporal relation of these lesions with dementia onset, as coexistence of AD pathologic change and vascular lesions in the brain is fairly common in the elderly.¹⁵⁴ Lack of imaging data may affect the diagnostic accuracy for AD and VaD, but not for overall dementia. As the boundaries between AD and VaD remain controversial, in *Study III*, we were able to confirm the association between diabetes and AD by dividing the AD cases into two groups: AD with stroke, and pure forms of AD when all major vascular diseases and risk factors were absent.

Assessment of diabetes. The possible misclassification of the exposure is another issue that needs to be addressed. In *Studies I-III*, diabetes and borderline diabetes were assessed at baseline only, thus some incident cases of diabetes or borderline diabetes might have been missed. This kind of non-differential misclassification is more likely to underestimate an effect. The annual incidence of diabetes is 1.0% in people aged ≥ 70 years,⁷⁵ yet the size of the effect would be modest because the proportion of people with undiagnosed diabetes in the total non-diabetic group should be small. Indeed, the risk of dementia in studies that actively screened for diabetes is largely similar to those that did not. In addition, type 1 and type 2 diabetes were not distinguished, but in view of the age of the populations involved, most participants probably have type 2 diabetes.¹⁷¹

In *Study IV*, diabetes was identified based on self- and informant-reported information and on inpatient medical history. Information on blood glucose concentration was not available. Because diabetes is commonly (around 30%) undiagnosed in elderly people,¹⁷² in this study a substantial proportion of subjects with diabetes might have been erroneously assigned to the non-diabetic group, which might have led to an attenuation of the risk attributable to diabetes. In addition, information from informants was used for participants who could not provide information about history of diseases due to impaired cognition (7.0%). However, the bias of using reports from an informant has been previously found to be minimal.¹⁷³

6.1.2.3 *Confounding*

Confounding is one of the central issues for epidemiological research, and is simply defined as the mixing of effects between an exposure, an outcome, and a third variable known as confounder.¹⁶²

Diabetes is a complex metabolic disorder that is closely associated with risk factors that are also related to accelerated cognitive decline and dementia, such as hypertension and atherosclerotic vascular disease. These factors, together with demographic and socioeconomic factors, diabetes-specific conditions, and genetic factors, could be important determinants of the increased risk of dementia in people with diabetes.

The possible confounders, including demographic features (age, sex and education), vascular risk factors (such as BMI), vascular comorbidities (heart disease, stroke and hypertension) and genetic factors (*APOE* genotype or shared genetic factors in twins) were taken into account in all four studies by using proper approaches (multivariable analysis, stratification and co-twin matched case-control analysis). Even after controlling for many confounding variables, residual confounding may still be an issue when the measured confounder is not a perfect measurement. Information on potential confounding variables, however, was generally reliable in this study due to the study design.

6.1.2.4 *Random error*

Random error is the inherent imprecision of a given process of measurement, and remains after systematic error is eliminated. Random error can be minimized if a sufficiently large sample is used or the study design is modified to increase the efficiency with a given number of study subjects.¹⁷⁴

The Kungsholmen Project is a large-scale cohort with long-term follow-up, and the HARMONY Study is the largest population-based twin study of dementia to date. In all *Studies*, the sample size and the high exposure prevalence led to meaningful estimates. In the large-scale population-based twin study (*Study IV*), the effect of diabetes on dementia risk varied according to age of diabetes onset. Even though all studies were

based on large samples, a chance finding could still not be ruled out, especially when the stratified or interactive analyses were performed. In *Studies I* and *II*, indeed, the statistical power was limited for the interactive analyses due to the small number of diabetic or prediabetic subjects with vascular factors (such as BMI ≥ 30 and *APOE* $\epsilon 4$) or vascular disorders at baseline.

6.1.3 Interaction

The term “interaction” is used in epidemiology to describe a situation in which two or more risk factors modify their separate effect with regard to the occurrence of a given outcome. This phenomenon is also known as effect modification.

In *Studies I* and *II*, the interaction between diabetes or borderline diabetes and vascular factors was evaluated as a departure from the multiplicative effect in Cox regression models. Whether this is a proper way to evaluate interaction is still under debate. Both effect-measure modification and statistical interaction depend on an arbitrary choice of measure or of scale. Statistical interaction, being ambiguous, can not correspond to the concept of biological interaction among component causes, which refers to a mechanistic interaction that either exists or does not exist. It has been suggested that the biological interaction should be evaluated as a departure from the additive effects.¹⁶² When multiplicative models that are used to measure (statistical) interaction may lead to estimates of interaction smaller than estimates derived from additive models based on risk differences.¹⁷⁴

6.2 INTERPRETATIONS OF THE FINDINGS

6.2.1 Diabetes, dementia and VaD

In *Study I*, we found that diabetes increased the risk of dementia, and of VaD in particular, independently of vascular disease. The risk for dementia and VaD was especially high when diabetes occurred together with severe systolic hypertension or heart disease. Previous prospective studies have shown that diabetes is associated with an elevated risk of dementia and VaD.^{116-119,121} The relation between diabetes and dementia could be explained through vascular damages or nonvascular effects of diabetes. Diabetes is notorious for micro- and macro-vascular complications, and it is a

well-established risk factor for cardiac and cerebrovascular diseases. Neuroimaging studies have demonstrated that people with type 2 diabetes had moderately elevated risk for lacunes, hippocampal atrophy, and deep white matter lesions.¹⁷⁵ Therefore, an increased risk of VaD resulting from diabetes can be expected. Despite this, there are indications that the effect of diabetes on dementia is not, or at least not entirely, mediated through vascular factors. Also, diabetic patients without clinical cerebrovascular disease were found to perform poorer on cognitive tests than healthy controls.¹⁷⁶ In addition, diabetes was associated with vascular cognitive impairment after adjusting for stroke, hypertension, and heart disease.¹¹⁶ Our results showed independent associations between diabetes and dementia, and VaD. Furthermore, a higher level of blood glucose was found to be associated with an increased risk for VaD, independently of other vascular diseases, suggesting that nonvascular pathways may be involved in the development of dementia. In this study, diabetes was marginally associated with the risk of AD. However, in the analysis of the combined effect between diabetes and vascular disorders on dementia, we found that subjects with both diabetes and severe systolic hypertension had a higher risk for developing dementia, and both AD and VaD. This is in agreement with a study in which a strong interaction between diabetes and hypertension on cortical atrophy was reported.¹⁷⁷

6.2.2 Borderline diabetes, dementia and AD

The natural history of type 2 diabetes is preceded by impaired glucose regulation, which may last for years before it is clinically manifested.¹⁷⁸ Clinical and cross-sectional studies have suggested that impaired glucose regulation is related to worse cognitive performance.^{137,140,179} A prospective study has shown that pre-diabetes increased the risk of developing cognitive impairment in elderly women.¹³⁹ No prospective cohort study has investigated the relationship between borderline diabetes and the risk of dementia. In *Study II*, we found that borderline diabetes was independently associated with nearly a 70% increased risk of developing dementia and AD. With this study, we were able to expand our previous findings by showing that borderline diabetes is also associated with AD. It is well established that diabetes increases the risk of vascular disease, which is one of the components for the diagnosis of VaD. It is not surprising, therefore, that an increased risk of VaD is linked to diabetes. It is likely that demented persons who are suffering from diabetes tend to be

diagnosed with VaD. However, in the current study, it is unlikely that borderline diabetes played a role in dementia diagnosis, because neither the examining physicians nor the subjects per se were aware of this condition when the diagnoses of dementia and its subtypes were made.

We assessed the joint effects of borderline diabetes with other vascular or genetic factors. First, borderline diabetes appeared to have a multiplicative effect with severe systolic hypertension (≥ 180 mm Hg) on the risk of AD, which is in agreement with the previous findings that comorbid type 2 diabetes and hypertension exacerbated cognitive decline, and contributed to a much higher risk of developing AD.^{110,112,180} Second, borderline diabetes and obesity (BMI ≥ 30) showed no joint effect on dementia risk in our very old population. Third, we found that, among non-carriers of *APOE* $\epsilon 4$, borderline diabetes led to a higher risk of AD, which is in accordance with a recent report that the association between diabetes and incident AD was present only in *APOE* $\epsilon 4$ negative individuals.⁵⁵ This finding might be due to selective survival.¹⁸¹ However, the power of the interactive analyses was limited due to the small number of borderline diabetes subjects with severe systolic hypertension, obesity (BMI ≥ 30), or *APOE* $\epsilon 4$ at baseline.

6.2.3 Diabetes and AD

The association of diabetes with the Alzheimer type of dementia remained inconsistent.¹⁸² In fact, some longitudinal studies reported an association between diabetes and AD^{110,114,117,119,121} or observed such an association only in specific subgroups,^{55,108,112} but others did not.^{116,118,127} In *Study III*, we found that diabetes in general increased the risk of VaD, but undiagnosed diabetes did not predispose to any type of dementia, and was associated with increased risk of both AD and VaD. However, well-controlled diabetes was not significantly related to dementia risk after adjustment for vascular diseases. Our findings may contribute to the explanation of controversial results among previous studies by taking into account antidiabetic treatment and glycemic control. Finally, the association of borderline diabetes with dementia seems to be restricted to the pure AD cases.

Diabetes is closely associated with vascular diseases that may act as confounders or mediators of the association between diabetes and dementia. It is also possible that vascular disease can serve both as an independent risk factor and as a mediator in the association between diabetes and dementia.¹⁸³ One study, however, reported a decreased risk of dementia in patients with both diabetes and hypertension compared to those with diabetes alone.¹¹⁰ In the present study, we examined the role of vascular comorbidities by grouping the AD cases according to the presence or absence of various vascular diseases. The finding that borderline diabetes and undiagnosed diabetes were associated with the risk of “pure” AD (AD with no vascular disease) suggests a possible causal relationship between glucose dysregulation and neurodegeneration.

6.2.4 Diabetes and dementia in twins

In *Study IV*, there was a moderately increased risk of dementia, AD and VaD in twins with diabetes. The risk tended to be stronger for VaD. These results are in agreement with findings from The Honolulu-Asia Aging Study, which reported an association between diabetes and increased risk of dementia, AD and VaD.¹¹⁷ We also found that patients with an onset of diabetes before age 65 had a greater dementia risk than those with diabetes onset after age 65. Recent reports showed that long-term diabetes has a stronger risk effect for the development of cognitive impairment and dementia.¹⁸⁴ However, in our study the association between midlife diabetes and dementia was still significant after adjustment for diabetes duration, suggesting that time at exposure to diabetes may also be relevant for the development of dementia.

In co-twin control analyses, the risk effect of midlife diabetes on dementia remained significant, but the association between diabetes occurring in late life and dementia risk was largely reduced. Thus, the association between diabetes in late life and dementia may be attributed to genetic and early environmental factors (such as maternal nutrition status and childhood socioeconomic situation). These findings suggest that the association observed in the unmatched case-control analysis between late-onset diabetes and dementia is more likely to be endogenous. Our findings give support to recent evidence, which has suggested that the molecular defects associated with the development of diabetes also contribute to an increased risk of all types of dementia.¹⁸⁵

Several genetic studies have revealed that chromosome 10 contains potentially important novel genes for late-onset AD as well as for type 2 diabetes.^{186,187} Since the IDE (Insulin Degrading Enzyme) gene is located on chromosome 10, and since IDE demonstrates the ability to degrade insulin and amyloid- β (A β), it may be hypothesized that IDE is a candidate gene for both type 2 diabetes and AD.¹⁸⁸ Furthermore, there is now abundant evidence that early-life growth and development have an effect on the risk of disease in adult life.¹⁸⁹ Studies have reported the relationship between low birth weight and increased risk of diabetes.¹⁹⁰ In addition, childhood low socioeconomic status may also contribute to the risk of both diabetes¹⁹¹ and dementia.¹⁹² Thus, the link between diabetes and dementia is probably determined by the complex interplay of genetic and environmental exposures throughout the life course.

In contrast to late-life diabetes, midlife diabetes was associated with an increased risk of dementia, even when controlling for genetic and familial factors, suggesting that the midlife diabetes-dementia association might be exogenous, and it is more likely attributable to adulthood environments (e.g., occupation and lifestyle factors such as exercise, diet, smoking, and social activities).¹⁹³

6.3 POSSIBLE MECHANISMS

Taken together, all studies included in this thesis strongly support the hypothesis that the risk of dementia is increased in people with diabetes and borderline diabetes. This increased risk includes both AD and VaD. There are many pathological mechanisms through which diabetes could affect the initiation and promotion of underlying pathological lesions leading to dementia. These mechanisms include those that are common to both AD and VaD, as well as aging itself. It has been recognised that the brains of demented patients, especially in the very old, are likely to show a mixture of alterations, particularly Alzheimer type lesions and vascular changes. In some diabetic patients, vascular damage will predominate leading to vascular dementia, whereas in other patients, amyloid-related mechanisms may predominate leading to a clinical picture of “pure AD”. However, it is likely that most patients will have both types of brain lesions and develop mixed dementia. At least six major mechanisms that may act separately or at the same time have been suggested:

1. **Vascular pathways.** Diabetes is a known risk factor for atherosclerosis and stroke,¹⁹⁴ which lead to vascular pathology in the brain.¹⁹⁵ Diabetes may develop in a cluster of risk factors including obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. These factors constitute the metabolic syndrome, which is reported to be a predictor of cerebrovascular disease, ischemic stroke, and accelerated cognitive decline and dementia.¹⁷¹
2. **Glucose toxicity.** Toxic effects of higher blood glucose could lead to progressive functional and structural abnormalities in the brain.¹⁹⁶ Chronically hyperglycemic rodents have been found to express cognitive impairments and abnormalities in synaptic plasticity.¹⁹⁷ These processes could affect brain tissue directly, but can also lead to microvascular changes. The glucose mediated effects on cognition and brain structure could be referred to as “accelerated brain aging”. Hyperglycemia is often accompanied by an accelerated rate of formation of advanced glycation end products (AGE), which is associated with increased amyloid deposition, tau formation, and oxidative stress.¹⁹⁸
3. **Hyperinsulinemia.** Glucose dysregulation is associated with hyperinsulinemia, which gives rise to Alzheimer-type pathology. Alterations in insulin and glucose homeostasis could affect amyloid metabolism through changes in the brain of insulin and its receptor, and by the formation of AGE.¹⁹⁹ Insulin appears to stimulate A β secretion, and inhibits the extracellular degradation of A β by competing for insulin-degrading enzyme. In addition, the signaling defects in insulin may lead to hyperphosphorylation of tau, which can form neurofibrillary tangles.
4. **IDE.** Dysfunction of the IDE may also be a possible pathologic link between diabetes and AD. Chromosome 10 contains the genes for IDE and potentially the genes for both late-onset diabetes and AD.¹⁸⁸
5. **Inflammation.** Inflammatory markers, including C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and tumor necrosis factor (TNF)- α have been associated with diabetes¹⁹⁹ and AD.⁴⁸ Increased oxidative stress has been proposed to be one of the major causes of the hyperglycemia-induced trigger of diabetic complications.²⁰⁰ Oxidative damage may play a role in amyloid deposition in AD.²⁰¹

6. **Molecular connections between dementia and diabetes.** Recent evidence suggests that the molecular defects such as protein kinase B (PKB) and glycogen synthase kinase 3 (GSK3) associated with the development of diabetes also contribute to an increased risk of dementia.¹⁸⁵

6.4 GENERALIZABILITY

The validity of a study is usually separated into two components: the internal validity and the external validity (or generalizability). The internal validity has been discussed earlier. Generalizability is the validity of the inference that the findings of a study pertain also to people outside the studied population. However, no study population is fully representative of all populations; the unique characteristics of any given population should be kept in mind when interpreting the major findings even of population-based studies.

The Kungsholmen population consisted of individuals aged ≥ 75 years that were living in a geographically defined central area of Stockholm. This population had comparable age and sex compositions as well as a similar health care system as in the city of Stockholm. However, the Kungsholmen population did differ from the rest of the urban area of Sweden in terms of the proportion of pensioners, women, highly educated persons, and marital status. Cautions are needed when generalizing the findings from the Kungsholmen population to a younger population or to rural areas. The major findings from this population may be generalized to the urban population aged over 75 in Western society.

The HARMONY population included twins aged ≥ 65 years derived from the Swedish Twin Registry that covers the whole of Sweden. If twins are different from the general population (non-twins) in terms of the outcome of interest, the results will not be applicable to the general population. The age-specific prevalence of dementia in this population is similar to the Kungsholmen population.¹⁵⁶ Twins surviving into late life are similar to a representative sample of non-twins of the same age in healthy status and biobehavioral functioning.²⁰² Nevertheless, the comparison of the results from the cohort as a whole with the matched pairs provides important information about the

potential role of genetic and familial influences. The major findings from this population may also be generalizable to the population aged 65 years and older in Western society.

7 CONCLUSIONS

1. Diabetes increases the risk of dementia, and of VaD in particular, in the elderly. The risk for dementia and VaD is especially high when diabetes occurs together with severe systolic hypertension or heart disease.
2. Borderline diabetes is associated with an increased risk of dementia and AD; the risk effect is independent of the future development of diabetes. Borderline diabetes may interact with severe systolic hypertension to multiply the risk of AD.
3. Uncontrolled diabetes is associated with increased risk of dementia including vascular and neurodegenerative dementia. Borderline diabetes and undiagnosed diabetes are related to an increased risk of pure AD as well. The detrimental effect of diabetes on dementia might be alleviated by effectively controlling blood glucose.
4. The risk effect of diabetes on risk of dementia, AD and VaD seems to be stronger in patients with diabetes onset at midlife compared to patients with diabetes onset in late-life. Genetic and environmental factors in early life might account for the association between late-life diabetes and dementia, but could not explain the midlife diabetes-dementia association, thus suggesting the lifespan development of a diabetes-dementia association.

8 RELEVANCE AND IMPLICATIONS

Diabetes and dementia, two of the most common disorders in the elderly, are posing a tremendous burden on public health in the society. Moreover, the absolute number and the proportion of older people who are affected by diabetes, borderline diabetes and dementia are expected to further increase over the next few decades. Our population-based study provides a better insight into how diabetes and borderline diabetes affect the development of dementia and its main subtypes. The major findings of this thesis are of scientific relevance for theoretical aspects, clinical practice and prevention of both diabetes and dementia.

Diabetes is a risk factor for vascular disorders. Therefore, an increased risk of VaD resulting from diabetes can be expected. However, our studies demonstrated that the effect of diabetes on dementia and VaD is independent of vascular disease, suggesting that nonvascular pathways may be involved in the development of dementia. Indeed, we found that borderline diabetes and undiagnosed diabetes are associated with an increased risk of AD, and pure AD. Further, we found that genetic and early life environmental factors, as well as adulthood lifestyle may contribute to the development of a diabetes-dementia association. These findings have relevant implications for the understanding of the mechanisms linking diabetes to dementia, and for the development of effective therapeutic measures and preventative strategies against dementia.

Our findings highlight the need to detect borderline diabetes and undiagnosed diabetes in order to effectively prevent dementia, as previous studies have shown that prediabetes and diabetes could be improved by interventions addressed towards lifestyle changes and antidiabetic treatment.^{203,204} Our data also indicate the beneficial role of effective glycemetic control in mitigating the risk of dementia.

As far as clinical practice is concerned, it is important to bear in mind that prevention, timely diagnosis, and the optimum treatment of diabetes and borderline diabetes may help to reduce the occurrence of dementia.

9 FUTURE DIRECTIONS

There is convincing evidence that shows an increased risk of dementia in people with diabetes. This increased risk of dementia clearly demands our attention. But there are few detailed epidemiological data for diabetes-related factors such as diabetes duration, glycemic control, diabetes treatment, and comorbidities. Some experimental studies provided several biologically plausible pathways for the association of diabetes with dementia, but did not indicate which of these are clinically relevant. This gap in evidence between epidemiological and experimental studies needs to be closed.

Future studies need to identify patients who have an increased risk of dementia, clarify the underlying mechanisms and potentially modifiable determinants, and assess the effects of treatments. The risk factors and mechanisms that drive the association between diabetes and accelerated cognitive decline and dementia need to be identified before adequate treatment measures can be developed. This process will require longitudinal studies that include detailed assessment of cognition, preferably in combination with neuroimaging, detailed assessment of diabetes- and prediabetes-related factors, comorbid conditions, insulin resistance, inflammatory markers (such as CRP, IL-6 and TNF- α) as well as genetic factors (such as *APOE* genotype and IDE gene). Studies based on large population-based cohorts of elderly people with diabetes and prediabetes, and longitudinal studies of at-risk populations that examine the progression of vascular disease, metabolic syndrome, diabetes, prediabetes, insulin resistance and cognition will be optimal to pursue this aim.

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12 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2008

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

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