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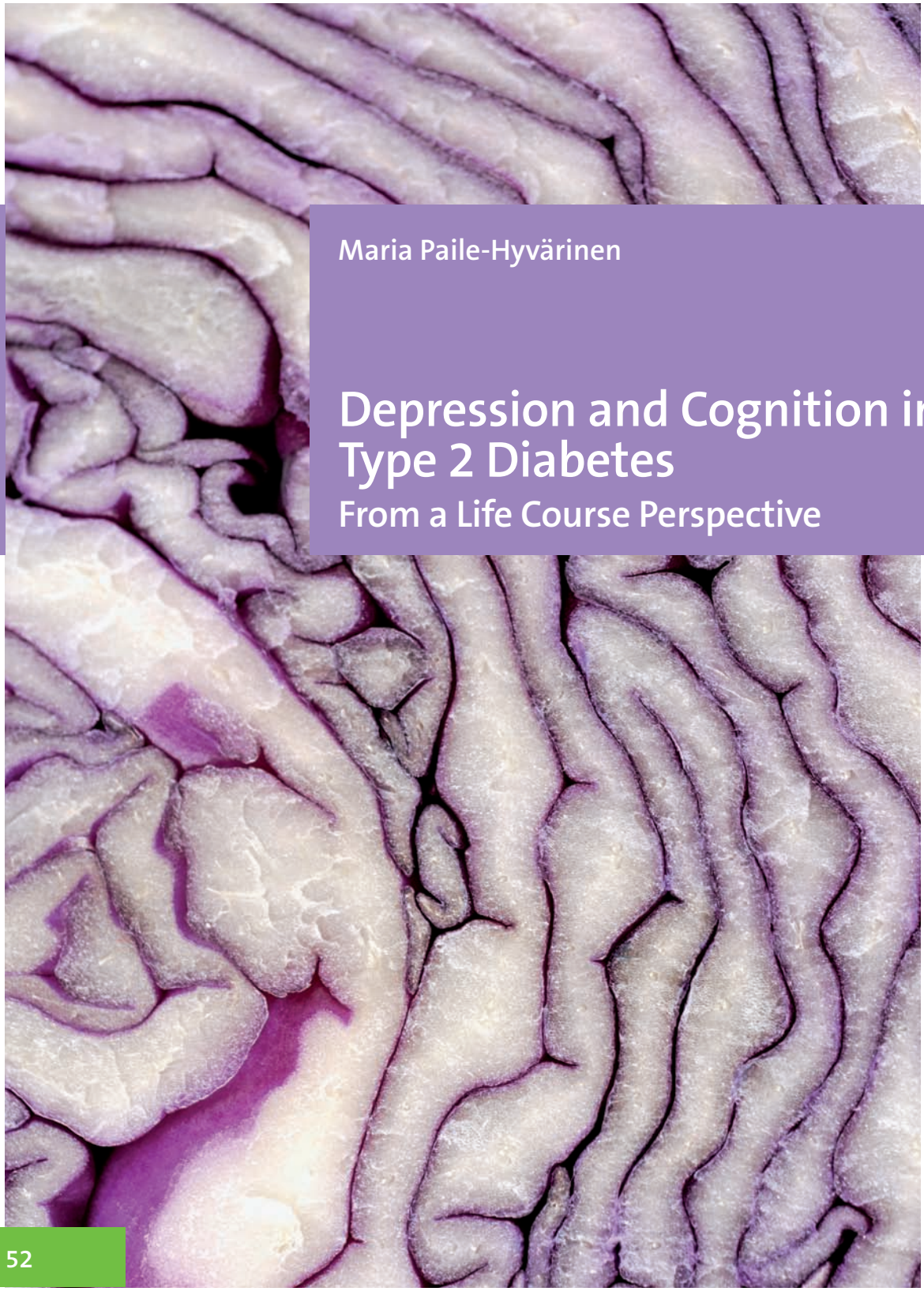

RESEARCH

Maria Paile-Hyvärinen

Depression and Cognition in Type 2 Diabetes

From a Life Course Perspective

Maria Paile-Hyvärinen

Depression and Cognition in Type 2 Diabetes

From a Life Course Perspective

Academic dissertation

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Department of Chronic Disease Prevention,
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To my Father

"How sad and bad and mad it was,
but then, how it was sweet!"
—Browning (1864)

Abstract

Maria Paile-Hyvärinen. Depression and Cognition in Type 2 Diabetes. From a Life Course Perspective. National Institute for Health and Welfare (THL), Report 52/2011. 118 pages. Helsinki, Finland 2011.
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Background

The aetiology of type 2 diabetes is multifactorial; both genetic and environmental factors interact in complex manners which are still poorly understood. Furthermore, diabetes is linked to several complications which add to both physical and mental distress.

Depression is a common co-morbidity of diabetes which can occur both as a cause and a consequence of type 2 diabetes. Depression has been shown to correlate with glucose regulation and treating depression might prove beneficial for glucose regulation as well as for mental well being.

Another complication which might affect diabetes management is cognitive decline. Type 2 diabetes is associated with a ~1.5 fold risk of cognitive decline but it is not known which subjects with diabetes eventually develop cognitive impairment and which ones are likely to be spared. Several other risk factors and complications of diabetes might modify the risk for developing cognitive impairment.

Type 2 diabetes, depression and impaired cognitive performance have all been linked to low birth weight. In addition, birth size has been found to modify the effect of some previously known risk factors on diabetes. This thesis aimed to explore the effects and interactions of birth weight, depression and cognitive ability in relation to type 2 diabetes from a life course perspective.

Subjects and methods

Studies I, II and V were part of the Helsinki Birth Cohort Study. 2003 subjects from the original cohort of 8,760 participated in an extensive clinical examination at an average age of 61 years. A standard 75 g oral glucose tolerance test (OGTT) was performed and depressive symptoms were assessed using the Beck Depression Inventory (BDI). BDI scores of 10 or more were regarded as mild to moderate depressive symptoms. In addition data was obtained from child welfare clinics and national registers. A subset of the cohort (n = 1247) also performed a test on cognitive performance (CogState®) at the average age of 64. Furthermore 642 of the men had completed a test on intellectual ability during their compulsory military service at the average age of 20 years.

Studies III and IV were randomised clinical trials where mildly depressed diabetic subjects were treated with paroxetine or placebo and the effect on

metabolic parameters and quality of life was assessed. The first trial included 14 women and lasted 10 weeks, while the second trial included 43 subjects, both men and women, and lasted 6 months.

Results

Type 2 diabetes was positively associated with the occurrence of depressive symptoms. Among diabetic subjects 23.6% had depressive symptoms, compared to 16.7% of subjects with normal glucose tolerance (OR = 1.77, 95% CI = 1.30 to 2.43, $p<0.001$). Formal mediation analysis revealed that cardiovascular disease (CVD) is likely to act as a mediator in the association between type 2 diabetes and depressive symptoms (Sobel's test statistic = 4.00. $p<0.001$). Furthermore, low birth weight was found to modify the association between type 2 diabetes, CVD and depression. The association between BDI score and having type 2 diabetes or CVD was twice as strong in the subgroup with low birth weight (≤ 2,500g) compared with the group with birth weight > 2,500g (p for interaction 0.058).

In the six months long randomised clinical trial (study IV) the antidepressive agent paroxetine had a transient beneficial effect on glycosylated haemoglobin A_{1c} ($GHbA_{1c}$) and quality of life when compared to placebo after three months of treatment.

In study V we found that subjects with known diabetes had a consistently poorer level of cognitive performance than subjects with normal glucose tolerance in most of the tested cognitive domains. This effect was further amplified among those born with a small birth weight (p for interaction 0.002). Intellectual ability in early adulthood was not related to any impairment of glucose tolerance at the age of 61 years (study I).

Conclusions

Type 2 diabetes is associated with a higher occurrence of depressive symptoms compared to subjects with normal glucose tolerance. This association is especially strong among subjects with CVD and those born with a low birth weight. Treating depressed diabetic subjects with paroxetine has no long term effect on glucose regulation.

Physicians should be aware of depression as an important co-morbidity of type 2 diabetes. Further research is needed regarding the optimal treatment in case of co-morbidity. Both depression and the cognitive decline often seen among diabetic subjects are increased if the subject is born with a low birth weight. Physicians should recognise low birth weight as an additional risk factor and modifier of diabetic complications.

Keywords: antidepressant, birth weight, cognitive ability, depression, developmental origins, glucose tolerance, intellectual ability, paroxetine, type 2 diabetes.

Tiivistelmä

Maria Paile-Hyvärinen. Depression and Cognition in Type 2 Diabetes. From a Life Course Perspective [Masennus ja kognitiiviset toiminnot tyypin 2 diabeteksessa elinkaarinäkökulmasta]. National Institute for Health and Welfare (THL), Report 52/2011. 118 pages. Helsinki, Finland 2011.
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Tausta

Tyypin 2 diabeteksen taustatekijät ovat moniulotteisia ja sekä geenit, että ympäristötekijät vaikuttavat yhdessä, toistaiseksi osittain tuntemattomalla tavalla. Diabetes on myös yhteydessä moniin komplikaatioihin, jotka lisäävät niin fyysistä kuin henkistäkin kärsimystä.

Masennus on eräs diabeteksen yleinen liitännäissairaus, joka voi ilmaantua diabeteksen seurauksena, mutta myös olla diabeteksen riskitekijä. Masennuksen ja sokerinsietokyvyn välillä on todettu olevan yhteys ja masennuksen hoitaminen saattaa parantaa psyykkisen hyvinvoinnin lisäksi myös sokeritasapainoa.

Kognitiivinen heikentymä on toinen komplikaatio, joka voi vaikeuttaa diabeteksen hallintaa. Tyypin 2 diabeetikoilla on todettu olevan noin 1,5-kertainen riski heikentyneeseen kognitiiviseen suoriutumiseen, mutta on epäselvää mihin diabeetikoiden alaryhmään tämä vaikutus eniten kohdistuu. Useat diabeteksen riskit ja komplikaatiot saattavat olla mukana muokkaamassa kognitiivisen heikentymän todennäköisyyttä.

Tyypin 2 diabeteksen, masennuksen ja kognitiivisen toiminnan on kaikkien todettu olevan yhteydessä alhaiseen syntymäpainoon. Lisäksi alhainen syntymäpaino on osoittautunut muokkaavaksi lisätekijäksi kun tarkastellaan jo ennestään tunnettuja diabeteksen riskitekijöitä. Tässä väitöskirjassa tullaan tarkastelemaan syntymäpainon, masennuksen, tyypin 2 diabeteksen ja kognitiivisen toiminnan yhteisvaikutuksia elämänkaarinäkökulmasta.

Tutkittavat ja menetelmät

Osatyöt I, II ja V olivat osa Helsingin syntymäkohorttitutkimusta. Alun perin 8 760 henkilöstä koostuvasta kohortista yhteensä 2003 vapaaehtoista osallistui laajaan kliiniseen kartoitukseen keskimäärin 61 vuoden iässä. Heille tehtiin mm. vakioitu 75 g oraalinen sokerirasitustesti ja kartoitettiin masennusoireet Beck Depression Inventory (BDI) kyselyn avulla. Lieviksi tai keskivaikeiksi masennusoireiksi tulkittiin BDI pisteet ≥ 10. Lisäksi tietoja kerättiin syntymätodistuksista, neuvolan ja kouluterveydenhuollon rekistereistä sekä valtakunnallisista terveydenhuollon rekistereistä. 1247 henkilöstä koostuva alaryhmä osallistui kognitiivista toimintaa mittaavaan testiin (CogState®) keskimäärin 64 vuoden iässä. Lisäksi 642

ryhmän miehistä olivat pakollisen asepalveluksensa aikana suorittaneet älyllisen suorituskyvyn mittaavan testin keskimäärin 20 vuoden iässä.

Osatyöt III ja IV olivat kliinisiä lääketutkimuksia, joissa hoidettiin lievästi masentuneita diabeetikoita paroksetiinilla tai plasebolla ja tutkittiin vaikutusta metabolisiin ja elämänlaatuun liittyviin tekijöihin. Ensimmäisessä kokeessa tutkittiin 14 naista 10 viikon ajan. Toiseen kokeeseen osallistui 43 henkilöä, joita seurattiin 6 kuukautta.

Tulokset

Masennusoireita oli 23,6 % diabeetikoista ja 16,7 % henkilöistä, joilla oli normaali sokerinsietokyky (OR = 1.77, 95 % CI = 1.30 to 2.43, $p < 0.001$). Yhteys tyypin 2 diabeteksen ja masennuksen välillä saattoi välittyä sepelvaltimotaudin kautta. Lisäksi havaittiin, että alhainen syntymäpaino muokkaa diabeteksen, sepelvaltimotaudin ja masennuksen yhteyttä. Yhteys BDI pisteiden ja diabeteksen tai sepelvaltimotaudin välillä oli kaksinkertainen niillä, jotka olivat syntyneet pienipainoisina (≤ 2 500 g) verrattuna muihin (interaktion p-arvo = 0.058).

Kolmen kuukauden paroksetiinihoito alensi glykohemoglobiiniia (GHbA1c) ja paransi elämänlaatua paremmin kuin lumelääke. Tämä vaikutus oli kuitenkin ohimenevä (osatyö III).

Viidennessä osatyössä havaittiin, että henkilöillä, joilla oli ennestään tiedossa oleva diabetes, oli usealla kognitiivisella osa-alueella heikompi suorituskyky verrattuna niihin, joilla oli normaali sokerinsietokyky. Tämä yhteys oli voimakkaampi pienipainoisina syntyneillä (interaktion p-arvo = 0.002). Nuorella aikuisiällä testattu älyllinen suoriutuminen ei ollut yhteydessä sokerinsietokykyyn vanhemmalla iällä (osatyö I).

Päätelmät

Tyypin 2 diabetesta sairastavilla on enemmän masennusoireita verrattuna niihin, joilla on normaali sokerinsietokyky. Tämä yhteys on vielä voimakkaampi henkilöillä, joilla on sepelvaltimotauti tai pieni syntymäpaino. Hoidettaessa masentuneita diabeetikoita paroksetiinilla ei saada pitkäaikaista hyötyä sokeritasapainoon.

Lääkäreiden kannattaa pitää mielessä masennuksen ja diabeteksen välinen yhteisesiintyminen. Näiden sairauksien optimaalisesta yhtäaikaisesta hoidosta tarvitaan vielä lisätietoa. Sekä masennus, että diabeetikoilla yleisesti esiintyvä kognitiivinen alenema, ovat yleisempiä pienipainoisina syntyneillä. Pienipainoisuus on yksi tyypin 2 diabeteksen komplikaatioita muokkaava riskitekijä.

Avainsanat: kognitiivinen suoriutuminen, masennus, masennuslääke, paroksetiini, sokerinsietokyky, syntymäpaino, tyypin 2 diabetes, varhainen ohjelmoituminen, älyllinen suorituskyky

Contents

List of Original publications

I Paile-Hyvärinen M, Kajantie E, Räikkönen K, Henriksson M, Leskinen J, Laaksonen I, Forsén T, Eriksson J. (2009). "Intellectual ability in early adulthood and type 2 diabetes in later life." Acta Diabetologica 46(3): 249–252.

II Paile-Hyvärinen M, Räikkönen K, Forsén T, Kajantie E, Ylihärsilä H, Salonen MK, Osmond C, Eriksson J.(2007). "Depression and its association with diabetes, cardiovascular disease, and birth weight." Annals of Medicine 39(8): 634–640.

III Paile-Hyvärinen M, Wahlbeck K, Eriksson J. (2003). "Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: A single-blind randomised placebo controlled trial." BMC Family Practice 4(1): 7.

IV Paile-Hyvärinen M, Wahlbeck K, Eriksson J. (2007). "Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomised placebo controlled 6-month trial." BMC Family Practice 8(1): 34.

V Paile-Hyvärinen M, Räikkönen K, Kajantie E, Darby D, Ylihärsilä H, Salonen MK, Osmond C, Eriksson J (2009). "Impact of glucose metabolism and birth size on cognitive performance in elderly subjects." Diabetes Research and Clinical Practice 83(3): 379–386.

Abbreviations

ADA	American Diabetes Association
AL	Associate Learning
ANCOVA	Analysis of Covariance
APA	American Psychiatric Association
BDI	Beck's Depression Inventory
BMI	Body Mass Index
CES-D	Center for Epidemiological Studies Depression Scale
CHD	Coronary Heart Disease
CI	Confidence Interval
CRT	Choice Reaction Time
CVD	Cardiovascular Disease
C-peptide	Connecting Peptide
CRP	C - reactive protein
CRP	C-Reactive Protein
DA	Divided Attention
DM	Diabetes Mellitus
DOHaD	Developmental Origins of Health and Disease
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
FPG	Fasting Plasma Glucose
GHbA1c	Glycosylated Haemoglobin A_{1c}
HAM-A	Hamilton's Anxiety Scale
HADS	Hospital Anxiety and Depression Scale
HPA-axis	Hypothalamic Pituitary Adrenal-axis
IA	Intellectual Ability
ICD	International Classification of Disease
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IL-6	Interleukin-6
IQ	Intelligence Quotient
MADRS	Montgomery-Åsberg's Depression Rating Scale
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PPAR-γ	Peroxisome Proliferator Activated Receptor – γ
RAND-36	RAND-36 item health survey
SD	Standard Deviation
SES	Socio-economic Status
SF-36	36-Item Short Form Health Survey
SHBG	Sex Hormone Binding Globulin
SRT	Simple Reaction Time
SSRI	Selective Serotonin Re-uptake Inhibitor
T2D	Type 2 Diabetes Mellitus
TNF-α	Tumour Necrosis Factor-α
WHO	World Health Organization
WM	Working Memory

1 Introduction

Type 2 diabetes comprises a vast health care problem which continues to grow in all parts of the world (King and Rewers 1993; Harris, Flegal et al. 1998; Connolly, Unwin et al. 2000; Wild, Roglic et al. 2004; Peltonen, Korpi-Hyövälti et al. 2006). In addition to changes in lifestyle (Ramachandran, Snehalatha et al. 2004), the accelerated ageing of the population in many countries also increases the prevalence and incidence of type 2 diabetes (Harder, Rodekamp et al. 2007). The aetiology of type 2 diabetes is multifactorial; both genetic, environmental and life style factors interact. Many risk factors are known, others are certainly yet to be found, and the complex relationships and interactions between risk factors need to be explored.

During the past decade low birth weight has been introduced as a new risk factor for type 2 diabetes and cardiovascular disease (Forsén, Eriksson et al. 1999; Eriksson, Forsen et al. 2001; Harder, Rodekamp et al. 2007; Whincup, Kaye et al. 2008). Low birth weight has also been linked to depression (Thompson, Syddall et al. 2001; Gale and Martyn 2004; Alati, Lawlor et al. 2007), which is a common co-morbidity of type 2 diabetes. In addition, birth size has been found to modify the effect of some previously known risk factors on diabetes (Eriksson, Lindi et al. 2002; Ylihärsilä, Eriksson et al. 2004). It remains to be explored how birth weight affects the relationship between type 2 diabetes and depression.

Depression can be both a risk factor and a complication of diabetes and co-morbid depression complicates the management of glucose homeostasis. It is important to recognize this co-morbidity and greater insight is needed in how depression and treatment of depression influence the diabetic patient's treatment and overall quality of life.

Another complication which affects diabetes management is cognitive decline. Type 2 diabetes is associated with a ~1.5 fold risk of cognitive decline (Cukierman, Gerstein et al. 2005) but it is not known which subjects with diabetes eventually develop cognitive impairment and which ones are likely to be spared. Other risk factors and complications of diabetes might modify the risk for cognitive decline. On the other hand baseline intellectual ability might affect both the development of diabetes and the risk for future cognitive decline.

This study aimed to explore the effects and interactions of birth weight, depression and cognitive ability in relation to type 2 diabetes from a life course perspective.

2 Review of the litterature

2.1 Definition and diagnosis of type 2 diabetes

Diabetes mellitus is a group of diseases characterized by hyperglycaemia. The most common subgroups are type 1 and type 2 diabetes. In type 1 diabetes hyperglycaemia is a result of absolute insulin deficiency whereas relative insulin deficiency and insulin resistance are the key elements in type 2 diabetes (WHO 1999; ADA 2007).

Type 2 diabetes (T2D) can be asymptomatic for a long period of time but when marked and prolonged hyperglycaemia occurs some of the following symptoms are often present: polyuria, polydipsia, involuntary weight loss and sometimes blurred vision.

The standard diagnostic test for type 2 diabetes is the 75g 2-hour oral glucose tolerance test (OGTT) where plasma glucose concentrations are measured at fasting and two hours after an oral glucose load. Different diagnostic criteria have been proposed during the past decades but since 1997 the cut-off points for diabetes have been fasting plasma glucose ≥ 7.0 mmol/l or post load plasma glucose ≥ 11.1 mmol/l according to both the American Diabetes Association (ADA) (ADA 1997) and the World Health Organisation (WHO) (WHO 1999). Lesser impairments in glucose tolerance are defined as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The cut-off points for the various disturbances in glucose regulation are presented in Table 1.

TABLE 1. WHO 1999 criteria for diagnosing type 2 diabetes based on a 75 g oral glucose tolerance test.

NGT	Fasting plasma glucose Plasma glucose 2 hours after glucose load	≤ 6.0 mmol/l and < 7.8 mmol/l
IFG	Fasting plasma glucose Plasma glucose 2 hours after glucose load	6.1 - < 7.0 mmol/l and < 7.8 mmol/l
IGT	Fasting plasma glucose Plasma glucose 2 hours after glucose load	< 7.0 mmol/l and 7.8 - < 11.1 mmol/l
DM	Fasting plasma glucose Plasma glucose 2 hours after glucose load	≧ 7.0 mmol/l or ≧ 11.1 mmol/l

NGT = normal glucose tolerance, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, DM = diabetes mellitus.

2.2 Prevalence of type 2 diabetes

The registry on medication reimbursement, which is maintained by the Social Insurance Institution of Finland provides a means for estimating the prevalence of drug treated diabetes in Finland. During the year 2006 there were 169 332 people in Finland who were using oral antidiabetic medication either alone or in combination with insulin (Reunanen, Virta et al. 2008). This number corresponds to the majority of drug treated Type 2 diabetics, although those on insulin treatment only will not be included in this group. There are is probably a large proportion of diagnosed diabetic patients that are treated with diet only and are thus not recognised by drug registers, although according to the more recent treatment guides drug treatment should be initiated immediately when the diagnosis is made (Laakso, Reunanen et al. 1991; Groop, Virkamäki et al. 2007). Moreover several population based studies have shown that around half of those who would fulfil the diagnostic criteria for diabetes are yet undiagnosed and thus untreated (King and Rewers 1993; Peltonen, Korpi-Hyövälti et al. 2006).

The prevalence of type 2 diabetes in Finland has been estimated in population-based studies using oral glucose tolerance tests. In the years 2004–2005 the FIN-D2D study estimated that the prevalence of type 2 diabetes among 45–74-year-olds was 16% in men and 11% in women (Peltonen, Korpi-Hyövälti et al. 2006). The prevalence has increased markedly since 1992 when another population-based study found it to be 10% in men and 7% in women aged 45-64 years (Ylihärsilä, Lindström et al. 2005). Based upon these numbers one could estimate that there are ~ 500 000 Type 2 diabetics in Finland.

The prevalence of type 2 diabetes is increasing in all age groups but most rapidly among the young (Lammi, Taskinen et al. 2007; Lammi, Blomstedt et al. 2008; Reunanen, Virta et al. 2008). The increasing prevalence of type 2 diabetes in Finland is partly explained by the ageing of the population since the incidence increases with increasing age (IDF 2007). Other reasons are increasing prevalence of obesity and decreased physical activity (Männistö, Lahti-Koski et al. 2004).

2.3 Pathophysiology of type 2 diabetes

The main feature in type 2 diabetes is an increased insulin demand due to insulin resistance in peripheral tissues. Insulin is produced and released from the pancreatic β-cells. Its main action is to increase glucose uptake in splanchnic and muscle tissue, to inhibit glucose production in the liver and to suppress lipolysis and the release of free fatty acids from adipose tissue. Insulin resistance denotes the inability of insulin to achieve these effects at normal concentrations. There is also a progressive deterioration of β-cell function seen in subjects with type 2

diabetes. When the pancreatic β-cells fail to compensate for the increased insulin demand hyperglycaemia follows (Pickup and Williams 2003; Stumvoll, Goldstein et al. 2005).

Type 2 diabetes develops gradually through milder forms of glucose intolerance. Impaired fasting glucose (IFG) is a condition where a mild hyperglycaemia is present during fasting, whereas in impaired glucose tolerance (IGT) hyperglycaemia occurs especially in the postprandial state. Both are risk factors for developing type 2 diabetes and are associated with an elevated risk for micro- and macrovascular complications (ADA 2007).

2.4 Risk factors for type 2 diabetes

A large number of risk factors have been associated with type 2 diabetes (Table 2) including both modifiable and non-modifiable ones. Genetic factors (Altshuler, Hirschhorn et al. 2000; Grant, Thorleifsson et al. 2006; Owen and McCarthy 2007; Lyssenko, Jonsson et al. 2008), increasing age, male sex (Wild, Roglic et al. 2004), a small birth size (Forsén, Eriksson et al. 2000; Whincup, Kaye et al. 2008) and low socio-economic status (Connolly, Unwin et al. 2000; Tang, Chen et al. 2003; Ramachandran, Snehalatha et al. 2004) can be considered as non-modifiable. The potentially modifiable risk factors include obesity and excess visceral fat (Lean, Han et al. 1999; Han, Williams et al. 2002), dietary factors (van Dam, Willett et al. 2002; Montonen, Knekt et al. 2003), exercise habits (Jeon, Lokken et al. 2007) and smoking (Patja, Jousilahti et al. 2005). The risk factors are however very much intertwined, often occurring simultaneously and interacting with each other. The role of birth size will be discussed in greater detail below.

TABLE 2. Risk factors associated with type 2 diabetes.

Genetic predisposition	High intake of saturated fat
Male sex	Low intake of dietary fibre
Increasing age	Lack of exercise
Low socio-economic status	Depression
Hypertension (Gress, Nieto et al. 2000)	Cigarette smoking
Dyslipidemia (Ley, Harris et al. 2009)	Decreased sleep duration (Yaggi, Araujo et al. 2006)
Obesity and overweight	Birth size
Central obesity	

2.4.1 Prenatal factors

During the past decades the research on risk factors for several adult diseases has evolved from comprising interactions between genes and life style to involving foetal and childhood programming effects. The concept of early life origins of adult disease was first established in the late 1970's by Forsdahl (Forsdahl 1977). He noticed that there were considerable variations in mortality from coronary heart disease between different regions in Norway in a cohort of people born in 1896–1925. Since the differences could not be explained by socio-economic status in adulthood, Forsdahl sought for differences in standard of living in early life using infant mortality as an index marker. He found that infant mortality in 1896–1925 was an independent risk factor for adult cardiovascular mortality in Norway in 1964–1967.

The theory of early life origins of adult disease was further developed by Barker who expanded the concept and brought to attention the association between low birth weight and adult disease. Using a cohort of people born in Hertfordshire during 1911–1930 he showed that men who had the lowest weights at birth had the highest death rates from ischemic heart disease (Barker, Osmond et al. 1989). Later on Barker and his colleagues found associations between low birth weight or small size in infancy and several other adult diseases including type 2 diabetes, hypertension and the metabolic syndrome (Barker, Osmond et al. 1989; Barker, Hales et al. 1993; Barker 1995; Ylihärsilä, Eriksson et al. 2003).

After Barkers findings many other researchers from around the world have continued on the same path and today the field of research is commonly referred to as the Developmental Origins of Health and Disease (DOHaD) (Barker 2004; Kajantie 2008; Wadhwa, Buss et al. 2009). It has expanded to comprise infant and childhood growth as well as foetal development on one end of the life span and many different physical, mental and sociological aspects of health and disease on the other end. Several intervention studies conducted on animals have confirmed the hypothesis of developmental origins of later health outcomes (Ozanne, Wang et al. 1996; Fernandez-Twinn, Wayman et al. 2005; McMullen and Mostyn 2009).

Foetal growth is influenced by many factors: the genome of the foetus, maternal nutrition and use of tobacco and alcohol, glucocorticoids, maternal body composition, pelvic size and several other pregnancy-specific factors. According to the original DOHaD hypothesis suboptimal conditions in utero, often reflected in a small size at birth, lead to adaptive changes in the foetus, which may have adverse consequences in later life (Barker 1995; Barker 2004). An essential characteristic of all living things is the capacity to adapt. The adaptive changes aim to guarantee the ability to thrive and reproduce successfully. However, the conditions in utero might not be a good forecast of what postnatal and adult life will be and therefore the programming might be suboptimal and even predispose to greater health risks.

The potential mechanisms behind the programming are referred to as epigenetic alterations, i.e. changes in the regulation of gene transcription and expression rather than changes in the genome itself. Factors that regulate gene expression are e.g. DNA methylation and histone methylation, acetylation and phosphorylation (Bird 2002; Villeneuve and Natarajan 2010). Epigenetic changes have been shown to be sensitive to intrauterine conditions and interestingly enough can even be inherited (Morgan, Sutherland et al. 1999; Waterland and Jirtle 2004). Possible pathways of foetal programming are demonstrated in Figure 1.

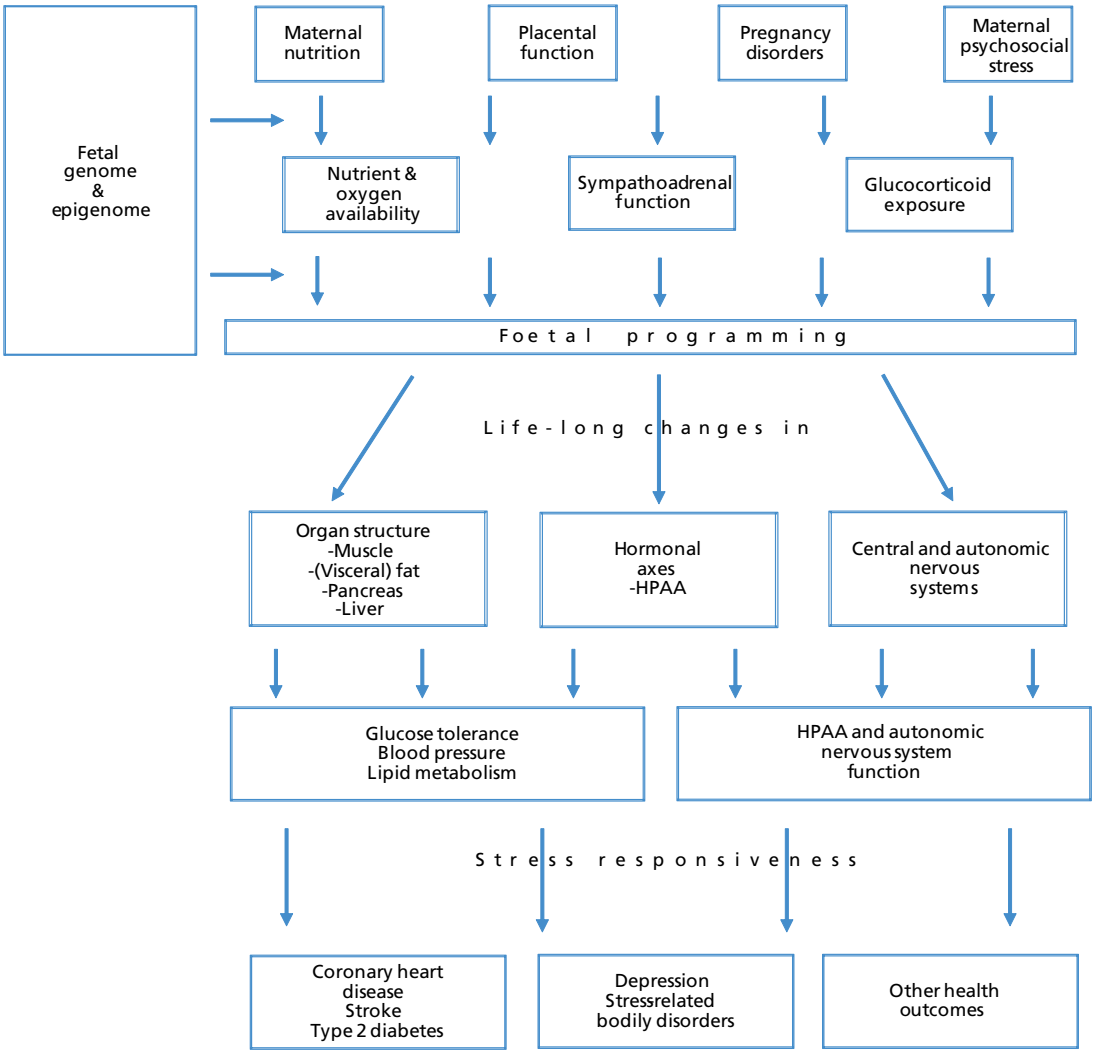

FIGURE 1. Possible pathways of foetal programming of adult disease. Modified from Annals of the New York Academy of Sciences (Kajantie 2006).

Birth size and type 2 diabetes

As first reported by Hales et al. (Hales, Barker et al. 1991) and recently reviewed by Whincup et al there is substantial evidence that links birth size to the risk of type 2 diabetes (Whincup, Kaye et al. 2008). The risk for type 2 diabetes is increased among subjects born small for gestational age as well as among those born large for gestational age (Wei, Sung et al. 2003; Harder, Rodekamp et al. 2007). Macrosomia is associated with maternal gestational diabetes which is an independent risk factor for type 2 diabetes in the offspring (Silverman, Metzger et al. 1995). This work will be restricted to discuss the effects of small birth size.

Low birth weight is associated with both insulin resistance and impaired insulin secretion in non-diabetic individuals (Pulizzi, Lyssenko et al. 2009) and with a smaller lean body mass and proportionally less muscle tissue at any BMI in adulthood (Eriksson, Forsén et al. 2002; Ylihärsilä, Kajantie et al. 2007). Since muscle tissue plays an important role in glucose storage and utilisation, reduced muscle tissue leads to a higher risk of insulin resistance and could be one possible mechanism by which a low birth weight increases the risk for type 2 diabetes. Another hypothesized mechanism by which low birth weight may cause type 2 diabetes is alteration of the HPA-axis, which leads to imbalanced cortisol secretion and thus increased insulin resistance (Kajantie 2006; Kajantie 2008). There is some evidence that adverse programming in utero can result in a permanent alteration of the HPA axis and consequently altered cortisol concentrations throughout life (Meaney, Szyf et al. 2007). This may occur as a consequence to intrauterine growth retardation as reflected by a small body size at birth (Phillips, Barker et al. 1998; Kajantie and Räikkönen 2010).

Birth size as a modifying factor

Small birth size is not only an independent risk factor for several adult diseases but has also been shown to modify the effect of previously known risk factors on adult disease. Results from the Helsinki Birth Cohort Study have shown that subjects born with a low birth weight are more vulnerable to the adverse effects of a low socio-economic status with respect to coronary heart disease (Barker, Forsen et al. 2001; Eriksson, Yliharsila et al. 2004). In addition, low birth weight has been shown to modify the effect of exercise and genetic susceptibility on the risk of type 2 diabetes (Eriksson, Lindi et al. 2002; Eriksson, Ylihärsilä et al. 2004; Pulizzi, Lyssenko et al. 2009). It remains to be seen whether birth weight has a modifying effect on the development of diabetic complications as well.

2.4.2 Intellectual ability as a predictor of adult disease

During the past decade low intellectual ability has been shown to be a risk factor for mortality in several epidemiological cohorts (Hart, Taylor et al. 2003; Batty, Shipley et al. 2008). Studies attempting to explain this association (Batty, Deary et al. 2007) have observed that low intellectual ability is associated with an unhealthier life style (e.g. higher rate of smoking and heavier alcohol consumption), more obesity and an increased risk for coronary heart disease which are all known to increase overall mortality. The role of socio-economic factors has been explored by Hart et al. who claim that IQ is an independent and stronger predictor of mortality than overall socio-economic status (SES) (Hart, Taylor et al. 2003). Batty et al. again found that education, occupational prestige and income taken together mediated the association between IQ and mortality (Batty, Shipley et al. 2008).

Low SES, smoking, obesity and CHD are all associated with type 2 diabetes as well and therefore a direct or indirect association between intellectual ability and type 2 diabetes might be expected. There are only a few studies in which this association has been examined. Batty et al. have shown that individuals with lower IQs are at increased risk for developing the metabolic syndrome. However, the negative association which they found between blood glucose and IQ was non-significant after adjusting for education.

There are only three published studies where the relationship between early life IQ and type 2 diabetes has been explored (Batty, Deary et al. 2007; Batty, Deary et al. 2007; Olsson, Hulting et al. 2008). Batty et. al found no association between the two in either of their studies while Olsson found a 40% increase in diabetes risk for every one standard deviation (SD) decrease in general ability test score (Olsson, Hulting et al. 2008). All of these studies have relied on questionnaires for the diagnosis of diabetes. However, it has been shown that only around 50% of subjects with diabetes are aware of their disease (King and Rewers 1993) and therefore the results from these studies could be biased. Moreover, in all of these studies the prevalence of type 2 diabetes was assessed at an age less than 55 years. Those who develop the disease and have it diagnosed at an early age represent an extreme of the type 2 diabetes spectrum and may have different disease and risk factors profiles. Therefore there is a need for studies using OGTT to identify diabetic subjects and for studies performed in older populations in whom the disease is more prevalent.

2.5 Complications and co-morbidities of type 2 diabetes

Diabetes is associated with several complications which are related to the duration of the disease and to metabolic control. Sustained hyperglycaemia, increased concentrations of free fatty acids and inflammatory markers seen in type 2 diabetes are risk factors for developing micro- and macroangiopathy, including neuropathy, retinopathy, nephropathy, and cardiovascular disease (ADA 2007). There is also an increased mortality associated with type 2 diabetes, which is mainly due to macrovascular complications (Hu, Stampfer et al. 2001; Eliasson, Talback et al. 2008). In addition diabetes has a negative effect on quality of life and mental well being (Anderson, Freedland et al. 2001; Grandy S, Chapman RH et al. 2008) and on cognitive performance in the elderly (Strachan, Deary et al. 1997). These complications can be direct consequences of the metabolic impairments seen in type 2 diabetes or they can share a common origin with type 2 diabetes and develop side by side. In some cases, e.g. in the case of depression, the same phenomenon can be a risk factor predisposing to type 2 diabetes as well as a consequence of type 2 diabetes (Mezuk, Eaton et al. 2008). Depression and cognitive impairment will be discussed in greater detail below.

2.5.1 Depression

Prevalence

Depression is an expanding public health problem with major consequences for the individual as well as the society as a whole (Mathers and Loncar 2006). It is one of the most common reasons for work disability in Finland (KELA 2008). In the Finnish Health 2000 study the 12-month prevalence of major depression according to DSM-IV criteria was 4,9% among adults over 30 years of age (Pirkola, Isometsä et al. 2005). This is consistent with the world wide prevalence of 4–11 % reported by WHO (WHO 2000). In Europe the lifetime prevalence for major depression has been estimated to be as high as 12.8% to 30%, (Paykel, Brugha et al. 2005).

Aetiology and diagnosis

The aetiology of depression is multifactorial and the manifestation of clinical depression is always a consequence of several factors interacting. Stressful life events have long been known to play a role in the development of depression (Agid, Kohn et al. 2000). Also genetic predisposition has repeatedly been described (Levinson 2006). Genetic susceptibility has mainly been linked to polymorphisms and epigenetic modifications in genes involved in serotonin and glucocorticoid

metabolism (Caspi, Sugden et al. 2003; Levinson 2006; McGowan, Sasaki et al. 2009).

The main symptoms of depression are depressed mood, loss of interest and pleasure, low self-esteem, fatigue and loss of energy. Alterations in cognitive functions, sleep and appetite are also common. Depression and depressive symptoms can be assessed in different ways according to the purpose of assessment. For clinical purposes there is a diagnostic convention based on ICD-10 (WHO 1992) and DSM-IV (APA 2000) criteria. The severity of depression can be assessed according to certain threshold values based on the number of symptoms. However, the threshold values are arbitrary (Kendler and Gardner 1998) and for many purposes it makes more sense to use continuous scales. Beck's Depression Inventory (BDI) (Beck, Ward et al. 1961) is a widely used scale for assessing depressive symptoms. It is a 21-item self-report scale where the patient is asked to rate the severity of symptoms related to mood, pessimism, self-esteem and body image, self-destructive thoughts, social functioning and different somatic manifestations. The BDI score ranges between 0 and 63 points and different threshold values have been used to indicate severity (Roivainen 2008). In this work ≥10 points was used as a cut-off for mild or moderate depressive symptoms as suggested by Beck et al.(Beck 1988).

T2D and depression co-morbidity

The co-morbidity of depression and type 2 diabetes has been established and reviewed on several occasions (Gavard, Lustman et al. 1993; Talbot and Nouwen 2000; Eaton 2002). The most recent meta-analysis found that type 2 diabetes is associated with a 60% increased risk for having concomitant depression or depressive symptoms and with a 17,6% prevalence of clinically relevant depression among type 2 diabetes subjects (Ali, Stone et al. 2006).

It has been speculated that the association between diabetes and depression is merely a reflection of the psychological burden of having a chronic disease (Kessing, Nilsson et al. 2003; Knol, Heerdink et al. 2007). However, the results of Timonen et al.. argue against this simple explanation by showing that insulin resistance was associated with higher depressive symptoms among subjects without a previous diagnosis of diabetes (Timonen, Laakso et al. 2005).

Conversely, as reviewed by Knol et al., depression has been shown to increase the risk for onset of diabetes (Knol, Twisk et al. 2006). In fact in light of the most recent evidence depression seems to be a stronger predictor of diabetes than diabetes is of depression. As reviewed by Mezuk et al. depressed subjects without a previous diagnosis of diabetes had a 60% increased risk to develop diabetes during follow up when compared to non-depressed subjects. Diabetic subjects had only a 15% increased risk of developing depression compared to non-diabetic subjects (Mezuk, Eaton et al. 2008).

Moreover it has been suggested that depression may lead to deterioration in glycaemic control in diabetes (Lustman and Clouse 2005). An obvious mechanism underlying this association is the fact that depressed individuals are less adherent to their treatment and less physically active (Ciechanowski, Katon et al. 2000; Lin, Katon et al. 2004; Kilbourne, Reynolds et al. 2005; Pirraglia and Gupta 2007). Another explanation is that there may be a common underlying hormonal or metabolic pathway connecting depression and diabetes (Bjorntorp 2001; Musselman, Betan et al. 2003; Golden 2007; Champaneri, Wand et al. 2010).

Treating diabetic subjects with SSRI

If depression deteriorates glycaemic control, whether through behavioural or biological mechanisms, this deterioration could possibly be reversed by treatment of depression. Indeed, some antidepressant drugs have been shown to improve insulin sensitivity and glucose metabolism. For example, the selective serotonin reuptake inhibitor (SSRI), fluoxetine lowers blood glucose levels in type 2 diabetics (Gray, Fujioka et al. 1992; O'Kane, Wiles et al. 1994). Some SSRI's have also been shown to promote weight loss, which in itself would improve insulin sensitivity. In a recent meta-analysis the mean short-term weight loss induced by fluoxetine was found to be 0,94 kg. The long-term effect (0,31 kg after > 4 months of treatment) was less marked but still significant (Serretti and Mandelli 2010). Interestingly, the effect of fluoxetine on insulin sensitivity also occurs independently of weight loss (Maheux, Ducros et al. 1997). There are only a few controlled trials where the effect of antidepressive treatment on glucose tolerance has been assessed in type 2 diabetic patients particularly treated for depression (Lustman, Griffith et al. 1997; Lustman, Griffith et al. 1998; Lustman, Freedland et al. 2000; Amsterdam, Shults et al. 2006; Lustman, Clouse et al. 2006; Lustman, Williams et al. 2007). The question whether the improvement in glycaemic control is linked to improvement in depressive symptoms or to a physiological effect of the antidepressant drug is still unanswered. Further studies are needed to elucidate this issue.

2.5.2 Cognitive decline

Cognitive ability declines with age and the prevalence of dementia among people over 65 years is estimated to be between 5 and 9 % in Finland (Viramo and Sulkava 2006).

Cognitive ability can be assessed in different ways depending on the purpose of assessment. Some tests are designed to measure global cognitive function while others evaluate different cognitive domains more specifically. The different domains which are usually assessed include processing speed/psychomotor performance, executive function, short-term and long-term memory, learning and attention. One widely used cognitive test is the Mini Mental State Examination (Folstein, Folstein

et al. 1975). It is a test designed to measure global cognitive function and is best suited to screen for dementia. When assessing more subtle changes in cognition, e.g. in epidemiological research, it may be useful to use more sensitive tests such as the Cogstate® test battery which will be described in detail below (Darby, Maruff et al. 2002).

Type 2 diabetes has been linked to an elevated risk for cognitive impairment. It was first reported in the early twenties by Miles and Root (Miles and Root 1922) and the continuously growing literature on the subject has been reviewed several times (Strachan, Deary et al. 1997; Allen, Frier et al. 2004; Cukierman, Gerstein et al. 2005; Biessels, Staekenborg et al. 2006; Kodl and Seaquist 2008). Longitudinal studies have shown that diabetes is not only associated with lower cognitive performance but also with a higher risk for cognitive decline over time and for development of dementia. As reviewed by Cukierman et al. people with diabetes have a 1.5 fold risk of cognitive decline compared to people without diabetes. It is possible that not all cognitive domains are affected equally by diabetes (Awad, Gagnon et al. 2004). Therefore it may be beneficial to assess cognitive ability in diabetic subjects with a method designed to detect changes in several different cognitive domains.

Most published studies have focused upon the impact of manifest diabetes on cognition (Awad, Gagnon et al. 2004), while evidence regarding pre-diabetic stages is more scarce. Findings on the effect of impaired glucose tolerance on cognitive performance are not consistent and need further scrutiny (Kalmijn, Feskens et al. 1995; Vanhanen, Koivisto et al. 1998; Lindeman, Romero et al. 2001; Messier, Tsiakas et al. 2003; Kumari and Marmot 2005; Bonito, Fraia et al. 2007).

The mechanisms leading to cognitive decline in diabetes are diverse and not fully understood. Both micro- and macrovascular disease, which are common complications of diabetes, may affect the brain (Biessels, van der Heide et al. 2002; Mankovsky and Ziegler 2004; Manschot, Biessels et al. 2007). Depression is another common co-morbidity of diabetes (Anderson, Freedland et al. 2001) which can affect cognition and can be difficult to differentiate from early stages of dementia (Swainson, Hodges et al. 2001). However, it is also possible that hyperglycaemia and hyperinsulinaemia *per se* can affect brain tissue and its metabolism. Several insulin receptors and insulin sensitive glucose transporters have been found in brain tissue. Also patients with Alzheimer's disease have been shown to have an impaired insulin action in the brain and an elevated concentration of insulin in their cerebral spinal fluid. Still, research on the role of insulin in the brain is just beginning to evolve (Fujisawa, Sasaki et al. 1991; Manschot, Biessels et al. 2007; Kodl and Seaquist 2008).

Thus, it is not known which aspect of the complex cluster of diabetes and its co-morbidities mainly accounts for the association between diabetes and cognitive impairment. Likewise it is not known which subjects with diabetes eventually develop cognitive impairment and which ones are likely to be spared (Biessels,

Staekenborg et al. 2006). Mounting evidence exists linking low birth weight with alterations in cognitive abilities at various stages in life (Richards, Hardy et al. 2001; Viggedal 2004; Räikkönen, Forsén et al. 2009). It remains to be seen whether birth weight can modify the effect of diabetes on the brain.

2.6 Summary of the review

Type 2 diabetes is a disease that develops gradually during a long period of time and there are many factors throughout the life course which may influence the development. Only three studies have attempted to answer the question whether type 2 diabetes is predicted by intellectual ability in early adulthood. Therefore there has been a call for further investigation of this matter.

The co-morbidity between type 2 diabetes and depression has been established but there are still no guidelines for their simultaneous treatment. Some SSRI:s have been proven beneficial in the management of both depression and hyperglycaemia but the knowledge about other SSRI:s has been scarce.

Type 2 diabetes is also associated with an increased risk of developing cognitive impairment. However, the literature on the association between IGT and cognitive impairment is less abundant. Moreover the different modifiers and risk factors need to be further explored.

A low birth weight has been linked to type 2 diabetes both as an independent risk factor and as a modifier of other risk factors. It is also a risk factor for both depression and cognitive impairment. The role of birth weight as a modifier of the co-morbidity between type 2 diabetes, depression and cognitive impairment has not yet been explored.

3 Aims of the study

1. To explore intellectual ability as a potential risk factor for T2D. (Study I)
2. To explore associations between glucose tolerance and depression. (Study II)
3. To test the effect of paroxetine on mood and glucose tolerance in diabetic subjects. (Studies III–IV)
4. To explore associations between glucose tolerance and cognitive ability. (Study V)
5. To explore whether birth weight acts as a modifying risk factor for T2D and its complications. (Studies II, V)

4 Subjects and methods

4.1 The Helsinki Birth Cohort Study

Studies I, II and V were part of the Helsinki Birth Cohort Study. The original epidemiological cohort includes 8760 men and women who were born at the Helsinki University Central Hospital in 1934-1944. Subjects were included in the cohort if they were resident in Finland in 1971, when each member of the Finnish population was given a unique personal identification number.

In the year 2000, postal questionnaires were sent to all cohort members still living in Finland (n = 7,078). Out of 3,944 men and women who answered the questionnaire and consented to further contact we randomly selected 2,902 subjects to be invited to a clinical examination. Finally, 2003 of these subjects participated in an extensive clinical examination during the years 2001–2004.

Data collection

Data on the cohort members was obtained from hospital birth records, child welfare clinic records, school health care records as well as national Finnish registers. The birth records include information on birth weight, birth length and date of mother's last menstrual period, based on which gestational age was calculated. Socio-economic status in childhood was established based on father's highest recorded occupation, obtained from birth records, child welfare clinic records and/or school health care records.

Clinical examination

A standard 75 g oral glucose tolerance test (OGTT) was performed. For subjects who were on insulin treatment (n = 45) only fasting plasma glucose was obtained.

Height was measured to the nearest centimetre and weight with 0.1 kg precision. Body mass index (BMI; kg/m^2) was calculated. We assessed depressive symptoms using the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961). The subjects also filled out detailed questionnaires on current health status and medication. The level of education was also obtained from these questionnaires and defined by the following four categories: elementary school, vocational school, senior high school, college/university degree.

Testing of intellectual ability

Out of the 2003 subjects who participated in the clinical examination 642 men had completed a test on intellectual ability during their compulsory military service

at the average age of 20 years (range 17–27). These men comprised the study sample in study I. The intellectual ability test was designed by the Finnish Defense Forces Education Development Centre for the purpose of leadership training selections during the military service. It comprises three subtests measuring verbal, visuospatial and arithmetic reasoning. Visuospatial intellectual functioning is measured by a test analogous to the Raven's Progressive Matrices which are considered to be largely independent of education or socio-cultural factors (Raven 2000). Each subtest is composed of 40 multiple-choice questions. The test has been described in detail by Tiihonen et al. (Tiihonen, Haukka et al. 2005).

Cognitive testing

For the study on cognitive performance (study V) we invited those subjects from the original clinical cohort, who were still living in the greater Helsinki area (n= 1586). 67 subjects were deceased or lost to follow up, 227 subjects declined to participate, 5 subjects were not willing or capable of taking the test due to physical disabilities, 8 subjects were not capable of taking the test due to poor vision. The 1,279 subjects who attended were administered a test of cognitive performance in the years 2004–2006.

The test used is a standardised, language independent computerised battery of cognitive tests (CogState®, version 3.0.5). This battery has been validated and shown to be a sensitive indicator of mild impairments in the following cognitive domains: psychomotor speed, attention, working memory and episodic learning and memory (Collie, Darby et al. 2001; Darby, Maruff et al. 2002; Collie, Maruff et al. 2003). The test consists of five tasks where subjects are asked to pay attention to playing cards on a computer screen. Each task consists of 30 to 50 repeated stimuli described in detail below. The test battery takes approximately 15 minutes to complete and is preceded by a practice round. The five tasks are as follows:

1. Simple reaction time task (SRT) assessing psychomotor function and speed of processing. A single card is presented face-down on the computer screen. The subject is asked to press the spacebar as soon as the card turns face-up. This is repeated 35 times with random time intervals. This task is administered twice, first and last in the test, and the mean reaction time from both tasks is calculated.
2. Choice reaction time task (ChRT) assessing visual attention and requiring a binary decision. Subjects are asked to indicate whether the turning playing card on the screen is red by pressing either K ("yes") or D "(no"). The stimulus is repeated 30 times and the mean reaction time is calculated.
3. Divided attention task (DA). Five playing cards are presented next to one another on the computer screen. Two horizontal lines are shown on the screen, one above and one below the cards. The five cards move in a disorganised manner up and down towards the lines. The subject is asked to monitor all five cards simultaneously and press the spacebar as soon as any one of the cards

touches either of the lines. The stimulus is repeated 30 times, and the mean reaction time is calculated.

4. Working memory task (WM). A new playing card is presented 30 times and the subject is asked to indicate whether this card is identical to the preceding one. Mean reaction time is calculated and the number of correct responses is obtained.
5. Associate learning task (AL) assessing visual learning and memory. In this task five pairs of cards are initially presented face-up at the top of the screen. At the bottom of the screen a random card pair turns face-up 50 times and each time the subject is asked to indicate whether the random pair matches exactly any of the pairs above. Upon initial matching, the corresponding card pair turns face-down and subsequent matching has to be judged by memory. After every match the corresponding card pair is presented for a short while, allowing learning by repetition. Speed and the number of correct matches are obtained.

Reaction times were measured in milliseconds and mean reaction times were calculated for each subject for each task. Accuracy of responses was recorded as the number of correct answers divided by the number of answers given.

Definition of variables

Type 2 diabetes (T2D) and other stages of glucose tolerance were defined according to the World Health Organisation (WHO) criteria (WHO 1999) (Table 1). Subjects who were taking medication for diabetes and/or reported that they had been previously diagnosed with diabetes were categorised as known diabetics (known DM). Subjects who were diagnosed with diabetes for the first time by the OGTT performed at the clinic where categorized as new diabetics (new DM). Subjects who reported being diagnosed with diabetes at an age of 30 years or less were categorised as type 1 diabetics if they were on insulin treatment only (n = 4).

Coronary heart disease (CHD) was defined based upon self-report. Subjects were asked whether they had a physician-diagnosed history of angina pectoris (n= 103) or myocardial infarction (n = 67). If not recognised by the previous question, subjects using nitrate medication were also defined as having CHD (n = 41, no unrecognised). Subjects were defined as having cardiovascular disease (CVD) if, in addition to the previously mentioned criteria for CHD, they had a history of stroke (n = 53) or claudication (n = 37).

When appropriate, birth weight was dichotomised and a birth weight of ≤ 2,500 g was regarded as low. When BDI score was dichotomised the cut point was set at 10 points and scores of 0 to 9 points were regarded as normal, whereas scores of 10 or more were regarded as mild to moderate depressive symptoms (Beck, Ward et al. 1961).

4.2 Clinical trials

Subjects

For studies III and IV we conducted two clinical trials testing the effect of paroxetine on glucose tolerance and mental well being in diabetic subjects. Both clinical trials included mildly depressed subjects with type 2 diabetes. For trial 1, which was a pilot study, we invited only postmenopausal women over 50 years of age. Trial 2 included both men and women within an age range of 50 to 70 years. All subjects were diagnosed with type 2 diabetes at least a year prior to study entry and received standard diabetes treatment by their primary care physicians prior to and during the trials. They had been on stable antidiabetic medication for at least three months before entering the studies.

In trial 1 we included subjects with an unsatisfactory glycemic control, defined as glycosylated haemoglobin A_{1c} ($GHbA_{1c}$) ≥ 6.5% or fasting blood glucose ≥ 7.0 mmol/l, and with a depressive symptoms score between 2.5 and 12 on the Montgomery-Åsberg's Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). This range indicates mild to moderate depressive symptoms but not a severe depression requiring immediate treatment. In trial 2 we aimed to investigate subjects with worse glycaemic control and set the inclusion criteria at $GHbA_{1c}$ > 7.0%. The definition of mild to moderate depression was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (APA 2000). Subjects with 1–6 depressive symptoms according to DSM-IV were included in trial 2.

Subjects with major diabetes complications (e.g. major cardiovascular disease, renal insufficiency, blindness, amputations) were excluded from both trials. Furthermore, subjects were excluded if they had glaucoma (Eke and Bates 1997) and if they were using warfarin (Duncan, Sayal et al. 1998) because of possible adverse effects of paroxetine in these conditions. Patients who used any kind of antidepressants were also excluded.

The subjects who met the inclusion criteria were randomly assigned to take either placebo or 20 mg paroxetine once a day. In trial 1 this was done in a single-blind fashion while trial 2 was double-blind. The randomisations were computerised and concealed to both the patients, research personnel, and treating physicians until inclusion and informed consent was established. In trial 1 the allocation remained concealed to the patient, treating physician and laboratory staff, in trial 2 the allocation remained concealed to all parties. The research personnel did not take part in the clinical treatment of the study subjects.

Measurements

In trial 1 we analysed the patients at baseline and after 10 weeks of treatment. Mental well being was evaluated using two clinician-rated evaluation scales,

Hamilton's Anxiety Scale (HAM-A) (Gjerris, Bech et al. 1983) and Montgomery-Åsberg's Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), and two patient-rated scales, Beck's Depression Inventory (BDI) (Beck, Ward et al. 1961) and the RAND-36 Item Health Survey (RAND-36) for assessment of quality of life (Hays, Sherbourne et al. 1993). In trial 2 we evaluated mental well being using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) and quality of life using the the SF-36-Item Short Form Health Survey (SF-36) (Ware and Sherbourne 1992; McHorney, Ware et al. 1993). The patients were analysed at baseline and at 3 and 6 months.

In both trials fasting blood samples were drawn for the following analyses: blood glucose, $GHbA_{1c}$, serum cholesterol, serum HDL-cholesterol, serum cortisol and sex hormone binding globulin (SHBG). LDL cholesterol was calculated using the Friedewald formula (Friedewald, Levy et al. 1972). Body mass index (kg/m^2) was calculated using body weight measured to the nearest 0.5 kg and height to the nearest cm. All measurements were made after an overnight fast (at least 8 h fasting).

The primary outcome measures in both trials were improvement of $GHbA_{1c}$ and the quality of life score. A mean difference between the treatment groups of 0.8 %-units in $GHbA_{1c}$ and of 20% in the total score of quality of life was considered to be clinically significant.

4.3 Statistical analysis

Studies I, II and V

The intellectual ability test scores in study I were converted into standard deviation scores and treated as continuous variables. In study II BDI score was treated as a continuous variable and when dichotomised the cut point was set at ≥ 10 points, to reflect at least mild severity of depressive symptoms, as suggested by Beck (Beck 1988). In study V cognitive ability scores were treated as continuous variables except for the working memory accuracy which was dichotomised with a cut point at two errors. Four subjects had missing information on education. In these cases we substituted the missing values with the median value (vocational school) of the whole sample.

Variables with skewed distribution (BDI score, blood glucose, reaction times in cognitive performance test) were log-transformed in order to obtain normality. Central values of skewed variables are presented as medians and interquartile ranges or as geometrical means and standard deviations.

Multivariate linear regression analyses were used to determine associations with continuous outcome variables. When outcome variables were dichotomous logistic regression analyses were used. In study I we assessed the association

between intellectual ability score and glucose tolerance and odds for having type 2 diabetes. In study II we assessed the association between BDI score and glucose tolerance. In study V the association between glucose tolerance and cognitive ability was explored. All analyses were controlled for age and sex. When appropriate we controlled for CVD, BMI, education and birth weight to explore potential mediation of the associations. In study V we conducted formal mediation analyses using Sobel's test for mediation (Sobel 1982; Baron and Kenny 1986).

Interaction tests and subgroup analyses were conducted to assess whether the measured effects varied by sex, birth size, depression or educational attainment.

Studies III and IV

In study III (clinical trial 1) we calculated mean changes from baseline in metabolic parameters and parameters of mental well being. Differences between the two treatment groups were calculated using the non-parametric Mann-Whitney U-test. The results were recalculated for this thesis using the parametric students t-test. Both tests rendered similar results. Only the parametric test results will be presented below. Subjects who dropped out of the trial after more than two weeks of participation were included in the analysis by last observation carried forward technique.

In study IV (clinical trial 2) differences between the two treatment groups were assessed with analysis of covariance (ANCOVA), where baseline measurements were used as covariates. Analyses were also controlled for sex, baseline $GHbA_{1c}$, HADS, SF-36 and BMI. Changes from baseline were calculated with a paired samples t-test and tabulated as means and 95% CI:s. Kolmogorov-Smirnov-test was used to test for normality of the data.

4.4 Ethical considerations

Studies I, II and V were approved by the Ethics Committee of epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. In addition study I was partly approved by the Headquarters of the Finnish Defense Forces. Studies III and IV were approved by the Ethics Committee of Helsinki University Central Hospital. Each subject participating in the clinical examination of the cohort studies and in the clinical trials signed an informed consent form.

5 Results

5.1 Intellectual ability as a potential predictor of type 2 diabetes

In study I we analysed 642 men from the clinical cohort who had completed a test on intellectual ability during their military service. 132 (20.6%) of them had type 2 diabetes, 132 (20.6%) had impaired glucose tolerance (IGT), 60 (9.4%) had impaired fasting glucose (IFG) and 317 (49.5%) had normal glucose tolerance (NGT). Intellectual ability scores and other basic characteristics of the study sample are listed according to educational level in Table 3.

TABLE 3. Intellectual ability scores and socio-economic status at 20 years and metabolic parameters at 61 years according to adult educational level in a sample of 641 men from the Helsinki Birth Cohort.

	Elementary school	n = 178	Vocational school	n = 142	Senior high school	n = 176	College or university	n = 145
	mean/n	SD/%	mean/ n	SD/%	mean/n	SD/%	mean/n	SD/%
Verbal zscore	-0.24	0.89	-0.43	0.87	0.38	0.79	0.89	0.75
Visuospatial zscore	-0.26	0.93	-0.25	0.96	0.48	0.83	0.80	0.81
Arithmetic zscore	-0.35	0.95	-0.28	0.87	0.47	0.78	0.86	0.63
Highest childhood SES	14	7.9	14	9.9	35	19.9	58	40.0
BMI (kg/m^2)	28.1	5.3	27.5	3.9	27.6	3.5	26.7	3.4
T2D	43	24.2	33	23.2	33	18.8	23	15.9

zscore = standard deviation score, BMI = body mass index, SES = socio-economic status in childhood, T2D = type 2 diabetes.

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Logistic regression models revealed no associations between any of the intellectual ability domains and T2D when NGT was used as reference. Neither did any of the intellectual ability scores correlate with fasting glucose or 2-hour glucose concentrations (Table 4). Analyses were adjusted for age at conscription and age at OGTT. Additional adjustment for education, childhood SES or adult BMI did not change the results.

Early intellectual ability was positively correlated with future educational attainment (all p-values < 0.001) but intellectual ability scores explained only 19 to 25% of the variability in education. Therefore, we also separately analyzed the association between educational attainment and glucose tolerance. Educational attainment was associated with both fasting and 2h-glucose as well as with type 2 diabetes. Adjusting for intellectual ability in early adulthood or childhood SES did not affect the results. However, these associations were somewhat attenuated when controlling for BMI (Table 4). There were no interactions between intellectual ability test scores and educational attainment in explaining impairments in glucose regulation (p-values > 0.5).

TABLE 4. Associations of intellectual ability and education with glucose tolerance. Effect sizes are given as % difference in plasma glucose or as odds ratios for having type 2 diabetes (T2D), for one standard deviation (SD) change in intellectual ability score or by category of educational attainment. Normal glucose tolerance (NGT) was used as reference.

		Fasting glucose	2h-glucose	T2D
		% (95% CI)	% (95% CI)	OR (95% CI)
One SD increase in IA-score	Visuospatial	-1.1 (-4.6 to 2.5)	-3.7 (-11.0 to 4.2)	1.02 (0.82 to 1.26)
	Verbal	-1.5 (-5.1 to 2.1)	-5.0 (-12.4 to 3.0)	0.90 (0.73 to 1.12)
	Arithmetic	-1.4 (-5.0 to 2.3)	-6.5 (-13.9 to 1.6)	0.93 (0.74 to 1.16)
Educational attainment	Lowest	Reference	Reference	Reference
	2	-5.0 (-13.7 to 4.6)	-10.7 (-27.8 to 10.6)	0.74 (0.43 to 1.29)
	3	-5.1 (-13.4 to 3.9)	-10.7 (-27.0 to 9.3)	0.69 (0.40 to 1.21)
	Highest	-14.8 (-22.6 to -6.3)	-26.6 (-40.5 to -9.4)	0.50 (0.28 to 0.91)
Highest vs. lowest education	Adjusted for total IA-score	-16.6 (-25.2 to -6.9)	-27.2 (-42.8 to -7.4)	0.44 (0.22 to 0.88)
	Adjusted for childhood SES	-14.6 (-22.7 to -5.6)	-24.3 (-39.3 to -5.7)	0.53 (0.28 to 0.98)
	Adjusted for BMI	-11.5 (-19.4 to -3.0)	-20.0 (-34.7 to -2.1)	0.75 (0.39 to 1.45)

IA = intellectual ability, SES = socio-economic status in childhood.

5.2 Depression in association with glucose tolerance

Table 5 shows the characteristics of the study sample in study II. Out of the 2003 men and women 15.7 % had DM, 10.4 % had CVD, 77.5% had neither CVD nor DM, and 3.4 % had both.

TABLE 5. Basic characteristics of 2003 subjects from the Helsinki Birth Cohort.

		Men		Women	
		N	Mean (SD)/ %	N	Mean (SD)/ %
Age (years)		928	61.5 (2.8)	1,075	61.5 (3.0)
Body mass index (kg/m2)		927	27.5 (4.2)	1,074	27.7 (5.0)
Glucose at 0-min (mmol/l)		928	5.8 (5.4 to 6.3)[a]	1,075	5.4 (5.0 to 5.8)[a]
Glucose at 120-min (mmol/l)		904	7.1 (5.8 to 9.2)[a]	1,049	7.1 (5.8 to 8.5)[a]
Glucose tolerance		926		1,073	
	Normal	441	47.5	612	56.9
	IFG	101	10.9	38	3.5
	IGT	203	21.9	293	27.3
	DM	181	19.5	130	12.1
Depression (BDI score)		928	4 (2 to 7)[a]	1,067	5 (2 to 9)[a]
	< 10 points BDI	804	86.6	808	75.2
	≥ 10 points BDI	124	13.4	259	24.1
Birth weight (g)		928	3,476 (501)	1,075	3,353 (465)
	≤ 2.5 kg	35	3.8	37	3.4
	> 2.5 kg	893	96.2	1,038	96.6
CVD	No	798	86.0	997	92.7
	Yes	130	14.0	78	7.3

[a] Median and 25th and 75th percentiles.

IFG = impaired fasting glucose, IGT = impaired glucose tolerance, DM = diabetes mellitus, BDI = Beck Depression Inventory, CVD = cardiovascular disease.

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The associations between glucose concentrations and depressive symptoms were assessed with linear regression analysis and adjusted for sex. The BDI score was positively associated with both fasting and 2h-glucose values. A 10% increase in fasting or 2h-blood glucose was associated with a 3.9% (95% CI = 1.9 to 5.9%, $p < 0.001$) and 2.0% (95% CI = 1.0 to 2.9%, $p < 0.001$) increase in BDI score respectively. These associations were slightly smaller but remained significant after controlling for age and BMI.

We also compared subjects with low BDI scores (< 10p) to those with high scores (≥ 10 p). Subjects with mild or moderate depressive symptoms (≥ 10 p) had significantly higher plasma glucose values throughout the OGTT, compared to subjects reporting low depressive symptoms (< 10 p) (Figure 2).

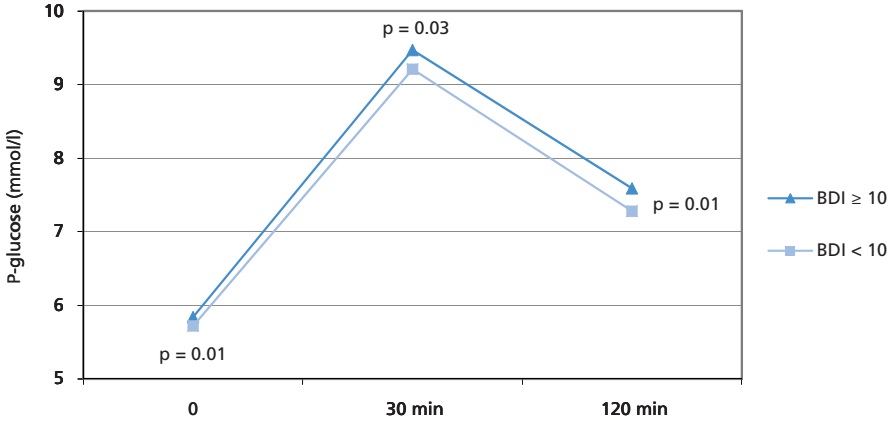

FIGURE 2. Plasma glucose concentrations during the oral glucose tolerance test according to mental well being among subjects from the Helsinki Birth Cohort. Adjusted for gender, age and BMI. BDI = Beck depression inventory score.

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Next we calculated the odds of having mild to moderate depressive symptoms in different categories of glucose tolerance. Among diabetic subjects 23.6% had depressive symptoms, compared to 16.7% of subjects with normal glucose tolerance (OR = 1.77, 95% CI = 1.30 to 2.43, p < 0.001). While further adjustments for age and BMI lowered the odds ratio, it still remained significant (OR = 1.43, p = 0.035) (Table 6). After adding CVD to the regression model depressive symptoms were no longer significantly more prevalent among diabetic subjects (Table 6). Formal mediation analysis revealed that CVD is likely to act as a mediator in the association between DM and depressive symptoms (Sobel's test statistic = 4.00. p < 0.001).

Subjects with CVD had more than a twofold risk of having depressive symptoms compared to those without CVD (OR = 2.61, 95% CI = 1.88 to 3.62, p < 0.001) Controlling for age and BMI did not significantly change the result and adding DM to the model did not further explain the variability in depressive symptoms. The results remained unchanged after excluding subjects with a history of stroke (n = 53). Differences in depressive symptom scores among subjects with DM versus CVD are presented graphically in Figure 3.

TABLE 6. Odds ratios (OR) for having a Beck Depression Inventory score (BDI) ≥ 10 in different categories of glucose tolerance and CVD among 2003 subjects from the Helsinki Birth Cohort. Normal glucose tolerance/no CVD was used as a reference category.

	Model 1		Model 2		Model 3		Model 4	
Glucose tolerance	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Normal	1.0		1.0		1.0		1.0	
IFG/IGT	1.41 (1.10 to 1.83)	0.007	1.38 (1.07 to 1.78)	0.014	1.27 (0.98 to1.64)	0.074	1.23 (0.95 to1.61)	0.111
DM	1.78 (1.30 to 2.44)	< 0.001	1.76 (1.28 to 2.41)	< 0.001	1.43 (1.03 to 2.00)	0.035	1.28 (0.91 to 1.80)	0.159
CVD								
No	1.0		1.0		1.0		1.0	
Yes	2.62 (1.89 to 3.64)	< 0.001	2.53 (1.82 to 3.51)	< 0.001	2.38 (1.70 to 3.31)	< 0.001	2.30 (1.64 to 3.22)	< 0.001

Model 1 gender adjusted, Model 2 + age, Model 3 + BMI, Model 4 + CVD/DM. IFG = impaired fasting glucose, IGT = impaired glucose tolerance, DM = diabetes mellitus, BDI = Beck Depression Inventory, CVD = cardiovascular disease, BMI = body mass index.

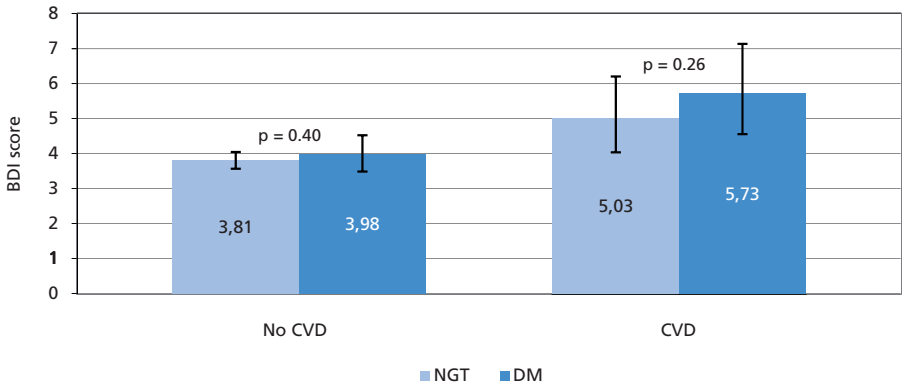

FIGURE 3. Depressive symptoms according to CVD and glucose tolerance among subjects from the Helsinki Birth Cohort. BDI = Beck Depression Inventory, NGT = normal glucose tolerance, DM = diabetes, CVD = cardiovascular disease.

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5.3 Treating diabetic subjects with an antidepressant

We performed two controlled clinical trials with diabetic patients treated with paroxetine (studies III and IV). In the first trial 14 women, and in the second trial 43 men and women entered treatment. Baseline characteristics of the subjects in the two trials are shown in Table 7.

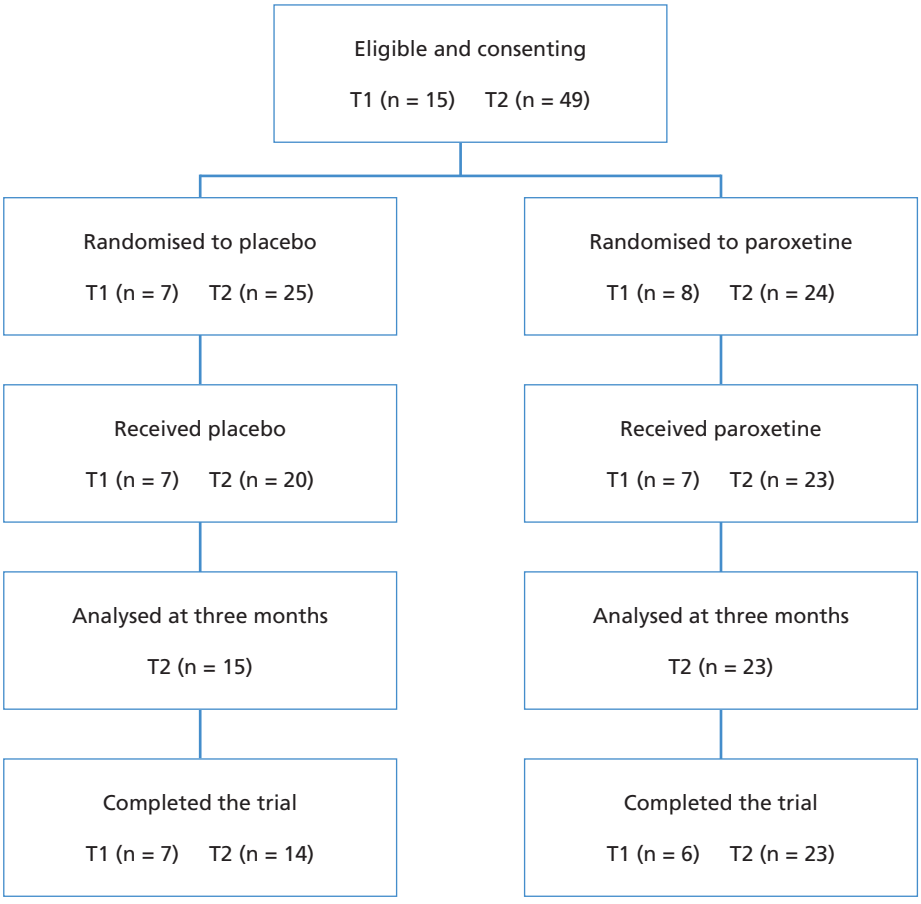

FIGURE 4. Flow chart on allocation and drop outs in two clinical trials where mildly depressed diabetic subjects were treated with paroxetine or placebo. T1 = 10 week pilot rial, T2 = 6 month double blind trial.

TABLE 7. Baseline characteristics of mildly depressed patients with type 2 diabetes. Subjects were treated with pareoxetine or placebo during 10 weeks (trial 1) or 6 moths (trial 2).

	Trial 1				Trial 2			
	Placebo (n = 6)		Paroxetine (n = 7)		Placebo (n = 20)		Paroxetine (n = 23)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sex (M/F)	0/6		0/7		16/4		17/6	
Age (years)	62.3	11.5	61.1	8.6	59.5	6.0	59.2	5.4
Body mass index (kg/m^2)	30.1	6.3	31.6	3.0	32.0	5.3	31.7	5.5
GHbA1c (%)	6.9	0.4	7.5	0.8	8.7	1.3	8.5	0.9
Fasting serum glucose (mmol/l)	8.4	1.3	8.9	2.8	10.4	3.4	10.4	3.7
Beck's Depression Inventory	13.0	9.2	13.7	7.4				
Hospital Anxiety and Depression Scale (total score)					15.7	5.5	14.0	5.2

Results from trial 1

After ten weeks of treatment the mean decrease in GHbA1c was 0.44%-units (95% CI= -0.78 to -0.10, p= 0.019) in the paroxetine group (Table 8). In the placebo group GHbA1c decreased only 0.07%-units (95% CI = -0.41 to 0.28, p = 0.64). When comparing the two groups to each other there was a trend towards a more beneficial outcome in the paroxetine group, although not statistically significant (p = 0.08). Fasting blood/serum glucose improved in both groups but the groups did not differ significantly from each other (Table 8).

Improvement in overall quality of life as measured by RAND-36 did not differ between the groups (p = 0.59). According to investigator-rated scales there was a decrease of anxiety and depressive symptoms in the paroxetine group, but a significant difference between paroxetine- and placebo-treated participants was not reached. All trial participants improved according to the patient-rated depression scale BDI, however, with no significant difference between the groups (paroxetine: -6.6 points, 95% CI = -11.9 to -1.2, placebo: -5.8 points, 95% CI = -12.4 to 0.7, p for difference between groups = 0.83) (Table 8).

TABLE 8. Means (and 95% CI) of metabolic and mental health parameters for type 2 diabetic subjects treated with pareoxetine or placebo during a 10 week trial.

	Placebo		Paroxetine		
	mean change	95% CI	mean change	95% CI	p for difference between groups
Body weight (kg)	-0.83	-1.87 to 0.20	-0.71	-2.83 to 1.40	0.908
Body mass index (kg/m2)	-0.31	-0.71 to 0.09	-0.26	-1.08 to 0.55	0.908
Fasting serum glucose (mmol/l)	-0.78	-1.39 to -0.17	-1.47	-3.80 to 0.86	0.529
HbA1c (%)	-0.07	-0.41 to 0.28	-0.44	-0.78 to -0.10	0.080
S-cortisol (nmol/l)	104.83	-53.68 to 263.35	-42.29	-165.97 to 81.40	0.089
Energy expenditure (kcal/d)	-33.33	-198.82 to 132.15	28.57	-135.17 to 192.32	0.523
Hamilton's Anxiety Scale	-0.67	-5.53 to 4.20	-5.43	-10.35 to -0.51	0.116
Montgomery-Åsberg's Rating Scale	-1.50	-5.67 to 2.67	-4.00	-7.20 to -0.80	0.251
Beck's Depression Inventory	-5.83	-12.38 to 0.72	-6.57	-11.93 to -1.21	0.829
RAND-36	129.37	-16.93 to 275.67	60.51	-189.76 to 310.79	0.586

Results from trial 2

After three months of treatment there was a statistically significant improvement in $GHbA_{1c}$ in the paroxetine group (mean change from baseline= 0.69%-units, p=0.001) and the difference between groups was significant. (Figure 5). Controlling for baseline $GHbA_{1c}$, HADS, SF-36 or BMI did not influence the result. After six months the change from baseline in $GHbA_{1c}$ was no longer significant in either group and there was no difference between the groups (Table 9).

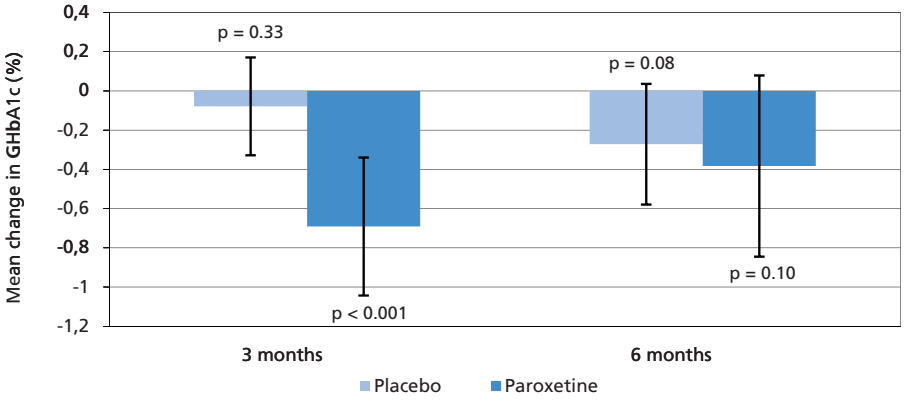

FIGURE 5. Mean changes in glycosylated haemoglobin A_{1c} ($GHbA_{1c}$) from baseline in 43 type 2 diabetic subjects receiving placebo or paroxetine. P-value for difference between groups at 3 months = 0.018, at six months = 0,693. P-values were calculated using ANCOVA with the baseline value as a covariate. Error bars represent 95% CI:s of means.

TABLE 9. Means (and 95% CI) of metabolic parameters for subjects who completed trial 2. Mean differences between groups were obtained with analyses of covariance with the baseline value as a covariate. Means at three and six months are estimated marginal means. GHbA1c= glycosylated haemoglobin A_{1c}

	Placebo (n = 14)	Paroxetine (n = 23)	Placebo–Paroxetine	P
	Mean (95% CI)	Mean (95% CI)	Mean difference (95% CI)	
GHbA 1 c (%)				
Baseline	9.0 (8.2 to 9.8)	8.5 (8.0 to 8.9)	0.54 (-0.24 to 1.31)	0.169
3 months	8.5 (8.2 to 8.9)	7.9 (7.6 to 8.2)	0.59 (0.11 to 1.07)	0.018
6 months	8.4 (7.9 to 8.9)	8.3 (7.9 to 8.7)	0.13 (-0.52 to 0.78)	0.693
Serum glucose (mmol/l)				
Baseline	10.7 (8.6 to 12.8)	10.4 (8.8 to 12.0)	0.27 (-2.27 to 2.81)	0.829
3 months	10.7 (9.8 to 12.5)	9.7 (8.2 to 11.1)	1.05 (-1.26 to 3.35)	0.362
6 months	10.8 (9.1 to 12.5)	10.2 (8.8 to 11.5)	0.59 (-1.56 to 2.74)	0.580
Serum C-peptide (nmol/l)				
Baseline	0.6 (0.3 to 0.8)	0.7 (0.5 to 0.9)	-0.15 (-0.46 to 0.15)	0.310
3 months	0.8 (0.6 to 0.9)	0.8 (0.7 to 1.0)	-0.04 (-0.25 to 0.16)	0.656
6 months	0.7 (0.6 to 0.9)	0.8 (0.7 to 0.9)	-0.04 (-0.21 to 0.14)	0.682
Body mass index (kg/m^2)				
Baseline	31.1 (29.3 to 34.1)	31.7 (29.8 to 33.1)	-0.66 (-4.14 to 2.82)	0.704
3 months	31.1 (30.7 to 31.6)	31.0 (30.6 to 31.3)	0.15 (-0.44 to 0.73)	0.614
6 months	31.4 (30.9 to 31.9)	31.2 (30.8 to 31.6)	0.15 (-0.47 to 0.77)	0.629

Overall quality of life, as measured by SF-36, was significantly improved in the paroxetine group (Figure 5). After three months of treatment there was a statistically significant difference between the two treatment groups in quality of life (mean difference = 11.0 points, p = 0.039) which remained significant after controlling for baseline SF-36 score, $GHbA_{1c}$ and BMI (Table 10). At the end of the six month trial the improvement in SF-36 score from baseline was still statistically significant in the paroxetine group, but there was no longer any statistically significant difference between the two treatment groups (Table 10) (Figure 6).

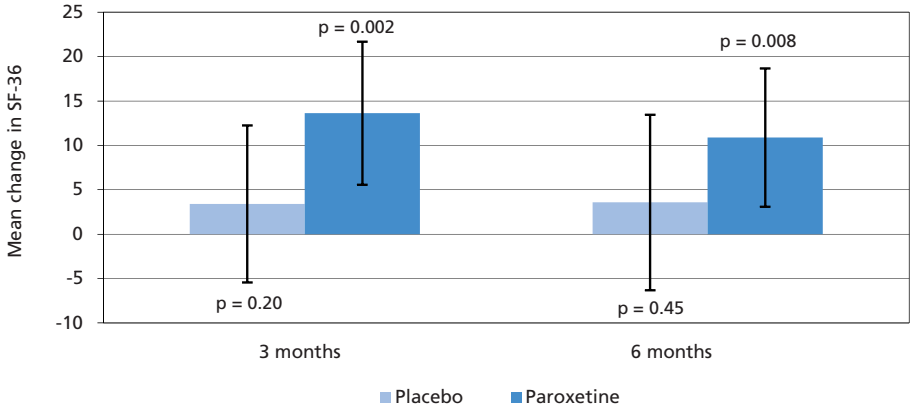

FIGURE 6. Mean changes in SF-36 quality of life score from baseline in type 2 diabetic subjects receiving placebo or paroxetine. P-value for difference between groups at 3 months = 0.039, at six months = 0,135. P-values were calculated using ANCOVA with the baseline value as a covariate. Error bars represent 95% CI:s of means.

Anxiety and depressive symptoms decreased in both groups with a trend for a stronger effect in the paroxetine group. However, no statistically significant difference between the groups was detected at any time point (Table 10). Neither was any difference observed in body weight, BMI, serum glucose, serum c-peptide, serum cortisol or serum SHBG.

TABLE 10. Means (and 95% CI:s) of quality of life and mental health rating scores for subjects who completed the study. Mean differences between groups were obtained with analyses of covariance with the baseline value as a covariate. Means at three and six months are estimated marginal means. HADS = Hospital Anxiety and Depression Scale.

	Placebo (n=14)	Paroxetine (n=23)	Placebo-Paroxetine	
	Mean (95% CI)	Mean (95% CI)	Mean difference (95% CI)	p
SF-36				
Baseline	51.2 (42.6 to 59.8)	56.2 (48.6 to 63.7)	-4.7 (-16.3 to 6.4)	0.381
3 months	59.1 (51.2 to 67.0)	70.1 (63.4 to 76.7)	-11.0 (-21.4 to -0.6)	0.039
6 months	56.9 (47.5 to 66.2)	65.8 (58.5 to 73.6)	-8.9 (-20.8 to 2.9)	0.135
HADS total score				
Baseline	15.8 (12.5 to 19.1)	14.0 (11.7 to 16.2)	1.8 (-1.9 to 5.6)	0.327
3 months	11.2 (9.0 to 13.5)	8.5 (6.6 to 10.4)	2.8 (-0.2 to 5.7)	0.066
6 months	12.1 (8.9 to 15.4)	10.2 (7.6 to 12.7)	1.9 (-2.2 to 6.1)	0.351
HADS depression score				
Baseline	8.2 (6.2 to 10.2)	7.3 (5.8 to 8.7)	0.9 (-1.4 to 3.4)	0.416
3 months	5.1 (3.8 to 6.3)	3.8 (2.7 to 4.9)	1.3 (-0.4 to 2.9)	0.129
6 months	6.2 (4.6 to 7.7)	5.5 (4.3 to 6.6)	0.7 (-1.2 to 2.7)	0.448
HADS anxiety score				
Baseline	7.6 (5.8 to 9.4)	6.7 (5.6 to 7.8)	0.9 (-1.1 to 2.8)	0.366
3 months	6.2 (4.8 to 7.6)	4.6 (3.5 to 5.8)	1.6 (-0.2 to 3.4)	0.085
6 months	6.0 (4.0 to 8.0)	4.7 (3.2 to 6.2)	1.3 (-1.2 to 3.8)	0.312

In order to elucidate whether the response to paroxetine was stronger among patients who fulfilled DSM-IV criteria for mild depression we performed a post hoc subgroup analysis of covariance. In the subgroup of subjects with five to six DSM-IV depressive symptoms [n(placebo) = 4, n(paroxetine) = 5] a significant benefit of paroxetine was seen in serum glucose levels after six months (mean difference between groups = 3.88 mmol/l, 95%CI = 0.47 to 7.29, p = 0.032).

5.4 Cognitive performance in different stages of glucose tolerance

In study V the sample consisted of 1,279 subjects from the original clinical cohort, who also completed a test on cognitive performance (CogState®). After exclusion of subjects with a history of stroke (n = 29), type 1 diabetes (n = 1) and invalid test results (n = 3), the sample consisted of 585 men and 658 women. The subjects who attended the cognitive test were similar in age, sex, education and prevalence and duration of DM to those who did not attend.

Inferior cognitive performance correlated with being female, being older, and having a lower educational attainment. Median test performance scores are shown in Table 11. In Table 12 we show the characteristics of the study participants according to glucose tolerance. Age, sex and education were added into all regression models since they were strongly associated with the cognitive test scores.

TABLE 11. Median reaction times and accuracy of performance in the CogState® test among subjects from the Helsinki Birth Cohort.

		N	Median (%)	25th percentile	75th percentile
SRT (milliseconds)		1,241	326	297	375
CRT (milliseconds)		1,229	564	510	628
DA (milliseconds)		1,233	483	423	560
WM (milliseconds)		1,235	855	756	1,009
WMhr (errors)	None	480	38.9		
	One	312	25.3		
	Two or more	443	35.9		
AL (milliseconds)		1,233	1,827	1,549	2,182
ALhr (%)		1,233	74.0	66.0	78.9

SRT = simple reaction time, CRT = choice reaction time, DA=divided attention (reaction time), WM=working memory (reaction time), WMhr = working memory hit rate, AL = associate learning (reaction time), ALhr = associate learning hit rate (% correct answers of all given).

TABLE 12. Characteristics of subjects from the Helsinki Birth Cohort Study, who took the CogState® test. Percents represent within glucose tolerance group values. P-value is given for the difference when each group is compared to known DM.

		N	% or Mean (SD)	p
Male sex	NGT	295	43.1%	<0.001
	IFG/IGT	188	48.7%	0.006
	new DM	50	52.1%	0.087
	known DM	52	67.5%	referent
Age at testing (years)	NGT	684	63.7 (2.8)	0.409
	IFG/IGT	386	64.2 (3.0)	0.014
	new DM	96	64.0 (2.8)	0.213
	known DM	77	63.3 (2.6)	referent
Birth weight (g)	NGT	684	3,433 (463)	0.004
	IFG/IGT	386	3,381 (486)	0.069
	new DM	96	3,406 (514)	0.080
	known DM	77	3,253 (571)	referent
Coronary heart disease	NGT	18	2.6%	<0.001
	IFG/IGT	24	6.2%	<0.001
	new DM	11	11.5%	0.002
	known DM	18	23.4%	referent
Lowest education	NGT	218	31.9%	0.677
	IFG/IGT	129	33.4%	0.875
	new DM	34	35.4%	0.997
	known DM	28	36.4%	referent
Highest education	NGT	152	22.2%	0.114
	IFG/IGT	80	20.7%	0.234
	new DM	12	12.5%	0.999
	known DM	10	13.0%	referent

NGT = normal glucose tolerance, IFG/IGT = impaired fasting glucose/impaired glucose tolerance, new DM = diabetes diagnosed at our clinic 2001–2004, known DM = diabetes diagnosed before clinical study.

Glucose tolerance and cognitive performance

We grouped the subjects according to different stages of impaired glucose regulation (IFG/IGT, new DM and known DM) and used subjects who had normal glucose tolerance as the referent group. Only subjects with known DM had longer reaction times and fewer correct responses than NGT subjects (Table 13). Controlling for BMI did not attenuate the results. Subjects with IFG/IGT or new DM did not differ from the NGT group in any of the tasks. After pooling new and known DM together the DM group did not differ from NGT in any of the cognitive tasks (all p-values > 0.05).

TABLE 13. Effect of glucose tolerance on cognitive performance. Numbers indicate per cent differences in reaction times and accuracy of performance (hit rate). For the working memory task accuracy of performance is given as odds ratios for having made two or more errors compared to none or one. Subjects with normal glucose tolerance were used as a reference category. Analyses were adjusted for sex, age and education.

		% (or OR*)	(95% CI)		p
SRT	IFG/IGT	1.6	-0.7	4.0	0.180
	new DM	2.3	-1.7	6.5	0.256
	known DM	3.7	-0.8	8.4	0.110
CRT	IFG/IGT	1.4	-0.7	3.5	0.190
	new DM	0.1	-3.3	3.7	0.954
	known DM	5.3	1.2	9.5	0.011
DA	IFG/IGT	0.8	-1.9	3.5	0.562
	new DM	-1.6	-6.0	3.0	0.485
	known DM	2.1	-3.0	7.4	0.433
WM	IFG/IGT	1.0	-1.6	3.7	0.442
	new DM	1.1	-3.3	5.6	0.630
	known DM	5.7	0.6	11.1	0.027
WMHR	IFG/IGT	*1.0	0.8	1.3	0.957
	new DM	*1.1	0.7	1.8	0.577
	known DM	*1.9	1.2	3.1	0.010
AL	IFG/IGT	-0.2	-3.2	2.8	0.879
	new DM	-1.2	-6.2	4.0	0.645
	known DM	6.7	0.8	13.0	0.027
ALHR	IFG/IGT	0.3	-1.0	1.7	0.629
	new DM	0.0	-2.3	2.3	0.994
	known DM	-3.1	-5.6	-0.5	0.018

NGT = normal glucose tolerance, IFG/IGT = impaired glucose tolerance, new DM = diabetes diagnosed at our clinic 2001–2004, known DM = diabetes diagnosed before clinical study, SRT = simple reaction time, CRT = choice reaction time, DA = divided attention (reaction time), WM=working memory (reaction time), WMh = working memory hit rate (two or more errors), AL = associate learning (reaction time), ALhr = associate learning hit rate (% correct answers of all given).

Differences between subjects with known and newly diagnosed DM

Subjects with known DM were different from those with new DM in several aspects. Coronary heart disease, high BMI, high BDI scores and low birth weight were more common among those with known DM after controlling for sex, age and education. However, their level of education was similar to that of the newly diagnosed subjects (Table 12).

The year of diagnosis was available for 82% (n = 63) of the subjects with known diabetes. The mean duration of diagnosed DM was 7.6 years (range 0.01 to 22.5 years). There was no linear association between known duration of diabetes and cognitive performance among these subjects.

Tests of mediation

We used Sobel's formal test for mediation (Sobel 1982; Baron and Kenny 1986) to test wether coronary heart disease (CHD) and depressive symptoms acted as mediators of the association between diabetes and poor cognitive performance. Presence of CHD was associated with a longer reaction time in the AL task (+9.6%, p = 0.002) and weakly associated with a longer reaction time in the CRT task (+3.9%, p = 0.058). When presence of CHD was added to the models predicting cognitive performance, the effect of known DM on AL reaction time was rendered non-significant (Table 13). The association between known DM and AL reaction time was found to be mediated by the presence of CHD (Sobel test statistic = 2.54, p = 0.011). CHD did not mediate the associations between other cognitive tasks and known DM.

The BDI score was positively associated with reaction time in the WM task (+1.6% for each point increase in BDI score, p = 0.019). Adding BDI score to the models predicting cognitive performance attenuated the association between known DM and WM reaction time by 17%. The association between known DM and WM reaction time was rendered non-significant (p= 0.067) but using Sobel's formal test for mediation did not reveal a statistically significant mediation by BDI (Sobel test statistic = 1.8, p = 0.070).

5.5 Birth weight as a modifying factor of risks and complications of diabetes

Birth weight and depression

In study II logistic regression analyses revealed that subjects who were born with a low birth weight (≤ 2,500 g, n = 72) had a significantly higher risk of having depressive symptoms (OR = 2.64, 95% CI = 1.42 to 4.91, p = 0.002) compared to those weighing over 2,500 g. Controlling for age, BMI, CVD, DM and gestational age did not influence the result.

We pooled subjects with DM or CVD or both into one group representing subjects with a chronic disease (n = 451). In a linear regression analysis with the BDI score as the dependent variable, the interaction between birth weight and having a chronic disease was marginally significant (p = 0.058). Subsequently, we analyzed subjects with low (≤ 2,500 g) and normal birth weight (> 2,500 g) separately. The association between BDI score and having a chronic disease was significant in both groups but it was twice as strong in the group with low birth weight as in the group with birth weight > 2,500 g (Figure 7). Thus low birth weight was found to strengthen the previously established association between chronic disease and depression.

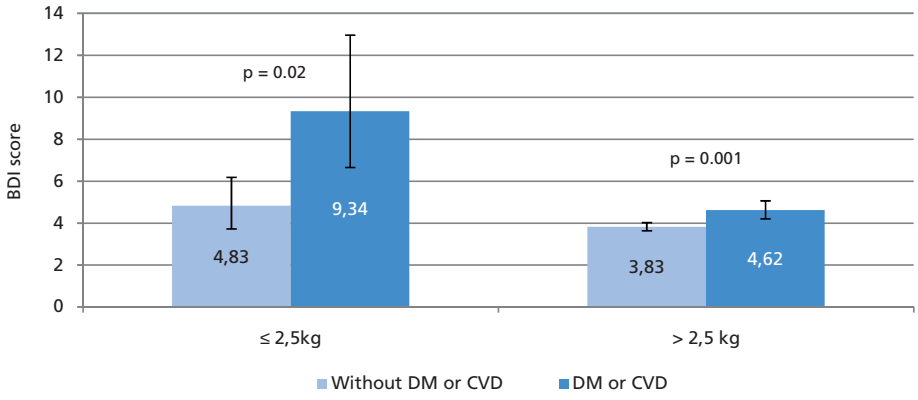

FIGURE 7. Depressive symptoms according to birth weight and presence of chronic disease among subjects from the Helsinki Birth Cohort Study. DM = diabetes, CVD = cardiovascular disease, BDI = Beck Depression Inventory.

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Birth weight and cognitive performance

In study V birth weight was negatively associated with reaction time in the DA task (-3.8%/kg, 95% CI = -6.5 to -1.1, p = 0.005) and with hit rate in the AL task (-1.5%/kg, 95% CI = -0.1 to -2.9, p = 0.036) after adjustment for age, sex and gestational age. The result was not altered by further adjustment for CHD, DM, depressive symptoms and education. We also found a significant interaction between birth weight and known DM when predicting the reaction times in the WM (p = 0.002) and AL (p = 0.009) tasks and a marginally significant interaction when predicting the CRT task (p = 0.052). A low birth weight was associated with longer WM and AL reaction times only among subjects with known DM, whereas the reaction times of

subjects in other glucose tolerance categories were not influenced by birth weight (Figure 8). Adding CHD to the interaction models did not affect this finding.

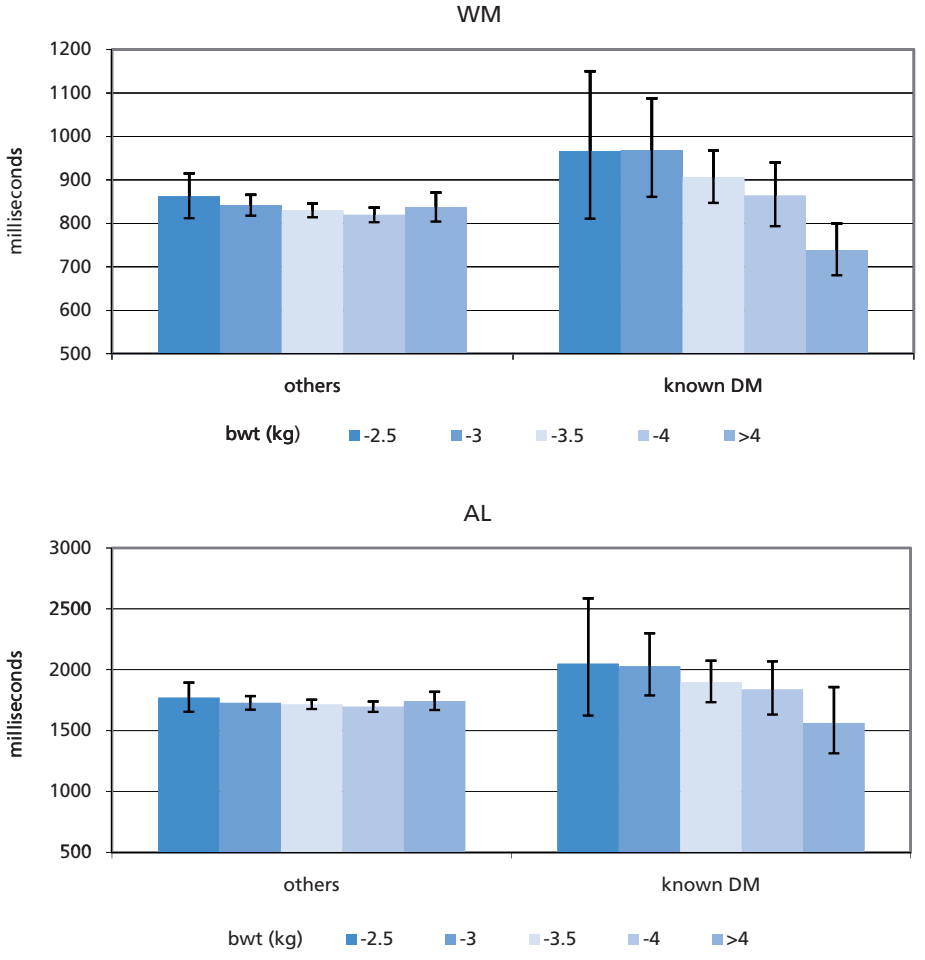

FIGURE 8. Reaction times in working memory (WM) and associate learning (AL) tasks for known diabetic subjects compared to others according to birth weight (bwt). P-values for interaction between birth weight and known DM in WM: p = 0.002, in AL: p = 0.009. Known DM = diabetes diagnosed before clinical study 2001–2004, other = subjects with normal glucose tolerance, impaired glucose tolerance or newly diagnosed diabetes.

6 Discussion

6.1 Depression and diabetes

The prevalence of diabetes in our study population was 15.5%, which is consistent with previous population based studies (Peltonen, Korpi-Hyövälti et al. 2006; Reunanen, Virta et al. 2008). The prevalence of depressive symptoms was 19.1%. This is somewhat higher than previously reported (Kessler, McGonagle et al. 1994; Kessler, Chiu et al. 2005; Pirkola, Isometsä et al. 2005), which is probably due to the older age of our study population and the fact that self report scales give a higher estimate of depression than formal diagnostic assessment (Musselman, Betan et al. 2003). In accordance with previous findings (Lustman, Anderson et al. 2000; Anderson, Freedland et al. 2001) we showed that type 2 diabetes was positively associated with the occurrence of depressive symptoms. Among diabetic subjects almost one fourth (23.6%) had a BDI score ≥10p.

The strength of our study is that we did not rely on hospital records or self-report for diagnosis of diabetes. Type 2 diabetes often goes undiagnosed for many years (King and Rewers 1993) and studies which rely on hospital records or self-report for diagnosis of their subjects are prone to selection-bias. We were also able to control the results for birth weight, which is essential since low birth weight has been associated with both type 2 diabetes and depression and might thus act a confounding factor.

Depression has previously been regarded as a co-morbid condition resulting from the daily burden of having diabetes and/or its complications, or from having a chronic disease. Some studies even suggest that it is the complications associated with diabetes that may induce depressive affect rather than having diabetes per se (Pouwer, Beekman et al. 2003; Bruce, Casey et al. 2006). In our study the association between diabetes and depressive symptoms was rendered non-significant after controlling for CVD, whereas the presence of CVD, regardless of diabetes, more than doubled the odds of having depressive symptoms.

Our findings are consistent with those of Pouwer et al. (Pouwer, Beekman et al. 2003) who compared diabetic subjects with co-morbid disease (CVD, asthma or emphysema) to subjects with diabetes without co-morbidities and found that only the ones who had diabetes in combination with another disease differed from healthy controls in terms of depression. These findings may be partly explained by the fact that subjects with DM but without CVD often have less symptoms of disease than those with both DM and CVD and would thus be less distressed by their condition.

However, during the past few years evidence has emerged arguing for another type of link. Depression has been shown to precede type 2 diabetes and has lately rather been regarded as a risk factor for the disease. In addition to behavioural pathways associated with depression, including altered dietary and exercise habits, there are several physiological mechanisms which may underlie the associations between diabetes, CVD and depression.

Subclinical hypercortisolism and other characteristics of an impaired HPA-axis are often seen in depressed subjects (Pariante and Lightman 2008; Champaneri, Wand et al. 2010). Furthermore there are elevated levels of inflammatory markers and cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6) and Tumor Necrosis Factor α (TNF-α) (Weinstein, Deuster et al.; Gimeno 2009; Stewart, Rand et al. 2009). Proinflammatory cytokines are known to activate the HPA-axis and both cortisol and cytokines can have damaging effects on the central nervous system thus contributing to the pathogenesis of depression (Miller and O'Callaghan 2005; Herbert, Goodyer et al. 2006).

Likewise a range of inflammatory components seem to play an important role in the development of diabetes. Several studies have found associations between various inflammatory markers and type 2 diabetes (Schmidt, Duncan et al. 1999; Champaneri, Wand et al. 2010). Most recently a longitudinal study by Bertoni et al. showed that the inflammatory markers CRP, IL-6 and fibrinogen predicted the incidence of type 2 diabetes. Another frequently observed feature of type 2 diabetes is hypercortisolism and alterations of the HPA-axis. Perturbation of the HPA-axis has been linked to insulin resistance and type 2 diabetes in several studies (Phillips, Barker et al. 1998; Björntorp, Holm et al. 1999; Chiodini, Adda et al. 2007).

Thus, several similar alterations are seen in depression and type 2 diabetes and the same factors seem to promote both insulin resistance and depression. Hence, a biological basis for the co-morbidity is conceivable.

6.1.1 Treating depression in diabetic subjects

Previous studies have shown that treating depression can improve glucose tolerance in addition to improving mood. We observed that the antidepressive agent paroxetine had a beneficial effect on $GHbA_{1c}$ and quality of life when compared to placebo after three months of treatment. However, when treatment was continued the difference between groups was no longer significant. In the preceding pilot study we found no statistically significant difference between the treatment groups in either glucose tolerance or mental well being.

The pilot study had several weaknesses, i.e. small sample size, (N = 15), lack of double-blindness, short duration (10 weeks), and a rather good baseline metabolic control (mean $GHbA_{1c}$ 7.5 %). We aimed at overcoming the weaknesses of the pilot trial by performing the 6-month double-blind trial with stricter inclusion criteria

for glycaemic control (>7 % vs. ≥ 6.5 % in the previous trial). In the 6 month trial we saw a minor effect of parxetine on $GHbA_{1c}$.

Our primary outcomes, which we considered to be clinically significant, were a 0.8%-units difference in $GHbA_{1c}$ and a 10 points difference in SF-36 when comparing paroxetine to placebo. Our finding of a 0.59%-units difference) but in $GHbA_{1c}$ did not reach our primary definition of clinical significance and the effect was transient. A similar transient treatment effect was seen in a study by Gray et al (Gray, Fujioka et al. 1992) exploring the effect of fluoxetine on $GHbA_{1c}$.

One explanation to the limited findings could be related to the low level of depression in our sample. Only ten subjects fulfilled the DSM-IV criteria for mild depression. A study by Weber-Hamann et al. suggests that the effect of antidepressants on glycaemic control is related to the improvement in depressive symptoms and showed that only the ones who responded to paroxetine treatment showed improved insulin sensitivity (Weber-Hamann, Gilles et al. 2006). We did not see a significant improvement in depressive symptoms by the end of six months, which could explain the lack of effect on glycaemic control. A statistically, significant improvement in SF-36 was reached after three months of treatment. However, by the end of the trial, the effect on quality of life was somewhat diminished and the difference between groups was no longer significant.

Our post hoc subgroup analysis suggested that a possible long term effect on glucose tolerance could be confined to those who fulfil criteria for clinical depression. Lack of power restricted our possibility to test whether this effect correlated with improvement in depressive symptoms.

Based on previous studies with fluoxetine we expected to see greater effects of paroxetine on metabolic parameters. It is possible that the effect of paroxetine differs from that of fluoxetine despite both being selective serotonin re-uptake inhibitors (SSRI). SSRI's are usually associated with weight loss. However, a recent meta-analysis found that the marginal weight loss seen in short term treatment of depression with paroxetine shifted into weight gain when treatment was continued for over four months (Serretti and Mandelli 2010). A study performed in vitro indicated that paroxetine could even induce insulin resistance in rat liver cells (Levkovitz, Ben-shushan et al. 2007). This could partly explain why we did not see the expected beneficial effect on glucose tolerance with paroxetine.

Our study was the first long-term double-blind placebo-controlled study where paroxetine was used to treat type 2 diabetic subjects with mild depressive symptoms and effects on mental well being and metabolic control were simultaneously assessed. Our findings suggest that diabetic patients with sub-threshold depression do not benefit from a long-term treatment with paroxetine.

6.2 Type 2 diabetes and cognitive ability

The association between type 2 diabetes and cognitive decline has been well established (Awad, Gagnon et al. 2004). Less has been published about how prediabetic stages affect cognition and about the effects of having previously diagnosed diabetes as opposed to newly diagnosed.

In study V we found no association between newly diagnosed diabetes or lesser impairments in glucose regulation and cognitive performance. However, subjects with known diabetes had a consistently poorer level of performance than subjects with normal glucose tolerance in most of the tested cognitive domains.

The absence of a correlation between IFG/IGT and cognitive performance is consistent with the findings of Lindeman et al. and Kumari et al. (Lindeman, Romero et al. 2001; Kumari and Marmot 2005). However there are also studies where a negative effect on cognitive performance has already been noted among subjects with IGT (Kalmijn, Feskens et al. 1995; Vanhanen, Koivisto et al. 1998; Bonito, Fraia et al. 2007).

Our finding regarding the effect of known DM on cognition might be attributed to a longer duration of the disease among those who already have a diagnosis. Although part of the subjects with newly diagnosed diabetes might have had DM for years without knowing it, we believe that those who have been diagnosed with DM have on average developed the disease earlier than those who have not been diagnosed. Thus, they have potentially been affected by impaired glucose regulation during a longer time period and developed more co-morbidities. Another possibility is that those who have a diagnosis have a more complicated and symptomatic form of disease to begin with. As shown in table 12 the subjects with known DM differed from the ones with newly diagnosed DM in several aspects. They had higher BMI, more CHD and were born with a lower birth weight.

One apparent mechanism by which cognitive impairment can develop in diabetic subjects is through the macrovascular and microvascular co-morbidity associated with diabetes. In our sample subjects with known DM had more CHD than those with newly diagnosed DM. However, CHD only mediated the effect of known DM in one task (AL reaction time). Even so, this does not exclude the possibility that vascular changes play a role in mediating impairment of other cognitive domains as well. In fact, a recent work by Park et al. shows that intracranial atherosclerosis can be present among subjects with the metabolic syndrome independently of extracranial atherosclerosis (Park, Kwon et al. 2007), which indicates that CHD may not always be a very sensitive marker for intracranial macrovascular disease.

Other possible mediators are hyperglycaemia, hyperinsulinaemia, dyslipidaemia and microvascular disease. Unfortunately we had no data on microvascular disease among the subjects, and their blood samples were not drawn at the time of cognitive testing. Thus we could not explore the mediating effects of

these factors. However, based on samples of blood glucose taken from a subgroup of the study subjects (unpublished data) we speculate that subjects with known DM have worse glucose homeostasis than subjects with new DM. This could give rise to more microvascular changes in the brain (Mäkimattila S, Malmberg-Cèder K et al. 2004) and thus explain part of our result.

6.2.1 Premorbid cognitive ability

The association between type 2 diabetes and low cognitive ability could also be influenced by pre-morbid cognitive ability. A low general ability might act as a risk factor for developing type 2 diabetes and thus subjects with diabetes would have lower cognitive ability already before developing the disease. Most studies on the effect of diabetes on cognition are controlled for education. However, our results from study I indicate that early intellectual ability test scores explain less than 25% of the variability in educational attainment. Thus controlling for education can only partly account for pre-morbid cognitive ability. But is pre-morbid cognitive ability a crucial confounding factor when assessing the effect of diabetes on cognition?

Since previous findings on the subject have been contradictory we set out to explore the effect of early intellectual ability on the risk of developing type 2 diabetes. We found no association between intellectual ability in early adulthood and impairment in glucose regulation at age 61 years. However, type 2 diabetes was predicted by low educational attainment. These results suggest that diabetes is predicted by aspects of educational attainment above and beyond those reflected in measures of intellectual ability. These may include factors related to socio-economic status, place of residence and lifestyle, which is illustrated by the fact that controlling for BMI attenuated the association between education and prevalence of diabetes.

Our results differ from those of Olsson et al. (Olsson, Hulting et al. 2008)# but there are several important differences between the studies which may explain the different results. The Olsson study did not control for current education or socio-economic status, which seem to be of major importance. Furthermore, the study samples differed in age at both the initial testing for intellectual ability and at assessment of diabetes. In the Olsson study subjects had an average age of 42 and diabetes diagnosis was based on interviews. The overall diabetes prevalence was low, being only 0.8%. This young population is likely to represent an extreme of the type 2 diabetes spectrum and thus the association with intellectual ability may be dissimilar in this subgroup. The public health burden of type 2 diabetes is more accurately indicated by our study, with a 21% prevalence of diabetes assessed by OGTT at 61 years.

To conclude, better educational attainment seems to protect men from developing type 2 diabetes whereas we found no evidence that intellectual ability

per se would do so. Longitudinal studies with assessment of cognitive ability at a young age and subsequent follow up with a focus on diabetes and cognition would shed more light into the association between pre-morbid and post-morbid cognitive ability in relation to diabetes.

6.3 Birth weight as a modifying factor

As discussed previously, the temporal and causal pathways linking depression, type 2 diabetes, and cognitive performance are complex. It seems likely that there are yet unresolved factors underlying all of these disorders which make certain people more vulnerable to this cluster of diseases. A possible common causal link between depression, type 2 diabetes, and cognitive decline is altered function of the HPA axis since elevated cortisol levels have been reported in all of these disorders (Nemeroff, Widerlov et al. 1984; Freeman, Nixon et al. 1987; Chiodini, Torlontano et al. 2005; Weber-Hamann, Gilles et al. 2006) (Rosmond and Bjorntorp 2000; Kajantie 2006). Altered HPA function has been associated with a small body size at birth (Phillips, Barker et al. 1998). Therefore we set out to explore the impact of birth size on the above mentioned disorders and their associations.

6.3.1 Depression

In accordance with previous findings we observed that low birth weight (≤ 2,500 g) was associated with depressive symptoms (Thompson, Syddall et al. 2001; Gale and Martyn 2004; Alati, Lawlor et al. 2007; Räikkönen, Pesonen et al. 2007). This association remained equally strong even after adjusting for the occurrence of cardiovascular disease and diabetes - i.e. disorders that might lie in the causal pathway between low birth weight and depression. A novel finding was that low birth weight increased the association between disease (CVD or DM) and depressive symptoms, which suggests that individuals with low birth weight are more vulnerable to depression associated with chronic disease such as DM or CVD.

6.3.2 Cognition

Subjects born with a low birth weight have on average lower cognitive performance throughout childhood and young adulthood (Richards, Hardy et al. 2001; Shenkin, Starr et al. 2004; Heinonen, Raikkonen et al. 2008; Räikkönen, Forsén et al. 2009). We are aware of only one previous study where the association between birth weight and cognitive performance in middle age or later life has been assessed (Martyn, Gale et al. 1996). That study found no association between the two. In our

study low birth weight was associated with a poor outcome in the DA and AL tasks independently of its association with DM, CHD or depressive symptoms.

We hypothesised that being born with a low birth weight might also make diabetic subjects more vulnerable to the effects of diabetes on cognition. Indeed, we found evidence to suggest that this is the case. We saw an interaction between birth weight and known DM which indicated that subjects born with a low birth weight seem especially vulnerable to the prolonged effect of diabetes on working memory and learning.

The mechanisms behind these interactions are not known but based on our findings we conclude that a lower birth weight seems to be a general indicator of vulnerability.

6.4 Strengths and limitations

This thesis is based on five original publications. Studies I, II and V were clinical epidemiological studies with a cross sectional approach. The conclusions which may be drawn from the results in such a setting are limited. Most importantly statistical associations should not be interpreted as causal relationships and we can only speculate about the temporal and mechanistic aspects behind the detected relationships.

The question of selection bias is always relevant. The original cohort consisted of subjects born as singletons at the University Hospital in Helsinki during the years 1934–1944. They attended the voluntary child welfare clinics, went to school in Helsinki, did not emigrate and were still alive in the years 2001–2006. Subjects who participated in the clinical study may differ in some aspects from the whole cohort and from the population at large. However, no statistically significant difference was found between participants in the clinical study and non-participants from the cohort regarding birth measures, socio-economic status and education. Whether they differed from the whole population is not known but since the results are based on internal comparisons within the sample they are likely to be representative.

In study I we have to consider the possibility of a survivors' bias. Those who attended the clinical examination in 2001-2004 are survivors and may have a different intellectual ability profile from those who died at an earlier age. It is possible that we could have found a correlation between intellectual ability and glucose tolerance if the non-survivors had been included in the analysis.

Despite the mentioned limitations these studies have a large sample size and comprise a representative sample of the elderly population in Helsinki. The diagnosis of diabetes was based on a standardized oral glucose tolerance test which allowed classification of the subjects into different glucose tolerance categories. Cognitive ability and depressive symptoms were assessed with sensitive, validated tools. However, while the BDI is a well validated measure of depressive symptoms,

it cannot be used as a diagnostic tool. Therefore we do not have information on clinical diagnosis of depression in the study subjects. Likewise we did not have information on clinical dementia.

Studies III and IV were placebo controlled clinical trials. Both of them were limited by small sample size. In addition to this it is possible that the limited findings were partly due to the low level of depressive symptoms. However, considering the double-blind placebo controlled setting it would have been unethical to include severely depressed subjects since there is always the possibility of receiving placebo.

7 Summary and conclusions

This thesis aimed to explore risk factors, complications and co-morbidities of T2D from a life course perspective. The key findings related to the specific aims are listed below:

1. Low intellectual ability per se is not an independent risk factor for T2D. However, regardless of intellectual ability or socio-economic status in childhood low educational attainment doubles the risk of future T2D among men.
2. T2D is associated with more depressive symptoms compared to subjects with normal glucose tolerance. This thesis adds to the literature by showing that this association is especially strong among subjects with CVD and those born with a low birth weight.
3. Treating depressed diabetic subjects with paroxetine has no long term effect on glucose regulation.
4. Subjects with known T2D have worse cognitive ability compared to both metabolically normal subjects and subjects with newly diagnosed T2D.
5. Low birth weight acts as a modifying risk factor with respect to diabetic complications. Both depression and cognitive impairment among diabetic subjects are increased if the subject is born with a low birth weight.

Conclusions

Type 2 diabetes is a vast and complex public health problem which is accompanied by several complications and co-morbidities. Depression and cognitive decline are common, but often overlooked, complicators of T2D and further research is needed regarding their optimal treatment and prevention. Moreover, it should be recognised that low birth weight is an additional risk factor and modifier of diabetic complications.

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