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Diabetes and cognitive functioning: The role of age and comorbidity

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ABSTRACT

This thesis deals with the influence of type 2 diabetes on cognitive function in adulthood and very old age. The effects of diabetes are studied both in populations free from dementia, and in a clinical Alzheimer's disease population. For Studies I & II, a non-demented, non-depressed, sample of very old (≥75 years of age) persons from the Kungsholmen Project in Stockholm, Sweden, was used. For Study III, data from the Betula prospective cohort study were employed. All selected participants (age-range 35 – 85 years) were non-demented at baseline, and did not develop dementia within ten years of cognitive assessment. For Study IV, a clinical sample, from the Massachusetts Alzheimer's Disease Research Center, of persons diagnosed with probable Alzheimer's disease (PRAD) was used. The main findings are summarized below.

Study I: The mini-mental state examination (MMSE) scores of 408 subjects (non-diabetics, *n*=356; diabetics, *n*=36) were examined. Total MMSE scores were significantly (*p*=.041) lower in diabetics than non-diabetics after controlling for demographics and cardiovascular disease (CVD). The scores in the subtests *attention and calculation* and *copy a design* were most highly related to diabetic status (*p*=.009, and *p*=.031, respectively). Among diabetics, a significant (*p*=.03) correlation between random blood glucose level and total MMSE score was observed. Among non-diabetics, the same correlation was not statistically significant.

Study II: Data from tests of episodic memory and verbal fluency among 338 subjects (non-diabetics, *n*=307; diabetics, *n*=31) were analyzed. In both types of tests, level of semantic support was varied. Diabetics performed significantly worse on tests with low cognitive support (*free recall of random words*, *p*=.048; *letter fluency*, *p*=.011) after control for demographics, CVD, and signs of CVD. No statistically significant difference between diabetics and non-diabetics was observed in tests with high level of cognitive support (*cued recall of organizable words*, *category fluency*). When controlling for impending death and preclinical dementia, only *letter fluency* remained significantly (*p*=.033) related to diabetes status.

Study III: Performance on tests of episodic memory with varying levels of support at encoding and retrieval in 2,765 non-demented subjects who would not develop dementia within 10 years (non-diabetics with normal levels of HbA1C, *n*=2,489; non-diabetics with elevated levels of HbA1C, *n*=151; diabetics, *n*=125) were analyzed. When the whole age-range was studied, diabetics performed at a lower level, than the two non-diabetic groups on an overall composite score of the cognitive tests (*p*=.017). Among persons 35 – 65 years of age, those with diabetes performed at a slightly lower level than persons with elevated HbA1C (*p*=.047), and at a lower level than the non-diabetic controls (*p*=.008). Among persons 70 – 85 years of age, non-diabetics with elevated levels of HbA1C performed at a slightly lower level than diabetics (*ns*) and at a significantly lower level than non-diabetics with normal levels of HbA1C (*p*=.001). High levels of cognitive support attenuated differences between groups, and high retrieval support resulted in the largest decrease of performance differences.

Study IV: Data on global cognitive performance (Blessed dementia scale; BDS) and activities of daily living (ADL) in a clinical population (total, *n*=693; non-diabetics, *n*=647; diabetics, *n*=46) of PRAD-patients were analyzed. Patients had been assessed with regard to ADL and BDS between 2 and 24 times during a period of 4.5 months to 12 years. Power analyses indicated good power (0.75) to detect small effect sizes.

Hierarchical linear modeling (HLM) analyses were performed. No difference in rates of cognitive or functional decline between diabetics and non-diabetics were detected.

In summary, non-demented diabetics performed at lower levels in tests of cognition than non-diabetics, both in an adult (35 – 85 years of age) and in a very old (75 – 96 years of age) population. Differences between diabetics and non-diabetics were smaller in subjects with preclinical dementia or impending death, and undetectable in subjects with PRAD. In general, persons with elevated HbA1C in the absence of a diabetes diagnosis performed at an intermediary level compared to diabetics and non-diabetics. In persons 70 years of age or older, however, persons with elevated HbA1C in the absence of a diabetes diagnosis performed at a lower level than diagnosed diabetics. This finding is discussed in relation to underdiagnosis of diabetes in the elderly population. Cognitive support, finally, attenuated differences between diabetic and non-diabetic groups.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Denna avhandling behandlar typ 2-diabetes och kognition. Typ 2-diabetes är den sorts diabetes som tidigare kallades åldersdiabetes. Kognition betyder ungefär förvärvande och användande av kunskap. I denna avhandling behandlar jag främst den kognitiva funktionen minne, men även annat kunskapsanvändande.

Tidigare forskning har visat att diabetessjukdomen påverkar minnet. Man vet inte exakt varför diabetes påverkar minnet, men det kan antingen bero på att diabetes ökar risken för andra sjukdomar, eller att någon del av diabetessjukdomen i sig påverkar hjärnan. Till exempel så ökar diabetes risken för demenssjukdomar, men gör också att personer utan demenssjukdom har påverkan på hjärnan och minnet. Troligen beror effekten av diabetes på en kombination av faktorer.

Jag har undersökt hur diabetes påverkar minnet hos vuxna personer (35-85 år gamla) som inte har någon demenssjukdom, hos mycket gamla personer (över 75 år) som inte har någon demenssjukdom, hos personer över 75 år som är på väg att få demens, samt hos personer som förutom diabetes också har diagnosen Alzheimers sjukdom.

Personer med diabetes har sämre minne än personer utan diabetes, och det gäller både för unga och gamla. Hos personer som är på väg att utveckla demens verkar inte diabetes påverka minnet lika mycket. Där är det nog så att den begynnande demenssjukdomen orsakar så stora besvär med minnet att den skillnad som diabetes-sjukdomen gör inte märks lika mycket. I vissa tester, som till exempel att på kort tid komma på så många ord som möjligt som börjar på bokstaven "F", ser man fortfarande att diabetespatienter presterar sämre än personer utan diabetes - även om både de med diabetes och de utan är på väg att utveckla demens. Personer som redan fått Alzheimers sjukdom, däremot, försämras lika snabbt i sina kognitiva förmågor oberoende av om de har diabetes eller inte.

Jag har också undersökt om det påverkar minnet att ha förhöjt långtidsblodsocker (HbA1C) utan att ha någon diabetesdiagnos. Att man har förhöjt långtidsblodsocker utan diabetesdiagnos kan antingen bero på att man inte har hunnit bli så dålig att man skall ha en diabetesdiagnos, eller på att man inte blivit läkarundersökt för att se om man har diabetes. Om man inte blivit läkarundersökt så kan man förstås redan egentligen ha diabetes, även fast man inte fått någon diagnos eller behandling. Tidigare forskning har visat att äldre personer som egentligen har diabetes går utan diagnos och behandling i större utsträckning än yngre personer. Ungefär varannan person som är över 65 år gammal och egentligen har diabetes saknar diagnos och behandling. Jag visar i denna avhandling att personer som har förhöjt långtidsblodsocker utan att ha någon diabetesdiagnos presterar olika bra i förhållande till personer med diabetesdiagnos (och i förhållande till personer utan förhöjt långtidsblodsocker) beroende på hur gamla de är. Hos personer som är upp till 65 år så har diabetespatienterna sämst minne, de som inte har någon diabetesdiagnos men har förhöjt långtidsblodsocker presterar på en mellannivå, och de som har normalt långtidsblodsocker har bäst minne. Bland de som är 70 år gamla eller äldre, däremot, så är det de som saknar diabetesdiagnos men ändå har förhöjt långtidsblodsocker som har sämst minne - sämre än de som har diabetesdiagnos. Detta skulle kunna bero på att det är fler i den äldre gruppen som egentligen har diabetes, men som inte fått diagnos och behandling.

Slutligen har jag också undersökt om det är skillnad på hur mycket diabetes påverkar prestationen i olika tester av kognition. Framförallt har jag undersökt effekten av kognitivt stöd. I tester med mycket kognitivt stöd får man hjälp att komma ihåg det man skall minnas, genom att till exempel utföra den handling man skall minnas, eller genom att få ledtrådar om vad det var man skulle minnas. I tester med mindre kognitivt stöd skall man istället minnas meningar som man bara läst, eller återge det man lärt sig utan att få några ledtrådar. Alla, både personer med och utan diabetes, kommer förstås ihåg mer i de tester som ger mycket stöd. Det intressanta är att skillnaden mellan hur mycket de med och utan diabetes kommer ihåg minskar om man ger mycket stöd. Det beror inte på att alla får alla rätt i testerna med mycket stöd, tvärtom är det väldigt få som får alla rätt. Det skulle kunna bero på att diabetes påverkar minnet selektivt, det vill säga att vissa delar av minnet påverkas mer. När man ger stöd så får diabetespatienterna möjlighet att utnyttja delar av minnet som är intakta, och de kan då prestera på samma eller nästan samma nivå som personer utan diabetes.

LIST OF PUBLICATIONS

I. Nilsson, E., Fastbom, J., & Wahlin, Å. (2002). Cognitive functioning in a population-based sample of very old non-demented and non-depressed persons: The impact of diabetes. *Archives of Gerontology and Geriatrics, 35*(2), 95-105.

I. Wahlin, Å., Nilsson, E., & Fastbom, J. (2002). Cognitive performance in very old diabetic persons: The impact of semantic structure, preclinical dementia, and impending death. *Neuropsychology, 16*(2), 208-216.

I. Nilsson, E., Wahlin, Å., & Nilsson, L.-G. (Submitted). Diabetes and Elevated Glycosylated Hemoglobin: Episodic Memory and Utilization of Cognitive Support. *Health Psychology*.

I. Nilsson, E., Wahlin, Å., MacDonald, S., & Growdon, J. H. (Manuscript). Diabetes does not influence rate of cognitive or functional decline in probable Alzheimer's disease.

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of daily living
AGEs	Advanced glycation end products
BDS	Blessed dementia scale
BMI	Body mass index
CNS	Central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
HbA1C	Glycated hemoglobin
IGF-1	Insulin like growth factor 1
IGFBP-1	IGF-1 binding protein
KP	Kungsholmen project
MADRC	Massachusetts Alzheimer's disease research center
MGH	Massachusetts General Hospital
MMSE	Mini-mental state examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
OGTT	Oral glucose tolerance test
PRAD	Probable Alzheimer's disease
Q-EEG	Quantitative electroencephalogram

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1 INTRODUCTION

The focus of my research, type 2 diabetes and cognition, is a field that has grown considerably since I started working on the present thesis. The growth has been both quantitative and qualitative, such that high-quality studies are now published at about the same rate per month as they were published per year in the late 90's. As the quality and volume of publications increases, so does the amount of unanswered research questions. An answer to the question "does diabetes affect cognitive performance?" gives rise to more detailed questions, such as "are the effects differential across cognitive domains?", and "does disease severity matter?". The answers to these questions in turn give rise to even more detailed or specific questions. In the present doctoral thesis, I attempt to give a brief summary of some of the questions that have been answered – by myself and others – and point to some questions that have yet to be answered.

The general disposition of the thesis is such that I first discuss larger conceptual domains, such as *Diabetes*. Then I move to more specific subjects, such as *Diabetes and cognition*. After that I give brief overviews of the empirical studies that form the basis of this dissertation, followed by a discussion about the limitations of the studies that I have performed. Finally, I present some questions that are as of yet unanswered, and describe how I intend to answer them in future studies.

Specifically, I attempt to answer questions regarding the effects of diabetes in non-demented old age (Studies I & II), in non-demented adulthood (Study III), and in Alzheimer's disease (Study IV). I also attempt to answer questions regarding the generality (Studies I & IV), and selectivity (Studies II & III) of diabetes related effects on cognition. In all studies, I have attempted to examine comorbidity. Some questions that I have not specifically addressed in the four empirical studies, such as whether diabetes affects the risk of dementia and AD, and diabetes as a part of a risk-factor complex, are briefly described next.

1.1 DIABETES

Diabetes mellitus is a group of common metabolic disorders. All types of diabetes mellitus are characterized by hyperglycemia, caused by defective insulin secretion, defective insulin action, or both. A simple and still formally correct way of subdividing most diabetic diseases is into type 1 and type 2 subcategories (Gavin et al., 2000). Type 1 diabetes accounts for 5-10% of diabetes cases in the population, and is characterized primarily by the autoimmune destruction of pancreatic islet cells, usually resulting in absolute insulin deficiency (American Diabetes Association, 2006a). Due to historical selective survival (i.e. that persons diagnosed with type 1 diabetes historically did not survive into old age), combined with low average age of diagnosis, type 1 diabetes prevalence is higher in younger than in older age-groups. Type 2 diabetes accounts for 90-95% of all diabetes cases in the population, and is more common in older than younger age groups (American Diabetes Association, 2006a). Prevalence of type 1 and type 2 diabetes also varies across different ethnical and cultural groups. In Sweden, data

indicate that type 2 diabetes accounts for about 90% of diabetes cases (Henriksson et al., 2000).

All conditions labeled as type 2 diabetes share the characteristic of *relative* insulin deficiency, i.e. the pancreas cannot produce enough insulin to give the desired effect in peripheral tissue. This deficiency may be primarily caused by abnormal insulin secretion or reduced insulin sensitivity (Zimmet, Alberti, & Shaw, 2001). Thus, in the development of type 2 diabetes – because peripheral tissue does not respond to "normal" insulin levels – the pancreas often increases insulin production. As the disease progresses, both the insulin sensitivity of peripheral tissue and the secretion of insulin from the pancreas become more impaired. Finally, the pancreas is unable to produce enough insulin to counter the insulin requirement, and the patient loses glycemic control. The loss of glycemic control constitutes the diagnostic criterion for diabetes (American Diabetes Association, 2006a). Importantly, there is not a single pathogenetic process that explains all instances of type 2 diabetes.

In the following text, type 2 diabetes will be treated as a homogenous disease – even though future criteria may define several specific diseases that replace the diagnosis. At present, there is simply not enough data to support differentiation between subtypes of type 2 diabetes, other than in endocrinological and diabetological studies specifically targeted at describing such differences (American Diabetes Association, 2006a).

Because type 2 diabetes may present itself gradually, it often goes unnoticed and undiagnosed for several years. Although specific hyperglycemic symptoms such as polyuria, polydipsia and blurred vision are not common in early type 2 diabetes, end-organ damage begins at the point when glucose regulation starts becoming dysfunctional. Often, by the time a diagnosis of type 2 diabetes is set, micro- and macrovascular complications are already present (American Diabetes Association, 2006a)[1]. Because the diabetes-related CVD risk increase reflects the prevalence of CVD in the studied population (WHO, 1985), it is likely that a larger proportion of older than younger persons that receive a diabetes diagnosis already have micro- and macrovascular complications.

Type 2 diabetes is a common disease among the elderly, with diagnosed prevalence figures as high as 10% in the 60+ population, and 20% in the 80+ population (Lipson, 1986). A studied sample of the general population in Australia, where the diabetes diagnoses were set as a part of the study examination, demonstrated prevalence figures of 0.3% in the 25 to 34 age range, with a gradual increase with increasing age, up to 13.1% in the 55 to 64 age range, and 23% in the 75 and older age group (Dunstan et al., 2002). The present thesis focuses mainly on the older segments of adult life. Several aspects of aging and type 2 diabetes are worth mentioning. First, the proportion of undiagnosed to diagnosed type 2 diabetics, increases with increasing age. Among those diagnosed with diabetes in the Dunstan et al. (2002) study, about one third of the diabetics in the youngest age group, and more than half of the diabetics in the oldest

[1] Microvascular complications refer to changes of small blood vessels, and may, e.g., include symptoms related to poor blood-supply to the retina. Macrovascular complications refer to changes in larger-diameter blood vessels, and include cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

age group were unaware of their diabetic status. A 50% underdiagnosis was also found in a Swedish study focusing on 64 year old women (Brohall, Behre, Hulthe, Wikstrand, & Fagerberg, 2006). Because there is such profound underdiagnosis in the general elderly population, it is desirable for most studies to include some form of objective measure of diabetes risk. Second, type 2 diabetes is part of a risk-factor complex that also includes hypertension, obesity, and cardiovascular disease. As these conditions are risk-factors not only for cognitive impairment but also for each other, it is essential to have good comorbidity data – particularly given that comorbidity increases with increasing age. The issue of comorbidity will be more thoroughly discussed in a later section of this thesis.

According to extant literature, disease severity is often difficult to grade in data from studies not specifically designed to assess diabetes. However, a proxy for studying the effects of disease severity may be to study the effects of fulfilling some of the laboratory criteria for diabetes without actually having received a diagnosis. This strategy is used in Study III, where persons with diabetes are contrasted with (i) persons with elevated glycated hemoglobin (HbA1C above normal range) in the absence of a diabetes diagnosis, and (ii) persons with normal HbA1C. Whereas HbA1C is not presently recommended as a diagnostic test for diabetes (American Diabetes Association, 2006a), an elevated level in the absence of a diabetes diagnosis is certainly a good risk indicator for diabetes. Even if persons that have elevated levels of HbA1C would not fulfill clinical diagnostic criteria, the elevated levels represent an early indicator of prodromal diabetes or insulin resistance. In fact, a large proportion of the population in western countries can be expected to have impaired glucose tolerance, based on the fact that a body mass index (BMI) above 30 is common, and a high BMI is correlated with insulin resistance (Williams & Pickup, 2004). Although waist circumference is a better indicator of insulin resistance than BMI (Janssen, Katzmarzyk, & Ross, 2004), the latter index is more common in large cohort- or population based studies.

1.2 AGING, COGNITION, AND DISEASE

In the study of diseases (e.g. type 2 diabetes) that increase in prevalence with increasing age, comparisons to normal aging are inevitable. However, the concept of "normal aging" is not easily defined. A nice summary of the potential pitfalls of viewing aging and disease as either dichotomous concepts or as endpoints of a continuum can be found in Blumenthal (2003). Should normal aging be defined as healthy aging? The World Health Organization's definition of health as "...a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (page 2, WHO, 1946) implies that aging and disease cannot be evaluated separately. Perhaps it is after all possible to consider aging – be it normal or not – as a continuum reaching from *biological* aging to *pathological* aging with regard to age-related functioning. Distinguishing between biological and pathological aging, rather than between normal and pathological aging, underscores the point that the term "normal" excludes the possibility of simultaneous pathological aging, whereas the term "biological" does not.

It is reasonable to view aging as composed of interrelated biological and pathological changes, or even to consider biological changes as passing over a pathology threshold when they limit function to a certain degree. For example, a common occurrence in

aging is reduced circulation in extremities. This may be due to biological aging, such as reduced flexibility in blood-vessels, but may also be exacerbated by pathological conditions such as diabetes. Even the biological component – the age-related reduction in vessel flexibility – may be considered pathological if it impairs function. Of course, we may not be able to distinguish a "pure" biological aging component in any person, but it is conceptually helpful to consider biological aging as a factor that interacts with numerous pathological aging factors for any specific individual. Thus, "normal" aging need not be defined in relation to the WHO-definition of health, or even the absence of disease. Rather, "normal" aging, in the sense that I will use it throughout this thesis, refers to the biological aging component and whatever pathological aging components not known or specifically targeted by research questions or comorbidity control.

Clearly, it is a difficult proposition to construct a definition of normal aging that holds true under all conditions. However, a definition that works in the context of a specific argument, or in the context of a specific study, may be a reasonable goal (e.g. a definition of normal aging that is practical in the context of cognition, diabetes, and aging). Characterizing normal aging as the absence of specific diseases means that there will be an artificial increase in the difference between the group of diabetics and the group of "normally aged". It is uncommon for a group of old people to be disease free, and failure to impose similar inclusion criteria on both the diabetics and the normally aged comparison group introduces bias into the study. Identifying a group of older type 2 diabetics who are free of other disease processes is, in most cases, not practically possible. It is more reasonable to define normal aging in this context as the absence of specific *neurodegenerative* diseases. Although it is difficult to argue that a given neurodegenerative disease is more pathological than other diseases (e.g. myocardial infarction), neurodegenerative diseases are clearly relevant to consider in the context of cognition.

After defining normal aging in the context of cognition, diabetes, and aging, it is necessary to discuss how aging in itself influences cognition. There is, of course, a plethora of studies showing that chronological age is a good predictor of cognitive function. However, I believe that a portion of the variance in cognitive function that is presently attributed to aging can in fact be better explained by specific disease processes. Even so, variance will remain unaccounted for by specific diseases despite improvements in diagnostic proficiency. This variance may in fact be best explained by age. Further evidence for age as an influence separate from disease is provided by analyses attempting to partial out the influence of health and age on cognition, showing relatively little overlap between health-related variance and age-related variance for most cognitive outcomes (e.g. Earles & Salthouse, 1995). Thus, when I use the term "normal aging" to refer to the absence of specific neurodegenerative disease, it is important to realize that it may be necessary to also control for other known comorbidity.

In the empirical studies of this thesis (Studies I-IV), I have to the best of my ability held the presence of neurodegenerative disease constant. In studies I-III, this was achieved through the exclusion of persons diagnosed with dementia, and in study IV it was achieved through excluding all persons *not* diagnosed with Alzheimer's disease. These exclusions reflect my belief that it is reasonable, in the context of cognition research, to attribute special significance to neurodegenerative disease.

The anatomical changes of the brain during normal aging are by no means dramatic, although measurable. A slight reduction in total volume (Albert, 1998), most visible through enlarged ventricles and widened sulci in the cortex of the brain, has been consistently shown to occur even in the absence of specific neurodegenerative disease. The overall brain volume is significantly different from younger controls when subjects are about 70 years of age (Stafford, Albert, Naeser, Sandor, & Garvey, 1988). Certain regions of the brain, such as the lateral prefrontal cortex, show significant decrease in volume as early as around 50 years of age (Raz et al., 2004). The efficiency of the cerebral blood-supply is also reduced through normal age-related changes in both cerebral and extra-cerebral vasculature (Raz, 2000).

There is evidence of selective cognitive deficits during normal aging – for example that certain memory systems are more affected than others. Of the memory systems (Schacter & Tulving, 1994), I focus on *semantic* and *episodic* memory in Studies I-IV. The following sections briefly summarize aging effects on these two systems.

Semantic memory, or memory for general knowledge, reveals a multifaceted picture with regard to aging related decline. The internal lexicon, a network of word- and concept-representations and associations, does not seem to be affected by aging. When controlling for education, word association experiments show similar results for old and young, category information is treated similarly, and vocabulary often improves into late life (Bäckman & Nilsson, 1996; Bäckman, Small, Wahlin, & Larsson, 2000; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Learning new semantic materials is, however, not as efficient in old age (Prull, Gabrieli, & Bunge, 2000). Moreover, additional time is required to access semantic information, indicating that the general semantic network may be intact albeit working more slowly. For example, the feeling of having something "on the tip of the tongue" is more common among older than younger persons. This speed-loss in retrieval could be explained by increasing difficulty in recalling phonological representations of words based on semantic cues. Tests that provide little support (e.g. world knowledge and verbal fluency) show some loss of performance with increasing age, but not tests that include higher levels of support (e.g. recognition vocabulary; Bäckman, Small, & Wahlin, 2001).

Episodic memory, the memory system that permits "mental time travel" (Tulving, 1999), is the memory system that is phylo- and ontogenetically most recent. Episodic memory can either be viewed as a system wholly separate from semantic memory (Squire, 1987), or as a system that shares many functions with semantic memory but also has unique features such as autonoetic awareness of personal past that semantic memory lacks (Tulving, 1999). Independent of which view is taken, the function of episodic memory depends to some degree on the function of semantic memory. Episodic memory is the memory system most sensitive to aging-related decline (see e.g. Nilsson, 2003). Longitudinal data from the Betula project (Nilsson et al., 1997) shows that, when controlling for training and cohort effects, episodic memory performance is stable up to about 60 years of age, and substantial decline starts after that age (Rönnlund et al., 2005). The change in episodic memory performance has been shown to generalize across many modalities of episodic memory information, such as words, sentences, faces, and actions (Nilsson et al., 1997). Even though a general decline in episodic memory performance is observed, there are still performance differences depending on the level of support provided during the test situation. Tests

that offer limited cognitive support (e.g. free recall) show larger age effects than tests (e.g. cued recall, recognition) that offer more cognitive support (Balota, Dolan, & Duchek, 2000).

Although some specific tests of cognitive function are more age invariant than others, the effect of aging – particularly in advanced years – is large enough to affect scores on global measures of cognition such as the mini-mental state examination (MMSE, Folstein, Folstein, & McHugh, 1975; Hill & Bäckman, 1995). Also, since detailed cognitive assessments are not always available, it is informative to note that tests of cognition originally devised for clinical usefulness and ease of administration (e.g. MMSE) can be analyzed on the item-level (Hill & Bäckman, 1995). This offers researchers with access to global measure data a possibility to examine also specific cognitive constructs.

1.2.1 Comorbidity

Prevalence[2] figures of certain chronic diseases (e.g. diabetes) increases with increasing age. For example, European data indicate that prevalence of hypertension grows dramatically between the age of 35-44 (27% prevalent hypertension) to the 65-74 year old cohorts, who have 78% prevalent hypertension (Wolf-Maier et al., 2003). In a different study, 46-month incidence[3] of cardiovascular disease in persons aged around 80 years was 85% (Aronow, Ahn, & Gutstein, 2002). As the risk of having any specific disease increases with age, so does the risk of having more than one disease. The concept of multiple diseases in a single patient is referred to as comorbidity, and this is an important factor to consider in studies of health and cognition in the elderly. Importantly, in subjects who are 80 years of age and older, the majority suffer from more than one diagnosed medical condition (Cauley, Dorman, & Ganguli, 1996).

Whereas incidence of disease tends to increase with increasing age, the prevalence of diseases that cause a large increase in mortality increases up to a point, but then decreases. Since most diseases are associated with increased mortality, the seemingly paradoxical finding that centenarians (admittedly an extremely select sample) are actually healthier than those slightly younger has been reported (Hitt, Young-Xu, Silver, & Perls, 1999). Since the maximum prevalence age is different for different diseases, it may be informative to include prevalence data for an age-matched stratum of the general population when assessing the prevalence of diseases in a specific data set.

Since comorbidity becomes more common with increasing age, it may be relevant to consider whether even those diseases that *in themselves* do not explain much variance in cognitive test performance may interact with other diseases (and biological changes that have not crossed the pathology-threshold) to explain age-related variance in

[2] Prevalence. The total number of cases of a disease in a specific population at a specific time.
[3] Incidence. The number of new cases of a disease in a specific population during a specified time-period.

performance. More elaborate descriptions of potential interaction effects are provided in the section describing *diabetes as a part of total comorbidity burden*.

1.2.2 Dementia

Dementia is a syndrome that is not defined by any specific pathogenetic process. Rather, it is defined by impairments that include acquired memory impairment, aphasia (deteriorated language), apraxia (deteriorated motor abilities), agnosia (loss of ability to recognize objects), and disturbed executive function (ability to plan and carry out complex behavior). In order to set a diagnosis of dementia, the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R, American Psychiatric Association, 2000) requires impairments to be severe enough to affect daily activities, and to include memory impairment and impairment in at least one other cognitive domain. There are several subtypes of dementia, including Alzheimer's disease (AD), and vascular dementia. AD is by far the most common form, representing about 60-70% of all dementia cases (Fratiglioni et al., 2000). In this thesis, AD is the only specific subtype of dementia that has been examined, and I will therefore limit my description to dementia, generally, and AD, specifically.

Prevalence of dementia increases with age. Data summarized from 12 studies conducted in Europe between 1980 and 1990 show that the prevalence of dementia in persons 65-69 years of age is 1.4%, in persons 70-74 years of age it is 4.1%, in persons 75-79 years of age it is 5.7%, in persons 80-84 years of age it is 13%, in persons 85-89 years of age it is 21.6%, and in persons 90-94 years of age the prevalence is 32.3% (Hofman et al., 1991).

AD is, in contrast to dementia in general, defined by its pathogenesis. Pathogenetic markers of AD are cerebral extracellular beta-amyloid depositions (senile plaques), and intraneuronal neurofibrillary tangles. Definite diagnosis of AD, based on both these markers, is at present possible only after death since no in-vivo visualization of the intraneuronal tangles is practically possible. The tangles are predominately present in medial temporal lobe structures such as the hippocampus, entorhinal cortex, and amygdala, whereas the plaques are more diffusely distributed (Carr, Goate, Phil, & Morris, 1997) but still aggregate to a greater extent in medial temporal lobe structures.

Clinical diagnoses of AD in demented persons are set according to either DSM-criteria, which require insidious onset and the exclusion of other possible causes of dementia, or according to a more detailed diagnostic procedure devised by the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA, McKhann et al., 1984). The main requirements are the same as the DSM-criteria, but a differentiation between possible, probable, and definite AD is made. Definite AD is the most certain diagnosis, followed by probable AD (PRAD). In practice, it is unlikely for a patient to receive a more certain diagnosis than PRAD before death.

There are many possible risk-factors for developing dementia, including apolipoprotein ε4 genotype, familial aggregation, midlife hypertension, and diabetes (Statens beredning för medicinsk utvärdering, 2006).

Treatment of dementia has shown little curative potential. At best, treatments such as cholinesterase inhibitors reduce the downward trajectory of cognitive function. Thus, risk-factor modification before dementia onset may be a more promising approach, although data so far only indicate that treatment of hypertension in midlife may reduce the associated risk of later developing dementia. No specific AD-preventive strategies have proven effective (Statens beredning för medicinsk utvärdering, 2006).

Since AD by definition has an insidious onset, the time before clinical diagnosis is characterized by decreased function in multiple cognitive domains. As a consequence, preclinical AD is an important factor to consider in studies assessing cognitive function in aging.

1.3 DIABETES AND COGNITION

Effects of diabetes on cognitive functioning were first described in the 1920s (Miles & Root, 1922). However, very little happened in the field until Bale (1973) published the first modern study on diabetes and cognition. Between the 70's and the 90's, a trickle of studies were put forth, and by the end of the 90's the field started growing at a fast rate. A Medline search in April of 2006 reveals 1,028 studies focusing on diabetes and cognition.

1.3.1 Mechanisms of diabetes-related cognitive impairment in non-dementia aging

How diabetes specifically affects the brain to impair cognitive functioning is not well understood. Given the complex end-organ effects of diabetes that are known, diabetes' effects on the brain are likely to be multi-factorial, similar to the causes of peripheral neuropathy. Also, evidence for the brain being an insulin-sensitive organ has recently emerged. Because of the impermeability of the blood-brain barrier to insulin, the brain was long thought to be independent of insulin. Insulin and insulin receptors have, however, been demonstrated throughout the CNS (Schulingkamp, Pagano, Hung, & Raffa, 2000), albeit in different concentrations in different structures.

Since the hippocampus is known to be sensitive to hypoxic conditions it is likely that decreasing vascular supply, causing inadequate oxygenation of brain tissue, is responsible for some of the hippocampal volume reduction that has been found in diabetics (den Heijer et al., 2003). However, even persons without diabetes diagnosis, but with reduced glucose tolerance, have been shown to have reduced hippocampal volume (Convit, Wolf, Tarshish, & de Leon, 2003).

Even though reduced glucose tolerance (postprandial hyperglycemia) in itself may cause vascular damage that may in turn lead to hypoxic conditions, perhaps another mechanism is also at work. Insulin and insulin receptors may play modulating roles in synaptic transmission in the brain. High densities of insulin receptors have been found in the hippocampus, olfactory bulb, cerebral cortex, cerebellum, and hypothalamus (Park, 2001; Unger, Livingston, & Moss, 1991), structures that are known to play important roles for memory proficiency (Squire, 1992). Acute elevation of serum insulin levels have been shown to increase insulin levels in the CNS (Wallum et al., 1987), and increased levels of brain insulin during euglycemic conditions have been

demonstrated to improve cognitive function in healthy humans (Kern et al., 2001). Since vascular insulin levels are often higher in type 2 diabetes patients than in persons without diabetes, this would ostensibly be a protective factor against cognitive impairment in type 2 diabetes. However, there are two factors that are important to take into consideration regarding the biological situation in diabetic brains. First, there is mounting evidence that the effects of chronically raised levels of peripheral insulin may actually induce a down-regulation of brain insulin. Chronic hyperinsulinemia causes down-regulation of the blood-brain barrier insulin receptors, leading to reduced brain insulin availability (Kaiyala, Prigeon, Kahn, Woods, & Schwartz, 2000). Second, the improvement of cognitive function that has been shown under euglycemic insulin administration has not been possible to replicate under hyperglycemic conditions (Watson & Craft, 2006). For further discussion regarding how different pathogenetic processes may explain how diabetes causes cognitive impairment in non-dementia aging, see Biessels (1999), and Gispen and Biessels (2000).

Aside from the direct pathogenetic effects of diabetes, one must also consider the possibility that diseases that are associated with diabetes may influence cognitive performance. Diseases associated with both diabetes and cognitive impairment include stroke, hypertension, depression (Stewart & Liolitsa, 1999), and cardiovascular disease (Barclay, Weiss, Mattis, Bond, & Blass, 1988). Diabetes-associated visual impairment influences performance in cognitive testing, and may indicate greater risk of central nervous system damage, but is not likely a cause of cognitive impairment.

There is always a risk of confounding due to a common cause, but there is no proof of a common cause of diabetes and neural damage with the exception of hypertension. Although available data do not confirm a causative link between hypertension and diabetes, they do tentatively indicate that hypertension is a risk-factor for diabetes (Sowers, Epstein, & Frohlich, 2001). I do not believe that type 2 diabetes is caused by any specific agent in very many cases, but rather by a complex interplay between genetic and lifestyle factors. Even if a diabetes-causing specific agent could potentially induce neural damage, it is unlikely to be a good explanation of the overall pattern of neuronal damage observed in diabetic patients.

1.3.2 Selective effects of diabetes in non-dementia aging

Early studies of diabetes and cognitive function showed discrepant results, with some studies indicating no diabetes effects (e.g. Atiea, Moses, & Sinclair, 1995; Robertson-Tchabo, Arenberg, Tobin, & Plotz, 1986), and the majority indicating clear effects. Whereas this discrepancy could also be explained by several other factors, one factor that seemed to merit detailed examination was the types of cognitive tests utilized. In the Robertson-Tchabo et al. study, subjects performed tests of vocabulary (Wechsler, 1981), and non-verbal memory (Benton, 1945). With current knowledge, it is easy to explain the absence of significant group differences in tests of this nature. The vocabulary subtest of the Wechsler adult intelligence scale (WAIS) taps semantic memory, known to be resilient to the effects of aging and most diseases, whereas the Benton visual retention test shows limited variability of results in persons that are relatively cognitively intact (ceiling effects). Robertson-Tchabo et al. (1986) hypothesized that persons with diabetes perform at a significantly lower level than non-

diabetic controls in tests requiring speedy response, and in tests with fixed response times. Whereas there is support for the notion that diabetes induces a cognitive slowing (e.g. Tun, Perlmuter, Russo, & Nathan, 1987), the results of previous studies seemed to indicate a more intricate pattern.

There is good evidence for selective cognitive effects in normal aging (reviewed in Bäckman et al., 2000), such that cognitive support attenuates differences between older and younger adults. This also holds true for other medical conditions, such as vitamin deficiency (Robins-Wahlin, Wahlin, Winblad, & Bäckman, 2001) and depression (Bäckman & Forsell, 1994). It should be noted that the beneficial effects of cognitive support in depressed persons are only demonstrable when support is given at both encoding and retrieval. Diabetes has been shown to induce selective effects in tasks that require fast and accurate processing of novel information (Tun et al., 1987; van Boxtel et al., 1998). An accelerated decline in tests of word fluency and digit-symbol substitution (Knopman et al., 2001) further demonstrates that semantically taxing and speed-requiring tasks may be most sensitive to diabetes-related cognitive impairment.

In Study II we showed that tasks relying less on semantic structures inherent in the test materials, and more on the ability to elaborate on and process information in a non-structured context, show the largest effects of diabetes[4]. If the results are viewed in accordance with the Tulving (1999) theory that episodic memory shares features with semantic memory but also has unique qualities that are phylo- and ontogenetically more recent, the selective effects may be taken to indicate that tasks using predominantly the features unique for episodic memory show the largest effects of disease. Expanding on this argument, there is also a relationship between level of cognitive support and the level of cognitive impairment at which it is possible to utilize the support. Previous research shows that depressed persons utilize low levels of cognitive support less efficiently than non-depressed persons, but when the level of support is increased such that support is provided both at encoding and retrieval, beneficial effects are apparent also for depressed patients (Bäckman & Forsell, 1994). Similarly, several studies on aging and cognitive support have indicated that there is a differential effect of cognitive support depending on the degree of support and the age of the "young" and "old" groups tested (for review, see Bäckman et al., 2000). In general, if the persons in the "old" group are old enough, limited support is no longer helpful. However, for organizability (encoding support) and cues (retrieval support), the benefits of the high support setting generalize into very old age (Bäckman & Wahlin, 1995).

Data from Study III indicate that diabetics benefit from both encoding and retrieval support, and that there is a greater beneficial effect of higher levels of support among diabetics than among non-diabetic controls. The overall appearance of the previous data on aging and medical conditions, together with my diabetes data, indicate that the usefulness of cognitive support is based on three variables: The severity of the cognitive impairment, the level of support, and the functional ceiling of the control group. If the cognitive impairment is severe, lower levels of support will not improve performance by much in the low performing group, but may produce performance improvement in the control group. If the cognitive impairment is less severe, the low

[4] If rephrased in terms of support, we demonstrated diabetes-related effects on cognitive performance only when support was low.

performing group may be able to utilize different abilities that are not as penalized by disease or old age, and improve more than the control group. Finally, if the tests tap an ability for which there is a functional ceiling, the difference between high and low performers may be decreased due to that the high performers are not able to perform better in the high-support condition than they already were in the low support condition. This situation needs not arise from a traditional ceiling-effect, such that the high-performing group are near the maximum score in the test, but may instead reflect that a high support setting helps the low performers recruit more intact abilities, whereas the high performers are already using all abilities relevant for the task at hand. Whether the cognitive performance difference between patients and controls decreases in high support settings because of functional ceiling effects in the control group, or because of utilization of abilities not penalized by disease in the patient group, is not always possible to disentangle.

The term *cognitive reserve* has been used to describe recruitment of more intact abilities by the group with lower performance. Data from my studies (I – III) indicate that whereas diabetes is detrimental enough to cognitive performance for relatively insensitive global tests of cognition (e.g. MMSE) to be affected, the impairment is not severe enough to reduce the cognitive reserve. Rather, in tests providing high levels of cognitive support diabetics perform at a similar level as non diabetics. This is the same thing as saying that the effects of diabetes on cognition are *selective*.

1.3.3 Diabetes and risk of Alzheimer's disease

Diabetes has in many studies been shown to increase the risk of dementia (e.g. Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004). The evidence of a risk increase for Alzheimer's disease specifically is slightly less well documented, but several studies have reported significantly greater risk for AD in diabetes patients. Ott and colleagues (1996; Ott et al., 1999) showed an approximately doubled risk of AD onset in subjects with diabetes. Leibson et al. (1997) reported a 66% increased risk of all dementias in persons with diabetes, with a doubled risk for developing AD in diabetic men relative to a non-significant risk elevation among diabetic women. It may be of interest to note that there is a kind of "dose-response" relationship for diabetes and dementia. Elevated random blood-glucose values in persons without diabetes diagnosis are an indication for increased risk of vascular dementia, but do not increase risk of other dementias. Diabetes does increase risk of all dementias, and if both systolic hypertension and diabetes are present, there is very strong evidence for an increased risk of AD. For an overview of studies linking diabetes to risk for AD, see Messier (2003), or Biessels, Staekenborg, Brunner, Brayne, and Scheltens (2006).

Although the biological mechanisms underlying diabetes and dementia are outside the scope of this dissertation, there are possible shared pathways for AD and diabetes. AD patients, irrespective of whether they have a diabetes diagnosis, show a pattern of elevated plasma insulin and depressed cerebrospinal fluid insulin (Craft et al., 1999) that is remarkably similar to what is observed in type 2 diabetes patients. Speculatively, this pattern may in part explain some of the pathologic processes of AD. For example, in vitro-studies have shown that insulin and glucose concentration affect metabolism of

amyloid precursor protein (Boyt et al., 2000). Also, insulin causes in vitro neurons to release beta-amyloid into the extra-cellular space (Gasparini et al., 2001), where it may in vivo be cleared. Finally, an effect of chronic hyperglycemia is an increase in advanced glycation end products (AGEs), and higher concentrations of AGEs have been found in the brain tissue of AD-patients. AGEs have been demonstrated to directly cause neuronal damage, and are involved in the neurotoxic pathway of beta amyloid in AD-development (Stewart & Liolitsa, 1999).

Several treatment strategies for AD have shown promise, but as of yet there is no evidence for any truly curative treatment. Thus, risk-factor management is at present probably the best way of reducing the impact of AD and other dementias. Since diabetes clearly increases the risk for developing dementia, and most likely increases the risk of AD, pre-AD diagnosis diabetes treatment may be a feasible way of limiting the incidence of AD.

1.3.4 Diabetes as a part of total comorbidity burden

Several medical conditions, such as cardiovascular disease and symptoms thereof, vitamin deficiency, thyroid disturbances, mood disorders, and diabetes, have been shown to affect cognition. As mentioned in the section on comorbidity, having more than one diagnosed chronic disease becomes increasingly likely with increasing age.

In relation to comorbidity, it is important to discuss disease severity. For diseases that are risk-factors for each other, comorbidity could be considered a measure of disease severity. Diabetes is a risk-factor for vascular disease, and the risk of vascular complications is related to the degree of diabetes severity. Thus, vascular disease could be viewed as a proxy of diabetes severity, as well as a risk factor for cognitive impairment in its own right, in diabetic patients. It is not uncommon for related diseases to show this type of relationship. For example, higher blood-pressure leads to increased risk of stroke, and both hypertension and stroke are associated with cognitive impairment. Thus, comorbidity as a proxy for disease severity is always a consideration when diseases serve as risk-factors for each other. However, diabetes and vascular disease are both risk factors for cognitive impairment, even when they are modeled simultaneously (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995), so obviously this can not be the whole story behind comorbidity effects.

It is important to realize that different combinations of diseases may act in different ways on cognition. The sum of diseases, or disease burden, do not always maximize explained variations in cognitive test performance. Instead, it may prove worthwhile to examine different types of interaction effects in the context of comorbidity. There are, for practical purposes, three different ways in which two diseases may affect cognition: (i) The effect on cognition in subjects with both disease A and disease B approximately *equals* the sum of effects found in subjects that have either disease A or disease B. This is actually a common finding (e.g. Wahlin, Hill, Winblad, & Bäckman, 1996), that is probably due to the fact that there are cognitive processes that are influenced to a certain degree by either disease, although the variance produced is not shared. Importantly, an additive interaction effect is not likely to be significant if examined as a cross-product interaction term. (ii) The effect on cognition in subjects with disease A

and B is *greater* than the sum of effects in subjects that have either disease A or disease B. This type of effect is statistically difficult to validate (McClelland & Judd, 1993), but has been shown in the context of effects on cognition of diabetes and hypertension (Elias et al., 1997; Hassing et al., 2004). (iii) The effect on cognition of disease A overshadows the effect of disease B (i.e. the effect of disease A alone is similar to the effect of disease A and B, even though disease B by itself has demonstrated an association with cognition). This type of effect is often found when examining other diagnoses in the context of post dementia diagnosis changes in cognition, such as in Study IV of this thesis. As already mentioned, the absence of a statistically significant interaction means that there is no detectable difference between the sum of effects in subjects that have either disease A or disease B and the sum of effects in subjects that have both diseases. Of course, data that point in this direction are by far the most common, since lack of significant interaction effects is the most common result. Non-significant interaction effects can either be caused by a true lack of meaningful effect modification of comorbidity, lack of power to detect such differences (due to small sample size, small effect size, or – relatedly – a large proportion of unexplained to explained variance in the data). For a more complete discussion on morbidity interaction effects and cognition, see Wahlin (2004).

Comorbidity may, as mentioned, in some cases serve as a proxy of disease severity. Thus, controlling for comorbidity (either statistically or through excluding persons with certain diagnoses from the study) may lead to unwanted dilution of effects in analyses of diabetes and cognition. On the other hand, if comorbidity effects are simply ignored, results are often trivial. For example, if no control for vascular diseases is done, a very strong association between diabetes and cognitive impairment may be demonstrated. However, because this association may result to a large extent from the "confounding" influence of vascular diseases, and thus does not imply a direct causative link, it is not as informative as an association demonstrated whilst controlling for known covarying conditions. The challenge in dealing with known comorbidity, therefore, is to simultaneously model diabetes and relevant comorbid conditions. I have dealt with this in different ways in the studies that form the empirical base of this thesis. In Study I, a correlation analysis was performed initially, and all predictor variables that were either correlated with diabetes or cognition were included in the main hierarchical regression analysis. In Study II, known vascular conditions and signs thereof were reduced into clusters by means of a factor analysis, and the factor-scores were then included and controlled for in the main hierarchical regression analysis. In Study III, similarly, a factor analysis was performed, and the resulting factor score was entered as a covariate in the main repeated measures analysis of covariance. In Study IV, several sets of potentially important comorbid conditions, or proxies of such conditions, were controlled for in separate models but not included in the final analysis since they influenced neither model fit nor main results.

A last aspect of comorbidity that I will briefly mention is unknown comorbidity. It is likely that all diagnoses that could potentially have been made are not made in all individuals participating in a study. Such undiagnosed conditions could potentially be related to both diabetes and cognitive impairment. Because type 2 diabetes is an exclusion diagnosis of sorts, it is also possible that several different subtypes of type 2 diabetes are represented in the group of diabetics, and that different comorbidity patterns are present for the different subtypes.

2 OBJECTIVES

I have studied the effects of diabetes on cognition in four consecutive studies. My aims were to assess:

(i) The effects of diabetes on global cognition and specific subsets of cognitive abilities in persons that are non-demented, non-depressed, and of very old age.

(ii) The effects of semantic structure in the test materials on the relationship between diabetes and cognitive performance.

(iii) The effects of encoding and retrieval support on the relationship between diabetes and cognitive performance.

(iv) The effects of elevated HbA1C on cognition in the absence of a diabetes diagnosis.

(v) The interaction of age and diabetes, with regard to cognitive performance.

(vi) The effects of preclinical dementia and impending death on the diabetes-cognition association.

(vii) The effects of diabetes on global cognition and functional ability in persons with diagnosed Alzheimer's disease.

(viii) The effects of comorbidity on the diabetes-cognition relationship.

Study I attempts to asses (i), and also assesses (v) in a limited age-span of very old subjects. Study II attempts to assess (ii) and (vi), and also assesses (v) in the very old. Study III attempts to assess (iii), (iv), (v), and (vi). Study IV, finally, attempts to assess (vii), and to a certain extent (v). In all Studies, (viii) was also taken under consideration.

3 MATERIALS AND METHODS

To fulfill the aims (i – viii), three different large databases were utilized. While the use of multiple databases may be unconventional in the context of dissertations, it has had the advantage of affording me data for answering questions that are highly related to each other without the risk of prior knowledge of the data-sets influencing the questions being asked. In other words, instead of repeatedly assessing highly interrelated questions in data from the same subjects, I have been able to start new analyses without knowing the relation between diabetes and cognition *in the database* in advance. This adds some credibility to the results. A disadvantage of utilizing different databases is that different sampling strategies, different diagnostical procedures, different cognitive measurements, and different laboratory analyses may influence the findings. In the following sections, I will provide brief overviews of the databases that I have utilized.

3.1 THE KUNGSHOLMEN PROJECT

The Kungsholmen project (KP) is a population based longitudinal study for which the original study population was all persons living in the Kungsholmen parish of Stockholm who were born before 1912. A detailed description of KP can be found in Fratiglioni, Viitanen, Bäckman, Sandman, and Winblad (1992).

All persons 75 years of age or older, residing in Kungsholmen, were invited to participate in baseline assessment between 1987-1989. Out of a total study population of 2,368 persons, 1,810 persons were alive, still living in Kungsholmen, and agreed to participate in the assessment. Baseline assessment was divided into a screening phase and an assessment phase. In the screening phase, subjects were tested with the MMSE. In addition, data on vital parameters such as blood pressure, height, weight, and multiple blood parameters (including blood glucose analyses) were collected. Persons scoring below 24 on the MMSE (n=314), and a random sample (stratified by age and gender) of persons scoring above 23 (n=354), were included in further baseline assessment. This second phase of baseline assessment comprised a complete medical examination, including diagnosis of dementia, specific diagnostic interviews, laboratory blood analyses, comprehensive cognitive testing, and renewed MMSE testing.

Three years after baseline assessment, a first follow-up assessment was conducted. The first follow-up involved repeated complete medical examination, laboratory blood analyses, and cognitive testing. Additionally, a merge of identification data on the participants of KP and a computerized inpatient discharge diagnosis register system covering all hospitals in Stockholm since 1969 was performed.

3.1.1 Measures

For both Study I and Study II, data from the screening phase (blood glucose), second phase baseline assessment (blood glucose, DSM III-R dementia, suspected dementia, or major depressive or dysthymic disorder (American Psychiatric Association, 1987)), and diabetes diagnoses from the computerized inpatient register were used.

For Study I, MMSE scores from second phase baseline assessment were used as cognitive outcome measures.

For Study II, DSM III-R diagnoses of dementia from first follow-up, and date and cause of death data from the computerized inpatient register were also used. Additionally, tasks tapping abilities in episodic word recall and verbal fluency, that were administered during second phase baseline assessment were used as cognitive outcome measures. The tests of episodic word recall were two different 12 word lists, with either random words or words divisible into four taxonomic categories, that were presented on printed cards and read aloud by the test leader. Recall tests started immediately after presentation. For the present purposes we examined free recall of the random word list, and category cued recall of the organizable word list. The tests of verbal fluency were two different tests of letter fluency and one test of category fluency. In the letter fluency tests, subjects were asked to generate as many nouns as possible in one minute, starting with either the letter N or S. In the category fluency test, subjects were asked to generate as many items found in a grocery store as possible in one minute.

3.1.2 Sampling procedure

For Study I, participants of the second phase baseline assessment who had completed the second-phase MMSE (*n*=668) were excluded if they fulfilled DSM III-R diagnostic criteria for dementia or suspected dementia (*n*=225), or major depressive or dysthymic disorder (*n*=35). Thus, 408 subjects (non-diabetics, *n*=356; diabetics, *n*=36) remained for analysis in Study I.

For Study II, participants of second phase baseline assessment who had completed the comprehensive cognitive test battery (*n*=528) were excluded if they fulfilled DSM III-R diagnostic criteria for dementia or suspected dementia at baseline, or failed, due to other reasons than death, to return three years later. Also, two persons were excluded based on clinical records of hyperlipidemia, thyroid disease, and renal failure. Thus, 338 subjects (diabetics, *n*=31; non-diabetics, *n*=307) remained for analysis in Study II.

3.2 THE BETULA PROJECT

The Betula Prospective Cohort Study (Betula) is a large study, sampling the population of the city of Umeå in northern Sweden. For an in-depth description of the study, see Nilsson et al. (1997) and Nilsson et al. (2004).

In total, Betula involves 4,261 persons randomly selected from a population of about 100,000. In the older cohorts, there is close to total participation in the study. For the present study, participants from the first three samples were used. The first sample (S1) comprises 1,000 participants who were aged 35, 40, 45, 50, 55, 60, 65, 70, 75, and 80 years when first tested in 1988-1990 (the first Betula test occasion; T1). Participants belonging to sample 2 (S2; *n*=996) were first tested in 1993-1995 (the second Betula test occasion; T2), and were in the same age at testing as the participants in S1. Sample 3 (S3; *n*=965) participants were also tested for the first time in 1993-1995 (T2), but belonged to the age cohorts 40, 45, 50, 55, 60, 65, 70, 75, 80, and 85 years of age. In

each of the three samples, there were about 100 participants in each age group. All participants of S1, S2, and S3 (*N*=2,961) were diagnosed as non-demented according to DSM-criteria (American Psychiatric Association, 1987) at the time of first testing.

The participants of Betula have been compared with the population of Sweden with regard to demographic factors, and the study population reflects the general levels of Sweden, aside from a slightly higher level of education (Nilsson et al., 1997).

3.2.1 Measures

Participants took part in an extensive health examination, including detailed medical history regarding conditions (e.g. diabetes) requiring health care contacts, and a comprehensive laboratory assessment. A total of 55 ml of blood was used for blood chemistry testing (including HbA1C).

Psychological assessment included tests of short-term and long-term memory processing (semantic memory, episodic memory, priming) and attention. The results analyzed in Study III were episodic memory assessments with varying degree of support at encoding (subject performed tasks and verbal tasks) and retrieval (cued recall and free recall). All combinations of encoding and retrieval support were assessed in each participant. The cognitive assessment lasted between 1.5 and 2 hours.

3.2.2 Sampling procedure

For Study III, participants who completed their first testing at T1 or T2 were selected. Participants who would become demented according to DSM-criteria (4th ed., American Psychiatric Association, 2000) within 10 years after data collection were excluded (n = 183). These persons were identified through the use of data from T3 (1998-2000), and T4 (2003-2005), respectively. Of these, 12 persons were diabetics, 16 were non-diabetics with elevated levels of HbA1C, and 155 were non-diabetic controls with normal levels of HbA1C. Remaining in the sample were 2,489 non-diabetic controls , 151 non-diabetics with elevated levels of HbA1C, and 125 diabetics. Data was missing on diabetes diagnosis for 13 participants. These participants were excluded.

3.3 THE MASSACHUSETTS ALZHEIMER'S DISEASE RESEARCH CENTER

The Massachusetts Alzheimer's Disease Research Center (MADRC) is a federally funded research center at the Massachusetts General Hospital (MHG). It was enacted in 1984, and has since provided care and treatment to individuals with AD and other forms of cognitive impairment. In conjunction with clinical work done at the memory disorders unit of MGH, data have been collected from patients who have agreed to participate in research. For general overview of the project, see (Locascio, Growdon, & Corkin, 1995).

The patients included in Study IV were examined at the MGH memory disorders unit between two and 24 times, and the time they were attached to the project varied between 4.5 months and 12 years. Mean time of involvement was 3.3 years.

3.3.1 Measures

Diabetes diagnoses were obtained through informant questionnaires, diagnosis register of MGH, information in referrals from primary care providers, or through diagnostic laboratory procedures at the memory disorders unit.

At each test occasion patients were assessed comprehensively by the treating physician. This assessment included past medical history, medications, and Blessed dementia score (BDS; Blessed, Tomlinson, & Roth, 1968). Also, a modified activities of daily living (ADL; Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) scale, designed for use with informants, was administered (Johnson, Barion, Rademaker, Rehkemper, & Weintraub, 2004). The rationale behind including ADL was that both diabetes and dementia have been shown to influence ADL-functioning in old age. The inclusion of ADL was intended to serve mainly as a control condition in this comorbidity context, and will therefore not be further dealt with in this thesis.

3.3.2 Sampling procedure

For Study IV, only persons with a diagnosis of PRAD who had visited the unit at least twice were included (n=701). Eight of the persons had missing data on when their mental capacity was last definitively normal. The final sample therefore comprised 693 persons (non-diabetics, n=647; diabetics, n=46).

3.4 ETHICS

The ethical committee at Karolinska Institutet approved the study proposal of the Kungsholmen Project (Dno. 87:148, Dno. 87:234, Dno. 90:251, 94:122, and Dno. 01-020). The ethical committee at Umeå University approved the study proposal of the Betula Project (Dnr. §7/870303, 97-173e99). The Massachusetts General Hospital Human Research Committee IRB approved the use of clinical and research data for Study IV (#2003-P-001973).

4 RESULTS

(i) Diabetes has detrimental effects on global cognition as measured by the MMSE in non-demented, non-depressed, very old age. The subsets *attention and calculation*, and *copy a design* show lower scores for diabetics than non-diabetics.

(ii) High levels of semantic structure in the test materials attenuates the difference in cognitive performance between diabetics and non-diabetics.

(iii) Encoding and retrieval support both attenuate the difference in cognitive performance between diabetics and non-diabetics.

(iv) Elevated levels of HbA1C in the absence of a diabetes diagnosis have different effects in different age-strata. In those ≤65 years of age, diabetics perform significantly worse in cognitive tests than controls, and those with elevated HbA1C in the absence of a diabetes diagnosis perform at an intermediary level. In those ≥70 years of age, those with elevated HbA1C in the absence of a diabetes diagnosis perform at a significantly lower level than controls, and persons with diabetes perform at an intermediary level.

(v) There were no significant multiplicative interaction effects on cognitive performance involving diabetes and age in the very old non-demented, non-depressed. When assessing cognitive functioning in a larger age-range, though, a significant age by diagnostic group interaction effect on performance was detected (see (iv)).

(vi) Diabetes does not add substantially to the cognitive deficits observed in persons who are close to death or suffer from preclinical dementia. However, performance in tests of letter fluency are significantly associated with diabetic status, even when controlling for impending death and preclinical dementia.

(vii) There were no significant differences in rates of cognitive or functional decline between diabetics with PRAD and non-diabetics with PRAD.

(viii) If known cardiovascular comorbidity is not controlled for, the effects of diabetes on cognitive function are larger than if cardiovascular comorbidity is controlled for, in non-demented adults. However, diabetes remains significantly associated with cognitive test performance even after controlling for known cardiovascular comorbidity. There is no significant effect of cardiovascular comorbidity on rates of cognitive decline in persons with PRAD, and no significant differential effect in diabetics and non-diabetics with PRAD.

More detailed results from the four studies now follow.

4.1 STUDY I

Non-depressed, non-demented very old subjects with diabetes were shown to perform worse than subjects without diabetes on the MMSE, after controlling for age, gender, education, and cardiovascular diseases. Alternative models, where diabetes was examined without discounting the influence of cardiovascular diseases showed similar results. The item-level analyses indicated that performance in the subtests *Attention and Calculation*, and *Copy a design*, were most highly related to diabetic status.

Furthermore, analyses of the influence of possibly elevated random blood glucose values (> 6.0 mmol/l), by the method used in the KP second phase baseline assessment, showed that MMSE total score was highly related to elevated blood glucose in the diabetic subjects, but not related to variations of blood glucose levels in the non-diabetic subjects. Figure 1 illustrates these findings.

4.2 STUDY II

The effects of diabetes on cognition in the very old were shown to be selective, such that diabetics performed significantly worse than non-diabetics on tests of free recall of random words and letter fluency, after controlling for age, education, vascular diseases, and signs of vascular disease. Tests with a higher level of cognitive support, namely cued recall of organizable words and category fluency, did not demonstrate any significant difference in results across diabetics and non-diabetics. When also controlling for impending death and preclinical dementia, only letter fluency performance remained significantly associated with diabetic status. Figure 2 illustrates letter fluency performance across groups.

4.3 STUDY III

Diabetics in the age-range 35 – 85 years were found to perform worse on an overall composite score of included cognitive tests than non-diabetics with elevated levels of HbA1C, and non-diabetics with normal HbA1C. When looking individually at the cognitive tests included in the study, cognitive support at encoding and retrieval both attenuated differences between the three groups.

Looking separately at young (≤ 65 years of age) and old (≥ 70 years of age) participants, an intriguing pattern emerged. In the young, the expected dose response effect of glycemic control was observed, such that non-diabetics with normal levels of HbA1C performed at the highest level, followed by non-diabetics with elevated levels of HbA1C, and with the diabetic persons performing at the lowest level. Among the old, however, persons with elevated HbA1C in the absence of a diabetes diagnosis performed at a non-significantly lower level than diabetics, and significantly worse than non-diabetics with normal HbA1C-levels.

When examining effects of cognitive support, through collapsing data across age-groups, retrieval support was shown to be most highly related with improvement of performance in the diabetic group relative to the non-diabetic groups. The group with elevated levels of HbA1C in the absence of diabetes diagnoses showed an intermediary gain relative to non-diabetics with normal HbA1C-levels in tests with high retrieval support.

When diabetics and non-diabetics with elevated levels of HbA1C were included in the same group, and contrasted against non-diabetics with normal HbA1C-levels, a stronger group difference in performance was observed than with the original three-group analysis. Reversely, when non-diabetics – irrespective of HbA1C-levels – were included in the same group and contrasted against diabetics, the group differences in performance were no longer significant.

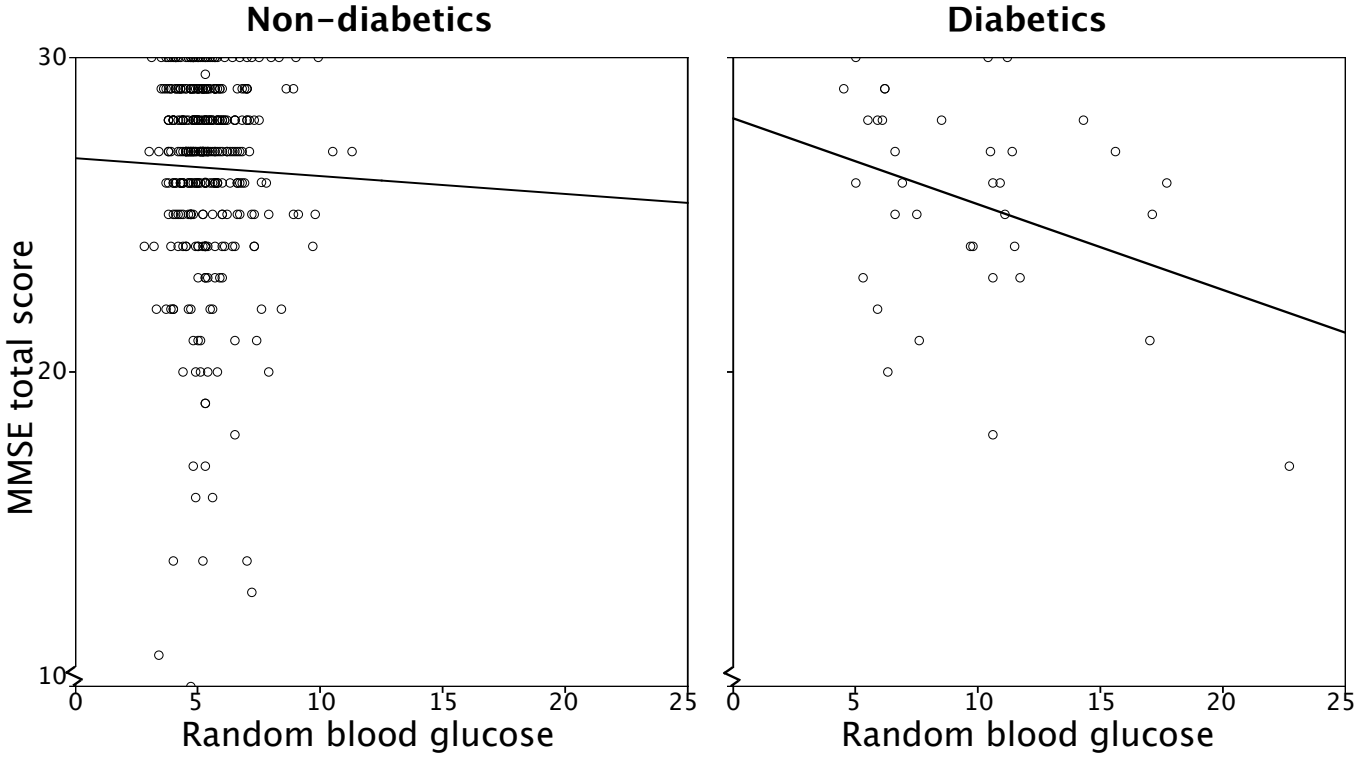

Figure 1. MMSE total score and random blood glucose in non-diabetics and diabetics. Regression lines indicate non-significant effect (r = -0.022, p = .68) in non-diabetics, and a significant effect (r = -0.356, p = .03) in diabetics, of random blood glucose on MMSE total score.

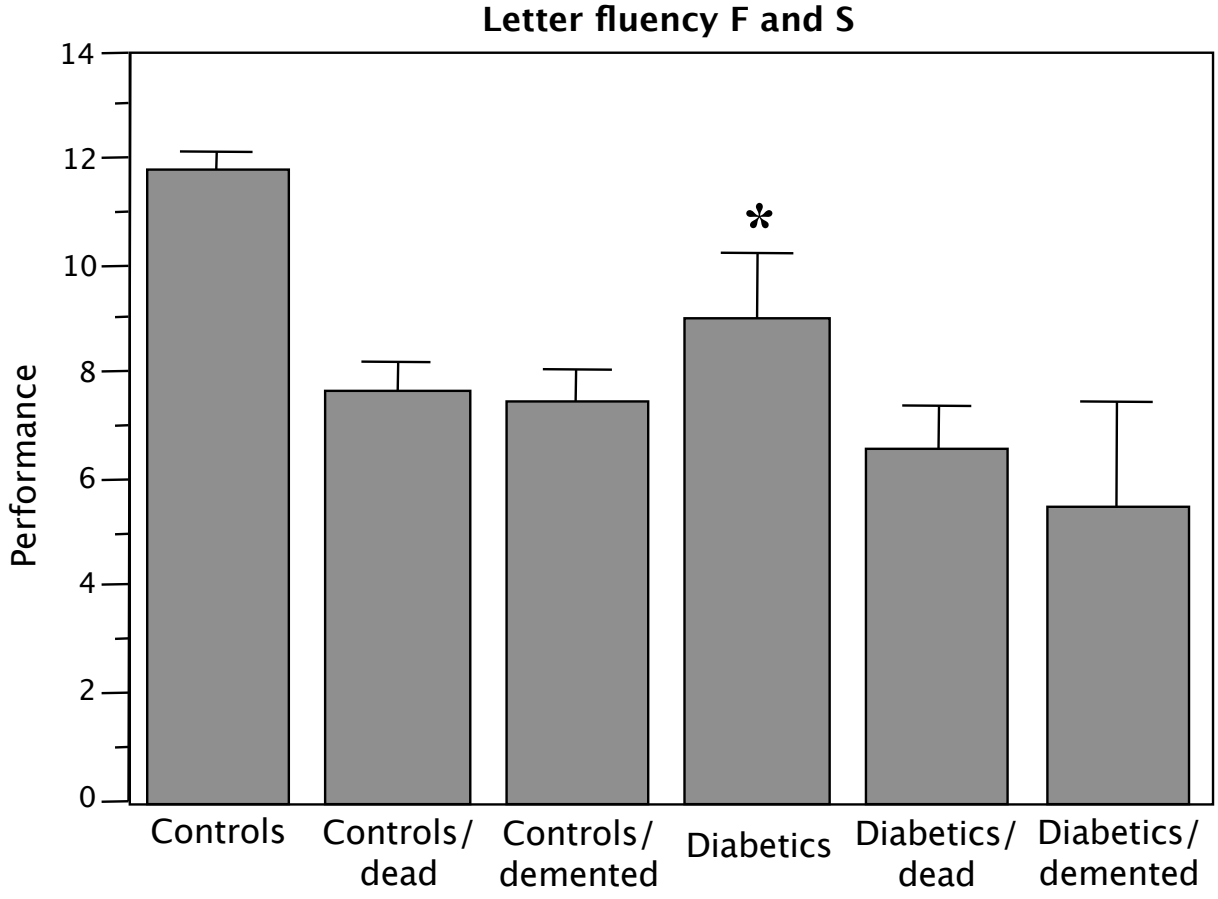

Figure 2. Letter fluency subdivided by impending death and preclinical dementia. Bars represent standard errors around the means. (*) Indicates significantly different (p<.05) than controls.

4.4 STUDY IV

There was no indication that diabetic status modified the rate of cognitive or functional decline in persons with a diagnosis of probable Alzheimer's disease. A power-maximizing analytical strategy was chosen, and power analyses confirmed that we had good power to detect even small effect sizes. Further, several different time metrics were examined, such as *chronological age*, *time since inclusion into study*, and *time since onset of dementia symptoms*. The best model fit was demonstrated for time since onset of dementia symptoms, but none of the time-metrics changed the main finding, that we could not demonstrate any differences in rate of performance decline between diabetics and non-diabetics.

No difference in model fit was demonstrated by inclusion of comorbidity data in the form of an index of cardiovascular disease, use of central nervous system drugs or cardiac drugs. The inclusion of these covariates also did not change the non-significant difference between diabetics and non-diabetics.

5 DISCUSSION

Previous studies have indicated that type 2 diabetes is associated with impaired cognitive performance. Study I extended these finding into very old age, and also demonstrated that among diabetic persons, high levels of random blood glucose were associated with poorer performance in the MMSE. This finding indicates, albeit tentatively, that good blood-glucose control in diabetics may be associated with attenuated cognitive impairment. The finding may also be taken to mean that persons with less severe diabetes are less cognitively impaired.

Studies on normal aging and other diseases than diabetes have indicated that in some situations, additional cognitive support in the test-materials can attenuate group differences. Other studies have indicated that in situations where the cognitive impairment is more severe (such as AD), group differences are, reversely, increased by additional cognitive support (see Bäckman, Mäntylä, & Herlitz, 1990, for a review). In some situations, group differences are increased when cognitive support is slightly increased, and reduced when a great deal of cognitive support is provided. A likely explanation of these findings is that persons who are sufficiently affected by disease or aging to have a reduced performance in tests with very low levels of support – such as free recall of random words – may still have a cognitive reserve capacity such that tests that provide support (e.g. in the form of retrieval cues, semantically structured encoding material, or other encoding support such as performing the actions described in the *to be remembered* material) may tap into less impaired memory systems and provide the low-performing group the means to increase their performance relative to the high-performing group. If, on the other hand, the cognitive performance of the group affected by disease or aging is more globally affected, utilization of cognitive support may also be impaired. Poor utilization of cognitive support in the low-performing group leads to increased group differences unless the control-group experiences functional ceiling effects. The intermediary result – that the low performing group can improve performance relative to the high performing group if large amounts of cognitive support is provided – indicates an intermediary generality of cognitive impairment.

Study II indicated that diabetics were able to utilize cognitive support in the form of semantic structure of the *to be remembered* material and retrieval cues. This indicates that diabetes causes a selective cognitive impairment to episodic memory, such that uniquely episodical abilities are most affected. The results showing larger diabetes-related effects on free recall than cued recall, as well as those showing that letter fluency (phonemic fluency) is more sensitive to diabetes-related impairment than category fluency (semantic fluency), can be interpreted to indicate that frontal structures are selectively impaired by diabetes. Phonemic fluency has been shown to rely more on frontal structures than semantic fluency, similar to a larger dependence on intact frontal function in free recall than cued recall (Lezak, 1995).

Study III indicated that diabetics utilized cognitive support at encoding and/or retrieval more efficiently than non-diabetic controls. Further, persons with elevated levels of HbA1C in the absence of a diabetes diagnosis utilized cognitive support at an intermediary level. Taken together, these two findings indicate that the difference

between diabetics, non-diabetics with elevated levels of HbA1C, and non-diabetic controls, were attenuated in a high-support setting. This is taken to indicate that uniquely episodic cognitive domains are selectively affected by diabetes. The attenuated group differences in the high-support setting indicate that diabetics may recruit more intact domains if the test supplies support making this possible. In other words, diabetics are able to utilize a cognitive reserve when the test materials permit the use of auxiliary brain-structures less affected by diabetes.

Previous studies have indicated that persons with reduced glucose tolerance in the absence of a diabetes diagnosis have reduced hippocampal volume. Also, an intermediary increase of dementia risk has been demonstrated in persons with elevated random blood glucose levels, compared to diabetics and non-diabetics with normal values of random blood glucose. The data from Study III indicate that there is an effect on cognition of elevated levels of HbA1C in the absence of diabetes diagnosis. The fact that analyses where diabetics and non-diabetics with elevated levels of HbA1C were treated as a single group, and contrasted against non-diabetic controls, showed similar effect sizes as the original three-group analyses, indicates that the persons in the group of non-diabetics with elevated HbA1C are likely cognitively more similar to diabetics than non-diabetics with normal HbA1C.

Older persons with elevated HbA1C in the absence of a diabetes diagnosis were in Study III shown to perform at a lower level in tests of cognition than diagnosed diabetics, whereas young persons with elevated HbA1C performed at an intermediary level between diabetics and non-diabetic controls. This, coupled with previous findings regarding age-variant underdiagnosis of diabetes, could be speculated to indicate that (i) The younger persons with elevated HbA1C in the absence of diabetes diagnosis are likely in the prodromal phases of diabetes development, (ii) The older subjects with elevated HbA1C in the absence of diabetes diagnosis are more likely to actually fulfill diagnostic criteria for diabetes, and (iii) that there is a protective effect on cognitive performance – at least in the oldest age group – of diabetes diagnosis in persons with elevated levels of HbA1C. The protective effect of diagnosis (iii) is likely to be an effect of diabetes treatment.

In Study II, the diabetes-cognition relationship was examined whilst controlling for impending death and preclinical dementia. The results indicate that whereas the effect of diabetes on cognitive function does extend into very old age, only performance in the letter fluency task remained significantly related to diabetes status when controlling for impending death and preclinical dementia. Since diabetes is a risk-factor for dementia and associated with increased mortality, this finding could be taken to indicate that – at least among the very old – a proportion of the diabetes-related variance in cognitive performance can be accounted for by incipient death and dementia related processes. However, effects of diabetes are difficult to separate from effects of dementia and impending death, but Study II also indicates a small but separate effect of diabetes in the preclinical dementia phase (see Figure 2). Future studies with better power may show whether diabetes adds to cognitive variation in preclinical phases of dementia.

In Study IV, finally, the effects of diabetes on rate of cognitive decline after diagnosis of PRAD were examined. Since (i) diabetes increases the risk of dementia, (ii) Study II

had shown that some of the diabetes-related variance in tests of cognition was explained by preclinical dementia, and (iii) there was a tendency for diabetes to influence cognitive performance also in preclinical dementia stages of dementia, a possible hypothesis was that diabetes would explain some variance in the rates of decline. However, previous studies on post dementia diagnosis rates of change have indicated that even potent risk-factors for development of dementia, and factors highly related to cognitive impairment in non-dementia aging (e.g. number of ApoE e-4 alleles, education, and cerebrovascular disease) are unable to explain differences in rates of decline post diagnosis (Growdon, Locascio, Corkin, Gomez-Isla, & Hyman, 1996; Morris, 2005). In fact, the only factor that has been shown to influence rate of cognitive decline after AD diagnosis is AD-severity (Morris, 2005). Thus, the null findings of Study IV are not completely surprising. However, since diabetes had not previously been assessed as a potentially influential factor in post PRAD-diagnosis cognitive decline, the findings of Study IV add to extant knowledge about modifying factors of AD progression.

5.1 LIMITATIONS

When a study is completed, analyzes performed, and tentative conclusions reached, it almost always becomes apparent that certain aspects of the study could have been changed to give greater efficiency or interpretability. When data are used that have been collected before the research question to be studied is formulated, limitations are sometimes identifiable even before commencing the study. Knowledge of the specific limitations of a study help the authors reach conclusions that are supported by the data. Thus, listing limitations is not only a way to improve future studies, but also to improve the interpretation of results in the study at hand.

5.1.1 Samples

The samples used in the empirical studies that form the basis of this dissertation share the characteristic of not being specifically designed to asses the effect of diabetes on cognition. Thus, the number of persons with diabetes in the studies is representative of prevalence levels in the general population (Studies I-III) or in the outpatient treated probable Alzheimer's disease (PRAD) population (Study IV), rather than being tailored to maximize statistical efficiency. It is possible to view this as a limitation, since the reduction in power means that certain differences that potentially would have been apparent (in a case-control study, for example) are not detectable. However, it is my belief that population-based studies add something that may be worth the price of reduced statistical efficiency.

Most case-control studies have used clinical diabetes populations. Either diabetes patients selected from outpatient units at hospitals, or patients selected from among the patients of primary care physicians that specialize in treating diabetes patients. It is reasonable to assume that – on average – a patient that is treated in an outpatient unit or by a physician interested in the treatment of diabetes is more severely ill than a patient that receives his or her treatment elsewhere. Therefore, studies that utilize clinical diabetes populations artificially increase the difference between diabetes patients and

control subjects. This may not always be a disadvantage, and maximizing the difference may in certain instances be the only feasible approach to certain questions. However, if the purpose of a study is to draw conclusions regarding the majority of diabetes patients, a population based sample is more likely to provide interpretable information.

5.1.2 Cognitive testing

The types of cognitive test data available for analysis vary greatly between the empirical studies included in this thesis. In Study I, the research question motivated the use of a global measure of cognition, and the MMSE was used. Although the MMSE was not designed to replace proper cognitive examination, it is possible to argue that MMSE scores vary slightly also for conditions with less serious impact on cognition. Indeed, several studies have demonstrated effects of diabetes on MMSE total score (e.g. Croxson & Jagger, 1995; Kalmijn et al., 1995; Launer, Feskens, Kalmijn, & Kromhout, 1996; Worrall, Moulton, & Briffett, 1993). However, in order to answer questions regarding selectivity of the cognitive effects of diabetes – and in order to assess the feasibility of Study II – item-level MMSE data were also analyzed. Although item level MMSE analyses have been used in a variety of settings (see, e.g. Braekhus, Laake, & Engedal, 1992; Hill & Bäckman, 1995), they are arguably less efficient than analysis of specific cognitive tests of the functions of interest. The loss of efficiency depends both on the psychometric properties of the MMSE, i.e. that it primarily differentiates between pathological and normal responses and, relatedly, that the variance in performance for non-demented persons is limited.

Study II and III have no such obvious limitations in the domain of cognitive testing. The tests used are validated and experimentally based tests, and as a consequence allowed specific hypothesis testing about utilization of cognitive support.

In Study IV, I use cognitive data obtained through the use of the Blessed Dementia Scale (BDS; Blessed, Tomlinson, & Roth, 1968). Whereas the BDS has not been used much in the study of cognitive effects of diabetes, MMSE has been used in several studies (see above). The subtests of BDS and MMSE correspond well with each other in content, are highly correlated, and it has actually been shown that the correlation between BDS and MMSE is of the same magnitude as the test-retest correlations of BDS and MMSE respectively (Fillenbaum, Heyman, Wilkinson, & Haynes, 1987). Thus, any limitations of the BDS are likely to be similar to the limitations of MMSE previously mentioned. In Study IV, however, I do not use item-level analyses of cognitive data. This, coupled with the fact that the variance in performance is greater in a dementia cohort than in a non-dementia cohort, should reduce the limitations of interpretability imposed by the use of BDS data. That is to say, since there are no ceiling effects in a dementia cohort, it is likely that any actual effect of diabetes on cognitive domains assessed by the BDS will also be reflected in the scores.

5.1.3 Diabetes diagnosis

The procedure for obtaining diabetes diagnoses varied between the empirical studies included in this thesis, but none of the diagnostic procedures would *in themselves* have been sufficient for a clinical diagnosis of diabetes. Data on fasting blood glucose or oral glucose tolerance tests (OGTT) at two occasions were not available. Instead, in studies I-III, the basic data on diabetic status was self-reported diabetes. There may be reasons to doubt self-reports of diseases, but it is important to realize that such self-reports are generally based on previous clinical diagnoses set by the subjects' physician, and explained by the physician to the subject (Ferraro, 1987). In general, better accuracy is obtained in self-reported diagnoses that are easily comprehended than in diagnoses that are, to the layman, less conceptually understandable (Paganini-Hill & Chao, 1993). Also, self-reports of chronic diseases with a clear lifestyle impact are in general more accurate than self-reports of more transient or less lifestyle-changing diseases (Kriegsman, Penninx, van Eijk, Boeke, & Deeg, 1996). Thus, given that diabetes is a fairly clear-cut and well-known disease in the general population, that it is a chronic disease, and that it necessitates daily medication and/or lifestyle changes, there is reason to believe that the accuracy of self-reported diabetes is high. Even so, accuracy may be further improved by adding additional diagnostic data.

For Study I & II, we started with self-reports of diabetes. In addition to the self-reported diabetes, however, we also required the patient to be rated as reliable by the test-leader, *or* have a random blood glucose level exceeding the normal range for the laboratory method employed. This procedure likely leads to close to zero false positive diabetics, but a somewhat higher "under-diagnosis" of diabetes in the setting of our studies. The procedure was chosen after careful consideration of the consequences of over- or under-diagnosis, respectively, for the interpretability of the data. I argue that an under-diagnosis of diabetes, in the setting of the analyses performed in Studies I & II, leads only to a dilution of the diabetes-related effect, and does not cause risk of false positives in the analyses. Over-diagnosis of diabetes, on the other hand, could conceivably cause much difficulty in interpreting the data. Consider, for example, the possible situation that false self-reports of diabetes were more common among persons with cognitive impairments than among persons without cognitive impairments. If we had not required persons to either be rated as reliable or have random blood glucose values indicating diabetes in addition to their self-reports, any results could be argued to arise from this non-random over-reporting.

For Study III, the self-reports of diabetes were in response to the question "Have you received treatment from a doctor or been treated in a hospital for diabetes, and if so how many times and at what dates?"[5] rather than the more imprecise self-report question "Do you have a diagnosis of diabetes?". Also, in Study III, glycated hemoglobin (HbA1C) laboratory data were available. All persons reporting to have been treated for diabetes also had elevated levels of HbA1C (values above normal range), strengthening the diagnosis obtained through self-reports. In Study III, a group of persons without diabetes diagnosis, but with elevated levels of HbA1C, was also included. Elevated level of HbA1C was defined as an HbA1C-level > 6.6% in sample

[5] Question in Swedish: "Har du sökt läkare eller vårdats på sjukhus [...] hur många gånger [...] vilket årtal, vid vilken ålder eller om det var före eller efter 20 års ålder?"

one, or >5.3% in samples two or three. The cutoffs for the HbA1C were based on the high end of normal variance for the different laboratory procedures, rather than on any guideline recommendation cutoffs (e.g. American Diabetes Association, 2006b). The reason for choosing the high end of the normal variance as a basis for dichotomization, was that the statistical properties of such cutoffs are known, even if the test-values themselves do not correlate perfectly with other methods of HbA1C-assessment (Sacks et al., 2002). Some of the persons in this group may have been in fulfillment of the diagnostic criteria for diabetes, although they had not received a diagnosis at the time of testing. If data from two fasting blood glucose measurements or OGTT had been available, more subjects could potentially have been included in the group of diabetics. However, none of the conclusions drawn from the data in Study III can reasonably be considered to be caused by this potential misclassification. It is my belief that the potential misclassification in Study III would also result in a dilution of effect, and does not give rise to false effects. The point could, of course, be made, that the effect of elevated HbA1C on cognition in the absence of diabetes among the older age-group is an effect of underdiagnosis of diabetes. This is, in fact, the interpretation that is suggested in the study. However, this point could have been more elegantly made had we had access to OGTT or fasting blood glucose measures.

Finally, in Study IV, the diagnosis of diabetes was made either through information given by the referring primary care physician (information that I believe should be considered as equally informative as if the diagnosis had been set at the Memory Disorders Unit itself), diagnostic tests at the unit, or informant questioning. Informant questioning is inevitable when dealing with a group of subjects that are included in the study on the basis of a diagnosis of probable Alzheimer's disease (PRAD), but may be considered to be associated with some of the same pitfalls as self-reported disease. Also, it is reasonable to assume that informants are influenced by some of the same factors as subjects giving self-reports, namely that diseases such as diabetes that are chronic, conceptually explainable for a layman, and require daily treatment or lifestyle management are more likely to be correctly reported. A factor that further mitigates the potential for misclassification in Study IV is that the informants are asked at each visit to the unit (two to 24 visits per subject) to give information on new or previously unmentioned diseases, and are read the list of diseases that were supplied at first visit plus any diseases mentioned at subsequent visits. One could argue that this procedure limits the risk of an informant forgetting to mention a disease.

6 FUTURE RESEARCH

The limitations of the research performed so far, by myself and others, are to some extent avoidable in future studies. Also, several research questions are not yet answered. In order to better study the impact of diabetes on cognition, it is necessary to do focused studies where there is some degree of control over the severity and treatment of diabetes. A problem that immediately arises is caused by the phylogenetic recency of episodic memory. Since animals that are possible to study as practical models of diabetes (predominately rats, mice, guinea pigs, and dogs) do not possess episodic memory in any sense that is quantitatively testable, full randomization of exposure is not possible. Thus, studies focusing on humans with diabetes are the most promising avenue of research. There are several problems with this strategy, of course. Most importantly, causal effects are difficult to establish without randomized exposure. A person that develops diabetes, may in some fundamental way, be different than a person that does not. We would ideally have wanted data from the diabetic person *had the person not developed diabetes* as a comparison. Since that is not possible, causal inference may be feasible through experiments with randomized treatment.

If we assume that there is a dose-response effect of disease severity on cognition, and that disease severity can be modified through treatment, we can design a study that may answer some profound questions regarding the relationship between diabetes and cognition. Surprisingly, such studies have not yet been devised. The studies thus far have been limited by unreliable or unvalidated cognitive measures, unstandardized cognitive test delivery, poor control over treatment effect, or insufficient randomization procedures. A Cochrane report on interventional studies of diabetes treatment and cognitive performance (Areosa & Grimley, 2004) found no studies that fulfilled inclusion criteria for evidence based medicine, and specified that studies aiming to explore the effect of treatment on the cognitive repercussions of type 2 diabetes should include reliable and validated measures of cognition. Further, test batteries that cover a wide range of cognitive domains should be used, in order to be able to detect differential effects. Steps should also be taken to avoid confounding from education and premorbid abilities. Finally, the report recommends studies to assess cognition at several time-points, and to also assess treatment efficacy with other objective outcome measures such as insulin and glucose levels.

The next study that I have planned fulfills the criteria set up by the Cochrane report. Although one single study will, admittedly, not be sufficient for any conclusions to be considered evidence based, I believe that this study will add greatly to our knowledge of diabetes-related cognitive impairment and potential treatments to minimize it. Data collection is well under way, and the study will be described it in some detail in the last section of this thesis.

6.1 PREVENTION OF COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES

The purpose of this project is to study strategies for the prevention of cognitive impairment related to type 2 diabetes. At present there is little information on the short- and long-term influence of type of treatment and level of metabolic control on

cognitive function of people with diabetes. In this project, intensity of treatment is randomized, and three groups of subjects are studied in order to determine how results of neuropsychological tests and quantitative electroencephalogram (Q-EEG) measurements are affected by diabetes treatment intensity. Multiple measurements are made before and after a period of intensified treatment, in order to study how interventions aiming to improve metabolic control influences the cognitive performance and brain electrical activity. The three groups studied are: (i) Diabetes patients that are randomly assigned to intensified treatment (n=20), (ii) Diabetes patients that are randomly assigned to standard treatment (n=20), and (iii) Healthy volunteers that receive no treatment (n=28).

Intensified treatment is defined as the patient receiving (i) A one-week course on diabetes, medication, and lifestyle changes, (ii) A consultation with an experienced endocrinologist with the purpose of optimizing individual pharmacological treatment, and (iii) A contact person in the form of an experienced diabetes-nurse, with whom bi-weekly telephone contact is maintained during the study period. Some telephone contacts may be replaced by in-person visits. Standard treatment is defined as the patient receiving no change of treatment from the diabetes outpatient unit at the Karolinska University Hospital, Solna. The patients included in the group receiving standard treatment may, however, have their treatment changed or improved for reasons outside our control (for example through contact with their primary care physician).

The two groups of diabetes patients are selected from the patients at the diabetes outpatient unit at the Karolinska University Hospital, Solna, and among patients in a primary care setting in Stockholm. Our recruitment and testing of non-diabetics is completed. They were recruited among persons who did not have any diabetes diagnosis. The three groups of participants are matched with regard to age, sex, and level of education. Initial glycemic status (as measured by HbA1C) is matched for the two diabetic groups. Inclusion criteria for the diabetic groups are:

Type 2 diabetes mellitus classified as clinically complication-free.
Target age of 60 +/- 10 years. Target duration of diabetes 5-10 years.
At least 7,5% HbA1C at latest measure before the study.

For all diabetic participants, plasma glucose variability is assessed through download of data from patients own validated electronic plasma glucose sensor. For all subjects, acute blood glucose values are taken immediately before cognitive testing. HbA1C samples are collected. Insulin-like growth factor 1 (IGF-1), IGF-1 binding protein (IGFBP-1), and insulin levels are assessed. Through the collection of these data, the group of non-diabetics is ascertained not to include any undiagnosed diabetics.

All three groups are tested twice, with a period of two months +/- five days between tests. The intensified treatment group is tested for the first time before treatment manipulation. The diabetic group receiving standard treatment, and the non-diabetic group, are tested twice without intervening manipulation.

The testing procedure on each occasion comprises two steps. First, a standardized test battery is administered by trained nurses. The test battery consists of five sets of

cognitive tests, assessing cognitive speed (2 tests), episodic memory (4 tests), verbal fluency (2 tests), visuospatial ability (2 tests), and semantic memory (2 tests). Second, QEEG testing is performed. On one occasion, a detailed structured anamnesis and limited physical examination is performed by a physician.

The cognitive test battery is based on the test battery of the Swedish National study on Aging and Care (SNAC, Lagergren et al., 2004). The two tests of cognitive speed are *digit cancellation* (Diller et al., 1974), and *compare figures*. The four tests of episodic memory are *random recall* (16 words), *recognition*, including remember/know/guess, *recall of organizable words* (16 words), and *cued recall* (five categories). The two tests of verbal fluency are *category fluency* (animals and occupations), and *letter fluency* (F and A; Lezak, 1995). The two tests of visuospatial ability are *mental rotations* (Vanderberg, 1971), and *block design* (Wechsler, 1981). Semantic memory, finally, was tested with a test of *vocabulary* (SRB:1; Nilsson et al., 1997), and *information* (Wechsler, 1981).

The procedure for QEEG testing and analysis is based on a test procedure developed for type 1 diabetics, and is described in detail in Brismar, Hyllienmark, Ekberg, and Johansson (2002), and Hyllienmark, Maltez, Dandenell, Ludvigsson, and Brismar (2005). Briefly, the test procedure involves the standardized placement of 23 Ag electrodes on the scalp, with recording reference on the nose, and four eye-movement detection electrodes. Recordings are made for 15 minutes on awake, resting subjects, following a strict protocol with cycles of 10 seconds with open eyes and 50 seconds closed eyes. During this recording, subjects are left undisturbed (except for instructions to open and close eyes). During the following 6 minutes the subjects perform a press-button task, followed by a 10 minute recording of EEG with deviant sound stimuli. Evoked responses (P300 and mismatch negativity) are calculated by post-processing the digital recordings.

This study has several advantages. First and foremost, it combines detailed cognitive testing with good clinical diagnostic procedures for ensuring the diabetic status of both the groups of subjects with type 2 diabetes and the healthy controls. Since a focus of my research so far has been to clarify the role of semantic or other cognitive support in the cognitive compensatory mechanisms of diabetes patients, tests that allow this are a significant advantage. The robust clinical diagnosis of type 2 diabetes mellitus provides data with minimized dilution of effects. Further, the study gives good ability to control for associated morbidity through the selection of participants rather than through statistical control procedures. Assessment of fasting blood glucose in association with testing provides good control for acute blood-glucose effects, minimizing the risk of effect dilution due to hypoglycemia of intensively treated diabetics, or accidental inclusion of undiagnosed diabetics in the non-diabetic control group. The ability to account for treatment effect through the assessment of HbA1C, blood glucose, insulin, IGF-1, and IGFBP-1, finally, is unique in combination with the extensive cognitive testing performed in this study.

Limitations of the study design may include that type 2 diabetics attending the diabetes unit of a university hospital, who form part of the groups of standard and intensively treated diabetics, are hardly representative of type 2 diabetics in general. Although we collect demographic information, there may be reasons for referral to the diabetes unit

which we were not able to assess or control for. This may limit the generalizability of the study.

Data collection is still ongoing, and no preliminary results of cognitive testing are available. Limited results are however available regarding laboratory analyses for the intensively treated group of diabetic subjects. For the intensively treated diabetics already tested (n=11), fasting blood glucose values have improved from an average of 11.1, to an average of 8.5 mmol/l over the two month study period.

When data are collected, it will be possible to analyze whether (i) Intensive treatment gives better control over blood glucose levels in diabetic patients, (ii) Intensive treatment attenuates differences between type 2 diabetics and non-diabetics in tests of cognition, (iii) Control of blood glucose levels in diabetics is associated with cognitive functioning, and whether (iv) Intensive treatment affects EEG-patterns among type 2 diabetics.

Since the test battery includes tests that are known to be sensitive to diabetes-related cognitive impairment, it is likely that differences between the diabetic groups and the non-diabetic group will be demonstrated at baseline testing. If intensified treatment gives reasonable effects on cognition during the study period, it is likely that we will be able to show a significant difference in cognitive change between the intensive treatment group and the standard treatment group of diabetic patients.

If effects of diabetes treatment intensity on cognition are too small to be demonstrable in the cognitive testing of this study, but there are trends towards an effect, Q-EEG-data may supply additional evidence of treatment efficacy.

7 ACKNOWLEDGEMENTS

I decided to be a scientist when I was around 11 years old. At that point, my main research questions were related to space travel and things that would explode. Even though the focus of my interest has changed slightly since then, the desire to find out what is really going on is as strong as ever.
Although I am truly fascinated by the human mind in general, and cognition in particular, I still wouldn't have gotten through the stress and misery of doctoral studies without the support of some important people who I hereby want to thank.

First, ***Åke Wahlin***, my main supervisor, who besides possessing a vast knowledge in the field of cognition, giving intelligent and detailed critique, and tolerating both my overly optimistic scheduling and the resulting telephone calls outside office hours, is also a thoroughly good person.
Stuart MacDonald, without whom I would not have been able to understand the wonderful world of hierarchical linear modeling, and who also provided substantial feedback on a previous version of this thesis.
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8 REFERENCES

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9 APPENDIX

List of dissertations from the Stockholm Gerontology Center and Aging Research Center 1991-2005

1991
Herlitz Agneta. Remembering in Alzheimer´s disease. Utilization of cognitive support. (Umeå University and Karolinska Institutet).
1992
Borell Lena. The activity life of persons with a dementia disease.

1993
Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994
Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University).
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995
Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996
Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis).
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997
Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis).

1998

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

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

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

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

1999

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

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

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