ACTA

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FACTORS, COMPLICATIONS AND HEALTH-RELATED QUALITY OF LIFE ASSOCIATED WITH DIABETES MELLITUS DEVELOPED AFTER MIDLIFE IN MEN

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Abstract

Type 2 diabetes is increasing overall in the world and is mostly associated with Western lifestyle including replete, unhealthy diet, sedentary life style and growing obesity. In the future the highest prevalence will be seen among older people due to longer life expectancy and changes in demography. Because diabetes is associated with increased morbidity, especially from cardiovascular causes, and a shortened life expectancy, an important aspect in the older population is the impact of diabetes on health related quality of life (HRQoL) and development of disability. To measure HRQoL we have many valid instruments, one of them the widely used RAND-36 survey. The 2-hour glucose value is important in screening subjects at high risk for diabetes, but it is time consuming and costly. Recently, 1-hour post load glucose has aroused interest in the prediction of diabetes. Few studies have focused on the effect of the age of onset of diabetes and how it effects on the HRQoL at an older age.

The aim of this study was to investigate the risk factors for future diabetes in men healthy in midlife; the interest was especially focused on 1-hour post load glucose. The other objective was to estimate the HRQoL in men who develop diabetes at an old age.

The present prospective study is based on the Helsinki Businessmen Study originally consisting of 3.490 men, born in 1919–1934 and followed since the 1960´s. All the men had socioeconomically similar status and belonged to the highest social group. The extensive baseline examinations were conducted in 1974, when the men were in midlife, mean age 48. At that time the men´s health, medication and cardiovascular risk factors were observed and self-related health (SRH) was rated on a five-step scale. The men who were healthy without medications were included in the follow-up group. The men were later investigated with postal questionnaires (1985/86, 2000, 2002/03, 2007). In 2000, at mean age of 73, the HRQoL of the survivors was examined using the RAND-36 instrument and was replicated in 2002/03, 2005 and 2007. Development of diabetes was evaluated using the National Drug Reimbursement register and self-reported diabetes in questionnaires.

Baseline 1-hour post-load blood glucose and weight gain from the age of 25 to midlife predicted future diabetes, and especially a combination of 1-hour glucose >8.9 mmol/L and body mass index (BMI) of ≥30 was associated with a 10.1-fold increase of diabetes risk independently of cardiovascular risk factors. Men with late-onset of diabetes (age >75) tented to be healthier in midlife. Diabetes did not affect the HRQoL until after diabetes onset. According to the evaluation in 2000, three RAND-36 scales, *i.e.* physical functioning, general health and social functioning, worsened already after 0–4 years from diabetes onset but did not deteriorate thereafter. There was no consistent impact on mental health.

In conclusion, this study demonstrates that in men, who develop diabetes later in old age, cardiovascular risk factors in midlife and elevated 1-hour post-load glucose and weight gain up to midlife are important predictors for future diabetes. Developing diabetes exerts clear effects on HRQoL, measured with RAND-36 very early after diagnosis, but affects only some of the domains.

Keywords: 1-hour post-load glucose, age, HRQoL, type 2 diabetes, weight gain

Pienimäki, Tuula, Myöhemmällä iällä puhkeava diabetes: Riskitekijät keski-iässä ja vanhuusiän elämänlaatu.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Terveystieteiden laitos, Geriatria; Oulun yliopistollinen sairaala; Helsingin yliopisto, Lääketieteellinen tiedekunta; Helsingin Yliopistollinen Keskussairaala

Tiivistelmä

Tyypin 2 diabetes on lisääntymässä maailmanlaajuisesti ja on suurelta osin yhteydessä länsimaisen elämäntyylin yleistymiseen. Keskeisimpinä tekijöinä ovat muuttunut, yltäkylläinen ruokavalio, vähentynyt fyysinen aktiivisuus ja niiden myötä lihavuuden lisääntyminen. Diabeteksen lisääntyminen näyttäisi olevan suurinta yli 65-vuotiaiden keskuudessa. Tähän vaikuttavat mm. eliniän pidentyminen ja väestörakenteen muutokset. Diabetesta sairastavien riski sairastua ja kuolla sydän- ja verisuonisairauksien komplikaatioihin on suurempi kuin ei-diabeetikoilla ja sairauksien myötä toimintakyky sekä elämänlaatu heikkenevät. Henkilön oma arvio hyvinvoinnista on tärkeä mittari. Elämänlaadun luotettava mittaaminen on tullut mahdolliseksi testattujen kysymyssarjojen myötä. Yksi laajasti käytetty mittari on RAND-36. Diabetesriskissä olevien henkilöiden löytämiseksi on käytetty 2-tunnin glukoosirasitustestiä, joka on aikaa vievä. Viimeaikoina onkin herännyt kiinnostus glukoosirasituksen jälkeistä yhden tunnin sokeriarvoa kohtaan. Useimmat tyypin 2 diabetekseen liittyvät tutkimukset ovat keskittyneet työikäiseen väestöön, minkä vuoksi tutkimuksia vanhemmalla iällä puhjenneesta diabeteksesta ja sen vaikutuksesta elämänlaatuun on vähemmän.

Tämän tutkimuksen tarkoituksena oli selvittää keski-iän riskitekijöitä, jotka ennustavat tulevaa tyypin 2 diabetesta myöhemmällä iällä. Yhtenä tutkimuskohteena oli yhden tunnin glukoosirasituksen jälkeinen sokeriarvo. Myöhemmällä iällä puhjenneen diabeteksen merkitystä elämänlatuun kartoitettiin RAND-36-mittarilla.

Tutkimusaineistona oli ns. Helsingin Johtajatutkimuksen mieskohortti, jota on seurattu 1960-luvulta alkaen. Kaikki miehet (n=3.490) olivat alkuaan terveitä, vuosina 1919–1934 syntyneitä miehiä, jotka kuuluivat ylimpään sosiaaliryhmään. Heidän terveydentilaansa on kartoitettu nykypäiviin saakka. Laajempi perustutkimus tehtiin vuonna 1974, jolloin miehet olivat keski-iässä (48 v). Seurantaan valittiin terveet henkilöt, joilla ei ollut säännöllisiä lääkityksiä. Tällöin kartoitettiin sydän- ja verisuonisairauksien riskitekijöitä, mitattiin glukoosirasituksen jälkeinen yhden tunnin sokeriarvo ja selviteltiin elämäntapoja, minkä lisäksi sen hetkistä itse koettua hyvinvointia mitattiin 5-portaisella asteikolla. Postitse lähetettyjä kyselytutkimuksia on tehty tietyin väliajoin ja aineiston tiedot tähän tutkimukseen on kerätty 31.12.2007 mennessä. Vuonna 2000 kyselytutkimukseen liitettiin elämänlaatumittarina RAND-36-mittarin suomalainen versio. Diabeteksen puhkeamista on seurattu Kelan lääkekorvausrekisteristä sekä itse ilmoitettuna postikyselyiden kautta.

Tässä keski-iässä terveessä mieskohortissa tulevan diabeteksen kannalta merkittävimmät ennusteelliset tekijät olivat painon nousu 25-vuoden iästä keski-ikään sekä keski-iässä mitattu glukoosirasituksen jälkeinen yhden tunnin sokeriarvo. Etenkin yhden tunnin sokeriarvo >8.9 mmol/L ja BMI ≥30 nostivat tulevan diabeteksen riskin 10-kertaiseksi. Näillä tekijöillä oli myös vahva yhteys sydän- ja verisuonisairauksien aiheuttamaan kuolleisuuteen. Glukoosirasituksen jälkeisellä yhden tunnin sokeriarvolla näyttäisi olevan merkitystä arvioitaessa tyypin 2 diabetesriskiä tulevaisuudessa, katkaisupisteenä plasman ≥7.8 mmol/L. Elämänlaatua diabetes näytti heikentävän pian diagnoosin jälkeen (0–4 vuotta diagnoosista), mutta sen jälkeen elämänlaatu ei huonontunut oleellisesti. RAND-36 mittarilla mitattuna elämänlaatu heikkeni merkittävästi diabeetikoilla ei-diabeetikoihin verrattuna fyysisen toimintakyvyn, yleisen elämänlaadun ja sosiaalisten toimintojen osa-alueilla, mutta mielenterveyteen diabetes ei näyttänyt vaikuttavan.

Asiasanat: elämänlaatu, ikä, painon nousu, tyypin 2 diabetes, yhden tunnin glukoosirasituksen jälkeinen sokeri

Tietämisemme on kuin pallo: mitä suuremmaksi sen tilavuus kasvaa, sitä suuremmaksi tulee myös sen tietämättömyyteen ja tuntemattomaan suuntautuva pinta-ala. (Mahatma Gandhi)

Dedicated to my son Juha

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When I was young I wanted to become a teacher in biology. In 1974 I graduated, received my M.Sc. from the University of Oulu. As a teacher in a high school in Rovaniemi I started to dream of studying medicine. In 1983 it was time to start in the Faculty of Medicine with some my own pupils becoming my fellow students. My secret dream has always been to write a doctoral thesis. It has been a long and arduous road, but now my dream is coming true.

This work was carried out at the University of Oulu, in the Faculty of Medicine, Institute of Health Sciences between the years 2008–2014. The research is based on the data of the Helsinki Businessmen Study, a follow-up study of originally over 3400 men starting in the 1960s and still going on.

I express my deepest gratitude to my principal supervisor Professor Timo Strandberg MD, PhD at the University of Helsinki, Department of Medicine and the Helsinki University Central Hospital and the University of Oulu, Institute of Health Sciences/Geriatrics for giving me the opportunity to do research under his tutelage.The Helsinki Businessmen Study cohort was an excellent collection of data to start with. He graciously helped me to understand the framework of this research.

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Abbreviations

ADA   American Diabetes Association
AHA   American Heart Association
ANCOVA   analysis of covariance
BMI   body mass index
BP   blood pressure
CAD   coronary artery disease
CI   confidence interval
CRP   C-reactive protein
CVD   cardiovascular disease
ECG   electrocardiography
GDM   gestational diabetes
HDL   high-density lipoprotein cholesterol
HbA_{1c} hemoglobin A_{1c}
HR   hazard ratio
HRQoL   health-related quality of life
IFG   impaired fasting glucose
IGT   impaired glucose tolerance
IL-6   interleukin 6
IQR   inter quartile range
MetS   metabolic syndrome
MI   myocardial infarction
MOS   Medical Outcomes Study
NFG   normal fasting glucose
NGT   normal glucose tolerance
NHANES   National Health and Nutrition Examination Survey
NHP   Nottingham Health Profile
OGTT   oral glucose tolerance test
RAND-36   RAND-36–Item Health Survey (Version 1.0)
SF-36   SF-36 the MOS–Item short form Health Survey
SE   standard error
SRH   self-related health
TNF-α   tumor necrosis factor α
WC   weist circumference
WHO   World Health Organization
WHOQOL   World Health Organization Quality of Life

List of original publications

I   Strandberg TE, Pienimäki T, Strandberg AY, Salomaa VV, Pitkälä KH, Tilvis RS & Miettinen TA (2011) One-hour glucose, mortality, and risk of diabetes: A 44-year prospective study in men. Arch Intern Med 171(10): 941–943.

II   Strandberg AY, Pienimäki T, Pitkälä KH, Tilvis RS, Salomaa VV & Strandberg TE (2013) Comparison of normal fasting and one-hour glucose levels as predictors of future diabetes during a 34-year follow-up. Ann Med 45(4): 336–400.

III Pienimäki T, Strandberg AY, Pitkälä KH, Tilvis RS, Miettinen TA, Salomaa V & Strandberg TE (2012) Modifiable risk factors in midlife and the age of onset of diabetes mellitus: A 34-year follow-up study. JAGS 60(1): 174–176.

IV Pienimäki T, Strandberg AY, Pitkälä KH, Tilvis RS, Salomaa VV & Strandberg TE (2013) Health-related quality of life as a function of diabetes onset in men. European Geriatric Medicine 4(4): 217–220.

Contents

1   Introduction

Diabetes mellitus (later in text diabetes) is increasing overall in the world and an increasing proportion of those affected will be older persons (McBean *et al.* 2004). Earlier it was estimated, that in 2030 we will have over 360 million people with diabetes in the world due to population growth, ageing, urbanization and increasing prevalence of obesity and physical inactivity (Wild *et al.* 2004). The newest global estimation of the prevalence of diabetes in 2030 is already 552 million, in 2011 the number of diabetic individuals was 366 million, most of them living in low- and middle-income countries (Whiting *et al.* 2011)

Diabetes is a major risk factor for cardiovascular disease (CVD) and mortality (Kannel & McGee 1979b, Stamler *et al.* 1993) and approximately 75–80% of diabetic people are reported to die of CVD (Alberti *et al.* 2007, Reunanen 1983). CVD events and the high incidence of other macro- and microvascular complications associated with diabetes (Stratton *et al.* 2000) are a major cause of illness and a remarkable economic burden (Hogan *et al.* 2003).

Early identification of those at risk of developing type 2 diabetes is essential for prevention of diabetes and its complications. Fasting plasma glucose (FPG) and the 2-hour oral glucose tolerance test (OGTT) are recommended for early detection of type 2 diabetes (American Diabetes Association 2010). These instruments reflect different pathophysiologic mechanisms (Nathan *et al.* 2007) and detect different individuals at high risk of developing type 2 diabetes (Levitan *et al.* 2004). Recently, 1-hour post-load glucose has aroused interest in the prediction of diabetes (Abdul-Ghani *et al.* 2008, Abdul-Ghani *et al.* 2009, Manco M. *et al.* 2010), but its clinical significance has not been studied sufficiently and its position as a risk-predicting tool has not been established. One-hour post-load glucose measurements have been reported to predict CVD mortality (Orencia *et al.* 1997, Strandberg *et al.* 1995) and to be associated with carotid intima-media thickness and chronic kidney disease (Succurro *et al.* 2009, Succurro *et al.* 2010).

Older people with diabetes are a heterogeneous group because of frequent co-morbidity and different history. They require special caution when handling their diabetes (Kesavadev *et al.* 2003). Few studies have considered the effect of the age at the onset of diabetes. The duration of diabetes may be important when assessing the risks of older individuals who have developed diabetes. The risk of CVD increases already before clinical diagnosis of diabetes (Qiao *et al.* 2002). People, who have developed diabetes earlier in life or later at older age are at the same risk of experiencing a coronary artery disease (CAD) event. Early onset

with duration > 10 years, showed a risk similar to those with previous myocardial infarction (MI) and no diabetes (Wannamethee *et al.* 2011, Whiting *et al.* 2011).

As a result of ageing, the morbidity of chronic diseases anticipates increasing disability and functional impairment among older people, affecting their quality of life. Validated questionnaires such as RAND-36 have made it possible to obtain information about various diseases and how they influence health-related quality of life (HRQoL). While diabetes is associated with increased morbidity and a shortened life expectancy (Morrish *et al.* 2001), an important factor in the older population is the impact of diabetes on HRQoL. Many studies show that diabetes with its complications has a significant and negative impact on HRQoL (Goodridge *et al.* 2005, Lloyd *et al.* 2001, Redekop *et al.* 2002), but there are only a few studies of the time course of this relationship between diabetes and HRQoL.

We need simple and cost-effective tools to find the individuals at high risk of diabetes and CVD. One possible tool could be the 1-hour post-load glucose level. In the older population insulin sensitivity is different from younger individuals (Short *et al.* 2003) and postprandial hyperglycemia is more sensitive in identifyiong persons with diabetes (Kesavadev *et al.* 2003). The duration of diabetes and the glycemic control affect the risks of complications companied with diabetes (Pirart 1977) and can impair HRQoL. It is also important to take into consideration the person´s age at diabetes onset and to avoid goals that are too strict for the older population (Bonds *et al.* 2010).

The aim of the present study was to study 1-hour post-load glucose as a predictor for future diabetes and mortality in men, who were healthy in midlife. Furthermore the aim was to compare fasting and 1-hour post-load glucose levels in predicting future diabetes. The Helsinki Businessmen study cohort also enabled us to evaluate the risk factors assessed in middle age for later CVD and diabetes. Finally, the aim was to study how diabetes developed in older age affects HRQoL.

2   Review of the literature

2.1   Definition and classification of diabetes

2.1.1 Definition

Diabetes is a disease, in which the blood glucose level is permanently abnormally high. It may result from many environmental and genetic factors with disturbances of carbohydrate, fat and protein metabolism. Several pathogenic processes are involved in the development of diabetes including processes that destroy beta-cells of the pancreas and factors resulting in insulin resistance. The long-term effects of diabetes can damage various organs such as kidneys, eyes and the autonomic nervous system (Alberti & Zimmet 1998). People with diabetes have also an increased risk of CVD (Deshpande *et al.* 2008, Kannel & McGee 1979a).

2.1.2 Classification

The tests used for diagnosis and classification of diabetes were brought into order by the National Diabetes Data Group of the USA and the second World Health Organization Expert Committee on Diabetes Mellitus in 1979 and 1980 (Alberti & Zimmet 1998). The World Health Organization (WHO) has published several guidelines for diagnosis of diabetes since 1965, and the diagnosis and classification were reviewed in 1999 and published in Part 1: Diagnosis and Classification of Diabetes Mellitus and its complications (World Health Organization 1999).

Diabetes was classified earlier in 1985 by the WHO into the following groups: 1) Type I, insulin dependent diabetes mellitus (IDDM), 2) Type II, non-insulin dependent diabetes mellitus (NIDDM), and 3) other types, including impaired glucose tolerance (IGT) and gestational diabetes mellitus (GDM). The new classification (1999) contains various degrees of hyperglycemia and subsequently NIDDM and IDDM should no longer be used. The main etiological groups are: Type I and Type II diabetes mellitus, other specific types, and GDM. The clinical staging contains IGT and impaired fasting glucose (IFG). These represent impaired glucose regulation referring to an intermediate metabolic state between normal glucose homeostasis and diabetes characterized by different abnormalities

of glucose regulation, one in the fasting stage (IFG) and one in the postprandial stage (IGT) (Alberti & Zimmet 1998).

Table 1. Disorders of glycaemia: aetiological types and clinical stages modified from Alberti & Zimmet (1998).

Etiological types	Clinical stages (impaired glucose regulation)
Type 1 diabetes mellitus	IGT: impaired glucose tolerance
Beta-cell destruction leading normally to absolute insulin deficiency, insulin is required for survival	IFG: impaired fasting glucose
An autoimmune process	
Idiopathic	
Type 2 diabetes mellitus	
Results from predominantly insulin resistance with relative insulin deficiency (secretory defect with or without insulin resistance)	
Other specific types (less common causes)	
Genetic defects of beta-cell function	
Genetic defects of insulin action	
Disease of the exocrine pancreas	
Drug- or chemical-induced	
Infections	
Other genetic syndromes	
Endocrinopathies	
Gestational diabetes	

2.2   Prevalence and incidence of diabetes

The number of people with diabetes is increasing overall in the world and among adults type 2 diabetes accounts for about 90% of all diagnosed cases of diabetes (World health Organization 1999). In 2011 the global burden of diabetes was 366 million people: by 2030 it is estimated to rise to 552 million. Most of these people live in low-income and lower middle-income countries and the largest increase is expected in the older age groups, but this varies according to countries´ income status (Whiting *et al.* 2011). The largest group of diabetic people in the world consists of persons between 40 and 59 years of age. It is estimated that altogether 183 million people (50%) with diabetes are undiagnosed. The global prevalence (20–79 years) of diabetes in 2011 was 8.3%, and in 2030 it is estimated to be 9.9% (Diabetes Atlas 2011). In the United States in 1999–2002 based on the National Health and Nutritional Examination Survey (NHANES), the prevalence of

diabetes was 9.3% and affected 19.3 million people in 2002 (Cowie *et al.* 2006)
Today, the number of diabetic individuals there is already 25.8 million people, of
those 18.8 million are diagnosed and 7.0 million undiagnosed (Diabetes Statistics
2011). In the United States among older people aged 65 and over, approximately
20% (about 7 million people) have diabetes (Kesavadev *et al.* 2003). The
prevalence of diabetes increases with age (Cowie *et al.* 2006) and in countries
classified as being high-income countries most people with diabetes are aged over
60 years, whereas in low- and lower middle-income countries diabetic people are
mostly of working age, between 40 and 60 years (Whiting *et al.* 2011). In Finland
diabetes affects approximately 10% of the adult population among whom the
great majority, 85%, have type 2 diabetes. About 200,000 Finns have diabetes
without knowing it. The number of people with type 2 diabetes being under
treatment will be double every 12th year (Koski 2011). The number of people
having IGT is estimated to be 500,000, and 5–10% of these convert to diabetes
every year (Winell & Reunanen 2006). A study published in 2005 showed, that
among 45 to 64 year-old Finns the prevalence of diabetes was 10.2% in men and
7.4% in women (Yliharsila *et al.* 2005). According to the National Health
Insurance of Finland (2012), 330,545 persons were reimbursed for anti-diabetic
medication.

2.3   Diagnostic criteria of prediabetes and type 2 diabetes

The term prediabetes was used in 1980 by the WHO but was later withdrawn to
avoid unnecessary worry, because people with slightly elevated glucose level do
not always convert to type 2 diabetes (World Health Organization 1985). In 2005
the American Diabetes Association (ADA) proposed again using the term
prediabetes for IGT and IFG (Nathan *et al.* 2009). Prediabetes is a stage of
intermediate hyperglycemia between normal glucose level and tolerance and type
2 diabetes mellitus (Table 2). IFG identifines a smaller number of people who are
at higher risk of developing diabetes mellitus than those with IGT (Gabir *et al.*
2000). Recently hemoglobin A_{1c} (HbA_{1c}) has been proposed by ADA at the range
of 5.7–6.4% as a tool to definite prediabetes (American Diabetes Association
2010). Prediabetes is a risk for future diabetes and CVD risk, but is also
associated with nephropathy, neuropathy and other CVD complications (Tabak *et
al.* 2012).

   The development of type 2 diabetes takes place a long time before the clinical
diagnosis is made, when insulin resistance develops and beta-cell function starts

to deteriorate (Cheng 2005). The diagnostic criteria for diabetes have not been changed since 1999, when fasting plasma glucose value was lowered from ≥ 7.8 mmol/L to ≥ 7 mmol/L to facilitate identification of undiagnosed diabetes and to reduce the discrepancy between FPG and 2-hour post-load plasma glucose (2-h PG) cut-off points used in OGTT (Gabir *et al.* 2000). The most recent diagnostic criterion of diabetes is HbA_{1c}, which WHO accepted in 2011 with the cut-off value $HbA_{1c} \geq 6.5\%$ (World Health Organization 2011) (Table 2).

Table 2. Diagnostic criteria for normoglycemia, prediabetes and diabetes according to WHO and ADA.

Variables	NGT	IGT	IFG	Prediabetes	Diabetes
FPG (mmol/L)	≤ 6.0 WHO		6.1–6.9 WHO	6.1–6.9 WHO	≥ 7.0
	≤ 5.5 ADA		5.6–6.9 ADA	5.6–6.9 ADA	
2-hour glucose (mmol/L)	< 7.8	7.8–11.0		7.8–11.0	≥ 11.1
HbA_{1c} (%)	< 5.7%			5.7–6.4% ADA	≥ 6.5%

NGT = normal glucose tolerance, IGT = impaired glucose tolerance; IFG = impaired fasting glucose,
FPG = fasting plasma glucose

2.3.1 OGTT, FPG and HbA_{1c}

Two-hour post-load glucose measurement is recommended for early detection of diabetes (American Diabetes Association 2010) and has become the standard method for identifying individuals at risk for type 2 diabetes. People, who have normal fasting glucose (NFG), may have hyperglycemia during OGTT and vice versa (Levitan *et al.* 2004). If OGTT is performed in individuals having fasting glucose between 5.7 mmol/L and 6.9 mmol/L, it improves the diagnostic strategy for diabetes and detects over 80% of patients at risk for diabetes (Botas *et al.* 2003). The OGTT identifies people with either IFG or IGT and finds thus more people who are at increased risk for future diabetes (American Diabetes Association 2010).

OGTT is also an important method for screening individuals at high risk of type 2 diabetes, but it is time-consuming and costly.

For decades FPG has been used for the diagnosis of diabetes. FPG tells the glucose level at the moment of measurement and two separate assessments are required to confirm the diagnosis. FPG does not reflect the glucose level during the daytime as it is measured after a long nocturnal period without any intake of food and with no special stress on pancreatic beta-cells. The two-hour OGTT

reflects the pathophysiology of diabetes during the postprandial state because the health of the beta-cells is essential for normal postbrandial glucose values (Bonora & Tuomilehto 2011).

HbA$_{1c}$ has recently been accpeted as a part of the diagnostic criteria of diabetes (Word Health Organization 2011). HbA$_{1c}$ reflects the average glucose level of the past two of three months. Additionally, it has low intravidual variability. Therefore it may be a better measure than FPG for long-term macrovascular risk stratification (Selvin *et al.* 2010). Earlier, HbA$_{1c}$ was used as a control measurement to determine the glucose balance when the diagnosis of diabetes was received. HbA$_{1c}$ values reflect chronic hyperglycemia and are assosiated with microvascular diseases (American Diabetes Assosiation 2010). The community-based stydy of 11.092 middle-aged adults without diabetes showed that HbA$_{1c}$ was similarly associated with the risk of diabetes and especially with risks of CVD and death compared with the fasting glucose (Selvin *et al.* 2010).

The advantages diagnosing diabetes with HbA$_{1c}$ compared with FPG and vice versa are shown below modified according Bonora & Tuomilehto (2011)

HbA$_{1c}$ better than FPG for determination for diagnosis of diabetes

- chronic hyperglycemia is captured by HbA$_{1c}$ but not by FPG (even repeated)
- HbA$_{1c}$ is better related to cardiovascular disease than FPG
- fasting is not needed for HbA$_{1c}$ assessment
- HbA$_{1c}$ has a greater pre-analytical stability than blood glucose
- biological variability of HbA$_{1c}$ is lower than FPG and 2-hour post-load plasma glucose
- microangiopathic complications (retinopathy) are associated with HbA$_{1c}$ as strongly as with FPG

FPG better than HbA$_{1c}$ determination for diagnosis of diabetes

- diabetes is clinically defined by high glucose and not by glycation of proteins
- HbA$_{1c}$ is a poor marker of important pathophysiological abnormalities featuring diabetes
- HbA$_{1c}$ levels of 6.0–6.5% do not predict diabetes as effectively as FPG and 2-hour post-load plasma glucose

- HbA$_{1c}$ has significant differences in various ethnic groups, which are poorly understood and characterized
- cost of assey: glucose is cheaper than HbA$_{1c}$ and HbA$_{1c}$ assay is not available on a large scale in most ot the countries
- using HbA$_{1c}$ will deley the diagnosis of diabetes in about 60% of incident cases

2.3.2 One-hour post-load glucose as a predictor of type 2 diabetes

Subjects with IGT and IFG have an increased risk for future type 2 diabetes. Those with IGT about 50% convert to type 2 diabetes during 10-year follow-up. At the same time however about 40% subjects with normal glucose tolerance (NGT) at baseline will develop diabetes (Unwin *et al.* 2002). For identification of individuals at high risk of future type 2 diabetes, many models have been proposed (McNeely *et al.* 2003, Stern *et al.* 2002, Wilson *et al.* 2007, Tuomilehto *et al.* 2010, Wannamethee *et al.* 2011).

One-hour post-load glucose testing has recently aroused interest in the prediction of diabetes (Abdul-Ghani *et al.* 2008, Abdul-Ghani *et al.* 2009, Manco M. *et al.* 2010). One-hour plasma glucose stratifies subjects with NGT as well as subjects with IGT into high- and low-risk groups (Abdul-Ghani *et al.* 2008). Subjects who develop type 2 diabetes have impaired beta-cell function and insulin resistance in the liver and skeletal muscle (DeFronzo 1988). It has been shown, that during OGTT, the plasma glucose concentration at the 30–60 min time interval depends on insulin sensitivity in skeletal muscle and on beta-cell function (Abdul-Ghani *et al.* 2006, Abdul-Ghani *et al.* 2007, DeFronzo 1988, Graham *et al.* 2007). The increase in 1-hour post-load plasma glucose concentration would correlate with insulin resistance in liver and skeletal muscle and impaired beta-cell function (Abdul-Ghani *et al.* 2008). In individuals who have NGT with high 1-hour post-load glucose concentration to the same level as individuals with IGT, beta-cell rate sensitivity is impaired and characterizes the difference in their metabolic phenotype. Increased value of 1-hour post-load glucose (> 8.95 mmol/L) in individuals with NGT identifies insulin resistance and beta-cell dysfunction (Manco M. *et al.* 2010).

A cut-off point of 155 mg/dL (8.6 mmol/L) for the 1-hour post-load plasma glucose during the OGTT can identify subjects with NGT at high risk for future diabetes (Abdul-Ghani *et al.* 2008, Abdul-Ghani *et al.* 2009), but also those with increased risk for cardiovascular disease (Succurro *et al.* 2009). A new study

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concerning obese Hispanic youth shows that 1-hour post-load glucose ≥ 155 mg/dL during OGTT predicted independently beta-cell deterioration and progression to prediabetes over a follow-up-time of 8 years (Kim *et al.* 2013).

One-hour post-load plasma glucose level a cut-off point of 155 mg/dL during OGTT in non-diabetic subjects has been shown to be a strong predictor for future type 2 diabetes (Abdul-Ghani *et al.* 2007, Abdul-Ghani *et al.* 2008). In a large cohort of 1,611 non-diabetic participants in the San Antonio Heart study, subjects with NGT and 1-hour post-load plasma glucose concentration > 155 mg/dL, altogether 16.7%, developed type 2 diabetes over 7 to 8-year period, while the annual risk was 2.2%. Among those with 1-hour post-load plasma glucose level during OGTT < 155 mg/dL, the annual risk for onset of diabetes was 0.4%. One-hour post-load plasma glucose > 155 mg/dL among persons with metabolic syndrome (MetS) increased the annual risk to 4.3% for future type 2 diabetes and exceeding the risk of those with IGT. Using the cut-off point 155 mg/dL for 1-hour post-load glucose level in conjunction with MetS, non-diabetic subjects with NGT, IFG and IGT can be divided into three risk groups, low, intermediate, and high risk, independent of their 2-hour plasma glucose concentration (Abdul-Ghani *et al.* 2008).

Similarly in the Botnia study after 7–8 years of follow-up, subjects with NGT with 1-hour post-load plasma glucose concentration over 155 mg/dL (8.6 mmol/L), and the presence of the MetS, had a significantly increased risk for future diabetes (8.5%) compared with people, who had NGT and a 1-hour post-load plasma glucose concentration below 155 mg/dL (1.3%). Also among the groups IFG and IGT, the value of 1-hour post-load plasma glucose concentration during OGTT identifies high-risk individuals for future type 2 diabetes. Those with 1-hour post-load plasma glucose concentration > 155 mg/dL compared with those < 155 mg/dL, the risk was 10% and < 2%, respectively (Abdul-Ghani *et al.* 2009).

In these the San Antonio Heart and the Botnia studies 1-hour post-load plasma glucose seemed to correlate strongly as a measure of insulin resistance and beta-cell dysfunction instead of 2-hour post-load plasma glucose.

One-hour post-load plasma glucose with levels > 155 mg/dL has also been proposed to be a new possible marker for CVD (Bardini *et al.* 2010). Higher white blood cell count and fibrinogen levels that are signs of subclinical inflammation and worsening lipid profile were measured in subjects with higher levels of NGT than with lower NGT.

2.4 Type 2 diabetes and its risk factors

2.4.1 Obesity and insulin resistance

A tendency to be overweight and obese is increasing in the world (Must *et al.* 1999, Shields & Tjepkema 2006, Shields *et al.* 2011). A crude measure of obesity is the body mass index (BMI), a measure of body fat, where a person´s weight (in kilograms) is divided by the square of the person´s height (in metres). Obesity is defined as BMI ≥ 30 kg/m^2 and overweight as BMI ≥ 25 to < 30 kg/m^2 (World Health Organisation 2011). According to WHO estimates there will be over 1.6 billion overweight people and over 400 million obese people by 2015 (Drew *et al.* 2007). Over a 20-year period in the United States and Canada the highest weight increase among men was in the age group 60–74 years, but among women among those aged 20–30 (Shields *et al.* 2011). In the United States the prevalence of diabetes is high exceeding over 30% in most age and sex groups. Within racial and ethnic groups the prevalence ranged in 2007–2008 from 31.9% among non-Hispanic white men to 37.3% among non-Hispanic black men, and among women 33.0% to 49.6%, respectively (Flegal *et al.* 2010). In Finland the prevalence of obesity has increased during a 20-years period (1978–1980 to 2000–2001) from 17.9% to 24.1% in women and from 11.3% to 20.7% in men (Lahti-Koski *et al.* 2010).

Obesity is an important risk factor for type 2 diabetes, particularly obesity of long-term duration (Hu *et al.* 2001, Manson & Spelsberg 1994, Pi-Sunyer 1996, Wannamethee & Shaper 1999). The tools of preventing type 2 diabetes consist of weight control with lifestyle changes (Saaristo *et al.* 2010, Tuomilehto *et al.* 1992). In a prospective study BMI was the dominant risk factor for diabetes among middle-aged British men, and moderate physical activity reduced the risk for type 2 diabetes more than 50% (Perry *et al.* 1995). It has been known for a long time that obesity enhances insulin resistance, because glucose uptake to the tissues (liver, muscle, adipose tissue) is disturbed leading to an increase in insulin production and type 2 diabetes (Olefsky *et al.* 1982). In the background there are many metabolic disorders and the resistance to insulin-stimulated glucose uptake and hyperinsulinaemia are related apart from type 2 diabetes, also to hypertension and CAD (Reaven 1988).

The excess of body fat can be estmated with magnetic resonance imaging or computed tomography. These methods measure regional adiposity such as visceral and subcutaneous adipose tissue (Cambi *et al.* 2011). In practice BMI is

used as an indicator of overall obesity and waist circumference (WC) is employed to measure abdominal obesity. In a stydy, where fat distribution was measured by magnetic resonance, BMI had the stongest correlation for non-abdominal and abdominal subcutaneous fat, whereas WC was associated with an increase of visceral fat in white men and women. In this stydy BMI and WC independently contributed to prediction of non-abdominal, abdominal subcutaneous and visceral fat. This finding reinforces the useability of BMI and WC in clinical paractise (Janssen *et al.* 2002). Some differences, however, have been found between sex and race in the relationship between WC and BMI and visceral fat, subcutaneous adipose tissue and fat mass (Cambi *et al.* 2011).

In overweight people the abundant adipose tissue releases increased amounts of biologically active factors such as hormones, pro-inflammatory cytokines and non-esterified fatty acids, which are responsible for insulin resistance accompanied by dysfunction of pancreatic beta-cells releasing insulin. These factors result in failure to control blood glucose levels and are critical in defining the risk and development of type 2 diabetes. Therefore studies of type 2 diabetes and its reasons have moved on to the molecular and genetic basis providing new possibilities to treatment and prevention of this disease. (Kahn *et al.* 2006).

Adipokines are polypeptides released by adipose tissue. They are biologically active substanties and many of these are pro-inflammatory cytocines as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and interleukin-1 (IL-1) (Fatuzzi *et al.* 2005, Lago *et al.* 2007). TNF-α acts locally by redusing insulin sensivity in adipocytes and increases also the secretion of other inflammatory mediators (Lau *et al.* 2005). An attenuated insulin sensivity produces the release of free fatty acids and leads to atherogenic dyslipidemia (Krauss *et al.* 2004). IL-6 is a pleiotropic cytokine and a central mediator in many acute-phase events (Heinrich *et al.* 1990). IL-6 impairs insulin sensivity and increases the hepatic production of C-reactive protein (CRP) (Lago *et al.* 2007, Despres 2006). Many studies suggest that IL-6 and CRP which are sensitive physiological markers of subclinical systemic inflammation, coud be associated with insulin resistance and type 2 diabetes (Sandler *et al.* 1990, Pickup *et al.* 1997, Ford 1999, Frohlich *et al.* 2000). A prospective study among middle-aged women, who were at baseline free of diabetes, showed that elevated levels of CRP and IL-6 predicted the development of type 2 diabetes (Pradhan *et al.* 2001).

2.4.2 Physical inactivity

Many diabetes prevention studies have shown that diabetes is preventable by lifestyle interventions (Tuomilehto *el al.* 2001, Alberti *et al.* 2007, Laaksonen *et al.* 2005, Lindstrom *et al.* 2003). The protective benefits are seen especially in persons who are at the highest risk for diabetes (Helmrich *et al.* 1991). Physical activity is often recommended as a basic treatment for diabetic people, because physical exercise increases the sensitivity of skeletal muscles to glucose uptake and to insulin (Goodyear & Kahn 1998). Regular physical activity may prevent diabetes or delay it and its complications (Balducci *et al.* 2006, Zoppini *et al.* 2006) and improves blood glucose control (Duncan *et al.* 2003, Hamman *et al.* 2006). In spite of this many people with type 2 diabetes are not active (Morrato *et al.* 2007). Already moderate exercise for 20 min or 10 min of strenuous exercise twice per day reduced the risk of diabetes by 46% (an exercise-only treatment arm) in the Da Quig IGT and Diabetes Study in China (Pan *et al.* 1997).

One of the controlled, randomized trials was the Finnish Diabetes Prevention Study, in which the risk of diabetes was reduced by 58% in the intensive lifestyle intervention group the mean follow-up duration of 3.2 years. Exercise per day in the intervention group was at least 30 min (Tuomilehto *et al.* 2001). It has been shown that low cardiorespiratory fitness and physical inactivity independently predicted all-cause mortality in men with type 2 diabetes (Wei *et al.* 2000). Similar results have also been reported in some Finnish studies, in which good cardiorespiratory fitness was associated with a slower progression of early atherosclerosis and lower CVD and non-CVD mortality in middle-aged men (Lakka *et al.* 2001, Laukkanen *et al.* 2001). According to some studies low cardiorespiratory fitness as a notable risk is comparable to that of diabetes (Laukkanen *et al.* 2001, Wei *et al.* 1999).

The technical recommendations of exercise and type 2 diabetes were published by ADA in 1990. In a new review article the researchers have concentrated on major developments since 1990 (Sigal *et al.* 2004). It is recommended that the people with IGT should include in their weight control at least 150 min/week moderate to vigorous physical activity and a healthful diet. Many cohort studies have shown that low aerobic fitness and low physical activity level predict increased risk of CVD mortality in diabetic subjects. The structured exercise intervention in type 2 diabetes has reduced HbA_{1c} independent of body weight. New data of the benefit of resistance training in glycaemic

control and its safety among persons at high risk for CVD has also been found (Sigal *et al.* 2004).

2.4.3 Other risk factors

Many of the persons with type 2 diabetes have metabolic syndrome, which is a cluster of risks factors for CVD and also for diabetes including hypertension and disorders in lipid metabolism (Lakka *et al.* 2002). There is no internationally agreed definition for the metabolic syndrome, but the following components according to WHO (World Health Organization 1999) described below can be used as a working definition.

Clinical criteria for metabolic syndrome (WHO 1999)

–   impaired glucose regulation (IFG, IGT) or diabetes
–   insulin resistance

and any two of the following

–   raised arterial pressure $\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic
–   plasma triglycerides $\geq$ 1.7 mmol/L
–   HDL cholesterol < 0.9 mmol/L in men and < 1.0 mmol/L in women
–   BMI > 30 kg/m^2 and /or waist/hip ratio > 90 cm in men and > 85 cm in women
–   microalbuminuria: urinary albumin excretion rate $\geq$ 20 ug/min

Some studies have shown that major stress-related events associate with an increased risk of having metabolic syndrome (Chandola *et al.* 2006, Vogelzangs *et al.* 2007). The results in the Finnish study were in agreement with previous findings based on population in the Prevalence, Prediction and Prevention of diabetes (PPP)-Botnia Study, where stressful life events, such as financial difficulties increased the risk for MetS. Stress may be associated with metabolic changes through smoking, alcohol use and physical inactivity (Pyykkonen *et al.* 2010).

In some studies patients with hypertension had a 2.5-fold risk of developing diabetes compared to their normotensive partners (Gress *et al.* 2000, Weycker *et al.* 2009). Age also has a strong effect on the development of diabetes. The prevalence of diabetes is increasing in the world especially among older persons (Wild *et al.* 2004). There are also racial and ethnic differences. The risks for

diabetes are higher in Hispanics than among whites, blacks and Asians (McBean *et al.* 2004). Genetic factors and family history have a marked influence on ethnic and racial habits increasing the risk for diabetes (Haffner 1998, Harrison *et al.* 2003).

Some studies have shown that moderate alcohol consumption is associated with lower insulin secretion (Crandall *et al.* 2009, Waki *et al.* 2005) while smoking increases insulin resistance (Houston *et al.* 2006). A meta-analysis of smoking and type 2 diabetes found an association between active smoking and increased risk of type 2 diabetes (Willi *et al.* 2007). In conclusion of the meta-analysis of the relationship between depression and type 2 diabetes, is suggested that depression is a risk factor for developing type 2 diabetes, comparable in size to smoking and physical activity (Knol *et al.* 2006).

A relationship between socioeconomic status and type 2 diabetes was showed among people aged 40–69 years in the U.K. The prevalence of type 2 diabetes was increased in deprived areas and was higher among men (13.4 per 1000) than women (10.8 per 1000). According to researches the explanation to this probably relates to increased exposure to lifestyle and environmental risk factors for type 2 diabetes among people from areas of low socioeconomic status (Connolly *et al.* 2000). A study performed in Western European countries compared individuals with a high educational level with those with low educational status. The results indicated an inverse relationship between educational level and risk of type 2 diabetes which was only partially explained by variations in BMI (Sacerdote *et al.* 2012).

Recently has been dicussed also statin therapy and risk of developing type 2 diabetes. In a population based study was found a possible risk with atorvastatin and simvastatin compared with pravastatin (Carter *et al.* 2013). A large meta-analyzes of 13 randomized trials over 90.000 participants found a 9% risk for incident diabetes among statin users after 4 years follow-up. The risk was found particularly among older people. The researchers mention that risk is low and must remember also statins advantages in reduction of coronary events (Sattar *et al.* 2010). Some studies suggest that the antihypertensive drugs can increase the risk of new onset of diabetes especially beta-blockers and diuretics (Kostis *et al.* 2005, Elliot & Myer 2007).

People with obstructive sleep apnea have often same clinical findings as people with type 2 diabetes, such as obesity, hypertension and impared glucose tolerance. A resently published stydy found that about half of aduts with type 2 diabetes may be at high risk of obstructive sleep apnea and many may be

undiagnosed (Cass *et al.* 2013). But sleep apnea can also be a risk factor for type 2 diabetes. In a cohort study 544 participants without diabetes, but with sleep apnea were divided into quartiles according the severity of sleep apnea (Botros *et al.* 2009). The researches found that sleep apnea was an independent risk factor of developing type 2 diabetes (HR per quartile 1.43, confidence interval 1.10–1.86).

Many of the risk factors for type 2 diabetes can be controlled with lifestyle. Table 3.

Table 3. Modifiable and non-modifiable risk factors and associated disorders for type 2 diabetes. Modified from Alberti *et al.* 2007.

Modifiable	Non-modifiable
Overweight BMI ≥ 25 to < 30 kg/m^2 and obesity BMI ≥ 30 kg/m^2	Family history
Sedentary lifestyle	Gender
Metabolic syndrome	History of gestational diabetes
IGT or/and IFG	Polycystic ovary
Hypertension	Ethnicity
Increased triglycerides, low HDL-cholesterol	
Dietary factors	

BMI = body mass index, IFG = impaired glucose tolerance, IFG = impaired fasting glucose

2.5   Type 2 diabetes and cardiovascular disease

2.5.1 Cardiovascular disease and mortality

CVD is the leading cause of death and disability in the world as reported in the book *Global Atlas on cardiovascular disease prevention and control* (2011). About 17.3 million people in the world died from CVD in 2008, and over 80% of these deaths took place in low- and middle-income countries. CVD is the leading cause of death in many developed countries as well (Yusuf *et al.* 2004).

Diabetes seems to be an independent risk factor for CVD death (Butler *et al.* 1985, Pan *et al.* 1986, Stamler *et al.* 1993). In a large Finnish prospective population study CVD accounted for 70% of the causes of death among diabetic people (Reunanen 1983). In another large study researches have investigated risk factors for CVD mortality and morbidity among diabetic individuals. According to the results the assessment of CVD risk in diabetes must also include ´diabetes-related´- variables such as glycemic control, proteinuria and retinopathy, within the classic risk factors, blood pressure, smoking and dyslipidemia (Fuller *et al.*

2001, Turner 1998). Severe hypoglycaemia can be associated with increased risk with vascular events and death. Important risks are older age, duration of type 2 diabetes and use of many anti-diabetic drugs (Zoungas *et al.* 2010). Previous analysis based on the cohort of the Helsinki Businessmen Study concerning multifactorial prevention of CVD, the traditional risk factors smoking, blood pressure and cholesterol were significantly associated with CVD mortality, but factors related to glucose tolerance (1-hour post load glucose) explained in part the excess mortality (Strandberg *et al.* 1995). The mortality of people with diabetes diagnosed at an older age is lower than that reported for general older population with diabetes (Barnett *et al.* 2006). People with early- and late-onset diabetes are likely to experience major CAD events, but only early onset of diabetes and its duration of longer than 10 years seemed to be equivalent to CAD in predicting a CAD event (Wannamethee *et al.* 2011).

2.5.2 Cardiovascular disease and risk factors

Diabetes belongs to a special category of risk factors increasing the risk of CVD and is considered an independent risk factor for CVD both in men and women (Grundy *et al.* 1999, Wilson 1998). There is a lot of evidence showing that diabetic people are at high risk for several cardiovascular disorders such as coronary heart disease, stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure (Adler *et al.* 2002, Gaede *et al.* 2003, Pan *et al.* 1986). Individuals with type 2 diabetes without signs of myocardial infarction are at the same risk to have cardiac event than non-diabetic people with previous myocardial infarction (Haffner *et al.* 1998). CVD risk factors are often seen in conjunction with MetS including hypertension, increased waist circumference, atherogenic dyslipidamia, and hyperglycemia (Wilson *et al.* 2005) Both obesity and physical inactivity as predisposing conditions are recognized as CVD risk factors often accompanying the MetS (Lakka *et al.* 2002). In the United Kingdom Prospective Diabetes Study (UKPDS:23) researchers found, that many of potentially modifiable risk factors for CAD exist in patients with type 2 diabetes including disorders of the lipoprotein metabolism, raised blood pressure, hyperglycemia, and smoking (Turner *et al.* 1998). The data based on Euroaspire I and II surveys showed that among patients under 70-years with acute coronary syndrome, 18% and 20%, respectively, had diabetes. There was a high prevalence of adverse lifestyle and modifiable risk factors (smoking, hypertension, obesity and elevated total cholesterol) among diabetic and non-diabetic patients with

CAD, but the risk factor status was more adverse among diabetic individuals (Pyorala *et al.* 2004). Hypertension alone has been considered a major risk factor for CVD (Wilson 1998). Prospective studies such as the Framingham, Honolulu, and San Antonio Heart Studies, have documented the excess CVD risks in diabetic patients (Kannel & McGee 1979b, Rodriguez *et al.* 1999, Wei *et al.* 1998).

The risks for CVD can be divided into two groups: modifiable and non-modifiable risk factors. The majority of CVD is caused by risk factors that can be controlled, treated or modified. Table 4.

Table 4. Risk factors for CVD modified from Kannel *et al.* 1979.

1. Modifiable	2. Non-modifiable
Hypertension	Age
Raised blood glucose	family history
Physical inactivity	Gender
Smoking	
Cholesterol/lipids	
Overweight and obesity	

2.6   Complications associated with type 2 diabetes

The risks of developing diabetic complications are strongly associated with previous hyperglycemia. High blood glucose is a risk for development of microvascular and macrovascular complications (Fowler 2008). In the prospective observational study UKPDS 35 it was shown that the incidence of clinical complications was significantly associated with glycemia. Each 1% reduction in updated mean HbA_{1c} reduces the risk for microvascular complications by 37% (Stratton *et al.* 2000). A study conducted among older diabetic patients compared to a non-diabetic group indicated a significant increase in retinopathy, neuropathy, impotence and macrovascular complications such as CAD among diabetic individuals. The duration of diabetes was not associated with macrovascular diseases but was associated with the occurrence of retinopathy and neuropathy (Nathan *et al.* 1986). Improved blood glucose control decreased the progression of diabetic microvascular complications (retinopathy, neuropathy, nephropathy), but not macrovascular disease. On the other hand, goals that are too strict increase the risks of hypoglycaemia (Turner 1998). A cross-sectional study conducted in Sweden showed that risks for micro- and

macrovascular complications differ between men and women. Among men the important risk for macrovascular compications as well as for retinopathy and nephropathy was hypertension. Among women age and duration of diabetes were risks both for micro- and macrovascular complications (Wandell 1999). A value of 7.0% for HbA_{1c} was suggested to avoid hypoglycaemia and to prevent microvascular complications (Reusch & Wang 2011). Studies of the complications of type 2 diabetes normally concern a long-term period, but also glycemic control during a daily period is significant. In the study among older diabetic people the results suggest a significant relationship between acute glucose swings and cognitive performance impairment (Rizzo *et al.* 2010).

2.7   Health-related quality of life

2.7.1 Quality of life

Quality of life (QoL) is a wide-ranging concept and refers to the general well-being of individuals and societies. The term is multidimensional and does not include only wealth and employment, and may be categorized into five dimensions: physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing, and development and activity (Felce & Perry 1995). In 1948 the WHO definition of health as "a state of complete physical, mental and social well-being and not merely the absence of a disease or infirmity", contributed to the concept of quality of life (World Health Organization 1948).

The World Health Organization Quality of Life (WHOQOL) project started in 1991. The aim was to develop an international cross-culturally comparable instrument to assess individuals´ perceptions in the context of their culture and value system, and their personal goals, standards and concerns. The WHOQOL-BREF instrument comprises 26 items measuring physical and psychological health, social relationships and environment and is a shortened version of the WHOQOL-100 quality of life assessment (WHOQOL Group 1998).

According to the report of the National Institute for Welfare and Health (THL) in 2010 the QoL of Finnish people is in generally high until old age, but in a socially selective manner. In all 80% of Finns found their QoL to be good until the age of 70 years, but after this it decreased to 73% and after 80 years of age only 57% perceived their QoL to be good. The WHO QoL-instrument (WHOQOL-BREF) was used in this report (Vaarama *et al.* 2010).

2.7.2 Health-related quality of life

Health is a wide concept denoting more than just absence of illnesses. According to the WHO health is complete state of physical, mental and social well-being. This was criticized later and in 1993 WHO presented a definition of QoL linked to health: "An individual´s perception of his/her position in life, in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns" (WHOQOL Group 1993).

The concept of HRQoL is narrower than the concept of the QoL. The HRQoL includes the influence of illnesses and the care on the ability to function and welfare. It also usually includes self-reported measures of physical and mental health. (Guyatt *et al.* 1993, Kaukua 2006).

In addition to morbidity and mortality, we need more information about chronic diseases and their care and how they affect individuals from their own point of view. An essential goal of the health care system is to improve the HRQoL. For this we need measures that are reliable and valid.

According to Guyatt *et al.* 1993 two basic approaches to measure the quality of life are available: generic and specific instruments. The generic instruments provide a summary of HRQoL including health profiles and instruments that generate health utilities. Specific instruments focus on specific aspect of health such as single disease states or areas of function. The first meeting of the International Health-related Quality of Life Society was held in Brussels in February 1994 and the focus of many abstracts was on the development of new disease-specific scales of quality of life (Bowling 1999). Generic HRQoL is indicative in the areas of physical, emotional and social functioning of the patient´s sense of his own health and well-being (Polonsky 2002). Generic HRQoL is a multidimensional concept and involves domains which contribute independently to HRQoL. Disease-specific measures include the categories treatment satisfaction, disease-related self-efficacy, disease-related coping styles, and other feelings and beliefs about the disease. The disease-specific HRQoL has been more difficult to elucidate than generic HRQoL.

There are many generic instruments to measure HRQoL. In Finland the most commonly used instruments have been WHOQOL-BREF, 15D, EQ-5D and RAND-36/SF-36. There are validated Finnish versions available of all these, and the questionnaires can be completely self-administered. 15D and EQ-5D are utility surveys (single index score measure) and they are suitable for estimating health care measures and their impact and cost effectiveness for quality adjusted

life years (QALY). 15D, which was originally developed in Finland, can be used also as a profile instrument (describes the state of patient in many health-dimensions) (Sintonen 2001, Sintonen 2013).

Table 5. Some instruments to measure the health-related quality of life.

Instrument, year, country	Profile/utility	Questions	Domains	Dimensions		
				Social	Physical	Mental
WHOQOL BREF, HRQoL instrument by WHO, 1994 UK.	profile	26	4	11	9	6
15D 1989 Finland	utility/profile	15	15	1	9	5
EQ-15D EuroQoL 1987 UK.	utility	5+VAS*	5+VAS	0	4	1
RAND-36-Item Health survey 1993 USA	profile	36	8	2	25	9
SF-36 the MOS-item short form health survey 1992 USA	profile	36	8	2	25	9
SF-20 the MOS-item short form health survey 1988 USA	profile	20	6	1	14	5

* visual analogue scale

Rand-36

The RAND 36-item health survey (Version 1.0) is perhaps the most widely used HRQoL survey in the world today (Hays & Morales 2001). It has been developed in the United States as a measure of HRQoL. The RAND-36 consists of eight domains including 36 items reflecting functioning and well-being (Appendix 2). These 36 items are identical to the MOS 36-Item Short Form Health Survey (SF-36) described (Ware & Sherbourne 1992) and developed in 1988–1990 based on the data in the Medical Outcomes Study (MOS) (Hays *et al.* 1993, Hays & Morales 2001).

RAND-36 and the eight main domains

1. Physical functioning (PF)

   Includes ten items, describing health limits in physical activities such as to climbing stairs, walking distance, lifting objects At best, the patient has the ability to perform even demanding physical activities. At worst, the patient has great difficulty in moving around

2. Role limitations caused by physical health problems: (RP)

   Four items describing limitations in activities caused by physical problems. At best during the last 4 weeks there have been no limitations. At worst the patient´s work performance has been unusually poor and it has been necessary to reduce working hours and tasks.

3. Role limitations caused by emotional problems (RE)

   Three items that describe limitations in activities caused by emotional problems.

4. Social functioning (SF)

   Two items covering limitations in normal social activities due to physical or mental factors. At best the patient´s social life has been normal without limitations. At worst social life has been severely limited by the condition.

5. Mental health (MH)

   Five items covering happiness, anxiety and depression. At best the patient has been calm and happy, but at worst continuously nervous and depressed for the last 4 weeks.

6. Energy/fatigue (VT)

   Four items reflecting the respondent´s vitality and tiredness. At best the patient has been feeling energetic and vital over the last 4 weeks and at the worst the patient has been constantly tired.

7. Bodily pain (BP)

   Two items measuring the magnitude of pain and how it is present with daily activities. At best, there is no pain. At worst, the patient experiences intense, crippling pain.

8. General health perception (GH)

    Five items on self-perceived conception on one`s current health, state
    compared to others, future health and resistance to illness. At best, the
    perceived health is excellent and at worst poor and weakening.

Scoring the RAND-36 Item Health Survey is a two-step process. First all items
are scored so that a high score defines a more favorable health state. Each item is
scored on a 0 to 100 range, so that the lowest and highest possible scores are set at
0 and 100, respectively. The scores represent the percentage of total possible
score achieved. The second step lists the items averaged together to create each
scale. Missing data are not taken into account when calculating the scale scores.
Scale scores thus represent the average for all items in the scale that the
respondent answered. The RAND-36 questionnaire is distributed freely without
copyright protection.

    It has been shown in many clinical studies in the United States that RAND-36
is a reliable and valid instrument in measuring HRQoL (Garratt *et al.* 1993,
Jenkinson *et al.* 1994). The RAND-36 is suitable when studying HRQoL in a
heterogeneous population including older people or comparing different patients
groups (Haywood *et al.* 2005, Lyons *et al.* 1994). The Finnish version of the
RAND-36 was developed together with Stakes and Kansanterveyslaitos in 1994
and validated as a posted questionnaire for general population with age- and sex-
matched in the Finnish population (Aalto *et al.* 1999).

2.7.3 Diabetes and Health-related quality of life

Background

People with diabetes must deal with their illness every day by checking blood
glucose and their medications. QoL is a very important aspect of life for persons
with diabetes. Diabetes affects many areas of life, including diet, activity,
employment, and daily routines. (Norris 2005). Diabetes therapy, for example
administering insulin, can affect the quality of life positively or negatively
reducing or increasing symptoms according to blood glucose level. Some studies
have shown that HRQoL is reduced in type 2 diabetic patients compared to the
general population (Rubin & Peyrot 1999) and is somewhat lower also than in
patients with other chronic diseases.

The interest in HRQoL has increased in recent years (Rubin & Peyrot 1999). In evaluating HRQoL, patient´s subjective rather than objective health status is important (Polonsky 2002). According to Polonsky, disease-specific measurement of HRQoL refers to how the disease compromises a person´s well-being in three domains: physical, psychological, and social function. He has presented the six-component model of HRQoL in diabetes. He divides diabetes-specific physical aspects of HRQoL into four major categories: long-term complications, short term complications, blood glucose alternatives, and side effects of medications.

Generic physical aspects of HRQoL concern diabetic people, include many major medical issues such as arthritis, cancer, alcoholism, chronic pain, and are not directly attributable to diabetes, but they can affect diabetes management. (Polonsky 2002).

The impact of diabetes on HRQoL

Diabetes is a serious disease and has significant effects on quality of life. In several studies diabetes has been shown to have a negative impact on the HRQoL, especially in the presence of complications (Goodridge *et al.* 2005, Lloyd *et al.* 2001, Redekop *et al.* 2002, Smith 2004). A study, conducted in the United States in a heterogeneous sample of adults with diabetes, with an average age of 59 years using a generic HRQoL instrument (the SF-20 survey) showed that older persons reported more impairment in physical and social function and less impairment in mental health than younger diabetic persons. Females reported significantly lower quality of life than males in physical and social functioning and mental health (Glasgow *et al.* 1997). The effects of diabetes on physical, psychological and social function has been reviewed in a study which show that persons with diabetes have more disability days and more restrictions on daily activities than non-diabetic subjects (Revicki 1990).

Using the SF-36 survey studying urban African Americans with type 2 diabetes, researchers found that during follow-up mean SF-36 change scores for usual care revealed lower vitality and mental health. The scores were lower also in physical functioning, physical role functioning, and bodily pain, but were not statistically significant. The intervention groups showed modest improvement in some clinical measurements (HbA_{1c}, blood pressure) compared with usual care but they did not improve HRQoL (Hill-Briggs *et al.* 2005). In a recently published study using EQ-5D to describe differences in HRQoL in individuals with type 2 diabetes, co-morbidity but not average glycemic control reduced HRQoL. Age

over 66 years, female gender, hypertension, peripheral neuropathy and clinically relevant depression, were independent predictors for EQ-5D, whereas dysglycemia had no influence on the EQ-5D scores (Wasem *et al.* 2013).

The relationship between diabetes and depression is known well. Diabetes doubles the risk of depression impairing effective self-care and clinical management as well as glycemic control (Leppävuori 2010, Lustman *et al.* 2000).

Studies on how the newly diagnosed diabetes affects HRQoL are scarce. In a study researches have compared persons with type 2 diabetes diagnosed one year before and those detected at the time of study by screening. The differences were statistically significantly worse for the domains of role emotional, mental health, vitality and general well-being during the first year after diagnosis compared to those whose diabetes was detected by screening. However, general health and vitality scores improved over time in the newly diagnosed group, indicating a positive effect of diabetes treatment on HRQoL (Adriaanse *et al.* 2004).

There are a few Finnish studies of diabetes and HRQoL. In most of these studies researches have used SF-20 or the Nottingham Health Profile (NHP) questionnaires to assess HRQoL (Hanninen *et al.* 1998, Hanninen *et al.* 2001, Hiltunen & Keinanen-Kiukaanniemi 1999, Keinanen-Kiukaanniemi *et al.* 1996). In these studies there was a moderate worsening impact on HRQoL among diabetic people compared with non-diabetic controls. Existence of diabetes, CAD and other macrovascular disease were associated with impaired physical and social functioning, whereas mental status was not affected (Hanninen *et al.* 1998). Regular clinical check-ups at least twice per year, and education by a diabetes nurse and satisfaction with diabetes education seemed to improve HRQoL among diabetic people (Hanninen *et al.* 2001). A review article of the quality of life among patients with diabetes in the Nordic countries indicated that diabetes affects the HRQoL through macrovascular complications and is very highly associated with non-vascular co-morbidity, whereas microvascular complications, age and metabolic level are weaker predictors (Wandell 2005).

3 Purpose of the study

The aim of this study was to assess

1. how one-hour post-load glucose among men healthy in midlife predicts future diabetes
2. whether there are differences between normal fasting glucose and 1-hour glucose levels as predictors of future diabetes
3. how risk factors in midlife affect the those of onset of diabetes in older age
4. how diabetes developed in older age affects the HRQoL

4 Subject and methods

4.1 Helsinki businessmen cohort

The present thesis is part of the prospective study named The Helsinki Businessmen Study started in the 1960´s. The participants took part in examinations and answered to the postal questionnaires between the years 1964–2007. The schedule is presented in Table 6. A more detailed timeline for the study is summarized in Appendix A.

Table 6. The schedule of the investigations between 1964–2007.

The year of the investigation	Contents
1964–1973	3,490 men in leading positions took part in voluntary health examinations performed at the Institute of Occupational Health of Helsinki
1974	baseline examinations for 2,375 men, among them 1,815 clinically healthy men without diabetes, investigations for CVD risk factors and questions of SRH on a 5-step scale
1985/86	postal questionnaire and clinical examinations
2000	postal questionnaires including RAND-36 HRQoL, mortality retrieved from national registers
2002/03, 2005	postal questionnaires with RAND-36 survey, mortality from national registers
2007	mailed questionnaires, mortality from national registers

CVD = cardiovascular disease, HRQoL = health related quality of life, SRH = self-related health

4.2 Baseline examinations in 1964–1973

The men who took part in this study were in leading positions, mostly business executives or managers in different companies mainly in the field of industry or commerce. Between 1964 and 1973, altogether 3,490 men born in 1919–1934 participated in the examinations. Baseline examinations including measurements of 1-hour post-load blood glucose level and CVD risk factors are presented in Table 7.

Table 7. The health evaluation performed between 1964 and 1973.

Assessment	Contents
Clinical examination	performed by a physician
	height and weight measured
	blood pressure
	smoking status
Laboratory tests	serum cholesterol
	serum triglycerides (from 1969 onwards)
	1-hour post-load blood glucose
	1g/kg of body weight of glucose orally

At this point risk factor levels were available for 3,313 men, 95% of the original study population. This originally healthy and socioeconomically homogenous population with a follow-up time of over 40 years offers an appropriate basis for evaluating CVD risk factors in midlife and the risk of developing diabetes later at an older age and its impact on the HRQoL.

4.3 Baseline examinations in 1974 (midlife examination)

In 1974 CVD risk factors and weight gain from age 25 were assessed in 1,815 men. Mean age of the cohort was 48 years (SD 4). The men were asked about past and current diseases and medication and to describe their present health on a 5-step scale (self-related health, SRH): very good, fairly good, average, fairly poor and very poor. Smoking status was divided into never smoker, ex-smoker, and current smoker, alcohol consumption was calculated as g/week. To measure the glucose concentration was used whole blood according to the method of Hultman (Hultman 1959). The fasting glucose was measured after an overnight fast of 12 hours (mmol/L) as well as 60 minutes after an oral load of 1 g of glucose per kg of body weight which was standard procedure at that time (Pelkonen *et al.* 1981). The blood samples were analyzed immediately after drawing. Methods of the measures are presented in Table 8.

Table 8. Methods of the measures in 1974.

Variables	Measurement
Blood pressure	in sitting position after a 10-min rest measured with a mercury sphygmomanometer
Heart rate	calculated from resting electrocardiography (ECG)
Cholesterol and triglycerides	in the fasting state by standard methods
Blood glucose	in the fasting and one hour after a glucose load (1g/kg of body weight of glucose orally)
Smoking status	never smoker, ex-smoker, current smoker. number of cigarettes/day in self-reported questionnaire
Alcohol consumption	calculated as grams of ethanol/week assessed with a self-reported questionnaires
Weight	measured and BMI calculated as weight (kg) divided by height (metres) squared
Self-reported current health and physical fitness	5-step scale: very good, good, fair, poor very poor

Baseline characteristics in 1974 and diabetes developed during follow-up are presented in Table 9.

Table 9. Baseline characteristics in 1974 (n = 1,815) and onset of diabetes during follow-up (until 31 December 2007).

Variable	No diabetes during follow-up n = 1,599	Diabetes during follow up n = 216
Age, year	47.7 (4.1)	46.9 (4.0)
BMI kg/m^2	25.6 (2.6)	27.2 (3.0)
BMI at 25 years of age, kg/m^2	22.7 (2.1)	22.7 (2.3)
Weight gain until 1974, kg	9.1 (8.0)	14.4 (8.9)
Smokers, n (%)	477 (29.8)	74 (34.1)
Alcohol consumption g/week	155.2 (142.2)	185.1 (214.0)
Systolic BP	142.2 (18.6)	146.7 (19.2)
Diastolic BP	91.3 (11.2)	94.8 (11.3)
Resting heart rate beats/min	63.7 (10.9)	65.4 (11.3)
Serum cholesterol mmol/L	6.2 (1.0)	6.2 (1.1)
Serum triglycerides mmol/L	1.57 (0.88)	2.00 (1.14)
Fasting blood glucose mmol/L	4.7 (0.6)	5.1 (0.9)
1 hour post-load glucose mmol/L	6.8 (1.9)	8.7 (2.5)

BMI = body mass index, BP = blood pressure

Data are mean (SD) unless otherwise indicated

4.4 Examinations in 1986

In 1986 examinations included the third scientific evaluation in this male cohort. Postal questionnaires were sent to the participants who were healthy in 1974 and alive in 1986. Altogether 1,399 men (82%) replied, but some of the responses were incomplete. The men were asked to have their blood pressure, weight gain, electrocardiography (ECG) and blood samples taken at their local health care centre. Smoking status and alcohol consumption were assessed by the questionnaires.

4.5 The 2000 survey and later questionnaires

In 2000 a postal questionnaire including the Finnish version of the RAND-36–Item Health Survey 1.0, a HRQoL instrument practically identical to the SF-36, was sent to all survivors of the original cohort (n = 2,286). The questionnaire included also the variables: weight, physical activity, alcohol consumption, blood pressure (the latest measured), current smoking status, current diseases including cardiovascular diseases and diabetes. A questionnaire was re-mailed once to non-respondents and altogether 1,864 (88%) responded.

The postal surveys with RAND-36 were replicated in 2002/2003, 2005 and 2007. The response rates diminished gradually due to aging of the cohort being 67.8% in 2007.

4.6 Development of diabetes

Development of diabetes during the follow-up time from 1974 up to December 31, 2007, was assessed using the National Drug Reimbursement Register (Reunanen *et al.* 2000)) and self-reported diabetes in questionnaires. In Finland all individuals needing prescription medication for diabetes are entitled to reimbursement of their expenses, which requires a detailed medical certificate from the attending physician. The Social Insurance Institution of Finland (KELA) checks that the case fulfils the criteria for diabetes and maintains a register of these cases. In the case of questionnaire-verified diabetes the year it was first mentioned was used, if the year of onset was not specifically given.

4.7 Mortality follow-up

For the mortality follow-up of the study population the National Population Information system of Finland was used from baseline through 31 December 2007. The total mortality of the initial cohort was 44%.

4.8 Ethical consideration

This follow-up study has been approved by the Ethical Committee of the Department of Medicine of Helsinki University Hospital.

4.9 Statistical methods

In studies I, II and III statistical analyses were performed with NCSS 2004 (NCSS, Kaysville, Utah, www.ncss.com), in study IV with NCSS 2007 version. Descriptive statistics, t-tests (log transformed values were appropriate), nonparametric tests, and analysis of covariance (ANCOVA) were used in these studies.

Descriptive statistics, analyses of covariance, and logistic regression were used to find independent midlife predictors of diabetes (study III). In logistic regression with forward stepping, odds ratios (ORs and their 95% confidence intervals (CIs) were calculated. Analyses were age-adjusted, and the covariates included age, serum lipids, 1-hour glucose, weight gain up to midlife, systolic blood pressure, and smoking. In these analyses odds ratios (OR) were calculated per standard deviation of continuous variables to facilitate comparisons.

Chi-square and trend tests were used to compare proportions in the studies. Cox proportional hazards models were used to find independent predictors of diabetes (study I). In these analyses only registry-verified diabetes was used because the exact year of onset was known. Hazard ratios (HR, with their 95 per cent confidence intervals [CI]) for baseline variables were calculated. In these analyses HR was calculated per SD of continuous variables (except age) in order to facilitate comparisons.

In the analyses of study II both fasting and 1-hour post load glucose values were divided into quintiles. Analysis of covariance (ANCOVA) was used to include continuous variables in the analysis. Differences in the development of diabetes were analysed using Kaplan-Meier curves and log-rank tests. Before 2007, cases were censored at the time of diabetes diagnosis, or death. Cox's

proportional hazards regression was used to calculate adjusted RR with their 95% CI.

In study IV t-tests (log-transformed values were appropriate) and non-parametric tests were used, and analysis of co-variance was used to compare diabetes onset groups. Two-tailed tests were used in statistical analyses in all studies and two-sided P values < 0.05 were considered significant.

5 Results

5.1 One-hour post-load glucose, BMI and future diabetes (I)

The first substudy evaluated how 1-hour post-load blood glucose in conjunction with BMI would predict mortality and development of diabetes during follow-up. At baseline 2,765 men with 1-hour post-load blood glucose values without diagnosed diabetes and CVD were included in the analyses. Maximum follow-up time was 44 years with a median of 37 years (interquartile range = IQR, 29–40 years).

At baseline in 1974, the median age of the cohort was 42 years (IQR, 39–46 years), the median age of the survivors by 2007 was 79 years (IQR, 76–83 years). Median 1-hour glucose during the follow-up was 108 mg/dL (6.0 mmol/L), (IQR, 88.2–133 mg/dL). To convert glucose to millimoles per litre, multiplying by 0.0555 was used. Median BMI was 25.7 (IQR, 24.1–27.5). The 1-hour post-load glucose levels were divided into quartiles. See Table 10.

Altogether 357 men (13%) developed diabetes; 289 cases were from the reimbursement register and 68 cases from questionnaire data only.

Table 10. 1-hour post-load glucose levels, BMI and mortality by quartiles, a 44-year follow-up.

Variable	I	II	III	IV
1-hour post-load glucose mg/dL	≤ 161	≤ 161	> 161	> 161
BMI	< 25	≥ 25	< 30	≥ 30
Deaths	367	627	213	56
Incident diabetes	56	171	95	33
n/men	920	1313	390	86
%/men	44.2	48.4	14.3	3.2

BMI = body mass index

One-hour post-load blood glucose level higher than 144 mg/dL (7.9 mmmol/L), (plasma value > 161 mg/dL, > 8.9 mmol/L), the cut-point used in the study by Manco *et al.* (2010.) and BMI of 30 or higher, was associated with 10.1-fold increase of diabetes risk independently of CVD risk factors. Only 3.2% (86 out of 2,709 men) of the cohort belonged to this subgroup. The results demonstrate the very high diabetes risk associated with elevated 1-hour glucose level measured in early midlife.

5.1.1 Mortality during follow-up (I)

In the cohort a total of 1,287 men died (46.5%), 509 (39.5%) of them of CVD.

The elevated 1-hour post-load blood glucose level measured in early midlife indicated higher mortality risk later in old age and was independent of traditional CVD risk factors. The impact of the combination of 1-hour post-load blood glucose level and BMI on total mortality was significant in all subgroups compared to reference group (1-hour glucose < 161 mg/dL and BMI < 25).

Table 11. Causes of death in the study groups up to 31 December 2007 according to the blood 1-hour post-load glucose quartiles at baseline

Variable	Quartile				Numbers	P-value between
	1 n = 668	2 n = 705	3 n = 700	4 n = 683	2,756	quartiles
OHPLG, mmol/L	4.4	5.4	6.6	8.5		
median, (IQR)	(4.1–4.6)	(5.2–5.7)	(6.3–6.9)	(7.9–9.5)		
CVD	89	124	122	174	509	< 0.001
CAD	68	92	82	127	369	0.03
Cancer	81	98	94	86	359	0.76
Accident and suicide	30	27	28	29	114	0.93
Other causes	58	56	61	66	241	0.73

OHPLG = 1-hour post load glucose, CVD = cardiovascular disease, CAD = coronry artery disease, IQR = inter quartile range

5.2 Comparison of normal fasting and 1-hour post-load glucose and future diabetes (II)

This study compared the value of fasting and 1-hour post load blood glucose to predict diabetes risk during a 34-year follow-up in an originally normoglycemic (FBG < 5.0 mmol/L) male cohort.

At baseline in 1974 the mean age of the men (n = 1,145) was 47.8 (SD 4) years and median FBG was 4.4 (IQ range 4.2–4.7) mmol/L. For 1-hour glucose the median level was 6.6 (IQ range 5.5–7.8) mmol/L and mean BMI was 25.7 (SD 2.7) kg/m^2.

The mean age of surviving participants (n = 689) was 80.7 (SD 4) years at the end of the follow-up in 2007. During the 34-year follow-up time 108 incident cases of diabetes developed. Of these 108 cases 33 were identified via self-reporting.

The unadjusted cumulative incidence of diabetes among quintiles of fasting glucose and 1-hour post-load blood glucose is presented in Figures 1 and 2. The varying power of these two glucose variables to predict the development of diabetes is seeing in these curves. The RRs (with 95% CI) of various quintiles, adjusted for age, smoking, and BMI, with lowest quintile as referent, are shown in Table 12.
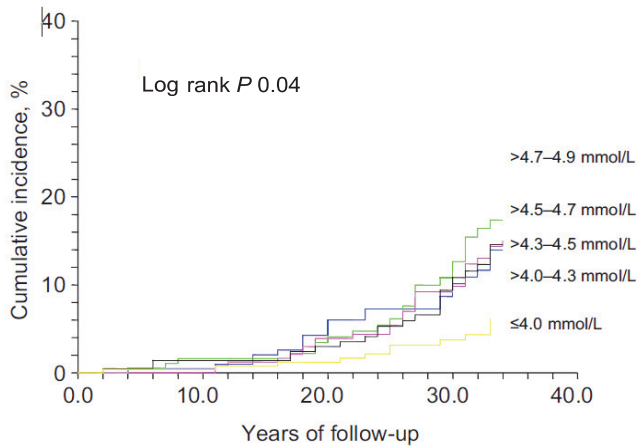

Fig. 1. Cumulative incidence of diabetes during 34 years of follow-up according to baseline fasting blood glucose in 1974. Unadjusted.
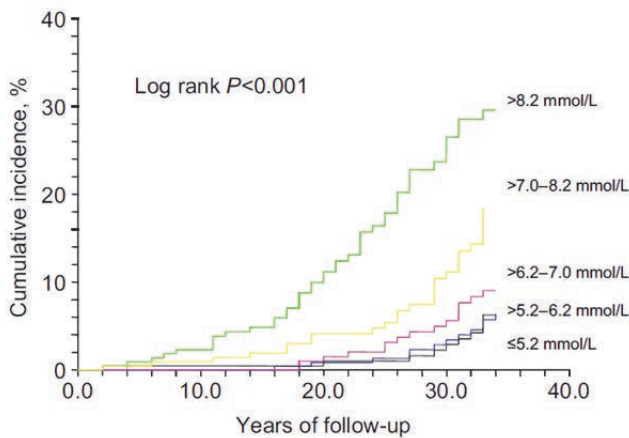

Fig. 2. Cumulative incidence of diabetes during 34 years of follow-up according to baseline 1-hour post-load glucose in 1974. Unadjusted.

Table 12. Risk ratios for type 2 diabetes among 1,145 men during 34 year of follow-up according to quintiles of normal fasting glucose in 1974.

Variable	Quintile 1 (n = 267)	Quintile 2 (n = 211)	Quintile 3 (n = 217)	Quintile 4 (n = 258)	Quintile 5 (n = 192)
Fasting blood glucose mmol/L	≤ 4.0	> 4.0–4.3	>4.3–4.5	> 4.5–4.7	> 4.7–4.9
Equivalent plasma glucose	≤ 4.5	> 4.5–4.8	> 4.8–5.0	> 5.0–5.3	> 5.3–5.5
Risk ratio, adjusted for age, smoking and BMI (95% CI)	1	1.90 (0.93–3.85)	1.92 (0.95–3.90)	2.03 (1.02–4.02)	2.22 (1.10–4.50)
Risk ratio for the register-verified cases, adjusted for age, smoking and BMI (95% CI)	1	4.14 (1.39–12.36)	3.94 (1.31–11.85)	4.04 (1.37–11.97)	4.92 (1.65–14.64)

Table 13. Risk ratios for type 2 diabetes among 1,145 men during 34 year of follow-up according to quintiles of 1-hour post-load glucose in 1974.

Variable	Quintile 1 (n = 214)	Quintile 2 (n = 256)	Quintile 3 (n = 230)	Quintile 4 (n = 221)	Quintile 5 (n = 224)
1-hour post-load blood glucose, mmol/L	≤ 5.2	> 5.2–6.2	> 6.2–7.0	> 7.0–8.2	> 8.2
Equivalent plasma glucose	≤ 5.8	> 5.8–6.9	> 6.9–7.8	> 7.8–9.2	> 9.2
Risk ratio, adjusted for age, smoking and BMI (95% CI)	1	0.86 (0.45–1.67)	1.55 (0.84–2.84)	2.79 (1.63–4.78)	4.23 (2.49–7.17)
Risk ratio for the register-verified cases of diabetes, adjusted for age, smoking and BMI (95% CI)	1	0.88 (0.29–2.61)	1.13 (0.39–3.28)	2.40 (0.93–6.14)	4.76 (1.94–11.62)

BMI = body mass index, CI = confidence interval

The number of register-verified diabetes cases was also 75, and the results were analyzed separately for these as well. In spite of less statistical power, these results did not change the conclusion of the study (Table 12 and 13).

5.2.1 Fasting blood glucose and risk for future diabetes

When analyzing the results, among the quintiles of FBG (below 5.0 mmol/L), the lowest quintile ≤ 4.0 mmol/L was associated with the lowest (4.9%) risk of diabetes. In the higher quintiles, RRs were greater, but fairly comparable, ranging from 1.9 to 2.2.

5.2.2 One-hour post-load glucose and risk for future diabetes

When comparing the lowest 1-hour post-load blood glucose quintile to the lowest FBG quintile, the incidence of new diabetes was similar, 4.7%. There were no significant differences in RR from the referent 1-hour post-load glucose in the second and third quintiles ($\leq$ 7.0 mmol/L), but RR rose to 2.8 in the fourth quintile (> 7.0–8.2 mmol/L) and to 4.2 in the highest quintile (> 8.2 mmol/L).

5.3   Modifiable risk factors in midlife and future diabetes (III)

The follow-up time in this substudy was 34 years, from 1974 through 2007. At the beginning the men in this cohort were healthy without diabetes, with mean age 48 years (SD 4). During the follow-up, register-verified diabetes developed in 166 men (median time to diagnosis 21 years) while 52 cases were based on self-report. Age at onset of diabetes could be determined in 214 men and was divided into age groups 45–64, 65–74, and 75–87. They were compared with men without diabetes during the follow-up.

5.3.1 Midlife characteristics at baseline in 1974

At baseline in 1974, cardiovascular risk factors and weight gain from age 25 were assessed in 1,815 healthy middle-aged men without diabetes. The weight gain from the age of 25 in men who did not develop diabetes was 9.1 kg and the mean 1-hour post-load glucose level 6.8 mmol/L. Those who developed diabetes later gained more weight and their 1-hour post-load glucose levels were higher. See Table 14.

Table 14. Midlife characteristics according to age of onset of diabetes.

Characteristics	No diabetes	Diabetes age groups			P-value
	n = 1.597	< 65, n = 65	65–74, n = 86	> 75, n = 63	between
Year of onset of diabetes, median (IQR)		1986 (1982–92)	1999 (1993–2003)	2005 (2004–07)	
Age at DM onset, median (IQR)		60 (54–63)	71 (67–72)	78 (76–81)	< 0.001
BMI at age 25, kg/m^2	22.8 (0.06)	22.7 (0.3)	22.4 (0.3)	22.9 (0.3)	0.41
Weight gain from age 25 to year 1974, kg	9.1 (0.2)	17.4 (1.1.)	14.8 (1.0)	11.5 (1.1)	0.002
Variable in 1974					
Age, mean (SE)	47.7 (0.1)	46.0 (0.5)	46.1 (0.4)	49.0 (0.5)	< 0.001
BMI kg/m^2 mean (SE)	25.6 (0.07)	28.2 (0.4)	27.1 (0.3)	26.6 (0.4)	0.009
Smoker, n (%)	478 (29.9)	24 (36.9)	34 (39.5)	14 (33.6)	0.07
BP, mmHg mean (SE)					
Systolic	142.1 (0.5)	152.6 (2.4)	145.0 (2.1)	142.5 (2.5)	0.01
Diastolic	91.3 (0.3)	98.3 (1.4)	92.1 (1.2)	94.4 (1.4)	0.003
Resting heart rate, beats/min, mean (SE)	63.7 (0.3)	69.9 (1.4)	65.2 (1.2)	61.9 (1.4)	0.003
Serum cholesterol, mmol/l, mean (SE)	6.1 (0.03)	6.2 (0.1)	6.1 (0.1)	6.1 (0.1)	0.62
Serum triglycerides, mmol/l mean (SE)	1.56 (0.02)	2.15 (0.14)	2.01 (0.12)	1.81 (0.14)	0.29
1-hour post-load glucose, mmol/l mean (SE)	6.8 (0.05)	10.0 (0.3)	8.4 (0.3)	7.8 (0.3)	< 0.001
Alcohol consumption, g/week, mean (SE)	154.9 (3.8)	208.6 (26.7)	189.8 (23.4)	153.5 (2.71)	0.38

age adjusted

Log-transformed values where appropriate

IQR = inter-quartile range; SE = standard error, BMI = body mass index, BP = blood pressure

Among the whole cohort, only baseline 1-hour post-load blood glucose (OR per SD = 1.9, 95% CI = 1.7–2.3), and weight gain from 25 years to midlife (OR per SD = 1.5, 95% CI = 1.3–1.8) predicted future diabetes. When compared to onset of diabetes at age < 64, onset at higher age was characterized by lower levels of midlife risk factors of which weight gain up to midlife, 1-hour post-load blood glucose, blood pressure, and pulse rate were statistically significant. Men with late-onset diabetes ≥ 75 also tended to have been healthier in middle age with less smoking and alcohol consumption. (Table 12).

5.4 Onset of diabetes in old age and HRQoL (IV)

In this substudy the aim was to evaluate the effect of diabetes onset on HRQoL.

During the 34-year follow-up (from 1974 to 31 December 2007), 634 men (34.9%) died and 216 (11.9%) developed diabetes, 161 of the cases were register-verified and 55 questionnaire-based. At baseline the men, who developed diabetes showed higher CVD risk and poorer glycemic status compared to men without diabetes during follow-up. The groups of diabetes (n = 216) onset were divided as follows: 1991 or before, n = 57; 1992 to 1995, n = 38; 1996 to 2000, n = 34; 2001 to 2003, n = 36; and 2004 to 2007, n = 61. The numbers of diabetes cases and deaths are compared in Table 14.

Table 15. Number of deaths during follow-up (1974 to 2007) and proportion of men with HRQoL assessment in 2000.

Diabetes onset (number)	No of men	No of deaths by 2000	No of deaths 2001–2007	HRQol assessed in 2000 (response %)
Diabetes during 1974–2007	1,599	396	250	1,067 (89)
Diabetes before 1992	57	18	13	32 (82)
Diabetes 1992–1995	38	10	15	23 (82)
Diabetes 1996–2000	34	2	9	32 (100)
Diabetes 2001–2003	26	--	8	23 (88)
Diabetes 2004–2007	61	--	2	52 (85)

HRQoL = health related quality of life

5.4.1 RAND-36 questionnaire

In 2000, all survivors (n = 1,390) were sent a postal questionnaire including the Finnish version of the RAND-36 item health survey 1.0 was sent to all survivors to evaluate HRQoL. The response rate was very good, 87.8%, the mean age of respondents being 73 years (SD 4)

Questionnaire data including HRQoL could be obtained from 162 men with diabetes (*i.e.* 75% of all) and from 1,067 men without diabetes during follow-up up to 2007.

According to the onset of diabetes, the scores of eight RAND-36 scales in 2000 were adjusted for age and SHR in 1974, when the men were free of diabetes. Statistically significant differences in old age between the onset groups were found in scores for physical functioning (p > 0.001), social functioning (p = 0.03), and general health (p = 0.01). In these scales HRQoL worsened rapidly and quite

constantly after diabetes developed (during 4 years after onset of diabetes). However there were no significant differences between "prediabetic" men and non-diabetic men during the 34-year follow-up. No consistent relationship was seen between mental health (p = 0.7) or vitality (p = 0.4) and diabetes.

5.4.2 Self-related health

To compare SRH at baseline in 1974 (five step scale) and at the end of follow-up in 2007 according to diabetes onset groups, the SRH question of RAND-36 reported in 2007 was used. The wording in RAND-36 (excellent, very good, good, fair, poor) differs somewhat from that in the 5-step scale used in 1974 (very good, fairly good, average, fairly poor, very poor).

At baseline there was no consistent association between the groups, but with longer duration of diabetes in 2007, SRH tended to worsen (global p = 0.07).

6 Discussion

6.1 Assessment of the study cohort

This present thesis was based on a prospective study cohort called the Helsinki Businessmen study, with follow-up from 1964 to the end of year 2007. All participants were Caucasian men of high socioeconomic status with similar working life positions. In the beginning all participants (3,490) were healthy men born in 1919–1934. The men took part in examinations and completed postal questionnaires during the follow-up.

In1974 when the men were in midlife, with a mean age of 48 years (SD 4), without diabetes, they were evaluated especially for CVD factors with questionnaires and clinical and laboratory investigations. Fasting blood glucose (FBG) and 1-hour post-load glucose levels have been measured during the follow-up offering an opportunity to examine the development of diabetes among normoglycaemic men from midlife to old age. The onset of diabetes was ascertained through registers (the National Drug Reimbursement register) (Reunanen *et al.* 2000) and from questionnaires up to 31 December 2007.

To assess their HRQoL, the men were asked about their present health (SRH) on a five-step scale in 1974, reflecting "global" quality of life at baseline. In 2000 all survivors (mean age 73 years, SD 4) were sent a postal questionnaire including the Finnish version of the RAND-36–Item survey 1.0 consisting of 36 questions assessing eight domains of HRQoL (Aalto *et al.* 1999, Hays *et al.* 1993) The response rates have diminished gradually, being 87.8% in 2000 and 67.8% in 2007, due to the ageing of the cohort.

Mortality was 34.9% from 1974 to the end of 2007 and retrieved from the National Population Information System of Finland.

6.2 Discussion of the methods

The results are based on a large, homogenous cohort with an especially long follow-up time from the 1960´s until 31 December, 2007. All the men were healthy without any chronic disease or medication at baseline. The participants were from higher socioeconomic class with similar job status and most of them belonged to the group of professional executives. This homogenous status has its advantages when evaluating QoL, but there are also disadvantages, because social

class has a clear impact on morbidity and mortality (Drever *et al.* 1997). Thus the generalization of the results to the general population should be done with caution.

Development of diabetes with year of onset was evaluated using the National Reimbursement register, which indicates clinically well-established diabetes in Finland, even though the actual "break-out" may have happened several years before. Cases of self-reported diabetes in questionnaires were not reliably verified and were therefore not included in statistics, even though they did not seem to change the results.

The National Population Information System of Finland was used for the mortality follow-up. Data in this register include names, births and deaths and are 100% complete.

HRQoL was measured in 2000 and replicated later with the RAND-36 survey, which is a widely used and validated international instrument. At baseline in 1974 SRH-questionnaire (5-step scale) was used, with wording that differs somewhat from that used in RAND-36.

The data on the risk factors at baseline, later clinical examinations and in the questionnaires enabled multivariate adjustments for potential confounding factors and wide use of statistical analyses.

6.3   Major results of the study

6.3.1 One-hour post-load glucose, diabetes risk and mortality (I)

This 44-year follow-up study shows a very high diabetes risk associated with elevated 1-hour post-load glucose level measured in early midlife. In the quartiles, the combination of blood 1-hour post-load glucose level higher than 144 mg/dL (7.9 mmol/L), equivalent to plasma value > 161mg/dL (8.9 mmol/L) and BMI of 30 or higher was associated with a 10.1-fold increase of diabetes risk independently of CVD factors.

In this study there was a strong relationship between 1-hour glucose quartiles and both cardiovascular ($p < 0.001$) and total mortality and development of diabetes ($p < 0.001$) during the follow-up. Non-vascular mortality was not related to 1-hour post-load glucose in this cohort.

6.3.2 Comparison of normal fasting and one-hour glucose and future diabetes (II)

Fasting and 1-hour post-load glucose were measured in the originally normoglycaemic (FBG < 5.0 mmol/L, equivalent to plasma glucose FPG < 5.6 mmol/L), middle-aged male cohort, who were then followed up for34 years for development of diabetes. The median FBG and 1-hour post-load glucose values at baseline were 4.4 and 6.6 mmol/L, respectively.

The fasting blood glucose ≤ 4.0 mmol/L indicated protective effect compared to the mid-high normal range > 4.0 to 4.9 mmol/L. Among the quintiles the risk of incident diabetes was doubled for the highest quintile compared to the lowest quintile.

In the 1-hour post-load glucose quintiles, the incidence of diabetes was similar in the lowest quintile (< 5.2 mmol/L) as in fasting glucose (< 4.0), but quadripled in the highest quintile (> 8.2 mmol/L).

FBG could not separate the risk for those with higher levels of glucose in the range < 5.9 mmol/L, whereas 1-hour post-load glucose discriminated the risk better at higher values. The incidence of diabetes did not seem to increase steeply until after 15–20 years of follow-up.

6.3.3 Midlife risk factors and the age of onset of diabetes (III)

In this study the men with higher post-load glucose, blood pressure, and pulse rate at baseline or greater weight gain up to midlife appeared to develop diabetes earlier than 65 years of age compared to those with fewer risk factors. The men who developed diabetes later, ≥ 75 years, were shown to have been healthier in middle age, to have used less alcohol and have smoked less. In the whole cohort, only baseline 1-hour post-load glucose (p < 0.001) and weight gain from age of 25 to midlife (p = 0.002) predicted future diabetes.

6.3.4 Onset of diabetes and HRQoL (IV)

The results suggest that diabetes does not affect the quality of life until after diabetes onset. This worsening is seen in only some of the domains of RAND-36: physical functioning (p < 0.001), social functioning (p = 0.03) and general health (p = 0.01). Mental aspects seemed not to be affected by diabetes in this male

cohort. During the pre-diagnostic period of up to seven years no association was found between pre-diabetic state and HRQoL.

6.4 Strength and limitations

6.4.1 Strengths in the study

The major strength of this study was the large socioeconomically homogenous cohort at baseline consisting of subjects of the same ethnicity. The exceptionally long follow-up time of the study cohort allows a distinctive opportunity to observe subsequent health consequences of different cardiovascular risk factor and predictors of future diabetes from midlife to older age. The results are based on a male cohort, healthy at baseline without any diseases or medications.

To evaluate the HRQoL of the men the Finnish version of the RAND-36-survey was used. The RAND-36 survey is widely used in the world and reliable and validated to assess the HRQoL.

6.4.2 Limitations in the study

While the homogenous nature of the study population is an advantage, it has limitations too. The good socioeconomic status can diminish the important bias related to socioeconomic status and restricts the generalization of our results to the general population. Especially the lack of women is also a remarkable limitation, as is the lack of younger people. For instance, it has been shown that glucose absorption may differ between genders during OGTT (Anderwald *et al.* 2011).

Even though the long follow-up time has its benefits, it does have disadvantages as well. During this time the criteria for the diagnoses of diabetes have changed, as have measurements methods. Otherwise, missing data related to mortality should be taken into account concerning a longitudinal study and its duration. It is possible that some of the men who died during the follow-up of other causes would have developed diabetes. It is also possible that with advancing age and co-morbidities, diabetes may remain undiagnosed, untreated, or unreported in a long-term study.

The majority of diagnoses of diabetes were gathered from registers, but some of them were based on self-reports, which may be unreliable. The diagnoses taken

from the registers were not separated into type 1 and type 2 diabetes (taking into account the frequency of type 2 diabetes and the age of men). The exclusion of self-reported diabetes did not change the conclusions of our study.

The incidence of diabetes in the cohort was low. At baseline we had only a single sample of fasting and one-hour glucose and there could have been inconsistency among repeated measurements. This may diminish the accuracy and the reliability of this study.

Because the men belonged to a high socioeconomic group, their lifestyle may have been healthier compared to those in lower socioeconomic groups (Hulshof *et al.* 2003) and they may have assessed their HRQoL differently from other socioeconomic groups. On the other hand, the lifestyle of the participants may have changed during the long follow-up, affecting their predisposition to diabetes.

6.5 Discussion of the results

6.5.1 One-hour post-load glucose, normal fasting glucose and future diabetes (I, II)

To identify the people at risk for future diabetes the use of 2-hour OGTT is recommended, and the WHO also recommends the use of OGTT in people with fasting plasma glucose between 6.1 and 6.9 mmol/L (World Health Organization 1999). Botas *et al.* (2003) have compared the diagnostic criteria for diabetes according to WHO-1985, ADA-1997 and WHO-1999 in the adult population of Asturias (Spain), and they propose the use of OGTT for all those with fasting blood glucose between 5.7 mmol/L and 6.9 mmol/L to improve the diagnostic strategy for diabetes and detect up to > 80% of patients. In another study of 5.023 adult Pima Indians, the frequency of diabetes was 12.5% by the 1997 ADA criteria, 14.6% by the 1985 WHO criteria and 15.3% by the 1999 WHO criteria, and the incidence of diabetes was clearly related to higher FPG and 2-hour post load glucose. Even though IGT was more common than IFG (15% vs. 5%), the incidence of diabetes was higher among people with IFG than among those with IGT (37% vs. 24%) (Gabir *et al.* 2000).

Several studies have been carried out to find better models to improve the ability to predict future diabetes (McNeely *et al.* 2003, Stern *et al.* 2002, Wannamethee *et al.* 2005, Tuomilehto *et al.* 2010) and these are based on risk factors for type 2 diabetes. Stern *et al.* (2002) showed in their study that persons

at high risk for diabetes are better identified by using a simple prediction model than by relying exclusively on results of a 2-hour OGTT. They used a multivariable model measuring BMI, BP, lipids, FPG and 2-hour post-load glucose and medical history. In another multivariable model McNeely *et al.* (2003) found that clinical model (age, BMI, BP, FPG, HDL, family history, ethnicity) was better than FPG alone for predicting diabetes after 5–6 years but not after 10 years, in Japanese Americans aged $\leq$ 55 years. The model was not useful in older age, whereas 2-hour post-load glucose was useful in predicting diabetes regardless of age. In the Finnish model targeted to the general population, the risk screening based on risk assessment and subsequent glucose measurements predicted with 85% accurary future diabetes risk in 10 years follow-up. This tool detects also current asymptomatic diabetes and abnormal glucose tolerance (Lindstrom et Tuomilehto 2003, Saaristo *et al.* 2005)

OGTT is time-consuming, costly and inconvenient. Even though the OGTT diagnosis of IGT has high specificity (92%) in predicting subject at high risk for developing type 2 diabetes, it has a much lower sensitivity (51%) and half of those who convert to type 2 diabetes could not to be identified (Abdul-Ghani *et al.* 2007). We need less expensive and less time-consuming methods of identifying persons at high risk for type 2 diabetes.

One-hour post-load glucose has recently aroused interest in prediction of future type 2 diabetes (Abdul-Ghani *et al.* 2007, Abdul-Ghani *et al.* 2008, Abdul-Ghani *et al.* 2009, Manco M. *et al.* 2010). Individuals with NGT have low risk of developing type 2 diabetes, but about 40% of subjects who develop diabetes have NGT at baseline (Unwin *et al.* 2002). Abdul-Ghani *et al.*(2008) showed in their study, that 16.7% of subjects with NGT and 1-hour plasma glucose level during OGTT > 155 mg/dL developed diabetes during a 7- to 8-year period. NGT subjects with one-hour plasma glucose > 155 mg/dL with metabolic syndrome were at very high risk for type 2 diabetes and their risk exceeded that of subjects with IFG and IGT. The researchers suggest that the plasma glucose concentration at one hour during the OGTT is a strong predictor for future type 2 diabetes independent of the glucose tolerance status and a cut-point of 155 mg/dL divides individuals with NGT, IFG, and IGT into low-, intermediate-, and high-risk groups. In this present study the results point in the same direction.

In this study it was found that 1-hour post-load blood glucose level > 144 mg/dL (plasma value > 161 mg/dL) measured in early midlife combined with BMI $\geq$ 30 demonstrated very high diabetes risk, a 10.1-fold, independently of CVD risk factors, later in older age in men. Of all incident diabetes 84.2%

occurred among individuals who were either overweight (BMI ≥ 25), had 1-hour post-load blood glucose level higher than 144 mg/dL or both at baseline. A cut-off point of 1-hour post-load glucose level used in the study was the same as used by Manco (2010). Using the cut-off point of plasma glucose 155 mg/dL for the 1-hour post-load glucose concentration gave 50% greater sensitivity in predicting future diabetes compared with the OGTT diagnosis of IGT with only a modest (15%) decline in specificity (Abdul-Ghani *et al.* 2007). The cut-off values of plasma glucose used by Abdul-Ghani (2007) and Manco (2010) are quite close to each other: 155 mg/dL equivalent to 8.6 mmol/L and 161 mg/dL equivalent to 8.9 mmo/L.

FPG and 2-hour OGTT are recommended for screening of type 2 diabetes. They are both useful, reflecting different pathophysiologic mechanisms (Nathan *et al.* 2007). IGT and IFG are states of carbohydrate metabolism intermediate between normal glucose tolerance (NGT) and type 2 diabetes, and represent two partially overlapping conditions with different metabolic characteristics (Abdul-Ghani *et al.* 2006, Unwin *et al.* 2002). It is known that IFG reflects marked hepatic insulin resistance and near normal muscle insulin sensitivity, while this pattern is reversed in IGT (Abdul-Ghani *et al.* 2006). Earlier studies have shown that beta-cell glucose sensitivity and insulin sensitivity contribute to values of 2-hour plasma glucose independently of each other (Ferrannini *et al.* 2005). In the literature there are some studies concerning 1-hour post-load glucose and beta-cell function. A higher level of 1-hour post-load glucose might represent a surrogate marker on impaired beta-cell function (beta-cell glucose sensitivity and rate sensitivity) in individuals otherwise regarded as having NGT who are insulin-resistant (Manco M. *et al.* 2010). They showed that 1-hour post-load plasma glucose correlated better than 2-hour plasma glucose with total insulin secretion, beta-cell glucose sensitivity and beta-cell rate sensitivity. The best cut-off value for 1-hour plasma glucose was > 8.95 mmol/L. Participants with NGT and with 1-hour plasma glucose > 8.95 mmol/L had larger waist circumference, higher BMI, lower insulin sensitivity, higher fasting glucose and higher insulin secretion than their counterparts with 1-hour plasma glucose < 8.95 mmol/L. Also in the present study individuals at higher risk for future diabetes had higher BMI (> 25) and higher 1-hour post-load blood glucose level > 144 mg/dL (equivalent to plasma glucose 8.9 mmol/L) at baseline. Median BMI and 1-hour post-load blood glucose were 27.5 (IQR 24.1–27.5) and 108 mg/dL (IQR 88.2–133 mg/l), respectively. The risk for future diabetes was 2.2-fold in the quartile BMI ≥ 25 and 1-hour post-load blood glucose level ≤ 144 mg/dL, but 10.1-fold in the

quartile BMI ≥ 30 and 1-hour post-load blood glucose ≥ 144 mmol/dL equivalent to plasma glucose 161 mg/dL (8.9 mmol/L). These results with higher values of 1-hour post-load glucose may identify an intermediate condition between NGT and IGT characterized by greater insulin resistance, reduced beta-cell glucose sensitivity, and reduced beta-cell rate sensitivity as mentioned by Manco *et al.* (2010). In another study obese Latino youth with a family history of type 2 diabetes were divided into two groups based on 1-hour glucose threshold of 155 mg/dL and followed up for 8 years. The results suggest that a 1-hour post-load plasma glucose ≥ 155 mg/dL during an OGTT is an independent predictor of beta-cell deterioration and progression to prediabetes among obese Latino youth (Kim *et al.* 2013).

The present study investigated also individuals with normal FBG below 5.0 mmol/L, (equivalent to FPG below 5.6 mmol/L, median 4.4 mmol/L) and 1-hour post-load blood glucose levels (median 6.6 mmol/L) as predictors of future diabetes. Low normal FBG (≤ 4.0 mmol/L) showed a protective effect compared to the mid-high normal range (> 4.0–4.9 mmol/L), while 1-hour post-load blood glucose levels predicted diabetes more strongly in the highest quintile. FBG could not separate the risk for those in the range < 5.0 mmol/L. According to the studies fasting glucose and OGTT do not identify the same subjects at increased risk for type 2 diabetes (Nathan *et al.* 2007, Shaw *et al.* 1999) and this is suggested by the present findings as well. A study among young army personnel, demonstrated a progressive increasing risk for diabetes above fasting plasma levels of 4.8 mmol/L compared to levels below 4.5 mmol/L during a 6-year follow-up (Tirosh *et al.* 2005) The RR of 1.8 was similar to our finding in the same glucose category. Another study suggests that persons with normal FPG levels, 5.3–5.5 mmol/L, had a 2.3-fold risk for developing diabetes compared to those with FPG below 4.7 mmol/L (Nichols *et al.* 2008). In these studies IGT was not identified because OGTT was not performed. At baseline in the present study, there was a very low diabetes risk in this population. They all had FBG values below 5.0 mmol/L, only a few were obese, and the mean 1-hour post-load blood glucose value was < 7.0 mmol/L. The men belonged to the highest socioeconomic group. In the cohort 9.4% of the subjects developed diabetes. Individuals at low risk in midlife indicate the importance of early identification of those at risk of diabetes with advancing age.

In the present study the incidence of diabetes started to increase steeply after 15 to 20 years during the follow-up, also accelerating during the last years, when the mean age of participants was 81 year. The men who had arithmetic mean of

baseline fasting glucose and 1-hour post-load blood glucose value < 4.8 mmo/L had practically no risk of diabetes during later life.

One-hour post-load plasma glucose has been reported to predict CVD mortality (Orencia *et al.* 1997) and chronic kidney disease (Succurro *et al.* 2010). In this study an increased risk for diabetes and mortality was found to associate with elevated 1-hour post-load blood glucose level measured in early midlife.

6.5.2 *Predictors in midlife for future diabetes (III)*

It is important to recognize in time those, who are at risk of developing diabetes later in older age. Many studies have shown that weight gain and lifestyle are remarkable risks of future diabetes (Lindstrom *et al.* 2003, Manson & Spelsberg 1994, Must *et al.* 1999, Saaristo *et al.* 2010, Wannamethee & Shaper 1999) Diabetes is associated with many complications and the risk of complications depends on the duration of diabetes (Dankner *et al.* 2009). A unified national system was launched in the United States in 1989 to monitor trends in diabetes and diabetic complications and mortality in order to document the disease burden of diabetes and to identify high-risk groups (Wetterhall *et al.* 1992). In the UK, in a prospective study with a follow-up time of 12 years, researchers determined the risk factors for development of type 2 diabetes in middle-aged British men (Perry *et al.* 1995). This study showed a strong, graded association between BMI and risk of diabetes in this middle-aged male cohort, but evidence incriminating alcohol intake and cigarette smoking was lacking. Many CVD risk factors linked with insulin resistance (triglyceride, high density lipoprotein cholesterol and uric acid concentrations) predicted the development of type 2 diabetes already years before the onset of clinically manifest disease.

In this present study a statistically significant correlation was also found between weight gain (p = 0.002) and risk for diabetes at older age. Alcohol consumption and smoking did not seem to affect the risk of diabetes, although it has been found that the incidence of glucose intolerance is higher among smokers than among non-smokers (Houston *et al.* 2006). In one study the lowest association between alcohol consumption and the risk of diabetes was seen in moderate drinkers, 16–42 units/week (one unit is 10 ml pure alcohol) (Perry *et al.* 1995).

In this cohort baseline future diabetes was very strongly predicted by 1-hour post-load blood glucose. It has been shown that metabolic syndrome increases the risk of diabetes 3–6 times (Dankner *et al.* 2009), and in our study men with higher

post-load glucose, blood pressure, and pulse rate at baseline or greater weight gain up to midlife appeared to develop diabetes earlier (age < 65) than those with fewer risk factors. The men, who developed diabetes at age ≥ 75 years, showed less weight gain, better one-hour blood glucose levels and healthier lifestyles (less alcohol, less smoking) in middle age.

In accordance with earlier studies these findings show that obesity and elevated 1-hour post load glucose in midlife, are risks for future diabetes. One-hour post-load glucose level has earlier been used mainly as a marker for gestational diabetes. Interest in using it as a screening tool of type 2 diabetes has arisen recently. Screening the risks for diabetes is important for the prevention of this disease, but also for the prevention of CVD and mortality.

6.5.3 HRQoL and diabetes developed in old age (IV)

Among the older population type 2 diabetes is a growing problem everywhere in the world, and a larger proportion of newly diagnosed diabetic patients are older people, so that the prevalence is 13% among those older than 70 years, and many remain undiagnosed (McBean *et al.* 2004, Mokdad *et al.* 2000). In the older population an important aspect is the impact of diabetes on HRQoL and development of disability. Established diabetes and particularly its complications affect physical functioning and HRQoL (Brown DW. Balluz LS. Giles WH. Beckles GL. Moriarty DG. Ford ES. Mokdad AH. behavioral risk factor surveillance system (BRFSS) 2004, Hiltunen & Keinanen-Kiukaanniemi 1999, Redekop *et al.* 2002), and predict mortality (Graham *et al.* 2007, Kleefstra *et al.* 2008, Landman *et al.* 2010). In the literature there are few studies of the time course of this relationship concerning diabetes and HRQoL. Earlier studies of diabetes and HRQoL, have focused either on how HRQoL in diabetes affects prognosis (Kleefstra *et al.* 2008, Landman *et al.* 2010, McEwen *et al.* 2009) or how HRQoL in patients with diabetes differs from those without diabetes (Brown DW. Balluz LS. Giles WH. Beckles GL. Moriarty DG. Ford ES. Mokdad AH. behavioral risk factor surveillance system (BRFSS) 2004, Mata Cases *et al.* 2003, Redekop *et al.* 2002, Wandell & Tovi 2000).

In the present study developing diabetes was found to exert clear effects on HRQoL measured with RAND-36 very early after diagnosis, but diabetes affected only some of the domains of RAND-36: physical functioning, social functioning and general health. Mental aspects of HRQoL did not seem to be affected by diabetes in this cohort.

The ZODIAC-18 study of 1,353 men and women with diabetes showed, that poorer physical and mental HRQoL, assessed with RAND-36, was associated with higher total mortality and CVD mortality, although the dimension of mental health was significantly related to mortality in men only (Landman *et al.* 2010). In a population-based case-control study the objective was to explore the nature of functional impairment in older people with diabetes (median duration of diabetes 7 years and median age 75 years). The researchers found significant differences in the physical functioning domain of the SF-36 between control subjects and those with diabetes (Sinclair *et al.* 2008). In our study the results showed a similar trend concerning physical functioning, which worsened soon after diagnosis. Also in a Swedish study, older patients (64–84 years) with diabetes had poorer HRQoL, assessed with SWED-QUAL/MOS instruments, than general population, especially regarding physical health. In this study atheromatous complications were significant predictors of poor HRQoL and poor metabolic control was associated with reduced cognitive function (Wandell & Tovi 2000). Another study conducted in the Nordic countries, this time in Denmark, points in the same direction as a study above. In the Danish study, presence of complications had a significant effect on HRQoL (measured with EQ-5D) of patients with diabetes, whereas HRQoL of patients without complications was only slightly lower than among individuals in the general population (Redekop *et al.* 2002). In a Spanish survey of diabetes diagnosed after the age of 30 years and using the EQ-5 instrument, patients with complications, poor glycaemic control or using insulin, had worse HRQoL than people of the same age and gender in the general population (Mata Cases *et al.* 2003). In a recent study involving 2,205 healthy and 396 persons with diabetes, HRQoL (assessed with SF-36 instrument) was mainly predicted by complications of diabetes (Venkataraman *et al.* 2013). In a cross-sectional study of older Mexican Americans (60% women) with diabetes, researchers found no significant difference in the mental scale of SF-36 compared to individuals without diabetes, but people with diabetes had significantly lower scores on physical scales of HRQoL (Graham *et al.* 2007). The present findings point in the same direction concerning mental aspects and physical function.

This present study found no consistent effects on HRQoL observed in the pre-diagnostic period up to 7 years. The prevalence of prediabetes and associated health behaviours and chronic conditions among New Hampshire adults is described in the brief data from the New Hampshire Behavioral Risk Factor Surveillance Surveys (NH BRFSS). There were significantly more adults with

diabetes and prediabetes who reported having fair or poor health compared with adults without diabetes or prediabetes The subjects were also asked about physical and mental health in the past 30 days, and adults with prediabetes reported 6 physically and 6 mentally unhealthy days, whereas adult with diabetes reported 7 physically and 4 mentally unhealthy days. People without diabetes or prediabetes had 3 physically and mentally unhealthy days (Prediabetes in NH Issue Brief 2011). Findings from a study of physical activity and HRQoL in individuals with prediabetes demonstrated higher levels of physical and mental HRQoL in active than inactive people (Taylor *et al.* 2010).

Overall, the results are in accordance with earlier studies suggesting that worsening of HRQoL starts after the clinical diagnosis of diabetes and this worsening is mainly focused on physical functioning. HRQoL was assessed using RAND-36/SF-36, a widely used and validated generic instrument. With RAND-36 it is possible to distinguish both physical and mental aspects of HRQoL, which is important (Aalto *et al.* 1999).In Finland reimbursement for diabetes medication marks well-established diabetes, but the actual "break-out" may have happened several years earlier. This can have an effect on the findings that HRQoL worsened very early after diagnosis of diabetes affecting both physical and social function and general health. The finding that diabetes does not seem to affect mental HRQoL is somewhat surprising, although psychosocial factors have been considered as risk factors for diabetes onset at least in women (Strodl & Kenardy 2006). An explanation for this may be differences between the genders. A recent study suggested that psychosocial work environment increased diabetes risk among women but not among men (Smith *et al.* 2012).

These results suggest that worsening of HRQoL is not observed before clinical diagnosis of diabetes. In the future, the number of older people with diabetes will increase, and the worsened physical and social function due to this disease and its complications will increase the burden both to individuals and to society. These findings thus offer a possibility for prevention and hence encourage efforts for early detection of diabetes.

7 Conclusions

The findings in the present study indicate that 1-hour post-load glucose could be one option in midlife screening for the risk of future diabetes. Diabetes developed at an older age seems to affect HRQoL in some domains of the RAND-36 measurement. The main conclusions are:

I   One-hour post-load glucose measured in early midlife showed elevated diabetes risk at an older age. The risk was independent of traditional cardiovascular risk factors, and was accentuated when combined with BMI. A strong relationship was also seen between 1-hour post-load glucose quartiles and both total and CVD mortality.

II Comparing normal fasting and 1-hour post-load glucose in an originally fasting normoglycaemic middle-aged male cohort as predictors for future diabetes, higher values for both fasting and one-hour post-load glucose predicted long-term incidence of diabetes. One-hour blood glucose values > 7.0 mmol/L (equivalent to plasma glucose 7.8 mmol/L) in midlife could be regarded as a cut-off point for future risk of incident diabetes.

III Among middle-aged men healthy at baseline, assessed with CVD risk factors and without diabetes, only baseline 1-hour post-load glucose, and weight gain from 25 years to midlife predicted future diabetes.

IV HRQoL was affected by diabetes after diagnosis of diabetes after 0–4 years and did not deteriorate thereafter. Three RAND-36 scales physical functioning, social functioning and general health were significantly worsened compared with non-diabetic subjects. HRQoL was not worsened in prediabetic state compared with non-diabetic subjects.

8   Implications and future perspectives

Our results suggest that one possibility to assess the risk of future diabetes could be 1-hour post-load glucose, which is a less time- and resource-consuming method than 2-hour OGTT. Closer examination of high-risk men who survive to old age without diabetes and low-risk men who develop diabetes would give further information about pathways to diabetes. Our long-term results demonstrate that fasting and 1-hour post-load glucose even with normal values predicts the development of diabetes at a very early stage in population initially at low risk.

WHO (2011) has recently accepted HbA_{1c} as one of the diagnostic criteria for diabetes. It could be important to compare 1-hour post-load glucose with fasting and two-hour post-load glucose levels as well as HbA_{1c} in similar conditions and in various populations. We need reliable, fast and easy tests to find subjects who are at a risk to develope type 2 diabetes.

Diabetes is increasing among older people and worsened physical and social function will have an impact on the burden of this disease both to individuals and society. Results show that this worsening does not happen before clinical diagnosis of diabetes and offer an opportunity for prevention, and thus encouraging efforts for the early detection of diabetes. It may be important to treat older people according to the time when their diabetes emerged and avoid worsening HRQoL with too strict restrictions.

References

Aalto A, Aro AR & Teperi J (1999) RAND-36 terveyteen liittyvän elämänlaadun mittarina: mittarin luotettavuus ja suomalaiset väestöarvot. Tutkimuksia / Sosiaali- ja terveysalan tutkimus- ja kehittämiskeskus (101).

Abdul-Ghani MA, Abdul-Ghani T, Ali N & Defronzo RA (2008) One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. Diabetes Care 31(8): 1650–1655.

Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA & Groop L (2009) Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care 32(2): 281–286.

Abdul-Ghani MA, Matsuda M, Balas B & DeFronzo RA (2007) Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. Diabetes Care 30(1): 89–94.

Abdul-Ghani MA, Tripathy D & DeFronzo RA (2006) Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 29(5): 1130–1139.

Abdul-Ghani MA, Williams K, DeFronzo RA & Stern M (2007) What is the best predictor of future type 2 diabetes?. Diabetes Care 30(6): 1544–1548.

Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ & Holman RR (2002) UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 25(5): 894–899.

Adriaanse MC, Dekker JM, Spijkerman AM, Twisk JW, Nijpels G, van der Ploeg HM, Heine RJ & Snoek FJ (2004) Health-related quality of life in the first year following diagnosis of Type 2 diabetes: newly diagnosed patients in general practice compared with screening-detected patients. The Hoorn Screening Study. Diabet Med 21(10): 1075–1081.

Alberti KG & Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Med 15(7): 539–553.

Alberti KGMM, Zimmet P & Shaw J (2007) International Diabetes Federation: A consensus on Type 2 diabetes prevention. Diabetic Med 24(5): 451–463.

American Diabetes Association (2010) Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 33(Suppl. 1): S62–S69.

Anderwald C, Gastaldelli A, Tura A, Krebs M, Promintzer-Schifferl M, Kautzky-Willer A, Stadler M, DeFronzo RA, Pacini G & Bischof MG (2011) Mechanism and effects of glucose absorption during an oral glucose tolerance test among females and males. Journal of Clinical Endocrinology & Metabolism 96(2): 515–524.

Balducci S, Iacobellis G, Parisi L, Di Biase N, Calndriello E, Leonetti F, Falluca T (2006) Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Compilications 20(4): 216–223.

Bardini G, Dicembrini I, Cresci B & Rotella CM (2010) Inflammation markers and metabolic characteristics of subjects with 1-h plasma glucose levels. Diabetes Care 33(2): 411–413.

Barnett KN, McMurdo ME, Ogston SA, Morris AD & Evans JM (2006) Mortality in people diagnosed with type 2 diabetes at an older age: a systematic review. Age Ageing 35(5): 463–468.

Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B, Horowitz KR, Savage PJ, Seaquist ER, Simmons DL, Sivitz WI, Speril-Hillen JM & Sweeney ME (2010) The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 340: b4909.

Bonora E, Tuomilehto J (2011) The pros and cons of diagnosing diabetes with A1c. Diabetes Care 34(2): 184–190.

Botas P, Delgado E, Castano G, Diaz de Grenu C, Prieto J & Diaz-Cadorniga FJ (2003) Comparison of the diagnostic criteria for diabetes mellitus, WHO-1985, ADA-1997 and WHO-1999 in the adult population of Asturias (Spain). Diabetic Med 20(11): 904–908.

Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK (2009) Obstructive sleep apnea as a risk factor for 2type 2 diabetes. Am J Med 122(12): 1122–1127.

Bowling A (1999) Health-Relatied Quality of Life. A discussion of the concept, its use and measurement background: The quality of life. Health related Quality of Life - World Bank: s 10.

Brown DW. Balluz LS. Giles WH. Beckles GL. Moriarty DG. Ford ES. Mokdad AH. behavioral risk factor surveillance system (BRFSS) (2004) Diabetes mellitus and health-related quality of life among older adults. Findings from the behavioral risk factor surveillance system (BRFSS). Diabetes Res Clin Pract 65(2): 105–115.

Butler WJ, Ostrander LD,Jr, Carman WJ & Lamphiear DE (1985) Mortality from coronary heart disease in the Tecumseh study. Long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 121(4): 541–547.

Cambi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, Ravussin E, Ryan DH, Smith SR, Katzmaryk P. (2011) The relationship of waist circumference and BMI to viskeral, subcutaneous, and total body fat: sex and race differences. Obesity 19(2):402–408.

Cass AR, Alonso WJ, Islam J, Weller SC (2013) Risk of obstructive sleep apnea in patients with type 2 diabetes mellitus. Fam Med 45(7): 492–500.

Chandola T, Brunner E & Marmot M (2006) Chronic stress at work and the metabolic syndrome: prospective study. BMJ 332(7540): 521–525.

Cheng D (2005) Prevalence, predisposition and prevention of type II diabetes. Nutr Metab 2.

Connolly V, Unwin N, Sherriff P, Bilous R & Kelly W (2000) Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. Journal of Epidemiology & Community Health 54(3): 173–177.

Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS & Gregg EW (2006) Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999–2002. Diabetes Care 29(6): 1263–1268.

Crandall JP, Polsky S, Howard AA, Perreault L, Bray GA, Barrett-Connor E, Brown-Friday J, Whittington T, Foo S, Ma Y, Edelstein SL & Diabetes Prevention Program Research G (2009) Alcohol consumption and diabetes risk in the Diabetes Prevention Program. Am J Clin Nutr 90(3): 595–601.

Dankner R, Geulayov G, Olmer L & Kaplan G (2009) Undetected type 2 diabetes in older adults. Age Ageing 38(1): 56–62.

DeFronzo RA (1988) Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37(6): 667–687.

Deshpande AD, Harris-Hayes M & Schootman M (2008) Epidemiology of diabetes and diabetes-related complications. Phys Ther 88(11): 1254–1264.

Despres JP (2006) Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. Eur heart J 8(suppl.B): 4–12.

Development of the World health Organization WHOQOL-BREF quality of life (1998) The WHOQOL Group. Psychol Med 28(3): 551–558.

Diabetes Statistics (2011) Data from the 2011 National Diabetes Fact Sheet Jan. 26, 2011). URI: http://www.diabetes.org/diabetes-basics/diabetes-statistics/2013/8/26.

Drew BS, Dixon AF & Dixon JB (2007) Obesity management: update on orlistat. Vasc Health Risk Manag 3(6): 817–821.

Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW (2003) Exercise training without weight loss, increases insulin sensivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care 26(3): 557–562.

Fantuzzi G (2005) Adipose tissue, adipokiness, and inflammation. J Allergy Clin Immunol. 115: 911–919

Felce D & Perry J (1995) Quality of life: Its definition and measurement. Res Dev Disabil 16(1): 51–74.

Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A & DeFronzo RA (2005) beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. Journal of Clinical Endocrinology & Metabolism 90(1): 493–500.

Flegal KM, Carroll MD, Ogden CL & Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999–2008. JAMA 303(3): 235–241.

Fowler MJ (2008) Microvascular and macrovascular complications of diabetes. Clinical Diabetes 26(2): 77–82.

Ford ES (1999) Body mass index, diabetes, and C-reactive protein among U.S. adults. Diabetes Care 22: 1971–1977.

Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muche R, Brenner H, Koenig W (2000) Association between C-reactive protein and feature of the metabolic syndrome: a population based study. Diabetes Care 23: 1835–1839.

Fuller JH, Stevens LK & Wang SL (2001) Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. Diabetologia 44(Suppl 2): S54–64.

Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH & Knowler WC (2000) The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. Diabetes Care 23(8): 1108–1112.

Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH & Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348(5): 383–393.

Garratt AM, Ruta DA, Abdalla MI, Buckingham JK & Russell IT (1993) The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? BMJ 306(6890): 1440–1444.

Carter AA, Gomes T, Juurink DN, Shah BR, Mandani MM (2013) Risk of incident diabetes among patients treated with statins: population based study. BMJ 346: f2610.

Elliot WJ & Meyer PM (2007) Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 20;369(9557): 201–207.

Ford ES (1999) Body mass index, diabetes, and C-reactive protein among U.S. adults. Diabetes care 22: 1971–1977.

Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J & Chobanian L (1997) Quality of life and associated characteristics in a large national sample of adults with diabetes. Diabetes Care 20(4): 562–567.

Global Atlas on Cardiovascular Disease Prevention and Control (2011) Mendis S Puska P, Norrving B editors. World Health Organization, Geneva.

Goodridge D, Trepman E & Embil JM (2005) Health-related quality of life in diabetic patients with foot ulcers: literature review. J Wound Ostomy Continence Nurs 32(6): 368–377.

Goodyear LJ & Kahn BB (1998) Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 49: 235–261.

Graham JE, Stoebner-May DG, Ostir GV, Al Snih S, Peek MK, Markides K & Ottenbacher KJ (2007) Health related quality of life in older Mexican Americans with diabetes: a cross-sectional study. Health Qual Life Outcomes 5: 39.

Gress TW, Nieto FJ, Shahar E, Wofford MR & Brancati FL (2000) Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 342(13): 905–912.

Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC,Jr & Sowers JR (1999) Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 100(10): 1134–1146.

Guyatt GH, Feeny DH & Patrick DL (1993) Measuring health-related quality of life. Ann Intern Med 118(8): 622–629.

Haffner SM (1998) Epidemiology of type 2 diabetes: risk factors. Diabetes Care 21 (Suppl 3): 3–6.

Haffner SM, Lehto S, Ronnemaa T, Pyorala K & Laakso M (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339(4): 229–234.

Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, Regensteiner J, Venditti B, Wylie-Rosett J (2006) Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 29(9): 2102–2107.

Hanninen J, Takala J & Keinanen-Kiukaanniemi S (1998) Quality of life in NIDDM patients assessed with the SF-20 questionnaire. Diabetes Research & Clinical Practice 42(1): 17–27.

Hanninen J, Takala J & Keinanen-Kiukaanniemi S (2001) Good continuity of care may improve quality of life in Type 2 diabetes. Diabetes Research & Clinical Practice 51(1): 21–27.

Harrison TA, Hindorff LA, Kim H, Wines RC, Bowen DJ, McGrath BB & Edwards KL (2003) Family history of diabetes as a potential public health tool. Am J Prev Med 24(2): 152–159.

Hays RD & Morales LS (2001) The RAND-36 measure of health-related quality of life. Ann Med 33(5): 350–357.

Hays RD, Sherbourne CD & Mazel RM (1993) The RAND 36-Item Health Survey 1.0. Health Econ 2(3): 217–227.

Haywood KL, Garratt AM & Fitzpatrick R (2005) Quality of life in older people: a structured review of generic self-assessed health instruments. Qual Life Res 14(7): 1651–1668.

Heinrich PC, Castell JV, Andus T (1990) Interleukin-6 and the acute phase response. Biochem J 265(3): 621–636.

Helmrich SP, Ragland DR, Leung RW & Paffenbarger RS,Jr (1991) Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 325(3): 147–152.

Hill-Briggs F, Gary TL, Baptiste-Roberts K & Brancati FL (2005) Thirty-six-item short-form outcomes following a randomized controlled trial in type 2 diabetes. Diabetes Care 28(2): 443–444.

Hiltunen L & Keinanen-Kiukaanniemi S (1999) Does glucose tolerance affect quality of life in an elderly population?.Diabetes Res Clin Pract 46(2): 161–167.

Hogan P, Dall T, Nikolov P & American Diabetes A (2003) Economic costs of diabetes in the US in 2002. Diabetes Care 26(3): 917–932.

Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C & Kiefe CI (2006) Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. BMJ 332(7549): 1064–1069.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG & Willett WC (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345(11): 790–797.

Hulshof KF, Brussaard JH, Kruizinga AG, Telman J & Lowik MR (2003) Socio-economic status, dietary intake and 10 y trends: the Dutch National Food Consumption Survey. Eur J Clin Nutr 57(1): 128–137.

Hultman E (1959) Rapid specific method for determination of aldosaccharides in body fluids. Nature 183(4654): 108–109.

IDF Diabetes Atlas 5th edition (2012) The Global Burden. URI:http//www.idf.org/diabetesatlas/5e/the-global-burden/2013/8/26.

Janssen I, Heymsfield B, Allison DB, Kotler DP, Ross R. (2002) Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fa. Am J Nutr 75: 682–688.

Jenkinson C, Wright L & Coulter A (1994) Criterion validity and reliability of the SF-36 in a population sample. Qual Life Res 3(1): 7–12.

Kahn SE, Hull RL & Utzschneider KM (2006) Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 444(7121): 840–846.

Kannel WB & McGee DL (1979a) Diabetes and cardiovascular disease. The Framingham study. JAMA 241(19): 2035–2038.

Kannel WB & McGee DL (1979b) Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care 2(2): 120–126.

Kaukua J (2006) Terveyteen liittyvä elämänlaatu ja lihavuus. Duodecim 122(10): 1215–1224.

Keinanen-Kiukaanniemi S, Ohinmaa A, Pajunpaa H & Koivukangas P (1996) Health related quality of life in diabetic patients measured by the Nottingham Health Profile. Diabetic Med 13(4): 382–388.

Kesavadev JD, Short KR & Sreekumaran Nair K (2003) Diabetes in old age: An emerging epidemic. Journal of Association of Physicians of India 51(NOV): 1083–1094.

Kim JY, Goran MI, Toledo-Corral CM, Weigensberg MJ, Choi M & Shaibi GQ (2013) One-hour glucose during an oral glucose challenge prospectively predicts ß-cell deterioration and prediabetes in obese hispanic youth. Diabetes Care 36(6): 1681–1686.

Kleefstra N, Landman GW, Houweling ST, Ubink-Veltmaat LJ, Logtenberg SJ, Meyboom-de Jong B, Coyne JC, Groenier KH & Bilo HJ (2008) Prediction of mortality in type 2 diabetes from health-related quality of life (ZODIAC-4). Diabetes Care 31(5): 932–933.

Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ & Pouwer F (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49(5): 837–845.

Koski S (2011) Diabetesbarometri 2010. [Tampere], Suomen Diabetesliitto.

Krauss RM (2004) Lipids and lipoproteins with type 2 diabetes. Diabetes Care 27: 1496–1504.

Kostis JB, Wilson AC, Freudenberg RS, Cosgrove NM, Pressel SL, Davis BR, SHEP Collaborative Research Group (2005) Long-term effect of diuretic-based therapy on fatal outcomes in subjects wit isolated systolic hypertension with and without diabetes. Am J Cardiol 95: 29–35.

Laaksonen DE, Lindstrom J, Lakka TA, Eriksson JG, Niskanen L, Wikstrom K, Aunola S, Keinanen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hamalainen H, Rastas M, Salminen V, Cepaitis Z, Hakumaki M, Kaikkonen H, Harkonen P, Sundvall J, Tuomilehto J, Uusitupa M & Finnish diabetes prevention s (2005) Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. Diabetes 54(1): 158–165.

Lago F, Dieguez C, Gomez-Reino J, Guallino O (2007) Adipokines as emergin mediators of immune response and inflammation. Nature Clinical Practice Rheum 3: 716 –724

Lahti-Koski M, Seppanen-Nuijten E, Mannisto S, Harkanen T, Rissanen H, Knekt P, Rissanen A & Heliovaara M (2010) Twenty-year changes in the prevalence of obesity among Finnish adults. Obes Rev 11(3): 171–176.

Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J & Salonen JT (2002) The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288(21): 2709–2716.

Lakka TA, Laukkanen JA, Rauramaa R, Salonen R, Lakka HM, Kaplan GA & Salonen JT (2001) Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. Ann Intern Med 134(1): 12–20.

Landman GW, van Hateren KJ, Kleefstra N, Groenier KH, Gans RO & Bilo HJ (2010) Health-related quality of life and mortality in a general and elderly population of patients with type 2 diabetes (ZODIAC-18). Diabetes Care 33(11): 2378–2382.

Lau DC, Dhillon B, Yan H, Szmiko PE, Verma S, (2005) Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol heart Circ Physiol 288: H2031–2041.

Laukkanen JA, Lakka TA, Rauramaa R, Kuhanen R, Venalainen JM, Salonen R & Salonen JT (2001) Cardiovascular fitness as a predictor of mortality in men. Arch Intern Med 161(6): 825–831.

Leppävuori A (2010) Masennus ja diabetes. Duodecim 126(5): 521–527.

Levitan EB, Song Y, Ford ES & Liu S (2004) Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 164(19): 2147–2155.

Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J & Finnish Diabetes Prevention Study G (2003) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26(12): 3230–3236.

Lloyd A, Sawyer W & Hopkinson P (2001) Impact of long-term complications on quality of life in patients with type 2 diabetes not using insulin. Value Health 4(5): 392–400.

Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM & Clouse RE (2000) Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 23(7): 934–942.

Lyons RA, Perry HM & Littlepage BN (1994) Evidence for the validity of the Short-form 36 Questionnaire (SF-36) in an elderly population. Age Ageing 23(3): 182–184.

Manco M, Panunzi S, Macfarlane DP, Golay A, Melander O, Konrad T, Petrie JR, Mingrone G & Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) Consortium (2010) One-hour plasma glucose identifies insulin resistance and beta-cell dysfunction in individuals with normal glucose tolerance: cross-sectional data from the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study. Diabetes Care 33(9): 2090–2097.

Manson JE & Spelsberg A (1994) Primary prevention of non-insulin-dependent diabetes mellitus. Am J Prev Med 10(3): 172–184.

Mata Cases M, Roset Gamisans M, Badia Llach X, Antoñanzas Villar F & Ragel Alcázar J (2003) Effect of type-2 diabetes mellitus on the quality of life of patients treated at primary care consultations in Spain. Aten Prim 31(8): 493–499.

McBean AM, Li S, Gilbertson DT & Collins AJ (2004) Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, hispanics, and asians. Diabetes Care 27(10): 2317–2324.

McEwen LN, Kim C, Haan MN, Ghosh D, Lantz PM, Thompson TJ & Herman WH (2009) Are health-related quality-of-life and self-rated health associated with mortality? Insights from Translating Research Into Action for Diabetes (TRIAD). Prim Care Diabetes 3(1): 37–42.

McNeely MJ, Boyko EJ, Leonetti DL, Kahn SE & Fujimoto WY (2003) Comparison of a clinical model, the oral glucose tolerance test, and fasting glucose for prediction of type 2 diabetes risk in Japanese Americans. Diabetes Care 26(3): 758–763.

Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F & Marks JS (2000) Diabetes trends in the U.S. 1990–1998. Diabetes Care 23(9): 1278–1283.

Morrato EH, Hill JO, Wyatt RH, Ghushchyan V, Sullivan PW (2007) Physical activity in U.S. adults with diabetes and at risk for developing diabetes. Diabetes Care 30(2): 203–209.

Morrish NJ, Wang SL, Stevens LK, Fuller JH & Keen H (2001) Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 44(Suppl 2): S14–21.

Must A, Spadano J, Coakley EH, Field AE, Colditz G & Dietz WH (1999) The disease burden associated with overweight and obesity. JAMA 282(16): 1523–1529.

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B, American Diabetes A & European Association for Study of,Diabetes (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32(1): 193–203.

Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B & American Diabetes A (2007) Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 30(3): 753—759.

Nathan DM, Singer DE, Godine JE & Perlmuter LC (1986) Non-insulin-dependent diabetes in older patients. Complications and risk factors. Am J Med 81(5): 837–842.

Nichols GA, Hillier TA & Brown JB (2008) Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. Am J Med 121(6): 519–524.

Norris SL (2005) Health-related quality of life among adults with diabetes. Curr Diab Rep 5(2): 124–130.

Olefsky JM, Kolterman OG & Scarlett JA (1982) Insulin action and resistance in obesity and noninsulin-dependent type II diabetes mellitus. Am J Physiol 243(1): E15–30.

Orencia AJ, Daviglus ML, Dyer AR, Walsh M, Greenland P & Stamler J (1997) One-hour postload plasma glucose and risks of fatal coronary heart disease and stroke among nondiabetic men and women: the Chicago Heart Association Detection Project in Industry (CHA) Study. J Clin Epidemiol 50(12): 1369–1376.

Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P & Stamler J (1986) Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 123(3): 504–516.

Pan X, Li G, Hu Y, Wang J, Yang W, An Z, Hu Z, Lin J, Xiao J, Cao H, Liu P, Jiang X, Jiang Y, Wnag J, Zheng H, Zhang H, Bennet P, Howard B (1997) Effects of diabetes and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Quing IGT and Diabetes Study. Diabetes Care 20(4): 537–544.

Pelkonen R, Pyorala K & Kangas T (1981) [Diagnostic criteria and classification of diabetes; new recommendations of the WHO committee]. Duodecim 97(12): 920–924.

Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH & Shaper AG (1995) Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ 310(6979): 560–564.

Picup JC, Mattoc MB, Chusney CD, Burt D (1997) NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 40: 1286–1292.

Pirart J (1977) [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabetes et Metabolisme 3(4): 245–256.

Pi-Sunyer FX (1996) Weight and non-insulin-dependent diabetes mellitus. Am J Clin Nutr 63(3 Suppl): 426S–429S.

Polonsky WH (2002) Emotional and quality-of-life aspects of diabetes management. Curr Diab Rep 2(2): 153–159.

Pradhan A, Manson J, Rifai N, Buring J, Ridker P (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitu. Jama Vol 266(3): 327–334.

Prediabetes in NH issue brief (2011) New Hampshire Department of Healt and Human Services, Division of Public Health Services, Diabetes Education Program Reports.

Pyorala K, Lehto S, De Bacquer D, De Sutter J, Sans S, Keil U, Wood D, De Backer G, EUROASPIRE IG & EUROASPIRE II G (2004) Risk factor management in diabetic and non-diabetic patients with coronary heart disease. Findings from the EUROASPIRE I AND II surveys. Diabetologia 47(7): 1257–1265.

Pyykkonen AJ, Raikkonen K, Tuomi T, Eriksson JG, Groop L & Isomaa B (2010) Stressful life events and the metabolic syndrome: the prevalence, prediction and prevention of diabetes (PPP)-Botnia Study. Diabetes Care 33(2): 378–384.

Qiao Q, Pyorala K, Pyorala M, Nissinen A, Lindstrom J, Tilvis R & Tuomilehto J (2002) Two-hour glucose is a better risk predictor for incident coronary heart disease and cardiovascular mortality than fasting glucose. Eur Heart J 23(16): 1267–1275.

Quality of Life in Type 2 Diabetic Patients Is Affected by Complications But Not by Intensive Policies to Improve Blood Glucose or Blood Pressure Control (UKPDS 37). (1999) Diabetes Care 22(7): 1125–1136.

Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37(12): 1595–1607.

Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, Wolffenbuttel BH & Niessen LW (2002) Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 25(3): 458–463.

Reunanen A (1983) Mortality in type 2 diabetes. Ann Clin Res 15(Suppl 37): 26–28.

Reunanen A, Kangas T, Martikainen J & Klaukka T (2000) Nationwide survey of comorbidity, use, and costs of all medications in Finnish diabetic individuals. Diabetes Care 23(9): 1265–1271.

Reusch JE & Wang CC (2011) Cardiovascular disease in diabetes: where does glucose fit in? J Clin Endocrinol Metab 96(8): 2367–2376.

Revicki DA (1990) Quality of Life and non-insulin dependend diabetes mellitus. Diabetes Spectrum 3: 260–266

Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, Canonico S & Paolisso G (2010) Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care 33(10): 2169–2174.

Rodriguez BL, Lau N, Burchfiel CM, Abbott RD, Sharp DS, Yano K & Curb JD (1999) Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. Diabetes Care 22(8): 1262–1265.

Rubin RR & Peyrot M (1999) Quality of life and diabetes. Diabetes Metab Res Rev 15(3): 205–218.

Saaristo T, Moilanen L, Korpi-Hyovalti E, Vanhala M, Saltevo J, Niskanen L, Jokelainen J, Peltonen M, Oksa H, Tuomilehto J, Uusitupa M & Keinanen-Kiukaanniemi S (2010) Lifestyle intervention for prevention of type 2 diabetes in primary health care: one-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D). Diabetes Care 33(10): 2146–2151.

Sacerdote C, Ricceri F, Rolandsson O, Baldi I, Chirlaque MD, Feskens E, Bendinelli B, Ardanaz E, Arriola L, Balkau B, Bergmann M, Beulens JW, Boeing H, Clavel-Chapelon F, Crowe F, de Lauzon-Guillain B, Forouhi N, Franks PW, Gallo V, Gonzalez C, Halkjaer J, Illner AK, Kaaks R, Key T, Khaw KT, Navarro C, Nilsson PM, Dal Ton SO, Overvad K, Pala V, Palli D, Panico S, Polidoro S, Quiros JR, Romieu I, Sanchez MJ, Slimani N, Sluijs I, Spijkerman A, Teucher B, Tjonneland A, Tumino R, van der AD, Vergnaud AC, Wennberg P, Sharp S, Langenberg C, Riboli E, Vineis P & Wareham N (2012) Lower educational level is a predictor of incident type 2 diabetes in European countries: the EPIC-InterAct study. Int J Epidemiol 41(4): 1162–1173.

Sandler S, Bendtzen K, Eizirik M (1990) Interleukin 6 affects insulin secretion and glucose metabolism of rat pancreatic islets in vitro. Endocrinology 126: 1288–1294.

Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I (2010) Statins and risk of incident diabetes: a collaborative meta-analysis of randomised stain trials. Lancet 375(9716):735–742.

Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL (2010) Gycated hemoglobin, dioabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 362:800–811.

Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, Hemraj F, Fareed D, Tuomilehto J & Alberti KG (1999) Impaired fasting glucose or impaired glucose tolerance. What best predicts future diabetes in Mauritius?. Diabetes Care 22(3): 399–402.

Shields M, Carroll MD, Ogden CL (2011) Adult obesity prevalence in Canada and The United States. NCHS data brief (56): 1–8.

Shields M & Tjepkema M (2006) Trends in adult obesity. Health Rep 17(3): 53–59.

Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM & Nair KS (2003) Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. Diabetes 52(8): 1888–1896.

Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C (2004) Physical activity/exercise and type 2 diabetes. Diabetes Care 27(10):2518–2539.

Sinclair AJ, Conroy SP & Bayer AJ (2008) Impact of diabetes on physical function in older people. Diabetes Care 31(2): 233–235.

Sintonen H (2001) The 15D instrument of health-related quality of life: properties and applications. Ann Med 33(5): 328–336.

Sintonen H (2013) Terveyteen liittyvän elämänlaadun mittaaminen. Suomen lääkärilehti - Finlands läkartidning 68(17): 1261–1267.

Skevington SM, Lotfy M, O'Connell KA & WHOQOL G (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of Life Research 13(2): 299–310.

Smith DW (2004) The population perspective on quality of life among Americans with diabetes. Qual Life Res 13(8): 1391–1400.

Smith PM, Glazier RH, Lu H & Mustard CA (2012) The psychosocial work environment and incident diabetes in Ontario, Canada. Occup Med (Oxf) 62(6): 413–419.

Stamler J, Vaccaro O, Neaton JD & Wentworth D (1993) Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16(2): 434–444.

Stern MP, Williams K & Haffner SM (2002) Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? Ann Intern Med 136(8): 575–581.

Strandberg TE, Salomaa VV, Vanhanen HT, Naukkarinen VA, Sarna SJ & Miettinen TA (1995) Mortality in participants and non-participants of a multifactorial prevention study of cardiovascular diseases: a 28 year follow up of the Helsinki Businessmen Study. Br Heart J 74(4): 449–454.

Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC & Holman RR (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321(7258): 405–412.

Strodl E & Kenardy J (2006) Psychosocial and non-psychosocial risk factors for the new diagnosis of diabetes in elderly women. Diabetes Res Clin Pract 74(1): 57–65.

Succurro E, Arturi F, Lugara M, Grembiale A, Fiorentino TV, Caruso V, Andreozzi F, Sciacqua A, Hribal ML, Perticone F & Sesti G (2010) One-hour postload plasma glucose levels are associated with kidney dysfunction. Clin J Am Soc Nephrol 5(11): 1922–1927.

Succurro E, Marini MA, Arturi F, Grembiale A, Lugara M, Andreozzi F, Sciacqua A, Lauro R, Hribal ML, Perticone F & Sesti G (2009) Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. Atherosclerosis 207(1): 245–249.

Tabak AG, Herder C, Rathmann W, Brunner EJ & Kivimaki M (2012) Prediabetes: a high-risk state for diabetes development. Lancet 379(9833): 2279–2290.

Taylor LM, Spence JC, Raine K, Plotnikoff RC, Vallance JK & Sharma AM (2010) Physical activity and health-related quality of life in individuals with prediabetes. Diabetes Research & Clinical Practice 90(1): 15–21.

The National Health Insurance (2912) Lääkekorvausten saajat ja reseptitiedot. URI:http://raportit kela fi/ibi_apps/WFServlet 2013/8/29

Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T, Kochba I, Rudich A & Israeli Diabetes Research G (2005) Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med 353(14): 1454–1462.

Tuomilehto J, Knowler WC & Zimmet P (1992) Primary prevention of non-insulin-dependent diabetes mellitus. Diabetes Metab Rev 8(4): 339–353.

Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M & Finnish Diabetes Prevention Study G (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344(18): 1343–1350.

Tuomilehto J, Lindström J, Hellmich M, Lehmacher W, WestmeierT, Evers T, BrucnerA, Peltonen M, Qiao Q, Chiasson JL (2010) Development and validation of risk-scoremodel for subjects with impaired glucose tolerance for assessment of risk of type 2 diabetes mellitus–The STOP-NIDDM risk-score. Diabetes Research and Clinical Practise 87: 267–274.

Turner R (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352(9131): 837–853.

Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR & Holman RR (1998) Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 316(7134): 823–828.

Unwin N, Shaw J, Zimmet P & Alberti KG (2002) Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med 19(9): 708–723.

Vaarama M, Siljander E, Luoma M & Meriläinen S (2010) Suomalaisten kokema elämänlaatu nuoruudesta vanhuuteen. In: Anonymous Suomalaisten hyvinvointi 2010 / Marja Vaarama, Pasi Moisio & Sakari Karvonen (toim.) : 126–149.

Venkataraman K, Wee HL, Leow MKS, Tai ES, Lee J, Lim SC, Tavintharan S, Wong TY, Ma S, Heng D & Thumboo J (2013) Associations between complications and health-related quality of life in individuals with diabetes. Clin Endocrinol (Oxf) 78(6): 865–873.

Vogelzangs N, Beekman AT, Kritchevsky SB, Newman AB, Pahor M, Yaffe K, Rubin SM, Harris TB, Satterfield S, Simonsick EM & Penninx BW (2007) Psychosocial risk factors and the metabolic syndrome in elderly persons: findings from the Health, Aging and Body Composition study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 62(5): 563–569.

Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A, Ohashi Y, Kadowaki T, Tsugane S & JPHC Study G (2005) Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabet Med 22(3): 323–331.

Wandell PE (1999) Risk factors for microvascular and macrovascular complications in men and women with type 2 diabetes. Scand J Prim Health Care 17(2): 116–121.

Wandell PE (2005) Quality of life of patients with diabetes mellitus. An overview of research in primary health care in the Nordic countries. Scand J Prim Health Care 23(2): 68–74.

Wandell PE & Tovi J (2000) The quality of life of elderly diabetic patients. J Diabetes Complications 14(1): 25–30.

Wannamethee SG & Shaper AG (1999) Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 22(8): 1266–1272.

Wannamethee SG, Shaper AG, Lennon L & Morris RW (2005) Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 165(22): 2644–2650.

Wannamethee SG, Shaper AG, Whincup PH, Lennon L & Sattar N (2011) Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med 171(5): 404–410.

Ware JE,Jr & Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6): 473–483.

Wasem J, Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E & Tschöpe D (2013) Co-morbidity but not dysglycaemia reduces quality of life in patients with type-2 diabetes treated with oral mono- or dual combination therapy - an analysis of the DiaRegis registry. Cardiovascular Diabetology 12(1).

Wei M, Gaskill SP, Haffner SM & Stern MP (1998) Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care 21(7): 1167–1172.

Wei M, Gibbons LW, Kampert JB, Nichaman MZ & Blair SN (2000) Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 132(8): 605–611.

Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS,Jr & Blair SN (1999) Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 282(16): 1547–1553.

Wetterhall SF, Olson DR, DeStefano F, Stevenson JM, Ford ES, German RR, Will JC, Newman JM, Sepe SJ & Vinicor F (1992) Trends in diabetes and diabetic complications, 1980–1987. Diabetes Care 15(8): 960–967.

Weycker D, Nichols GA, O'Keeffe-Rosetti M, Edelsberg J, Vincze G, Khan ZM & Oster G (2009) Excess risk of diabetes in persons with hypertension. J Diabetes Complications 23(5): 330–336.

Whiting DR, Guariguata L, Weil C & Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94(3): 311–321.

Wild S, Roglic G, Green A, Sicree R & King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27(5): 1047–1053.

Willi C, Bodenmann P, Ghali WA, Faris PD & Cornuz J (2007) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 298(22): 2654–2664.

Wilson PW (1998) Diabetes mellitus and coronary heart disease. American Journal of Kidney Diseases 32(5 Suppl 3): S89–100.

Wilson PW, D'Agostino RB, Parise H, Sullivan L & Meigs JB (2005) Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112(20): 3066–3072.

Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM & D'Agostino RB,Sr (2007) Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 167(10): 1068–1074.

Winell K & Reunanen A (2006) Diabetesbarometri. Tampere, Diabetesliitto.

World Health Organization (1985) Diabetes Mellitus: report of WHO Study Group, Technical Series no. 727. Geneva.

World Health Organization (1999) Definition, Diagnosis and Classification of diabetes mellitus and its complications. Report of a WHO consultation. Part I: Diagnosis and Classification of diabetes mellitus. Geneva, World health Organization

World Health Organization (2011) Use of glycated hemoglobin (HbA$_{1c}$) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. Geneva, WHO Press.

World Health Organization (2011) Obesity and overweight. Fact sheet N 311. URI:http://www.who.int/mediacentr/factsheets/fs311/en/2013/8/22.

Yliharsila H, Lindstrom J, Eriksson JG, Jousilahti P, Valle TT, Sundvall J & Tuomilehto J (2005) Prevalence of diabetes and impaired glucose regulation in 45- to 64-year-old individuals in three areas of Finland. Diabetic Med 22(1): 88–91.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L & INTERHEART Study I (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364(9438): 937–952.

Zoppini G, Targher G, Zamboni C, Venturi C, Cacciatori V, Moghetti P, Muggeo M (2006) Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. Nutrition, Metabolism and Cardiovascular Diseases 16(8): 543–549.

Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S & ADVANCE Collaborative G (2010) Severe hypoglycemia and risks of vascular events and death. N Engl J Med 363(15): 1410–1418.

Appendix 1

The Helsinki Businessmen Study timeline

1964–1973

> 3.490 men of high sosioeconomic status, born 1919–1934 attend voluntary health checks at the Institute of Occupational Health in Helsinki. Data available n= 3.313
> Clinical examinations: weight, blood pressure,
> Laboratory examinations including cholesterol, fasting and 1-hour post-load blood glucose, triglycerides from 1969
> Medical history

> Dead n= 68

> No response/refused n= 867

1974–1975,
mean age 48 years

> Questionnaire and invitation to examination to all surving men, data available n= 2.375
> -Clinical examinations including weight, blood pressure
> -Laboratory examinations including cholesterol, triglycerides, fasting and 1-hour post-load blood glucose, EKG
> -Cardiovascular risk factors anf life style including : smoking, self-reported weight from age 25, alcohol consumption, physical activity
> -Self-rated health and fitness
>
> 1.   Healty, no CVD n=1.815
> 2.   Chronic disease or medication n= 536

> 1. Dead n=518
> 2. Dead n=244
> Dead n=285, no response/refused

2000,
mean age 73 years

> Mortality from registers , cumulative dead n=1023
> Postal questionnaire n= 2.286 , data available n= 1.864
> -RAND-36,
> -self-reported weigh and cardiovascular risk factors,
> -diseases, mediacations

> Dead n= 422

2007,
mean age 81 years

> Mortality from the registers. Cumulative dead 1537
> Postal questionnaires from the ability of function, the memory disorders, and B-gluc, weight, s-kol and latest blood pressure
> Data available n =1120

Appendix 2 RAND 36-Item Health Survey 1.0 Questionnaire Items

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago,** how would your rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing myself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

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20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How **TRUE** or **FALSE** is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

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Original papers

I   Strandberg TE, Pienimäki T, Strandberg AY, Salomaa VV, Pitkälä KH, Tilvis RS & Miettinen TA (2011) One-hour glucose, mortality, and risk of diabetes: A 44-year prospective study in men. Arch Intern Med 171(10): 941–943.
II   Strandberg AY, Pienimäki T, Pitkälä KH, Tilvis RS, Salomaa VV & Strandberg TE (2013) Comparison of normal fasting and one-hour glucose levels as predictors of future diabetes during a 34-year follow-up. Ann Med 45(4): 336–400.
III Pienimäki T, Strandberg AY, Pitkälä KH, Tilvis RS, Miettinen TA, Salomaa V & Strandberg TE (2012) Modifiable risk factors in midlife and the age of onset of diabetes mellitus: A 34-year follow-up study. JAGS 60(1): 174–176.
IV   Pienimäki T, Strandberg AY, Pitkälä KH, Tilvis RS, Salomaa VV & Strandberg TE (2013) Health-related quality of life as a function of diabetes onset in men. European Geriatric Medicine 4(4): 217–220.

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Original publications are not included in the electronic version of the dissertation.

1228. Niinimäki, Riitta (2013) Osteonecrosis in children, adolescents and young adults treated for cancer

1229. Mattila, Marja-Leena (2013) Autism spectrum disorders : an epidemiological and clinical study

1230. Vaaramo, Kalle (2013) Alcohol affects the outcome after head trauma

1231. Moilanen, Riina (2013) Heterotopic ossification in skin : special focus on multiple miliary osteoma cutis and the role of bone morphogenetic proteins

1232. Vatjus, Ritva (2014) Kohti suhdekeskeisyyttä lääkärin ja potilaan kohtaamisessa : laadullinen tutkimus potilas-lääkärisuhteen hahmottumisesta yleislääkäreiden koulutuksessa

1233. Mankinen, Katariina (2014) Neuropsychological performance and functional MRI findings in children with non-lesional temporal lobe epilepsy

1234. Karvonen, Henna (2014) Ultrastructural and functional characterization of myofibroblasts in lung diseases

1235. Sipola, Seija (2014) Colectomy in an ICU patient population : clinical and histological evaluation

1236. Lipponen, Kaija (2014) Potilasohjauksen toimintaedellytykset

1237. Jansson, Miia (2014) The effectiveness of education on critical care nurses' knowledge and skills in adhering to guidelines to prevent ventilator-associated pneumonia

1238. Turunen, Sanna (2014) Protein-bound citrulline and homocitrulline in rheumatoid arthritis : confounding features arising from structural homology

1239. Kuorilehto, Ritva (2014) Moniasiantuntijuus sosiaali- ja terveydenhuollon perhetyössä : monitahoarviointi Q-metodologialla

1240. Sova, Henri (2014) Oxidative stress in breast and gynaecological carcinogenesis

1241. Tiirinki, Hanna (2014) Näkyvien ja piilotettujen merkitysten rajapinnoilla : terveyskeskukseen liittyvät kulttuurimallit asiakkaan näkökulmasta

1242. Syrjänen, Riikka (2014) TIM family molecules in hematopoiesis

1243. Kauppila, Joonas (2014) Toll-like receptor 9 in alimentary tract cancers

1244. Honkavuori-Toivola, Maria (2014) The prognostic role of matrix metalloproteinase-2 and -9 and their tissue inhibitor-1 and -2 in endometrial carcinoma

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