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COGNITIVE FUNCTION IN GLUCOSE INTOLERANCE IN THE ELDERLY: THE ROLE OF HYPERINSULINEMIA

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MATTI VANHANEN

**COGNITIVE FUNCTION IN GLUCOSE INTOLERANCE IN THE ELDERLY:
THE ROLE OF HYPERINSULINEMIA**

Doctoral Dissertation

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Abstract

Aging is associated with various adverse physical changes, which can affect mental functions. Two increasingly common phenomena in the aging western populations are impaired glucose regulation and dementia. In general, both glucose intolerance and dementia are slowly progressive conditions with a long prodromal phase. Therefore, it is a challenging task to study the relationship between these common disorders. Previous studies have suggested that cognitive dysfunction may be present in patients with non-insulin-dependent diabetes (NIDDM). However, NIDDM is always preceded by a phase with a milder form of abnormal glucose tolerance, i.e. impaired glucose tolerance (IGT). An important predisposing factor for NIDDM and IGT is hyperinsulinemia, which recently has been associated with cognitive impairment. The principal aim of this series of studies was to investigate the association of glucose intolerance and hyperinsulinemia with cognitive function and Alzheimer's disease in the elderly. Altogether five studies with glucose tolerance determination and neuropsychological examination were conducted, furthermore, one study applied neurophysiological examinations, and the other dementia diagnosis. Impaired cognitive function was found in normoglycemic subjects at increased risk for NIDDM and in subjects with persistent IGT as well as in

patients with overt NIDDM. Minor changes were detected in the event related potentials in diabetic patients. Hyperinsulinemia was associated with cognitive dysfunction in subjects with normoglycemia, IGT and patients with NIDDM. In a population-based sample of 980 subjects Alzheimer's disease was strongly associated with glucose intolerance, only 28 % of the Alzheimer patients had normal glucose tolerance. Non diabetic subjects with hyperinsulinemia, who did not have a polipoprotein E e4 allele, had in creased p revalence of Al zheimer's di sease comp ared to th ose with normal in sulin lev els (hyperinsulinemic vs normoinsulinemic: 7. 5 % vs 1. 4 %). I n th e n ondemented p opulation, the association between NIDDM and cognitive dysfunction was weaker, although mental processing may be s lowed a lso in the no ndemented NIDDM pa tients. In co nclusion, g lucose i ntolerance a nd hyperinsulinemia were associated with cognitive dysfunction and Alzheimer's disease. These findings suggest that glucose intolerance and hyperinsulinemia can have an important role in the development of sporadic Alzheimer's disease.

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Medical Subject Head ings: aging; Alzheimer’s dis ease; dementia; epidemiology; diabetes mellitus, non -insulin-dependent; glucose into lerance; hyperinsulinemia; neuropsychological tests; risk factors.

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Kuopio, December 1998

Matti Vanhanen

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Apo E	Apolipoprotein E
BD	Block Design subtest from the Wechsler Adult Intelligence Scale
BMI	Body mass index
BSR	Buschke Selective Reminding Test
Db	Decibel
DS	Digit Span subtest from the Wechsler Adult Intelligence Scale
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSY	Digit Symbol subtest from the Wechsler Adult Intelligence Scale
ERPs	Event related potentials
FTT	Finger Tapping Test
HDL	High density lipoprotein
HbA_{1c}	Glycated haemoglobin
GDS	Geriatric Depression Scale
Hz	Herz
IGT	Impaired Glucose Tolerance
IQ	Intelligence Quotient
mmol/l	Millimoles per litre
MMSE	Mini-Mental State Examination
MMN	Mismatch negativity
ms	Milliseconds

mU/l	Milliunits per litre
N100	Auditory event related potential 100ms after stimulus
N2b	Auditory event related potential 200ms after stimulus
NGT	Normal Glucose Tolerance
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NP	Data not presented
P3, P300	Auditory event related potential 300 ms after stimulus
pmol/l	Picomoles per litre
S	Self reported depression
SD	Standard deviation
SPSS-PC+	Statistical Package for Social Sciences - Personal Computer
ST	Stroop Test
TM	Trail Making Test
VF	Verbal Fluency Test
WHO	World Health Organization
VRT	Visual Reproduction Test
VOC	Vocabulary subtest from the Wechsler Adult Intelligence Scale
WAIS	Wechsler Adult Intelligence Scale

List of original Publications

This thesis is based on the following original publications that are referred to in the text by the Roman numbers **I-V**.

I Vanhanen M, Karhu J, Koivisto K, Pääkkönen A, Partanen J, Laakso M, Riekkinen Sr. P. ERPs reveal deficits in automatic cerebral stimulus processing in patients with NIDDM. *NeuroReport* 7: 2767-2771, 1996.

II Vanhanen M, Koivisto K, Karjalainen L, Helkala E-L, Laakso M, Soininen H, Riekkinen Sr. P. Risk for non-insulin-dependent diabetes in the normoglycemic elderly is associated with impaired cognitive function. *NeuroReport* 8: 1527-1530, 1997.

III Vanhanen M, Koivisto K, Kuusisto J, Mykkänen L, Helkala E-L, Hänninen T, Riekkinen Sr.P, Soininen H, Laakso M. Cognitive function in an elderly population with persistent impaired glucose tolerance. *Diabetes Care* 21: 398-402, 1998.

IV Kuusisto J, Koivisto K, Mykkänen L, Helkala E-L, Vanhanen M, Hänninen T, Kervinen K, Yl Antero Kesäniemi, Riekkinen Sr.P, Laakso M. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *British Medical Journal* 315: 1045-1049, 1997.

V Vanhanen M, Koivisto K, Kuusisto J, Mykkänen L, Helkala E-L, Hänninen T, Riekkinen Sr.P Soininen H, Laakso M. Type-2 diabetes and cognitive function in a non-demented population. *(Submitted)*

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Contents

1. Introduction

Cognitive dysfunction and dementia are becoming increasingly prevalent in ageing western populations. The estimated prevalence of dementia at the age of 65 years is approximately 0.5 %, (Breteler et al. 1992) at the age of 75 years it is 4 % and at the age of 85 years it has risen to 23 % (Juva et al. 1993). Milder forms of cognitive dysfunction may be even more common (Koivisto et al. 1995b). Also the prevalence of non-insulin-dependent diabetes mellitus (NIDDM), which accounts for nearly all cases of diabetes in the elderly, increases rapidly with aging, doubling or tripling every ten years after the age of 40 years (Harris et al. 1987, Ohlsson et al. 1987, Laakso et al. 1991a). The concept of glucose intolerance includes also an intermediate category between normality and diabetes, so called impaired glucose tolerance (IGT). In elderly western populations, the prevalence of NIDDM has been estimated to be 10 - 19 % and prevalence of IGT 14 - 23 %, giving an overall prevalence figure of approximately 30 - 40 % for glucose intolerance (Mykkänen et al. 1990). Glucose intolerance is associated with increased mortality and morbidity, including cerebrovascular disease (Pyörälä et al.1987). Hyperinsulinemia as a result of peripheral insulin resistance is one of the most important risk factors for NIDDM, and it has also been associated with increased morbidity. Hyperinsulinemia has been associated with atherosclerosis and other risk factors for lacunar infarcts, thereby possibly affecting cognitive function.

In previous studies, NIDDM has been associated frequently with impaired cognitive function, mainly with impaired verbal memory (Strachan et al. 1997a). Most of these studies were small case-control studies, which can severely limit the generalization of the results obtained. There is also preliminary evidence that hyperinsulinemia would be associated with cognitive dysfunction (Kalmijn et al. 1995). Since hyperinsulinemia is major risk factor for NIDDM (Stern 1991, 1995), the possibility arises that frequently reported memory dysfunction could be present already in subjects in the prediabetic phase. Abnormal glucose and insulin metabolism have been reported in patients with Alzheimer's disease (Craft et al. 1993), which is the major dementing disease in Caucasian populations (van Duijn 1996). There is also evidence that late onset Alzheimer's disease is associated with cerebrovascular changes (Blennow et al. 1991, Brun et al. 1986). Therefore, the role of glucose intolerance and hyperinsulinemia may be of significance with respect to cognitive dysfunction and Alzheimer's disease. This series of studies was conducted in order to elucidate the association of glucose intolerance and hyperinsulinemia with cognitive function and Alzheimer's disease.

2. Review of the Literature

2.1 Glucose intolerance in the elderly

2.1.1 Definition and diagnosis of non-insulin-dependent diabetes mellitus and impaired glucose tolerance

Chronic hyperglycemia is the cardinal feature of diabetes mellitus (World Health Organization 1985). The two major forms are insulin-dependent diabetes mellitus (IDDM or type-1 diabetes) and non-insulin-dependent diabetes mellitus (NIDDM or type-2 diabetes). Insulin-dependent diabetes mellitus is a disease of the young, which is characterized by inadequate production of insulin. Non-insulin-dependent diabetes mellitus is principally a disease of the elderly, and it is characterized by a relative deficiency of insulin action due to the metabolic disorder of insulin resistance. In the state of insulin resistance, the ability of insulin to promote glucose uptake at the cellular level is decreased. To compensate for the diminished effect of insulin, insulin secretion is increased, and when this fails, hyperglycemia and NIDDM manifests itself. (Laakso 1993a).

The presence of diabetes can be verified by various methods. Weight loss, increased thirst and urine volume are signs which often accompany NIDDM. Diabetes can be verified using a random venous plasma glucose level equal or higher than 11.1 mmol/l or fasting plasma glucose equal or higher than 7.8 mmol/l. The most widely used criteria for diabetes is the World Health Organization (1985) criteria, which is based on measurement of venous plasma glucose level in the fasting state and two hours after a 75 g oral glucose load. Other criteria are the National Diabetes Data Group criteria (1979) and a suggestion for new classification of diabetes by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997), which has not yet been widely accepted. No description of these criteria is presented here, because they are not in general use in Finland.

Plasma glucose level measurement after an overnight fast combined with measurement of plasma glucose concentration two hours after a 75 g oral glucose load, is needed for determination of impaired glucose tolerance (IGT), an abnormal glucose tolerance class not meeting the criteria for diabetes. Impaired glucose tolerance period invariably precedes NIDDM, but IGT does not invariably deteriorate into NIDDM. Subjects with a high fasting glucose level have also high post-load level (World Health Organization 1985), whereas most elderly subjects with high postload glucose levels (³11.1 mmol/l) have a normal fasting plasma glucose level (Wingard et al. 1990). Criteria for diabetes mellitus and impaired glucose tolerance according to the WHO-criteria are shown in Table 1 (adopted from Mykkänen 1993).

Table 1. Diagnostic criteria for diabetes mellitus according to the World Health Organization criteria.

	Venous plasma glucose level (mmol/l)	
Class	Fasting	Two hour[1]
Diabetes mellitus	³7.8	or ³11.1
Impaired glucose tolerance (IGT)	< 7.8	and 7.8-11.0
Normal glucose tolerance[2] (NGT)	< 7.8	and < 7.8

[1]Two hour plasma glucose in an oral glucose tolerance test (75 g glucose).
[2]Although this criteria does not define 'normal' response in an oral glucose tolerance test, the NGT-term is used here to include subjects who do not meet the criteria for diabetes or IGT.

2.1.2 Prevalence of NIDDM and IGT

Non-insulin-dependent diabetes mellitus is the most common type of diabetes, accounting for 80-90% of all diabetes cases in western societies. The estimated global prevalence of NIDDM is 2 - 5 %, and in Finland it is 3.3 % (Laakso et al. 1991a). The prevalence of NIDDM varies considerably in different populations, partly due to different methodology to confirm the diagnosis of diabetes, i. e. history of diabetes, fasting hyperglycemia or oral glucose tolerance test (Wingard et al. 1990). The prevalence of NIDDM and IGT are strongly age dependent. After the age of 50 years, there is on average an increase in the two hour glucose 0.5 mmol/l and in the fasting glucose 0.06 mmol/l per decade (Davidson et al. 1979, Keen et al. 1982). Applying the World Health Organization (1985) criteria for diabetes, the prevalence of NIDDM in the elderly populations from the United States and Europe has been

estimated to vary between 10 - 19 % (Fuller et al. 1983, Escwege et al. 1985, Jarrett 1985, Pan et al. 1986). Also the prevalence of IGT increases with ageing, on average 1.5 fold per decade after the age of 40 years (McPhillips et al. 1990). In an elderly Finnish population aged 65-74 years, the prevalence of NIDDM was 15.7 % in men and 16.8 % in women, and respective prevalences of IGT were 17.8 % and 19.1 % (Mykkänen et al. 1990).

2.1.3 Pathogenesis of non-insulin-dependent diabetes mellitus

Hyperinsulinemia, insulin resistance and the insulin resistance syndrome

Hyperinsulinemia as a consequence of decreased insulin mediated glucose uptake (Laws and Reaven 1993) is one of the most important risk factors for NIDDM (Stern 1991, 1995). Pima Indians have the highest prevalence of NIDDM in the world, and therefore this population provides an excellent source to study deterioration in glucose tolerance. Saad et al. (1989) studied changes in serum insulin levels in subjects who preliminarily were normoglycemic but who later deteriorated in their glucose tolerance. Normoglycemic subjects who later developed NIDDM, had higher fasting and postload insulin levels than control subjects who remained nondiabetic. The transition from normal glucose tolerance to impaired glucose tolerance was associated with remarkable elevations in fasting and 2 hour insulin levels. Deterioration from impaired glucose tolerance to NIDDM was associated with a further increase in fasting insulin, but 2 hour insulin decreased. This observation provided the basis for the two phase model for the development of NIDDM. In the first phase, the transition from normal glucose tolerance to impaired glucose tolerance depends on presence of insulin resistance. In the second phase, transition from impaired glucose tolerance to NIDDM, which invariably precedes NIDDM, is dependent on impaired insulin secretion. According to this model, the primary deficit in NIDDM is insulin resistance, i.e. insulin does not have an adequate effect in skeletal muscle, but also concomitant impairment in insulin secretion is required to induce overt NIDDM. Both elevations in postload insulin and glucose values precede NIDDM. In a longitudinal analysis of the development of NIDDM, elevated 2 hour insulin levels were found 5 years before diagnosis, followed by sharply elevated 2 hour glucose levels approximately 2.5 years later (Hara et al. 1996). Hyperinsulinemia predicts diabetes also in Caucasian populations (Charles et al. 1991). Reaven (1988) introduced the term, insulin resistance syndrome (Syndrome X or metabolic syndrome), which is characterized by a defect in insulin mediated glucose uptake as the core feature. This syndrome describes a cluster of cardiovascular risk factors, i.e. insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia and hypertension, and it is also an important risk factor for NIDDM. Separate aspects of the insulin resistance syndrome, such as elevated blood pressure, a high triglyceride level and low HDL cholesterol predict NIDDM in the middle-aged subjects (Haffner et al. 1990).

Environmental risk factors for NIDDM

High body-mass index as an index of general obesity (Perry et al. 1995) and central obesity (Mykkänen 1990) are important risk factors for NIDDM. Obesity may partly be due to genetic predisposition, but also life style modification regulates body weight. Low level of physical activity increases risk the for NIDDM, consequently, moderate physical activity lowers the risk for NIDDM dramatically and even lighter exercise has parallel effects (Perry et al. 1995). Especially in the elderly subjects, physical inactivity is an important risk factor for NIDDM (Frisch et al. 1986). Smoking (Feskens and Kromhout 1989, Perry et al. 1995) and some antihypertensive drugs (betablocking agents and thiazides), may also increase the risk for NIDDM (Skarfors et al. 1989, Mykkänen et al. 1994).

Genetic risk factors for NIDDM

Laakso et al. (1991a) reported a higher prevalence of NIDDM in men than in women, but in the older age groups, the opposite has been found (Mykkänen et al. 1990). Twin studies have shown that concordance for NIDDM is high in monozygotic twins,

up to 90 %, whereas in dizygotic twins it is much lower, less than 20 %. First degree relatives have also an increased risk for NIDDM. The Apo E e4 phenotype has been associated with a high insulin level (Orchard 1994), which may therefore be also a risk factor for NIDDM.

2.2. Cerebral function in glucose intolerance

2.2.1 Glucose and memory

Glucose is the primary substrate for brain energy metabolism (Raichle et al. 1984). Neurons in the brain are unable to store or synthesize glucose, and therefore, the needed glucose is obtained from the systemic circulation and subsequently transported across the blood brain barrier (McCall 1992). The hippocampus, which plays a critical role in consciousness acquisition and recall of new information (i.e. declarative memory) (Squire et al. 1992), is vulnerable to excitotoxic damage during periods of glucose insufficiency (McCall 1992). Other medial temporal lobe structures for declarative memory include the entorhinal cortex, the parahippocampal cortex and the perirhinal cortex. Together with the hippocampus, these areas work in concert with neocortex (Zola-Morgan and Squire 1993).

Decreased glucose utilization has been hypothesized to play a role in the mild decline in memory function observed in normal aging (Gold 1986, Gold and Stone 1988). This idea has been supported by findings that elevating plasma glucose levels through glucose administration in elderly human and rodents improves memory without affecting motor and nonmemory functions (Gonder-Frederick et al. 1987, Manning et al. 1990). The specific way this occurs is still unclear, but a few mechanisms have been suggested. One hypothesis is that increased availability of glucose may increase the production of acetyl-CoA, a cholinergic substrate and thereby enhance cholinergic mediation of memory function (Gold and Stone 1988). Not only memory, but also attentional function are affected by the basal forebrain cholinergic system innervation, therefore attentional function may be improved by stimulated cholinergic system (Lawrence and Sahakian 1995). An alternative hypothesis is that hyperglycemia may modulate opiate inhibition of acetylcholine turnover in the hippocampus (Stone et al. 1991). Wenk (1989) presented a hypothesis that some cognition enhancing drugs produce their beneficial effects on memory through increasing the availability glucose in the brain.

2.2.2 Cognitive function in glucose intolerance

In 1922, Miles and Root demonstrated that subjects with diabetes performed poorer than non diabetic control subjects in tests measuring different cognitive domains. After that several studies have shown impaired cognitive function in both types of diabetes. The literature concerning NIDDM and cognitive function has been reviewed by Tun et al. (1990), by Richardson (1990) and recently by Strachan et al. (1997a). The most recent report of 19 studies, which were conducted during 1980-1995, included only studies with clearly identified type-2 diabetes patients. Subjects in these studies were aged from 53 to 80 years, and the number of cases varying from 19 to 140 and control subjects rom 13 to 195. Over 70 different psychological tests were applied, therefore it was not possible to perform any formal meta-analysis. In order to simplify the interpretation of the results in these studies, the various psychometric tests were summarized in six broad categories, based on the classification by Lezak (1995). The categories were attention / concentration, frontal lobe / executive function, visuospatial memory, verbal memory, psychomotor / performance IQ and the Mini-Mental-State Examination (MMSE). Verbal memory was the only cognitive domain, in which the majority of the studies (9/15) showed lower performance in patients with NIDDM in comparison with control subjects.

Verbal memory was assessed with story recall and word lists, which contain more information than one can maintain in the short-term memory. In studies, where both immediate and delayed recall were evaluated, both or neither of them were affected in subjects with NIDDM. Therefore, impairment in immediate or delayed recall did not separate NIDDM patients from control subjects in case control studies.

Visuospatial memory was affected in 5 out of 10 studies, again, NIDDM had no differential effects on immediate and delayed recall. Zaslavsky et al. (1995) found impaired visual memory in 20 NIDDM patients with autonomic neuropathy compared to the 34 nondiabetic control subjects, but this was not seen in patients without autonomic neuropathy. This cross-sectional study included subjects aged from 39 to 75 years, and therefore did not represent only the elderly.

Attention and concentration were assessed in 11 studies using a variety of tests. Subjects with NIDDM had unequivocal impairment in three of the studies, and they were impaired in three more studies at least in one test when several tests were applied. The forward and backward digit span subtests were most frequently used. Two studies reported impairment in the digit span forward (U'Ren et al.1990, Jagusch et al. 1992) and two in the digit span backward (Perlmuter et al. 1984, Tun 1987). In a more recent study, Dey et al. (1997) reported impaired attention and memory in younger type-2 diabetes patients.

Frontal lobe / executive function was impaired in three of the eight studies presented in the review by Strachan et al. (1997a). Subjects with NIDDM were impaired in the Verbal Fluency test in one study (Lowe et al 1994) but this was not found in four other studies (Atiea et al. 1995, Perlmuter et al. 1987, U'Ren et al. 1990, Helkala et al. 1995).

The psychomotor/performance IQ is a composite modality including a number of the Wechsler Adult Intelligence Scale subtests and reaction time measurements. Three of nine studies revealed poor performance at least in one test of this modality. Total reaction time was assessed only in three studies, and no differences were detected between diabetic subjects and controls. One study reported prolonged movement time, a component of reaction time in the diabetic subjects. Three studies utilized variations of the MMSE, a measure of overall cognitive function, and the diabetic subjects all demonstrated lower scores than the control subjects (Ciotti et al. 1986, Worrall et al. 1993, Croxson et al. 1995).

In addition to small case control studies, cognitive function have been examined in a few population studies. Kalmijn et al. (1995) studied a population based cohort of 462 men aged 69 to 89 years using the MMSE, a measure of cognitive function. Results were expressed as the number of erroneous answers given in the MMSE. Previously known diabetic patients made 1.23 times, newly diagnosed diabetic patients 1.16 times, and those with IGT 1.18 times more errors in the MMSE compared with the normoglycemic subjects. Elias et al. (1997) studied NIDDM and blood pressure as risk factors for poor cognitive function in the Framingham study investigating a prospective cohort sample with 187 NIDDM patients and 1624 nondiabetic subjects, aged 55-88 years. They used the following tests: logical memory with immediate and delayed recall, paired associates, digit span forward and backward, word fluency and similarities. Presence and duration of NIDDM were associated with poor performance in tests of visual memory. Patients receiving insulin treatment were at higher risk for poor cognitive function than those with diet or oral agents. Risk ratio for performing below the 25% percentile was 1.49 in the delayed logical memory, but in the remaining tests, the risk was not elevated. Elias et al. (1997) concluded that hypertensive people with NIDDM are at greater risk for poor performance on tests measuring visual organization and memory.

Subjects selection may have affected the results obtained in the previous case-control studies. Furthermore applying different neuropsychological methodology may have been a confounding factor. However, the pattern of cognitive impairment found in NIDDM resembles the changes found in early dementia of the Alzheimer type.

2.2.3 Electrophysiological brain findings in NIDDM

Electrophysiological studies have provided evidence of cortical changes in patients with NIDDM. Mooradian et al. (1988) reported a modest overall slowing of electroencephalographic frequencies in the elderly men with NIDDM accompanied by alterations in the P300 wave component. Cerizza et al. (1990) studied

somatosensory evoked potentials of median nerve calculating spino-thalamic central conduction velocity in 20 subjects with NIDDM aged 64-81 years and in 20 controls. No evidence was found for impairment of central conduction velocities. Kurita et al. (1996) studied auditory P300 event-related potentials in 60 patients with NIDDM (mean age 51 years) and detected longer latencies in patients with NIDDM than in the controls. Peripheral neuropathy, nephropathy, blood glucose levels and disease duration were not associated with the observed P300 latency alterations, but the authors suggested that microangiopathy and metabolic derangement during the preceding 1-2 months may contribute to pathophysiology of these changes. Dey et al. (1997) studied cognitive function and auditory evoked potentials (P 300) in 28 patients with NIDDM and 28 control subjects (mean age 47 years). They found significantly delayed latencies of P300 in patients with NIDDM, and concluded that mild central nervous system impairment should be recognized as a possible complication in relatively young patients with NIDDM.

2.2.4 Factors related to impaired cognitive function in NIDDM

When evaluating cognitive function in NIDDM, it is essential to decide whether to investigate pure diabetes or the syndrome of NIDDM. In order to investigate pure NIDDM, all subjects with any associated disorders should be excluded or these associated factors should be controlled (Strachan 1997a). In the elderly subjects, a more natural choice is to study the syndrome of NIDDM, because the disease as a distinct condition is uncommon.

Several mechanisms for cognitive impairment have been offered. Transient hypoglycaemia may impair cognitive function in NIDDM, and antidiabetic medication may have similar effects (Wredling et al. 1990, Langan et al. 1991). Neuropathy secondary to diabetes may result in impaired vision and hand coordination, which in turn can disturb neuropsychological performance (Colsher et al.1991). Also an elevated level of depression may affect cognitive function in patients with NIDDM (Palimkas et al. 1991, Lustman et al. 1992, Tun 1987). In a large well defined prospective study, hypertensive NIDDM patients have been shown to perform poorer in a test of visual memory than subjects with normotension (Elias et al. 1997).

Poor glycaemic control has been associated with cognitive dysfunction in some (Perlmuter et al 1984, Jagush et al. 1992), but not in all studies (Worrall et al. 1993, 1996, Lowe et al. 1994, Ryu et al. 1995, Zaslavsky 1995). The duration of diabetes have been associated with impaired cognitive function in a large prospective study (Elias et al.1997), but in small case-control studies this has not been reported (Perlmuter et al 1984, Zaslavsky 1995). Surprisingly, Ciotti et al. (1986) reported better cognitive function in those subjects with a longer duration of diabetes. This was most likely due to subject selection. On the other hand, the exact onset of diabetes is difficult define (Harris et al. 1992), unless glucose tolerance is measured on a regular basis (Elias et al. 1997). Cognitive dysfunction in NIDDM has been associated also with peripheral (Perlmuter et al. 1984) and autonomic neuropathy (Zaslavsky et al.1995). However, large studies investigating the association between neuropathy and cognition have not been conducted. A high triglyceride level has been associated with poorer cognitive function in patients with NIDDM (Helkala et al. 1995, Perlmuter et al. 1988), and interestingly, treating the hypertrigliceridemia has been reported to improve cognitive function (Heilman et al. 1974, Rogers et al. 1989).

Structural changes in the brain could also explain the cognitive dysfunction in NIDDM. The frequency of stroke is elevated in the elderly patients with diabetes (Meyer et al. 1988, Bell 1994, You et al. 1995), which may attenuate cognitive function. However, diabetes has been associated with with lacunar infarcts (Mast et al. 1995) and with cognitive dysfunction also in a stroke free cohort (Desmond et al. 1993). Hyperinsulinemia has been associated with atherosclerosis, thrombosis and abnormal haemodynamic processes (Feskens et al. 1992, Reaven 1988, DeFronzo 1992, Juhan-Vague et al. 1993), which could contribute to lacunar infarction and consequently to impaired cognitive function (Erkinjuntti and Hachinski 1993).

Hyperinsulinemia as a result of insulin resistance may have a detrimental effect on micro vascular function in the prediabetic state (Jaap et al. 1997). Therefore, both NIDDM and its cardinal risk factor share a potential mechanism for cerebrovascular disease, possibly affecting cognitive function. In addition to cerebrovascular disease, cortical (Araki et al. 1994) and central (Soininen et al. 1992, Pirttilä et al. 1992) atrophy have been reported in the elderly patients with diabetes.

2.2.5 Dementia in glucose intolerance

2.2.5.1 Major types of dementia

The distribution of dementia types varies in different populations. Alzheimer's disease is the major type of dementia in Caucasian populations, accounting for over 50% of all patients with dementia. The second most common type is vascular dementia with estimated prevalence of 12-30% (van Duijn 1996). A brief description of Alzheimer's disease is presented here to clarify features and risk factors.

Prevalence estimates of Alzheimer's disease increase rapidly with age, at the age of 65 its prevalence is 0.5% (Breteler 1992). Juva et al. (1993) present prevalence rates of 4.6%, 13.1% and 23.3% in a Finnish elderly population at ages 75, 80 and 85 respectively. The commonly used criteria for defining Alzheimer's disease are those of the third revised edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-III-R) (American Psychiatric Association 1987), the fourth Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) (American Psychiatric Association 1994) and the criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984). According to the DSM-IV-criteria, a subject must have memory impairment and at least one other impairment in cognitive function, and these disturbances should interfere with daily life. The course of the disease should be gradual and continuing, and other reasons of dementia should be excluded. Senile plaques, neurofibrillary tangles, cerebrovascular amyloid deposits, neuronal damage and loss of synapses can be found in the brain in Alzheimer's disease (Terry and Katzman 1983). In most patients, the etiology of the disease is unknown. However, known gene mutations may cause the early onset form of the disease. Mutations in the b-amyloid precursor protein gene on chromosome 21 have been found in families with early onset of the disease (< 55 years). Later, mutations in presenilin 1 gene on chromosome 14, and presenilin 2 gene on chromosome 1 have been reported in families with early onset disease. The e4 allele of the Apo E gene has been shown to be associated with increased risk for both early and late onset of the disease (van Duijn 1996, Farrer et al. 1997). In an elderly Finnish population, the risk of Alzheimer's disease was 2.7 in subjects with one e4 allele and 9.1 in subjects with two e4 alleles compared to those with no e4 alleles (Kuusisto 1994). Thus, the presence of Apo E e4 allele confers elevated genetic risk for Alzheimer's disease. Recent studies have indicated that the prevalence of Alzheimer's disease may be elevated in NIDDM (Ott et al. 1996).

Vascular dementia is a syndrome caused by several vascular lesions, including ischaemic, hypoxic and haemorrhagic brain damage. The clinical diagnosis requires the presence of dementia, cerebrovascular disease evidenced by neuroimaging and by neurological symptoms, and a temporal relation between the vascular disease and dementia. Subtypes of vascular dementia include multi-infarct dementia, lacunar state and Binswangers disease. Patients with vascular dementia have reduced life expectancy compared with the general population. Risk factors for vascular dementia include hypertension, diabetes and cardiovascular diseases. Vascular factors may be involved also in Alzheimer's disease, e.g. white matter changes have been detected this disease (VanDuijn 1996).

2.2.5.2 Dementia in NIDDM

Nielson et al. (1996) studied frequency of diabetes in 123 patients with Alzheimer's disease, in 51 patients with vascular dementia, in 57 patients with mixed Alzheimer's disease and vascular dementia patients and in 34 'other' dementia patients; of those

15 had diabetes. Diabetes was rare in patients with Alzheimer's disease (0.8 %), relative to vascular dementia (11.8 %), mixed dementia (8.8 %) and other dementia patients (8.8 %). Sinclair et al. (1997) studied 109 diabetic patients and 106 control subjects in nursing and residential homes in South Wales, aged on average 83 years (range 58 - 103 years). Dementia was more common in diabetic residents (49 %) than in nondiabetic residents (30 %), furthermore, the level of dependency was higher in patients with diabetes than in the age and sex matched control subjects.

There is a limited number of large population studies investigating the association between NIDDM and dementia. Bucht et al. (1983) reported the occurrence of diabetes in a population based study with 317 patients with Alzheimer's disease, 457 patients with multi-infarct dementia and 65 with confusional state. None of the Alzheimer's disease patients had diabetes, whereas 55 of the multi-infarct dementia patients and 5 of subjects with confusional state were diabetic. Ott et al. (1996) reported an association between NIDDM and dementia in the Rotterdam study, which is a large population based study to investigate a variety of disease in the elderly. Complete information of the presence of diabetes and dementia was available in 6330 subjects aged 55 to 99 years. The definition of diabetes was based on the use of anti-diabetic medication or random or postload glucose over 11 mmol/l, and dementia was diagnosed through a stepped approach including sensitive screening and a comprehensive diagnostic work-up. A positive association was found between NIDDM and dementia, patients with NIDDM had 1.3 times elevated risk for dementia after adjustment for age, education and sex. Relative risk for dementia in insulin treated patients was 3.2 compared with nondiabetic subjects. Diabetes was found in 30 % of patients with vascular dementia, in 21 % of patients with Alzheimer's disease and 19 % of patients with any other type of dementia. Leibson et al. (1997) studied risk of dementia in a population based historical cohort study including 1455 cases of adult onset diabetes mellitus. During the follow-up subjects with adult onset diabetes mellitus exhibited a significantly increased risk for all dementia, the relative risk being 1.66 compared with the nondiabetic subjects. Risk for Alzheimer's disease was more pronounced in men (relative risk 2.27) than in women (relative risk 1.37). Yoshitake et al. (1995) followed 828 nondemented subjects aged 65 years or older for 7 years and determined risk factors for dementia. In subjects with diabetes, the risk ratio for vascular dementia was 2.77 whereas for Alzheimer's disease it was 2.18.

In conclusion, large epidemiological studies indicate that AD and vascular dementia would be more prevalent in patients with NIDDM than in nondiabetic subjects. However, to a some extent differences in dementia diagnosis and definition of diabetes may have affected on the results.

2.3 Insulin and cognitive function

2.3.1 Acute insulin administration and cognitive function

Insulin receptors have been identified in different brain regions, e.g. in the hypothalamus (Shibata et al. 1985) and the hippocampus (Palovick et al. 1993). The former is an important factor in regulating feeding behavior and the latter in appropriate memory function (Baskin et al. 1987). Insulin is transported across the blood-brain barrier via specific receptors or is taken up into neural tissue from the cerebrospinal fluid. It may inhibit synaptic activity in the brain (Baskin et al. 1987). Insulin has been found to reversibly reduce cholinergic activity of striatal neuron cultures (Brass et al. 1992), and to accelerate turnover of monoamines in the brain (Kwok and Juorio 1987, 1988, Sauter et al. 1983). Therefore, insulin could affect cognitive functions through synaptic inhibition or by altered cholinergic and monoaminergic activity.

Raising plasma insulin levels by an intravenous infusion, causes a secondary reduction in plasma glucose level, which itself can impair cognitive function. Hyperinsulinemic euglycemic clamp technique, in which plasma glucose level is maintained at a stable baseline level, provides a way of investigating the independent effect of acutely raised insulin level (Craft et al. 1996). Kerr et al. (1991) studied the

cognitive changes in nine patients with insulin dependent diabetes, aged 21-50 years. During the euglycemic hyperinsulinemic clamp study, no differences were found in cognitive function. However, no appropria te test of declarative memory was included. Fanelli et al. (1994) investigated the relative roles of insulin and hypoglycaemia on cognitive function in 22 young nondiabetic subjects. During a three hour hyperinsulinemic euglycemic clamp study, the sum score of cognitive function did no t change, but during the hypoglycaemic condition cognitive impairment was detected. Craft et al. (1996) studied the effect of hyperinsulinemia on cognitive function in patients with mild Alzheimer's disease and in normal control subjects. They showed that raising the plasma insulin level via an intravenous insulin infusion while keeping glucose level at the b aseline level, produced a striking declarative memory enhancement in pati ents with Alzheimer's disease but not in the control subjects. In the nonmemory tests (word fluency, Stroop tests, line orientation, digit span) no improvement was found. Thes e results suggest, th at neuroendocrine may factors play an important role in th e pathophysiology of Alzheimer's disease. In the pa tients with i ncipient Al zheimer's di sease, acute insuli n admi nistration m ay have significant effects on memory, whereas in the control subjects this would be less likely.

2.3.2 The effect of chronic hyperinsulinemia

Rather recently, hyperinsulinemia has been associated with impaired cognitive function in large population studies. Kuus isto et al. (1993) reported impaired cognitive function in elderly nondiabetic subjects with essential hypertension. Hyperinsulinemic hypertensive subjects had, but normoin sulinemic hypertensive did not have, impairment in brief neuropsychol ogical tests. Kalmijn et al. (1995) found that nondiabetic elderly men with hyperinsul inemia made more errors in the MMSE than men with lower insulin levels. Stolk et al. (1997) studied 5510 elderly subjects, and detected an association between serum 2 hour insulin and the MMSE score in women, but not in men. Increased age-adju sted insulin levels were also found in women with dementia.

Studies into the plasma insulin level during fasting and oral glucose tolerance testing have given conflicting results in patients wit h Alzheimers' disease. Bucht et al. (1983) detected lowered fasting blood glucos e levels and elevated insulin levels in 317 patients with Alzheimers' disease co mpared with healthy control subjects. Kilander et al. (1993) studied peripheral insulin sensitivity with the hyperinsulinemic euglycemic clamp technique in 2 4 patien ts wi th Al zheimer's disease and in 24 control subjects, but d id not fin d any differences between the groups. Razay and Wilcock (1994) studied fasting plasma glucos e and insulin levels in 24 patients with Alzheimer's disease and in 24 control s ubjects aged 58 - 90 years. Women with Alzheimer's disease had higher insulin and gl ucose levels than the control subjects, whereas in men these differences were not si gnificant. Therefore a few studi es with small sample size which have reported no differences in insulin levels between patients with Alzheimers' disease and control subjects (Winograd et al. 1991, Fisman et al. 1988).

Craft et al. (1993) studied insulin levels in patients with Alzheimer's disease o f varying severity. Patients with very mild Alzheimer's disease were hyperinsulinemic, whereas those wi th more adv anced dem entia, had lower i nsulin le vels. Th e insulin response to oral glucose load was stronge r in patients with very mild demen tia compared with those having more severe dementia. This finding was co nfirmed in a follow-up experiment after 1.5 years. Subjects whose dementia progressed from very mild to more adva nced stages, init ially showed extreme elevations in plasm a insulin in response to hyperglycemia and a subsequent decline in those levels at follow-up.

Fujisawa et al. (1991) studied fasting and cerebrospinal fluid insulin in 54 patients with Alzheimer's disease, i n 4 4 pat ients with vascular dementia and in 26 control subjects. Fasting insulin levels did not differ in the groups, but elevated cerebrospinal fluid insulin levels were foun d in patients with Alzhe imer's di sease. Cra ft et a l. (1998) studied cerebrospinal fluid and plasma insulin levels in Alzheimer's disease in relation to severity of dementia an d Apo E genotype. Patients with Alzheimer's

disease had lower cerebrospinal insuli n, higher plasma insulin and reduced cerebrospinal t o pl asma insulin rat io, when c ompared with healthy adults. Th e differences were greater for patients wi th more advance d Alzheimer's disease. Patients who were not Apo E e4 homozygo tes had higher plasma insulin levels and reduced cerebrospinal to plasma insulin ratios, whereas Apo E e4 homozygotes with Alzheimer's disease had normal values. The authors concluded, that both plasma and cerebrospinal fluid insu lin levels are abnormal in patients with Alzheimer's disease, and there are metabolic differences in Apo E genotypes.

In conclusion, these stud ies indicate that both acute insulin administration and chronic hyperinsulinemia ar e asso ciated with changes in cognitive function, especially in patients with Alzheimer's di sease. As Craft (1993) suggested, patients in the early stage of Alzheimer's disease may have hyperinsulinemia, but those with more advanced demen tia have lower insulin levels. Low blood glucose levels, low blood pressures and increased prevalence of hyp othyreosis have been detected in patients with more advanced Alzheime r's d isease (Landin et al. 1993). These findings suggest that glucose and insulin metabolism change dramatically during th e progression of Alzheimer's disease, and that advanced Alzheimer's disease may be a catabolic state. Since abnorma lities in glu cose and insulin metabolism are present in Alzheimer's disease, this gives forms the foundation for the concept that these abnormalities might contribute to the development of certain subtypes of this form of dementia.

2.4. Classification of cognitive functions

Memory is not a single entity, but is composed of separate systems. Memory can be divided into declarative (explicit) and nonde clarative (implicit) memory. Declarativ e memory refers to memory for facts and events, whereas nondeclarative memory refers to skill and habit learning, priming, simple classical conditioning and nonassociative learning. Structures of the medial temporal lobe and diencephalon are essential for intact declarative memory function, whereas for nondeclarative memory function they are not necessar ily need ed (Squire and Knowlton 1995). Through th e book, 'memory' refers to declarative memory, unless other indicated.

Lezak (1995) has cla ssified cognitiv e functions into four major c lasses using analogies with c omputer syst ems. Firstly, recept ive func tions whic h cover th e abilities to sele ct, acquire, classify and i ntegrate information. Secondly, memory a nd learning, which refer to information storage and retrieval. Thirdly, thinking which is related to the mental organization and re organization of information. Fou rthly, expressive functions which refer s to ways through which information is communicated or acted upon. Each of th ese functional classes comprises many discrete act ivities, and th ese cla sses norm ally work in concert and interdependence (Lezak 1995). In addition to this crude cl assification, Lez ak (1995) presents a compendium of tests and assessment tech niques. These ar e divided into the major classes: orientation and attention, perception, memory, verbal functions and language skills, construction, concept formation a nd reasoning, executive functions and motor performance (Lezak 1995). Strachan et al. (1997) used a classification based on that of Lezak (1995) when reviewin g the lite rature concerning non-insulin -dependent diabetes and cognitive f unctions. Since very many psychological tests had been applied in thei r studies, t hey sum marized the result s for pract ical reasons in to si x major categories. These c ategories were 1. attention and concentr ation, 2. frontal lobe/executive function, 3. visuospatial memory, 4. verbal memory, 5. psychomotor/ performance intelligence quotient (includi ng variety of subtests of the WAIS performance scale) and 6. Mi ni-Mental Stat e Examination (representi ng overall cognitive level rather than any sp ecific cognitive domain). Although still crude, this classification provides the opportunity to compare results obtained in previous studies and gives signposts for future re search. Although psycho motor/performance intelligence quotient and Mini -Mental State Examination are not separate 'cognitive functions', these aggregat e sc ores are widel y used, and therefore they im prove comparability across different studies. The classification of cognitive functions used in the present study was based on that of Strachan et al. (1997) for these reasons.

3. Aims of the Study

The purpose of this series of studies was to investigate cognitive function in glucose intolerance and hyperinsulinemia in the elderly. More specifically the aims were the following:

1. To investigate if auditory event related potentials are affected in NIDDM. (Study I)

2. To investigate if risk for NIDDM in the normoglycemic subjects is associated with impaired cognitive function. (Study II)

3. To investigate if persistent impaired glucose tolerance is associated with impaired cognitive function. (Study III)

4. To investigate if hyperinsulinemia as a part of insulin resistance syndrome is associated with Alzheimer's disease. (Study IV)

5. To investigate if hyperinsulinemia is associated with impaired cognitive function independently of NIDDM. (Studies II, III, IV)

6. To investigate if cognitive function is affected in patients with NIDDM in a non-demented population. (Study V)

4. Subjects and Methods

4.1 Subjects

Participants in these studies were from three different sources. Study I included a small number of subjects collected from hospital records. Study II included subjects from a study examining risk factors for myocardial infarction in the Department of Medicine. Studies III - V included subsamples of subjects participating in a dementia epidemiology study in Kuopio, eastern Finland. All neuropsychological examinations in studies I and II were done by the author, whereas in the dementia epidemiology study they were performed by a psychologist, a doctor or a nurse. Glucose tolerance categories were defined according to the World Health Organization criteria (1985) in all studies. Table 2. shows the main characteristics of the study groups and a summary of the methods used

Study I

Subjects for study I were nine patients with previously known NIDDM (3 men, 6 women) and nine normoglycaemic control subjects (4 men, 5 women). The mean age of patients with NIDDM was 72.7 ± 2.5 years and in control subjects 74.6 ± 1.8 years, and education respectively 6.1 ± 1.6 and 7.1 ± 1.5 years, (both $p > 0.05$). Fasting plasma glucose and insulin levels were 13.4 ± 3.6 mmol/l and 17.9 ± 4.6 mU/l in patients with NIDDM and the corresponding values in controls were 5.3 ± 0.4 mmol/l and 7.3 ± 3.1 mU/l (both $p < 0.05$) (insulin level in pmol/l: 107.4 ± 27.6 and 43.8 ± 18.6 pmol/l). Subjects showing any condition (e.g. stroke, dementia, depression) that might interfere with cognition were excluded. The mean duration of diabetes was 8.2 ± 4.8 years (range 1 - 15 years). Two of the patients were on diet treatment only, five on sulphonylurea and two on metformin treatment. Hypertensive subjects and insulin-treated diabetic patients were excluded. Medications did not differ between the groups, except medication for diabetes.

Table 2. Summary of characteristics and methods in studies I - V.

Study	I	II	III	IV	V
n (control/case)[1]	9/9	26/22/35	506/80	915/46	732/183
Women (%)	56/67	62/77/63	63/64	65/70	64/65
Age (years)	75/73	63/65/67	73/73	73/74	73/73
Education (years)	7/6	8/7/7	7/7	7/5	7/6
Fasting glucose	5.3/13.4	5.2/5.6/9.3	5.4/6.0	6.2/6.9	5.6/8.8
2-hour glucose	NP	5.1/6.9/17.8	5.9/9.2	8.3/10.6	6.7/15.2
Fasting insulin	44/107	49/85/125	62/91	75/99	69/102
2-hour insulin	NP	170/505/593	360/721	501/682	462/672
Plasma lipids	NP	+	+	+	+
Blood pressure meas.	NP	+	+	+	+
Depression evaluation	NP	GDS	S	NP	S
Dementia diagnosis	-	-	NP	+	NP
ERPs	+	-	-	-	-
Tests of cognition:					
BSR	NP	+	+	+	+
VRT	NP	+	+	+	+
MMSE	+	+	+	+	+
TM	-	+	+	+	+
VF	-	+	+	+	+
DS	NP	+	-	-	-
ST	-	+	-	-	-
DSY	-	+	-	-	-
BD	-	+	-	-	-
VOC	+	-	-	-	-
FTT	NP	-	-	-	-

Glucose (mmol/l) and insulin (pmol/l) levels were measured from venous plasma, NP = data not presented, + = done, - = not done, GDS = Geriatric Depression Scale, S = self reported depression. ERPs = Event Related Potentials, MMSE = Mini-Mental State Examination, BSR = Buschke Selective Reminding Test, VRT = Visual Retention Test, TM = Trail Making Test, VF = Verbal Fluency Test, DS = Digit Span, ST = Stroop Test, DSY = Digit Symbol, BD = Block Design, VOC= Vocabulary, FTT = Finger Tapping Test. [1] Study II included two experimental groups. Values are means unless otherwise indicated.

Study II

Subjects for stud y II were a subsample of participants in a larger study examining primarily risk factors for myocardial infarction. Consecutive series of 73 normoglycemic subjects and 35 patients with NIDDM were included in the study. Normoglycaemic subjects were divided into two groups according to their risk of developing NIDDM: those considered to be at low risk (n = 26) had 2 hour plasma glucose and insulin values lower than the median, and those considered to be at increased risk (n = 22) had values higher than the median (median 2 hour plasma glucose was 5.9 mmol/l and median 2 hour pl asma insulin 279.6 pmol/l). In order to form groups with clearly different risk level for NIDDM, not all normoglycemic subjects were included in the risk groups. The NIDDM group was older than the low-risk group (ANOVA/Duncan $p < 0.05$), but th e groups did not differ signif icantly in education. As expected, the NIDDM group had higher fasting plasma glucose ($p < 0.05$) and 2-hour glucose levels ($p < 0.05$), glucose area ($p < .05$) and systolic blood pressure ($p < .05$) than the risk groups. The low -risk group had lower 2-hour insulin levels ($p < 0.05$), insulin areas ($p < 0.05$) and body -mass index ($p < .05$) than the group with increased risk or NIDDM, and al so lower fasting plasma insulin levels ($p < 0.05$) and higher HDL-cholesterol levels than the NIDDM group ($p < 0.05$).

Population based studies (III - V)

Subjects for the studies III - V were subsamples of the large population-based follow-

up study, which was primarily examining cardi ovascular risk factors in the elderly. This population has been describ ed in detail earlier by Mykkänen (1993) and by Kuusisto (1996). The baseline examination of this study was conducted between 1986 and 1988 at the Department of Medicine of the University of Kuop io. 1910 subjects born between th e year s 1912 - 1921 were randomly selected f rom the population register including all inhabitants of Kuopio. A postal questionnaire including questions about diabetes, ability to move and willingness to participate in the study was sent to each of subject. 83 subjects were too ill to participate and were excluded. Eventually 1299 o f the 1827 elig ible subjects participated in the examination at ba seline. One ma le subje ct wit h insulin -dependent diabe tes was excluded. The baseline examin ation was conducted during two visits to the C linical Research Unit of the University of Kuopio. The follow-up study was conducted between 1990 an d 1991 at Depar tment of Me dicine. The mean follow-up time was 3.5 years (range 2.7 - 5.2 years) . Of the 1298 subjects at baseline , 108 died during the follow-up. Of the 1190 eligible subjects, 136 were not willing or were too ill to participate. Therefore, 1054 s ubjects participated in the examination at th e Clinical Research Unit of the University of Kuopio. Measurement of cardiovascular risk factors was done 2 - 3 weeks prior to screening of dementia. Finally, 980 participated in the dementia screening at the Memory Research Unit in Department of Neurology. Clinical characteristics of the participants in this population study are shown by glucose tolerance group and sex in Table 3.

Table 3. Clinical characteristics of the subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and non-insulin-dependent diabetes mellitus (NIDDM) by sex.

	Men			Women			All		
	NGT n = 212	IGT n = 68	NIDDM n = 70	NGT n = 362	IGT n = 134	NIDDM n = 134	NGT n = 574	IG n = 202	NIDDM n = 204
Age (years)	73.2 ± 3.0	73.5 ± 3.1	72.9 ± 2.6	73.5 ± 2.9	73.2 ± 2.9	73.7 ± 2.8	73.4 ± 3.0	73.3 ± 0.3	73.4 ± 2.8
Education (years)	6.9 ± 3.6	6.9 ± 5.3	6.1 ± 2.6	6.9 ± 3.5	6.6 ± 3.4	5.7 ± 2.4*	6.9 ± 3.5	6.7 ± 4.1	5.8 ± 2.7*
Fasting plasma glucose (mmol/l)	5.6 ± 0.6	6.0 ± 0.5	8.7 ± 3.2*	5.4 ± 0.5	5.8 ± 0.6*	9.0 ± 3.5*	5.5 ± 0.6	5.9 ± 0.6*	8.9 ± 3.5*
2-hour plasma glucose (mmol/l)	5.9 ± 1.2	9.0 ± 0.9*	14.7 ± 5.1*	6.0 ± 1.0	8.9 ± 0.8*	15.8 ± 6.3*	6.0 ± 1.1	8.9 ± 0.9*	15.4 ± 5.9*
Fasting plasma insulin (pmol/l)	62 ± 30	80 ± 41*	97 ± 56*	65 ± 36	89 ± 51*	110 ± 64*	64 ± 34	86 ± 48*	107 ± 61*
2-hour plasma insulin (pmol/l)	360 ± 267	611± 323*	616 ± 552*	401 ± 319	770 ± 590*	712 ± 677*	384 ± 301	717 ± 520*	679 ± 638*
Glycated haemoglobin A_{1C} (%)	5.7 ± 0.8	5.9 ± 0.7	7.5 ± 2.0*	5.6 ± 0.7	5.7 ± 0.7	7.4 ± 2.3*	5.7 ± 0.8	5.8 ± 0.7	7.4 ± 2.1*
Total cholesterol (mmol/l)	6.2 ± 1.1	6.1 ± 1.0	6.2 ± 0.9	6.7 ± 1.1	6.7 ± 1.2	6.6 ± 1.5	6.5 ± 1.1	6.5 ± 1.2	6.5 ± 1.4
Total triglycerides (mmol/l)	1.4 ± 0.6	1.8 ± 1.3*	2.0 ± 1.0*	1.5 ± 0.6	1.8 ± 0.9*	2.4 ± 1.7*	1.5 ± 0.6	1.8 ± 1.0*	2.2 ± 1.5*
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.2 ± 0.4	1.1 ± 0.3*	1.5 ± 0.3	1.4 ± 0.3*	1.3 ± 0.3*	1.4 ± 0.3	1.3 ± 0.3*	1.2 ± 0.3*
Systolic blood pressure (mmHg)	147 ± 22	158 ± 23*	160 ± 22*	154 ± 22	163 ± 24*	161 ± 21*	152 ± 22	161± 24*	160 ± 26*
Diastolic blood pressure (mmHg)	82 ± 10	86 ± 11*	85 ± 11*	80 ± 9	82 ± 8	81 ± 9	81± 10	83 ± 9*	83 ± 12
Body mass index (kg/m^2)	25.5 ± 3.3	27.1± 4.1*	28.3 ± 3.9*	26.9± 4.1	28.5 ± 4.5*	28.7 ± 4.5*	26.4 ± 3.9	28.0 ± 4.4*	28.6 ± 4.3*
User of alcohol (>30g/week) %	23	24	23	3	1	0	10	8	8
Current smoker %	16	9	6*	5	0†	2	9	3†	3†
Self reported depression (often) %	4	4	1	7	3	5	6	3	3
Needs help in daily activities %	3	6	7	7	7	16*	6	6	14†
Hypertension %	39	56*	69‡	51	69	77‡	47	64‡	75‡
Angina pectoris %	18	18	29	19	13	30†	18	14	30*
History of myocardial infarction %	23	27	30	11	10	18	16	16	22
History of stroke %	3	3	7	4	5	2	3	5	5

Values are means ± SD or n (%). Compared with the NGT group, * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$. Analysis of variance with Duncan's post-hoc analysis and chi square test when appropriate.

Study III

Subjects of the study I II were a subsample of the 980 participan ts of the demen tia screening study. Glucose tolerance was de termined at baseline, 1986 - 1988, and on an averag e 3.5 y ears lat er. Only those subjec ts wh o remai ned normog lycemic (n = 506) (52 % of all par ticipants and 88 % of normoglycemic subjects at follow-up) or had IGT (n = 80) (8 % of all participants and 40 % of IGT subjects at follow-up) at the time of follow-up were included. Age, ed ucation and sex distribution did not differ between the study groups. Fasting and 2-hour glucose and insulin levels wer e higher in the IGT group than in the NGT group (Stud ent's t-test; $p < 0.001$), but glycosylated haemoglobin levels (HbA1c) a nd total cholesterol levels did not differ between the groups. HDL-cholesterol levels were lower ($p < 0.01$) and total triglyceride levels were higher ($p < 0.01$) in subjects with IGT c ompared to subjects with NGT. Systolic ($p < 0.001$) and diastoli c ($p < 0.01$) blood pressures as well as

body mass index values ($p < 0.001$) were higher in subjects with IGT. Alcohol consumption, smoking, self-reported depression and need for help in daily activities were comparable in the study groups. Hypertension was more prevalent in the IGT group ($p < 0.001$) than in the NGT group, whereas the frequency of angina pectoris and myocardial or cerebral infarcts did not differ.

Study IV

980 subjects of the cardiovascular risk factors study participated also in screening for dementia. Of the 980 subjects 19 had dementia of non-Alzheimer's type and were excluded, eventually leaving 961 subjects in the study 4. Of these 762 were nondiabetic and 199 were diabetic. Demographic and clinical data of the subjects in the study IV are given in Table 4.

Table 4. Characterics of study subjects with and without Alzheimer´s disease. Values are means±SD or percentages unless stated otherwise.

Characteristic	Nondemented controls n = 915	Alzheimer´s disease n = 46
Women (%)	65	70
Age (years)	72.9±2.9	74.1±2.6**
Education (years)	6.8±3.5	5.1±1.8**
Current smokers (%)	6.7	6.7
Alcohol users (%)	17.8	17.4
With hypertension (%)†	55.4	63.8
With myocardial infarction (%)	14.1	17.4
With stroke (%)	3.7	2.2
With diabetes (%)	19.9	32.6**
With impaired glucose tolerance (%)	19.9	37.0***
Body mass index (kg/m^2)	27.1±4.0	27.4±5.0
Waist:hip ratio	0.94±0.08	0.95±0.08
Systolic blood pressure (mmHg)‡	155±23	162 ±22*
Diastolic blood pressure (mmHg)‡	82±10	84±9
Total cholesterol (mmol/l)	6.5±1.2	6.2±1.0
High density lipoprotein cholesterol (mmol/l)	1.36±0.3	1.30 ±0.3
Triglycerides (mmol/l)	1.68±1.0	1.85±0.8
Apolipoprotein E e4 phenotype (%)	30.5	58.7***
Fasting plasma glucose (mmol/l)	6.2±2.1	6.9±2.8*
Two hour plasma glucose (mmol/l)	8.3±4.4	10.6±6.4**
Glycaeted Haemoglobin $A1_C$	6.0±1.3	6.3±2.0
Fasting insulin (pmol/l)	74.8±45.0	99.3±68.4***
Two hour insulin (pmol/l)	500.9±438	682.3±744*

*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

†systolic blood pressure 160 mmHg, diastolic blood pressure 95 mmHg, or drug treatment for hypertension. ‡measured twice on right arm in supine position after 5 minutes of rest. Second reading used in analyses.

Study V

Study V included 183 patients with NIDDM and 732 nondiabetic subjects (n = 915), who did not have dementia. Patients with NIDDM had higher glucose, insulin and HbA1C levels (all $p < 0.001$) than nondiabetic subjects. Sex distribution and age were comparable in the groups, but education was lower in patients with NIDDM ($p < 0.001$) than in the control subjects. The HDL-cholesterol level was lower, whereas total triglyceride level, systolic blood pressure and body mass index were higher in patients with NIDDM (all $p < 0.001$) than in the control subjects. Smoking was less

frequent in patients with NIDDM ($p < 0.05$), whereas need for help in daily activities was more common than in nondiabetic subjects ($p < 0.05$). The prevalence of hypertension, angina pectoris (both < 0.001) and myocardial infarction ($p < 0.05$) were higher in patients with NIDDM than in nondiabetic subjects.

4.2 Methods

4.2.1 Neuropsychological tests

The neuropsychological test battery applied in the epidemiological studies was primarily developed for dementia screening. This brief screening battery assessed visual and verbal memory, executive functions, and an overall estimate of cognitive function as evaluated by the MMSE. Evaluating memory and executive function is essential in neuropsychological dementia studies. Not all cognitive domains as presented by Strachan et al. (1997a) could be assessed with these methods in the epidemiological part of the study. Those categories evaluating attention /concentration and also category psychomotor/performance IQ remained unexamined. The following neuropsychological tests and behavioural scales were used during the study. Most of them have been described previously by Hänninen (1996). The Mini-Mental State Examination (MMSE) (Folstein et al. 1975) includes a selection of short items testing different aspects of cognitive function: orientation, repetition and recall of words, attention, language, and constructional ability. The score used was the sum of the scores of all items. The total score in the MMSE consists of several subitems, therefore it does not represent any specific cognitive function. The reliability coefficient was calculated for the MMSE score in the dementia screening population ($n = 980$). Cronbach's μ was relatively low 0.54. Removal any of the MMSE subitems did not increase the reliability coefficient to any major extent. The MMSE was applied in studies I - V.

In the Buschke Selective Reminding Test (BSR) (Buschke and Fuld 1974), subjects have to recall as many as possible of the ten words that have just been read out by the examiner. On the second trial, the examiner repeats only those words which the subjects have not recalled, and the subjects are asked to try to recall all the words again. This procedure is repeated six times and the scores obtained are the total number of words (BSR-T), and the number of words in long-term memory (BSR-L) (i.e., those words which were recalled in consecutive trials without being repeated). The BSR was used in studies I - V. In studies I and II the words were asked also after a delay of approximately 30 minutes filled with unrelated testing (BSR-D). The BSR is a test of verbal memory.

In the Russell's Adaptation of the Visual Reproduction Test (VRT) (Russell 1975), subjects must reproduce geometric figures from memory immediately after seeing them for ten seconds (VRT-I). To measure long-term retention, the subject is asked to reproduce the figures again after 30 minutes of unrelated testing (VRT-D). The VRT was applied in studies I - V. The same figures were also used as a visuo-constructive task by asking the subjects to copy them after the delayed recall task (VRT-C) (Studies III - V).

In the Finnish version of the Verbal Fluency Test on letters (VF-L) (Borkowski et al. 1967), the subjects are given 60 seconds to produce as many words as possible beginning with each of the letters P, A, and S, excluding proper names or different forms of the same word. The performance was scored by counting a sum score of words produced with the letters P, A and S. The VF-L was used in studies III - V. The Verbal Fluency Test on category (VF-C) (Butters et al. 1987) requires the subject to state as many animal names as possible in 60 seconds. The VF-L was scored by counting number of words produced within the time limit and it was applied in studies II -V. The VRT measures visual memory and visuoconstructive functions.

In Part A of the Trail Making Test (TM-A) (Reitan 1958), the subject must draw a line to connect consecutively numbered circles. In Part B, subjects have to draw a line alternating between numbers (1 - 13) and letters of the alphabet (letters A-L).

Due to the large amount of missing data, TM-B was removed from the analysis in the present study. In Part C (TM-C), the letters are replaced with the abbreviated names of the twelve months (JAN -DEC). Part C was developed because many eld erly persons at the area (eastern Finland) do not know the alphabet correctly (Koivisto et al. 1992). The scores were the time required to complete each trial, and the difference between parts A and C (in study V), which reflects the time of cognitive processing subtracted fr om the psychomotor speed involved in both tasks. TM -A and TM-C were used in studies III - V. The TM has been considered as a measure of executive function.

In the Stroop Test (ST) (Golden 1978), two naming trials ar e used. The first trial requires the naming of coloured dots on a sheet of paper, and th e second requires the naming of a colour when colour names are printed in a colour different from the word itself (interference condition). The shortened versions involving 50 do ts (ST-C) and words (ST-W) were used in both naming trials. The scores in the test were the time used to complete each naming trial. The Stroop test has been considered as a measure of executive functions.

Wechsler Adult Intelligence Scale (WAIS) subtests Vocabulary (study I), Digit Span, Digit Symbol and Block Desig n (study I and II) wer e used to assess cognitive function (Wechsler 1955). The Vocabulary subtest (VOC) requires ability to explain meaning of given words, and it has been used as an estimate of ge neral intellectual level (Lezak 1995). Subjects are required to ex plain the meaning of 32 words, and a score of two or one points was given for each compl etely or partially correct answer, from which the sum score was counted. The Dig it Span forward (DS -F) and backward (DS-B) require attention an d primary memory, and ar e considered to belong to the category attention/concentration, which has been described earlier.

The Digit Symbol subtest (DSY) requires perceptual organization, sustained attention and visuomotor coordination. The Block De sign (BD) is a test of visuospatial construction (Lezak 1995). The DSY a nd the BD be long in the a forementioned psychomotor/performance IQ category.

The Finger Tapping Test (FTT) (Lezak 1995) was used as a test of manual dexterity. It consists of a tapping key with a device for recording the number of taps. Five 10 seconds trials were made on the dominant hand and the score was the average number of taps. The FTT was applied in st udy I. FTT is a measure of motor speed. The Geriatric Depression Rating Scale (GDS) (Yesavage et al. 1983) was used to assess depressive symptoms. This scale includes thirty questions concerning different aspects of mood and activity. The answers are rated as true or false. The sum score of those answers indicating symptoms or fe elings of depression was used. GDS was applied in the study II.

An interview includin g questions about n eed for help in daily activities and mood was asked from the participants. Level of depression was gr aded as nonexistent, occasionally appearing and harmful to a such extent that it affects daily living.

4.2.2 Event-related potentials

Habituation of auditory N100 was ev aluated by delivering 50 trains of tones to the right ear at 60 dB above the hearing level. Each train consisted of four identical tones (800 Hz, duration 85ms) with an interstimulus interval of 1 s. The intertrain interval, i.e., the time from the offset of t he last tone in a train to the onset of the fi rst tone in the following train was 12 s econds. Auditory P3 and mismatch negativity (MMN) were measured in separate sessions using an auditory oddball paradigm with 85 % of standard (800 Hz, duration 85 ms) and 15 % of target (560 Hz, duration 85 ms) tones delivered randomly with an interstimulus in terval of 1 s to the right ear at 60 dB above the hearing level. The total number of stimuli was 600. During the sessions for habituation and MMN, the subject was instructed not to pay attention to the tones but instead to rea d a sel f-selected text. During the sessions for auditory P3, the subjects were asked to respond to each target stimulus by pr essing a button. The ERPs were recorded using Ag/AgCl electrodes placed on the scalp according to the International

10-20 System. Both vertical and horizontal eye movements were monitored. All electrodes were referred to the right mastoid. EEG and eye movement signals were filtered with a bandpass of 0.5 - 100 Hz, and digitized continuously at 256 Hz. The continuous data were transformed off-line to epochs of -100 to 900 ms relative to the onset of each stimulus. Epochs containing eye movement artefacts were rejected using both automatic and manual checking of data. The epoched data were averaged and filtered digitally with a low pass cut-off frequency at 20 Hz (3 dB point of 24 dB/octave roll-off). ERP amplitudes were measured relative to the 100 -ms pre-stimulus baseline except for auditory N100 which was measured from the preceding positive deflection at about 50 ms. MMN was measured as the mean amplitude of the deviant-standard difference curve over the 100 - 270 ms range (Pekkonen et al 1994). The neurophysiologist was not aware of the subject's clinical data or diagnosis.

4.2.3 Laboratory examinations

All subjects, except those receiving insulin, underwent an oral glucose tolerance test with a 75 gram glucose load (as 10 % solution). Venous blood samples for determination of plasma glucose and insulin levels were taken between 7.30 and 9.30 am after 12 hour fast, and 1 and 2 hours after the glucose load. Glucose levels were determined from samples by the glucose oxidase method (Glucose Auto & Stat HGA 1120 Analyser, Daichii Kyoto, Japan), and insulin levels by radioimmuno assay (Phasedeph Insulin RIA 100, Pharmacia, Uppsala, Sweden). Diabetic patients who were receiving insulin had C-peptide level measured at fasting and 6 minutes after intravenous glucagon administration. Glycated haemoglobin A1C was determined by a commercial liquid -chromatographic assay (Fast Protein Liquid Chromatography, Pharmacia Sweden). Commercial enzymatic methods were used in the determination of cholesterol and triglyceride levels. All the aforementioned laboratory methods, anthropometric measurements, blood pressure measurement, and diagnosis of stroke as well as diagnosis of cardiovascular disease have been described previously by Kuusisto (1996).

4.2.4 Diagnosis of dementia

Dementia diagnosis was based on three phase programme. Phase one involved a screening battery of five neuropsychological tests aimed at identifying subjects with dementia in all the study subjects (n = 980). The dementia screening battery included the five neuropsychological tests described above: MMSE, VRT, BSR, TM, VF. At phase two, subjects scoring at least 1 SD below the mean in the MMSE adjusted for education or below the cut off point score (£1 SD below the mean score in normal healthy elderly subjects of similar age), or both, in three of four other screening tests, were selected for an extensive neuropsychological and neurological examination to confirm the likelihood of dementia (n = 232). The detailed neuropsychological test battery included 12 tests, and this test battery have been described previously (Kuusisto 1994, Koivisto 1995b). The diagnosis of dementia was based on the criteria of DSM -III-R (American Psychiatric Association 1987). At phase three, all subjects with possible dementia (n = 66) were admitted to the Department of Neurology for further examinations. The final diagnosis and classification of dementia was set by the board of two neuropsychologists and two neurologists. All the subjects in whom the diagnosis was confirmed, underwent computed tomography. The classification of dementia was as follows: probable or possible Alzheimer's disease, vascular dementia, secondary dementia including other causes of dementia. The diagnosis of Alzheimer's disease was based on the criteria of NINCDS-ADRDA (McKhann et al. 1984) and the diagnosis of multi-infarct dementia on DSM-III-R criteria (American Psychiatric Association 1987).

4.2.5 Statistical analysis

The data were analysed by using the SPSS-PC software. The results for continuous variables are given as a mean ± SD, and the level of statistical significance was set at $p < 0.05$. Student's two-tailed t- test for independent samples, one-way analysis of variance and c2 test were used in the comparison of clinical and background data between the groups, when appropriate. The Mann -Whitney U-test was used in

comparing neuropsychological test scores and ERPs between NIDDM and control subjects (study I). Cognitive function between study groups was compared with analysis of covariance using education and age (studies III and V) and sex (study II) as covariates, and Student's t-test with the Bonferroni correction as a post hoc analysis (study II). Multiple stepwise linear regression analysis was applied to investigate the association between risk factors for impaired cognitive function and the MMSE score (study III) and the BSR-T score (study V). In study IV, Students two-tailed t-test for independent samples or the c2 test were used in the assessment of differences between the groups when appropriate. Univariate and multiple logistic regression analyses based on the maximum likelihood method were used to investigate the association of cardiovascular risk factors with the prevalence of Alzheimer's disease (study IV). Odds ratios (95 % confidence intervals) were calculated by logistic regression analysis (study IV). Pearson's two-tailed correlation coefficients were used in studying the association of glucose and insulin levels with cognitive function (study V).

Approval of the Ethics Committee

This study was approved by the Ethics Committee of the Kuopio University Hospital and all subjects provided an informed consent.

5. Results

5.1 Auditory event related potentials and cognitive function in patients with NIDDM

Auditory event-related potentials (ERPs) and cognitive function were compared in a small pilot study. The measures of automatic cerebral stimulus processing, habituation of auditory N100 and mismatch negativity were impaired in patients with NIDDM. No differences were found between the NIDDM and control groups in the N2b and P300 components, which presumably reflect conscious cognitive analysis of the stimuli. A trend towards impaired performance was found in the Digit Span backwards, but the NIDDM and control groups did not differ in tests of secondary or long-term memory.

5.2 Cognitive function in normoglycemic subjects with increased risk for NIDDM

The group with increased risk for NIDDM had impaired performance on the BSR-T, BSR-L, BSR-D, VRT-I, ST-C, DSY and VF-C compared with the low risk group ($p < 0.05$; Table 5). The NIDDM group showed impaired performance on the BSR-T, VRT-I, ST-C and DSY compared with the low risk group ($p < 0.05$) whereas no differences were found between the increased risk group and NIDDM group. Figure 1 shows the MMSE score in the risk groups and in patients with NIDDM.

Table 5. Cognitive function in the risk groups and in non-insulin-dependent diabetes patients (NIDDM).

	Low risk	Increased risk	NIDDM	p-value
MMSE	27.6 ± 1.9	25.7 ± 2.3	26.1 ± 2.6	0.07
BSR-T	41.8 ± 4.8	35.9 ± 6.6 **	37.7 ± 8.2 *	0.04
BSR-L	34.6 ± 7.3	26.2 ± 9.4 **	29.4 ± 11.8	0.03
BSR-D	6.7 ± 1.8	4.9 ± 2.0 **	6.0 ± 2.3	0.03
VRT-I	12.1 ± 3.0	9.0 ± 3.4 **	9.7 ± 2.5 **	0.01
VRT-D	9.5 ± 3.1	6.8 ± 4.2	7.2 ± 3.4	0.09
DS-F	6.3 ± 1.8	5.0 ± 1.5	5.6 ± 1.5	0.07
DS-B	6.0 ± 1.7	5.3 ± 1.8	5.3 ± 1.8	0.73
ST-C	31.4 ± 5.7	36.4 ± 8.6 *	40.7 ± 8.8***	0.01
ST-W	67.9 ± 18.7	87.6 ± 40.3	89.9 ± 32.6	0.13
DSY	41.1 ± 8.3	29.2 ± 8.5***	29.9 ± 10.3***	0.00
BD	29.7 ± 7.1	25.1 ± 7.1	24.7 ± 8.9	0.32
VF-C	23.2 ± 6.0	17.7 ± 4.5 **	19.9 ± 5.6	0.02

Values are means ± SD. Analysis of covariance, age, education and sex as covariates. Students t-test with Bonferroni correction in post-hoc analysis.

Differs from the low-risk group; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. No significant differences across the increased risk and NIDDM groups were found. MMS, Mini-Mental Status Examination; BSR, Buschke Selective Reminding Test; T, total score; L, long-term memory score; D, delayed memory score; VRT, Visual Retention Test; I, immediate memory; DS; Digit Span Test; F, forward; B, backward; ST, Stroop Test; C, colour dots; W, colour words; DSY, WAIS Digit Symbol Test; BD, WAIS Block Design; VF-C, Category Fluency

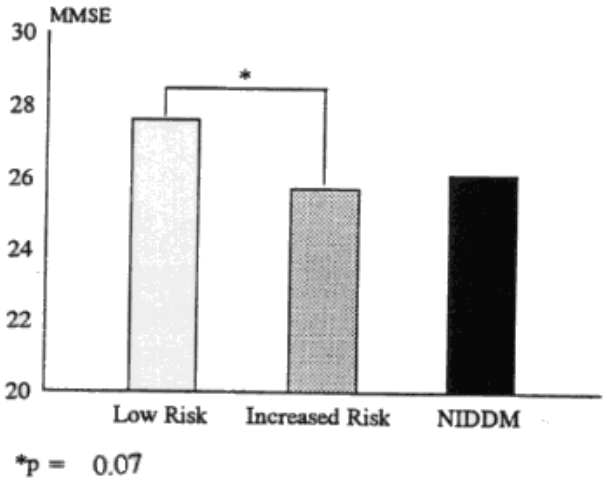

Figure 1 . The MMSE s core i n s ubjects at different ri sk lev els fo r n on-insulin-dependent diabetes (NIDDM) and in patients with NIDDM.

5.3. Cognitive function in subjects with persistent IGT

The subjects with persistent IGT were impaired compared to normoglycemic subjects in the MMSE (ANCOVA; $p < 0.02$) (26.6 ± 2.3 vs. 25.9 ± 3.0) and in the BSR-L ($p < 0.03$) (23.5 ± 11.8 vs. 22.1± 12.6), but not in the BSR-T, VR T-I, VRT-D, VRT-C,

TM-A, TM-C, VF-L or VF-C. When men and women were studied separately, only men with IGT were statistically significantly impaired in the MMSE ($p < 0.03$); however, a trend towards poorer cognitive function was also found in female subjects with IGT. The proportions of men belonging to the lowest tenth both in the MMSE and in the BSR-T were 14 % in IGT and 4 % in NGT group ($p < 0.05$), the respective proportions in women being 4 % in IGT and 3 % in NGT group (p = NS). In a multiple stepwise linear regression analyses, the association of age, education, sex, presence of hypertension, 2-hour glucose and 2-hour insulin levels with the MMSE score was investigated in subjects with IGT and NGT. In subjects with IGT, age, education and 2-hour insulin levels were significantly associated with the lower MMSE score, whereas in subjects with NGT, the insulin level was not associated with the MMSE. Figure 2 shows the MMSE score in subjects with persistent normoglycemia and IGT.

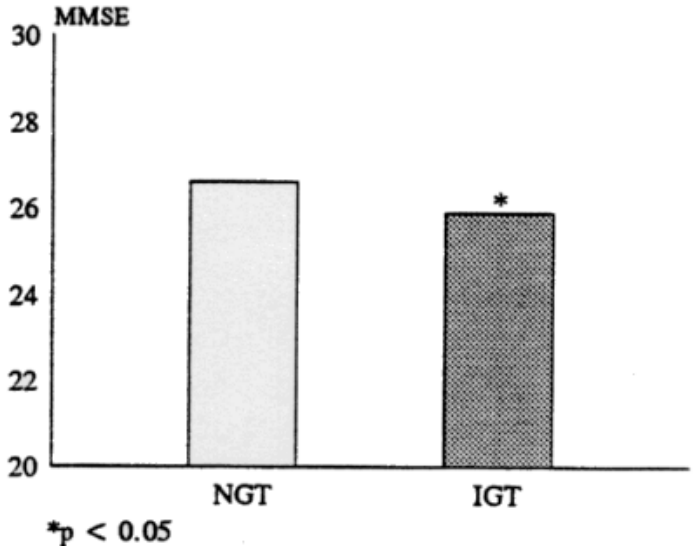

Figure 2. The MMSE score in subjects with persistent normoglycemia and IGT.

Table 6. Cognitive function in subjects with persistent normal- (NGT) and impaired glucose tolerance (IGT).

	All		Men		Women		p-value	
	NGT	IGT	NGT	IGT	NGT	IGT	All*	Men†
Mini-Mental State Examination	26.6 ± 2.3	25.9 ± 3.0	26.6 ± 2.3	24.9 ± 3.5	26.5 ± 2.3	26.4 ± 2.5	0.012	0.003
Buschke Selective Reminding Test								
total score	32.2 ± 8.4	30.8 ± 9.3	30.6 ± 8.0	28.0 ± 8.6	33.1 ± 8.4	32.3 ± 9.4	NS	NS
long-term memory	23.5 ± 11.8	22.1 ± 12.6	21.5 ± 11.5	16.9 ± 12.8	25.0 ± 11.8	23.1 ± 13.7	0.026	NS
Visual Reproduction Test								
immediate memory	8.9 ± 3.1	8.6 ± 3.3	9.3 ± 3.3	8.0 ± 3.1	8.7 ± 3.0	8.9 ± 3.4	NS	NS
delayed memory	6.0 ± 3.6	5.9 ± 4.2	6.2 ± 3.8	4.8 ± 4.2	5.8 ± 3.4	6.4 ± 4.1	NS	NS
copying	15.5 ± 2.0	15.2 ± 2.1	15.5 ± 2.2	14.7 ± 2.5	15.5 ± 1.8	15.4 ± 1.8	NS	NS
Trail-Making Test A (seconds)	71.0 ± 31.1	74.5 ± 31.1	70.7 ± 33.3	81.0 ± 31.0	71.0 ± 29.8	71.0 ± 30.8	NS	NS
Trail-Making Test C (seconds)	176.1 ± 81.3	180.7 ± 75.9	178.2 ± 82.8	187.6 ± 74.6	174.9 ± 82.8	177.3 ±77.0	NS	NS
Verbal Fluency Test on letters	33.7 ± 12.2	32.5 ± 14.1	33.9 ± 12.9	28.6 ± 11.3	33.7 ± 11.8	34.5 ± 15.1	NS	NS
Verbal Fluency Test on category	17.4 ± 5.3	16.6 ± 5.2	17.2 ± 5.7	16.0 ± 4.6	17.6 ± 5.0	16.9 ± 5.5	NS	NS

Values are means ± SD. The results were adjusted for *age, gender, education/ †age and education by the analysis of covariance.

5.4 Association between features of insulin resistance syndrome and Alzheimer's disease

46 subjects (4.7 % of the study population) were diagnosed as having Alzheimer's disease, and 38 of them were newly diagnosed (diagnosed in this study). Table 4

shows the levels of cardiovascular risk factors in subjects with and without Alzheimer's disease. Only 28 % (13/46) of the subjects with Alzheimer's disease had normal glucose tolerance. The risk of Alzheimer's disease was investigated in subjects with and without the Apo E e4 allele. Since fasting insulin level is a good marker for insulin resistance in nondiabetic subjects, but not in those with diabetes, this association was investigated in nondiabetic subjects. Hyperinsulinemia was defined as the highest fasting insulin quintile (> 89.4 pmol/l) in this subgroup. In subjects without the Apo E e4 allele (n = 532) hyperinsulinemia was associated with an increased risk for Alzheimer's disease; prevalence of Alzheimer's disease in hyperinsulinemic vs. normoinsulinemic, 7.5 % vs 1. %. In subjects with the Apo E e4 allele (n = 228), hyperinsulinemia did not have any effect on the risk for Alzheimer's disease; the prevalence in hyperinsulinemic subjects was 7.0 % and in normoinsulinemic subjects 7.1 %. Figure 3 shows the prevalence of Alzheimer's disease in nondiabetic subjects with and without ApoE e4 allele, and figure 4 the prevalence of Alzheimer's disease in subjects with normoglycemia, IGT and NIDDM.

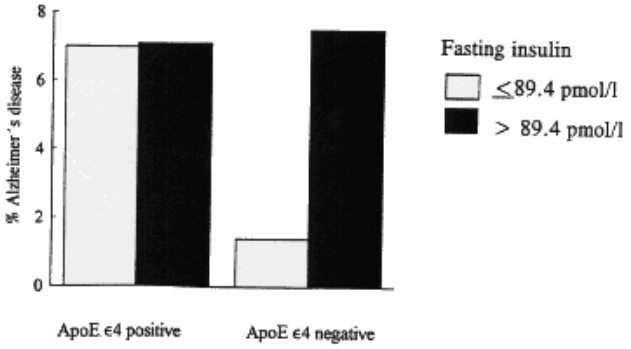

Figure 3. The prevalence of Alzheimer´s disease by hyperinsulinemia and ApoE e4 status.

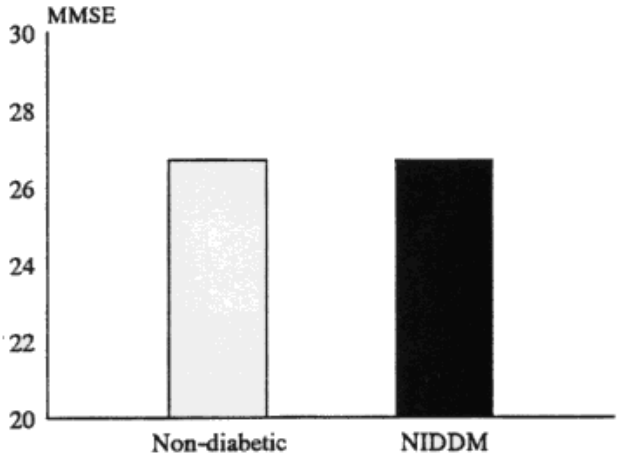

Figure 4. The prevalence of Alzheimer's disease in subjects with NGT, IGT and NIDDM

5.5 NIDDM and cognitive function in a nondemented population

Patients with NIDDM showed impaired performance in the TM-A and TM-C in the nondemented population. When the results were analysed by sex, women with NIDDM scored better than nondiabetic subjects in the MMSE, whereas diabetic men performed equally well compared with the nondiabetic men. A multiple stepwise linear regression analysis revealed that fasting insulin level was associated inversely with the BSR-T score, but fasting glucose level showed no such association. Figure 5 shows the MMSE score in control subjects and in patients with NIDDM.

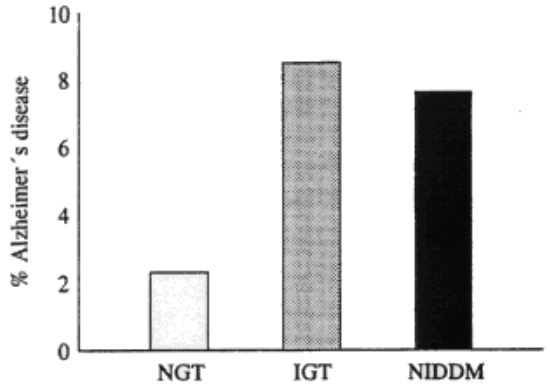

Figure 5. The MMSE score in control subjects and in patients with NIDDM in a nondemented population.

6. Discussion

Methodological considerations

This doctoral thesis is based on three separate patient populations. In study I only a small number of subjects were examined, and also in study II the selection of subjects may have affected the results. In contrast, studies III -V were based on a large population-based sample with relatively high participation rate (980/1192, 82 %). Therefore, the results obtained in studies III - V may be considered reliable, with respect to representativeness of the population. According to previous findings, subjects with diabetes and cognitive dysfunction may have a lower participation rate in epidemiological studies (Launer et al. 1994), this have been detected also in patients with stroke (Hoeymans et al. 1998). If this were the case also in the present study, the actual impairment in cognitive functions would be more prominent in subjects with NIDDM than reported here. Koivisto (1995a) presented background information of the nonparticipants in the dementia screening study. The prevalence of previously diagnosed diabetes was 16 % in the nonparticipants, but determination of glucose tolerance was done for only a minority of those who did not participate in dementia screening. Therefore, the true proportion of subjects with NIDDM among the nonparticipants was probably higher than 16 %. Due to higher morbidity and especially elevated frequency of stroke (participants vs. non participants; 4 % vs 22 %), cognitive function was most likely worse in the nonparticipants. It is a well known fact that stroke can often affect cognitive functions. However, direct information about cognitive abilities in the nonparticipants was not available.

The World Health Organization criteria (1985) for definition of glucose intolerance were used in this study. A standardized program in the determination of glucose tolerance provides a sound basis for definition of normality and abnormality. However, determination of optimal cut points for diabetes depends on how diabetes itself is defined (Engelgau 1997). Some epidemiological studies examining cognitive function in the elderly have applied more vague methods in their definition of diabetes, for example random glucose values (Ott et al 1996, Stolk et al. 1997). Furthermore, insulin secretion capacity was examined in insulin treated subjects to exclude those individuals with insulin dependent diabetes from the dementia screening study. The World Health Organization criteria (1985) for diabetes offers

the possibility to form an intermediate category between normal and diabetic glucose tolerance. Although this intermediate category, IGT, is a heterogenous group, it has an elevated risk for NIDDM, and may therefore be of significance in diabetes studies (Stern 1985, Yudkin 1990). The study design in the cardiovascular risk factor study (Mykkänen 1993, Kuusisto 1996) enabled to us to investigate cognitive function in subjects who maintained their impaired glucose tolerance category, which has not been done earlier. There are few large population based studies investigating cognitive function or Alzheimer's disease in subjects with well defined glucose tolerance categories.

There are no established criteria for hyperinsulinemia. Therefore, the highest fasting quintile was applied to represent subjects with hyperinsulinemia. However, clearly lower insulin levels (> 9.2mU/l; equals to > 55.2 pmol/l) have been used as being indicative of hyperinsulinemia (Feskens et al. 1995). Serum insulin levels are determined by both insulin resistance and insulin secretion. In patients with NIDDM, defects both in insulin secretion and insulin action are present, and postload insulin values reflect mainly impaired insulin secretion (Laakso 1993b). This means that postload insulin values do measure partly different factors in nondiabetic and in diabetic subjects. In order to improve comparability across the glucose tolerance categories, fasting insulin level should be preferred over postload values.

The neuropsychological test battery applied in the dementia screening study may be criticized. Firstly, the dementia screening battery included only five neuropsychological tests, and therefore not all aspects of cognitive function were evaluated. Secondly, lack of a test of delayed verbal memory may be considered a shortcoming, because according to some previous studies, verbal memory was frequently affected in patients with NIDDM (Strachan et al. 1997 a). Thirdly, it was not possible take into account the premorbid intellectual level when using these tests. Cognitive domains evaluated by this brief dementia screening battery were immediate visual (VRT-I) and verbal memory (BSR), delayed visual memory (VRT-D), frontal lobe/executive functions (TM, VF) and overall cognitive level assessed by the MMSE. These domains may be considered important with respect to dementia. Although the MMSE is an aggregate score with poor reliability, and it does not measure any specific cognitive domain, it has the advantage of being one of the most widely applied measures of cognitive function in the elderly. The MMSE permits one to do comparisons across different studies, which is practically impossible with any other of the dementia screening tests applied in this study. Age, educational level and sex should be taken into account when using this battery (Koivisto et al. 1992). The need for a standard neuropsychological test battery in cognitive evaluation in diabetes has been expressed recently (Strachan et al. 1997b).

Event related potentials in NIDDM (Study I)

Study I showed that elderly nondemented patients with NIDDM may have defects in cerebral automatic stimulus processing. Habituation of auditory N100 and mismatch negativity were impaired in patients, while no differences were seen the N2b and P3 components, which presumably reflect more conscious analysis of the stimuli. Since attended ERPs did not differ between the groups, the aforementioned impairment can be compensated by a conscious effort. In contrast, no significant memory dysfunction or impaired attention was detected in neuropsychological testing. The observation that abnormal electrophysiological findings are present in NIDDM agrees with previous studies (Mooradian et al. 1988, Pozzessere et al. 1988). In contrast to this study, however, prolonged P3 latencies have been reported in patients with NIDDM, but in younger subjects than those in the present study (Takeda et al. 1992, Kurita et al. 1996, Dey et al. 1997), and this could possibly explain the observed discrepancy. Ageing per se may affect P3 latencies, resulting in diminished differences between control subjects and NIDDM patients. Minor electrophysiological changes may be found in patients with NIDDM, although interpretation of the results should be made cautiously due to the small sample size.

Cognitive function in normoglycemic subjects with risk for NIDDM (Study II)

The main finding in study II was that normoglycemic subjects having increased risk for NIDDM had poor cognitive function compared with those having lower risk. Furthermore, the group with increased risk did not differ from patients with NIDDM in any cognitive function. The risk level for diabetes was defined by postload 2-hour insulin and glucose levels being simultaneously higher than the median in the normoglycemic subjects. There is evidence that these measures indeed are elevated before overt diabetes manifests itself (Hara et al. 1996). Already one to two decades before NIDDM is diagnosed, a reduced glucose clearance, hyperinsulinemia (Warram et al. 1990) and insulin sensitivity (Martin et al. 1992) have been found in normoglycemic subjects. Therefore, it is probable that subjects in the increased risk group were more likely to develop diabetes than those in the low risk group. We detected rather widely affected cognition, including indices of poor immediate and delayed memory, attention, visuomotor speed and verbal fluency in the increased risk group. To our knowledge, cognitive function has not been studied previously in normoglycemic subjects at different risk levels for NIDDM, therefore direct comparisons are not possible. The demarcation line between the risk groups was set using 2-hour postload glucose and insulin levels, however, the groups were different also in the fasting values and body mass index, all features of the insulin resistance syndrome.

Cognitive function in persistent IGT (Study III)

Study III included subjects with persistent normoglycemia and IGT. Due to the heterogenous nature of the IGT (Stern et al. 1985, Yudkin et al. 1990, O'Rahilly et al. 1994), it was necessary to elucidate cognitive function in subjects who maintained their impaired glucose tolerance category. Forty percent of subjects had persistent IGT during the follow-up period of 3.5 years, which fits well with previously reported figures. The proportion of persistent IGT according to the World Health Organization criteria (1985) has been reported to vary between 23% to 36 % in different populations with average follow-up times varying from six to seven years (Sasaki et al. 1982, King et al. 1984, Schranz 1989). Compared with the normoglycemic subjects, those with persistent IGT had elevated levels of glucose, insulin, total cholesterol, higher BMI, lower HDL-cholesterol and higher blood pressures. Subjects with persistent IGT were impaired in the MMSE and the BSR-L, these differences being greater in men than in women. Kalmijn et al. (1995) detected an elevated rate of erroneous answers (elevation 18 %) in the MMSE in the elderly men with IGT compared with the normoglycemic subjects. Our results are in accordance with those of Kalmijn et al. (1995), showing minor impairment. However, these studies do not represent similar IGT categories, because only a minority of the subjects in the aforementioned study had persistent IGT. In a subgroup analysis, we detected that the proportion of men belonging into the lowest tenth both in the MMSE and the BSR-T (scores in both tests £ 22) was elevated in men, but not in women with persistent IGT. This suggests elevated risk for dementia in men; which could be potentially related to cerebrovascular disease, because men have a higher risk for vascular dementia (Meyer et al. 1989). On the other hand, vascular factors may have a role in late onset Alzheimer's disease, which is often accompanied with white matter lesions (Blennow et al. 1991, Brun et al. 1986). Therefore, a subgroup of men with persistent IGT may have had mild dementia, although the average magnitude of the impairment was rather small.

Features of insulin resistance syndrome and Alzheimer's disease (Study IV)

The main result in study IV was that hyperinsulinemia and other features of insulin resistance syndrome were associated with Alzheimer's disease. These included the presence of glucose intolerance, high systolic blood pressure, low total cholesterol concentration, high fasting and 2-hour glucose and insulin values. The reason why an association between insulin resistance and Alzheimer's disease has not been found in previous studies is probably subject selection. Advanced Alzheimer's disease is a catabolic state with low blood pressure, glucose and total cholesterol levels (Landin et al. 1993), and this can interfere with insulin levels. Patients with early and late Alzheimer's disease have different insulin concentrations, those in the early stage of the disease have higher levels (Craft et al. 1993). Patients with NIDDM have elevated

prevalence of dementia, showing that hyperglycemia might increase the risk for Alzheimer's disease. Advanced glycation end products, which accumulate in tissues as a function of glucose level and time (Brownlee 1995), have been found in amyloid plaques of Alzheimer's patients (Vitek et al. 1994), suggesting a link between hyperglycemia and Alzheimer's disease. Accelerated atherosclerosis in subjects with insulin resistance syndrome (Hofman et al. 1997, Laakso et al. 1991b) may be responsible for the relationship between insulin resistance syndrome and Alzheimer's disease.

We detected an increased prevalence of Alzheimer's disease in hyperinsulinemic subjects, who were non diabetic and not carrying the Apo e4 allele, but not in those with an Apo E e4 allele. Craft et al. (1998) reported cerebrospinal and plasma insulin levels in Alzheimer's disease of varying severity and Apo E genotypes. Alzheimer patients had higher plasma insulin levels, lower cerebrospinal insulin levels, and a reduced cerebrospinal to plasma insulin ratio than healthy control subjects. These differences were greater in subjects with more advanced dementia. Interestingly, patients who were not ApoE e4 homozygotes had higher plasma insulin levels and reduced cerebrospinal to plasma insulin ratios, whereas ApoE e4 homozygotic Alzheimer patients had normal values (Craft et al. 1998). This finding is in accordance with our results and supports the notion that there are metabolic differences among different Apo E genotypes in patients with Alzheimer's disease.

Cognitive function in a nondemented population with NIDDM (Study V)

In the nondemented population the association between NIDDM and cognitive function was equivocal. When the results were analysed by sex, no differences were found between diabetic and nondiabetic men, whereas in women inconsistent findings were observed. Impaired performing in the TM was found, but in the MMSE, diabetic women performed better than control subjects. Slow performing in the TM could reflect sluggish mental processing, which has been associated with white matter changes in healthy elderly persons (Ylikoski et al. 1993). Since the MMSE is an aggregate score without any time limits, it is less sensitive in detecting slowing in cognitive function. Therefore it is possible that cognitive slowing may be present in nondemented women with NIDDM, but this can remain undetected if the MMSE only is applied.

In summary, depending on the control group, impaired cognitive function was found in subjects with NIDDM, IGT and in subjects with normoglycemia having elevated risk for diabetes. Elevated risk for NIDDM in normoglycemia and in IGT was associated with poorer cognitive function compared with those subjects having lower risk. These findings suggest that not only hyperglycemia appearing as NIDDM, but also hyperinsulinemia as a potential prediabetic phase of NIDDM, is associated with impaired cognitive function in the elderly. This is in accordance with previous studies (Kuusisto et al. 1993, Kalmijn et al. 1995, Stolk et al. 1997). There was a very strong association between glucose intolerance and Alzheimer's disease in the elderly population aged 69 - 78 years, only 28 % of the Alzheimer patients having normal glucose tolerance. A recent study failed to detect increased Alzheimer-type brain pathology in patients with diabetes in a retrospective postmortem study (Heitner et al. 1997). However, the role of previous hyperinsulinemia was not taken into account, and the control group included nondiabetic subjects, i.e. also those with IGT, which was strongly associated with Alzheimer's disease in this study. Hyperinsulinemia and features of insulin resistance syndrome were associated with Alzheimer's disease in subjects who did not have the ApoE e4 allele, but not in those carrying the e4 allele. Although NIDDM per se did not affect memory independently of dementia, it may be associated with mental sluggishness. Since hyperinsulinemia and IGT are closely related to NIDDM, they should be always taken into account when studying brain function in NIDDM.

7. Conclusions

1. Auditory ev ent related potentials show affected cerebral stimulus processing in patients with NIDDM. This was observed only in the auditory N100 and mismatch negativity, but not in later potentials, wh ich are more likely to reflect conscious cognitive processing. Although performing in neuropsychological tests would appear to be normal, disturbed cerebral stimulus processing may be foun d in NIDDM. However, this abnormality is unlikely to affect functional capacity or daily living.

2. A risk for NIDDM in the normoglycemic elderly subj ects was a ssociated with cognitive dysfunction. This study shows that changes in glucose and insulin metabolism, which have been detec ted in subjects who ca rry an e levated ri sk for future d iabetes, are associated with c ognitive impair ment. C hanges observed in glucose and insulin metabolism in the normoglycemic subjects may belong to a larger entity, i.e. insu lin resistance s yndrome. When studying cognitive or other aspects of brain function in NIDDM, the effect of prediabetic phases need to be taken into account, and therefore prospective st udy designs would be valuable in new studies.

3. Persistent impair ed gl ucose tolerance was a ssociated wit h m ildly a ffected cognitive function. Due to the heterogene ous nature of IGT, it was not known if persistent IGT wo uld affect co gnitive f unction. A subgroup of men with persistent IGT may have elevated risk for dementia , although on average, persistent IGT was only mildly associated with cognitive func tion. This suggests that persistent IGT alone does not account for the obser ved impairment, but a dementing disease associated with high insulin levels would be more probable explanation.

4. Hyperinsulinemia and features of insulin resistance syndrome were associated with Alzheimer's disease. In the nondiabetic population, this was found in subjects without the Apo E e4 allele, but n ot in those with this allele. Therefore, hyperinsulinemia and features of insulin resistance syndrome ma y represent a risk factor for sporadic Alzheimer’s disease, but not in those with a strong genetic risk factor. Treatment of hyperinsulinemia in su bjects without the ApoE e4 allele might improve cognitive function in Alzheimer’s disease.

5. An associatio n between hyperinsulinem ia and cognitive dysfunction indep endent of NIDDM was found in normoglycemic s ubjects at increased risk for NI DDM (study II) and in subjects with persistent IGT (study III). Hyperinsulinemia was associated with Alzheimer’s disease in th e nondiab etic population without the ApoE e4 allele (study IV). These results show that hyperinsulin emia is associated with cognitive d ysfunction in subjects wit hout diabetes. Factors, which normalize hyperinsulinemia may have positive effects on cognitive function in the elderly.

6. In the nondemented population the asso ciation between cognitive function and NIDDM was equivocal. Reduced speed of mental processing ma y appear in the frontal lobe/executive functions (study V) and minor changes using neurophysiological methods (study I) ca n be detected in nondemented NIDDM patients. A subject with NIDDM, who does not have not overt dementia as diagnosed by the DSM-I II-R criteria, may have mental sluggishness, but this is unlikely to affect daily living.

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