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Timo Saaristo

ASSESSMENT OF RISK AND PREVENTION OF TYPE 2 DIABETES IN PRIMARY HEALTH CARE

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FACULTY OF MEDICINE,
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ASSESSMENT OF RISK AND PREVENTION OF TYPE 2 DIABETES IN PRIMARY HEALTH CARE

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Abstract

Type 2 diabetes is one of the fastest increasing lifestyle diseases globally. Its cure is not yet possible, but there is firm evidence from scientific studies that it can effectively be prevented by lifestyle changes. There is limited evidence-based information on the prevention of diabetes in practice. This dissertation offers new desirable information on the issue.

The aim of this dissertation study was to describe the prevalence of risk factors for type 2 diabetes and hidden glucose disorders predicting the development of diabetes in the Finnish adult population, and to analyse whether the risk for developing diabetes could be reduced by simple lifestyle counselling. Furthermore, the ability of the Finnish Diabetes Risk Score (FINDRISC) to detect glucose disorders leading to diabetes and undiagnosed diabetes was analysed. In the dissertation data from large Finnish population surveys (the FINRISK 2002 glucose tolerance survey and the FIN-D2D 2004−2005 survey) were analysed. In addition, a prospective design and large-scale intervention were included.

We found that obesity and glucose disorders are very common in the Finnish middle-aged population. Prevalence of obesity was 24% for men and 28% for women, that of abnormal glucose metabolism 42% for men and 33% for women, and that of undiagnosed diabetes 9% for men and 7% for men. One quarter of individuals aged 45−64 years were at high risk for diabetes. Lifestyle interventions were offered to more than 10,000 high-risk individuals, 3,379 men and 6,770 women. Of the men, 43% were also at high risk for cardiovascular morbidity and 42% at high risk for cardiovascular mortality estimated through the FRAMINGHAM and SCORE risk engines, respectively. The FINDRISC, originally developed for predicting the risk of development of type 2 diabetes, also predicted the prevalence of diabetes in the population.

The effect of lifestyle interventions on weight and its association with glucose tolerance was evaluated in individuals at high risk for diabetes in a one-year follow-up. In total 17.5% of them lost ≥ 5% weight. Their relative risk for diabetes decreased 69% compared with the group that maintained their weight.

This study shows that FINDRISC predicts prevalent type 2 diabetes. A significant proportion of middle-aged Finnish population has a glucose disorder including undiagnosed type 2 diabetes. Lifestyle interventions in primary health care may promote weight loss, which decreases the risk of diabetes.

Keywords: abnormal glucose tolerance, cardiovascular disease, diet, FINDRISC, intervention, lifestyle, obesity, oral glucose tolerance test, physical activity, prevention, risk factors, screening, type 2 diabetes

Saaristo, Timo, Tyypin 2 diabeteksen riskin arviointi ja ehkäisy perusterveydenhuollossa

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Tiivistelmä

Diabetes on yksi nopeimmin lisääntyvistä elintapasairauksista maailmassa. Sitä ei vielä voida parantaa, mutta tieteellisissä tutkimuksissa on kiistattomasti osoitettu, että sitä voidaan tehokkaasti ehkäistä elintapamuutoksilla. Diabeteksen ehkäisystä käytännössä on hyvin niukasti tutkimustietoa. Tämä väitöskirja tuo kaivattua lisätietoa aiheesta.

Väitöstutkimuksen päätavoitteena oli selvittää diabeteksen riskitekijöiden ja piilevien diabetesta ennakoivien sokerihäiriöiden yleisyyttä suomalaisessa aikuisväestössä. Tämän ohella tavoitteena oli selvittää voidaanko yksinkertaisella elintapaneuvonnalla vähentää sellaisten henkilöiden sairastumisvaaraa, joilla oli suuri riski sairastua diabetekseen. Lisäksi arvioitiin diabetesriskitestin kykyä tunnistaa ennakoivat sokerihäiriöt ja aiemmin tunnistamaton diabetes.

Tutkimuksessa käytettiin laajoja suomalaisia väestötutkimusaineistoja: FINRISKI-2002 -tutkimusta, sen alaotosta ja D2D-väestötutkimusta 2004–2005. Mukana oli myös pitkittäisasetelma ja laajamittainen interventio.

Tutkimuksen perusteella huomasimme, että lihavuus ja sokerihäiriöt ovat hyvin yleisiä keskiikäisillä suomalaisilla. Merkittävästi lihavia (BMI $\geq$ 30 kg/m^2) oli 24 % miehistä ja 28 % naisista ja poikkeava sokeriaineenvaihdunta oli 42 %:lla miehistä ja 33 %:lla naisista. Tunnistamaton diabetes oli 9 %:lla miehistä ja 7 %:lla naisista. Suuressa diabetekseen sairastumisvaarassa oli neljäsosa 45−64-vuotiaista. Interventioon otettiin yli 10 000 suuressa diabeteksen sairastumisriskissä olevaa henkilöä, 3 379 miestä ja 6 770 naista. Miehistä 43 % oli suuressa sairastumisvaarassa myös sydän- ja verisuonisairauteen ja 42 % suuressa kuolemanvaarassa Framingham- ja SCORE-riskilaskureilla arvioituna. Tyypin 2 diabeteksen sairastumisriskin arviointiin kehitetty Riskitesti ennusti hyvin myös diabeteksen esiintymistä väestössä.

Elintapainterventioiden vaikutusta painoon ja sokeriaineenvaihduntaan analysoitiin vuoden seurannassa sellaisilla henkilöillä, joilla oli suuri diabetesriski. Paino laski 5 % tai enemmän 17,5 %:lla, jolloin sairastumisriski diabetekseen väheni 69 % verrattuna ryhmään, jonka paino ei muuttunut.

Tutkimuksen perusteella lihavuus, sokerihäiriöt ja tunnistamaton diabetes ovat yleisiä keskiikäisessä väestössä. Riskitesti on hyvä työkalu myös diabeteksen seulonnassa. Perusterveydenhuollossa tarjottavalla elintapaneuvonnalla voidaan saada aikaan laihtuminen, joka vähentää sairastumisvaaraa diabetekseen.

Asiasanat: elintavat, fyysinen aktiivisuus, heikentynyt glukoosinsieto, interventio, lihavuus, preventio, riskitekijät, riskitesti, ruokavalio, seulonta, sokerirasituskoe, sydän- ja verisuonisairaudet, tyypin 2 diabetes

To the memory of my brother Esa
and all other victims of diabetes

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This dissertation is based on data from the National FINRISK 2002 survey, from the FIN-D2D survey 2004–2005 and from the FIN-D2D high-risk cohort. The objective of the surveys was to identify risk factors associated with type 2 diabetes and cardiovascular diseases among middle-aged Finnish people. FIN-D2D 2003–2008 was the Implementation Project of the Programme for Prevention of Type 2 Diabetes, which was part of the Finnish National Diabetes Programme DEHKO.

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Abbreviations

ADA	American Diabetes Association
ADDITION	Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care
A1C	Glycosylated haemoglobin
AGT	Abnormal glucose tolerance
ANCOVA	Analysis of covariance
ANOVA	One-way variance analysis
aROC	Area under the receiver-operating (ROC) curve
BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
CI	Confidence interval
DECODE	Collaborative analysis Of Diagnostic Criteria in Europe
DEHKO	Development Programme for the Prevention and Care of Diabetes
DIET	Dietary
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
EXE	Exercise
FINDRISC	Finnish Diabetes Risk Score
FINRISK	National risk factor survey in Finland
FIN-D2D	Implementation project for the type 2 diabetes prevention programme in Finland
HDL	High density lipoprotein
HR	Hasard ratio
IDDP	Indian Diabetes Prevention Program
IDF	International Diabetes Federation
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
LDL	Low density lipoprotein
MONICA	Monitoring trends and determinants in cardiovascular disease
NA	Non available
NCEP	National Cholesterol Education Program
NGT	Normal glucose tolerance
NPV	Negative predictive value
NR	Non registered

OGTT	Oral glucose tolerance test
OR	Odds ratio
PPV	Positive predictive value
ROC	Receiver-operating characteristic
RCT	Randomized controlled trial
RR	Risk ratio or relative risk
SCORE	Systematic Risk Evaluation Formula
SD	Standard deviation
SENS	Sensitivity
SPEF	Specificity
ST2DM	Screen-detected type 2 diabetes
T2DM	Type 2 diabetes
TT2DM	Total type 2 diabetes
WHO	World Health Organisation

List of original publications

This dissertation is based on the following original articles referred to in the text by their Roman numerals (I–IV). In addition, unpublished results related to published articles are presented.

I Saaristo T, Peltonen M, Lindström J, Saarikoski L, Sundvall J, Eriksson J & Tuomilehto J (2005) Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. Diabetes and Vascular Disease Research 2: 67–72.

II Saaristo T, Barengo N, Korpi-Hyövälti E, Oksa H, Puolijoki H, Saltevo J, Vanhala M, Sundvall J, Saarikoski L, Peltonen M & Tuomilehto J (2008) High prevalence of obesity, central obesity and abnormal glucose tolerance in the middle-aged Finnish population. BMC Public Health 8: 423. DOI: 10.1186/1471-2458-8-423.

III Saaristo T, Moilanen L, Jokelainen J, Korpi-Hyövälti E, Vanhala M, Saltevo J, Niskanen L, Peltonen M, Oksa H, Cederberg H, Tuomilehto J, Uusitupa M & Keinänen-Kiukaanniemi S (2010) Cardiometabolic profile of people screened for high risk of type 2 diabetes in a national diabetes prevention programme (FIN-D2D). Primary Care Diabetes 4: 231–239. DOI: 10.1016/j.pcd.2010.05.005.

IV Saaristo T, Moilanen L, Korpi-Hyövälti E, Vanhala M, Saltevo J, Niskanen L, Jokelainen J, Peltonen M, Oksa H, Tuomilehto J, Uusitupa M & Keinänen-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: 2146–2151.

Contents

1 Introduction

Type 2 diabetes (T2DM) is a global health problem in developed and developing countries (King *et al.* 1998, The DECODE study group 2003a, Wild *et al.* 2004, International Diabetes Federation 2009). The worldwide number of people with diabetes is estimated to rise from the current estimate of 285 million to 438 million in 2030 (International Diabetes Federation 2009). Around every tenth middle aged European develops T2DM in a ten-year period. The estimated lifetime risk of diabetes in the United States for individuals born in 2000 is 33% for males and 38% for females (Narayan *et al.* 2003).

T2DM is a devastating disease because of the associated microvascular complications (renal failure, blindness, neuropathy) and macrovascular complications (cardiovascular disease, CVD). Individuals with diabetes have high excess mortality and their life-expectancy can be shortened 5 to 15 years, with up to 75% dying of CVD (Hu *et al.* 2005, Roglic *et al.* 2005 and 2010, Franco *et al.* 2007, Forssas *et al.* 2010). Diabetes causes a human, social and medical impact and heavy financial burden to the society (Ryan *et al.* 2009). The rapid increase in the incidence of T2DM among young adults is a new and worrying health problem (The Writing Group for the SEARCH for Diabetes in Youth Study Group 2007, Lammi *et al.* 2007, Kautiainen *et al.* 2010).

The risk factors for T2DM and stages of abnormal glucose tolerance (AGT) can be detected early before the clinical onset of T2DM (Harris 1992, WHO 1999). The slow progression from the earliest detectable glucose disorder to clinical diabetes offers the opportunity to prevent T2DM. It has been shown in clinical randomised controlled trials (RCTs), that prevention of T2DM is possible among high-risk individuals by lifestyle changes (Tuomilehto *et al.* 2001, Knowler *et al.* 2002) or by pharmacological treatment (Knowler *et al.* 2002, Chiasson *et al.* 2002). The opportunity to prevent T2DM is based on the detection of individuals at high risk of T2DM and on interventions to reduce risk of diabetes and its complications.

Evidence on the prevention of T2DM on community level is almost completely lacking (Uusitupa *et al.* 2011b). An important challenge is how to identify at-risk individuals and how to implement the evidence of the RCTs in health care. In the present study, the methods and tools to identify people at high risk for T2DM, the yield of their identification, and the effectiveness of lifestyle interventions aiming at prevention of T2DM carried out among high-risk individuals in the primary health care setting have been evaluated.

2 Review of the literature

2.1 Diabetes as a disease

2.1.1 Definition and classification of diabetes and other abnormalities of glucose metabolism

Diabetes mellitus is a complex of diseases of abnormal metabolism, most notable hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association 2011). The World Health Organization (WHO) has classified diabetes into four categories that are defined as type 1 diabetes and type 2 diabetes (T2DM), gestational diabetes and other forms of diabetes (WHO 1999). T2DM is the most common form of diabetes affecting about 85–90% of individuals with diabetes. Clinically, T2DM is at one end of a continuous glucose spectrum with normal glucose value at one other end and clinical diabetes at the other end (Edelstein *et al.* 1997). In between there is the long period of abnormal glucose tolerance (AGT) defined as impaired fasting glucose, impaired glucose tolerance (IGT) or both (Unwin *et al.* 2002).

Diabetes and AGT can be diagnosed on the basis of WHO recommendations (WHO 1999), incorporating both fasting and 2-h after glucose load criteria into a diagnostic classification (Table 1). An individual with elevated glucose levels just below the threshold defined for diabetes has IFG if only the fasting levels are high (The Expert Committee on the Diagnosis and Classification of Diabetes mellitus 1997) or IGT if the 2-hour glucose values in the OGTT are high (WHO 1999). Identification and classification of AGT and diabetes relies on the measurement of blood glucose concentrations. These can be random glucose samples independent of prandial status, fasting plasma glucose sampling, a standardised glucose load test i.e. 75-g oral glucose tolerance test (OGTT) (WHO 1999), and glycosylated haemoglobin (A1C) screening (The International Expert Committee 2009). The source of the blood glucose measurement sample can be whole blood, plasma or serum, and the origin of the test sample can be a capillary or vein.

Table 1. The diagnostic criteria for normal and abnormal glucose tolerance (including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus) (fasting and 2-h post glucose load values by source of plasma vs. whole blood and sample site of capillary vs. vein) (WHO 1999).

Glucose tolerance	Glucose concentration, mmol/l		
	Plasma	Whole blood	
	Venous	Venous	Capillary
Normal glucose tolerance, NGT			
Fasting glucose	≤ 6.0	≤ 5.5	≤ 5.5
2h-post glucose load	≤ 7.7	≤ 6.6	≤ 7.7
Impaired fasting glycaemia, IFG			
Fasting glucose	6.1–6.9	5.6–6.0	5.6–6.0
2h-post glucose load	< 7.8	< 6.7	< 7.8
Impaired glucose tolerance, IGT			
Fasting glucose	< 7.0	< 6.1	< 6.1
2h-post glucose load	7.8–11.0	6.7–9.9	7.8–11.0
Diabetes mellitus, T2DM			
Fasting glucose	≥ 7.0	≥ 6.1	≥ 6.1
2h-post-glucose load	≥ 11.1	≥ 10.0	≥ 11.1

Abbreviations: NG = Normoglycaemia, IFG = Impaired fasting glucose, IGT = Impaired glucose tolerance

Recently the American Diabetes Association published new criteria for the diagnosis of diabetes based on the measurement of A1C (American Diabetes Association 2011).

Gestational diabetes is the most common medical complication of pregnancy and affects up to 10% of all pregnant women and accounts for 90% of all cases of diabetes diagnosed during pregnancy (Rosenberg *et al.* 2005, Hunt *et al.* 2007, Zhang *et al.* 2011). Incidence rates of gestational diabetes are increasing, possibly as a consequence of lifestyle factors (Babtiste-Roberts *et al.* 2009). The incidence of diabetes during pregnancy has increased the incidence of T2DM in children (Lu *et al.* 2001).

Because T2DM is usually asymptomatic in its earliest stages, many cases remain undiagnosed for a long time. It has been shown that up to half of people having T2DM are undetected in most countries (Rathmann *et al.* 2003, Gregg *et al.* 2004, Mayor 2005, Cowie *et al.* 2006, Bonaldi *et al.* 2011). The absence of a diagnosis of diabetes prevents patients from receiving adequate intensified treatment in time and predisposes them to the development of diabetic complications (Bartnik *et al.* 2007, Lenzen *et al.* 2006, Roberts *et al.* 2011). Interventions that could prevent or delay these complications cannot be

administered to patients with diabetes, unless their disease has been detected. In patients with T2DM, active therapy may reduce the risk of these complications and hence should be initiated early (Davis *et al.* 1999, Gaede *et al.* 2003 and 2008).

2.1.2 Pathophysiology of type 2 diabetes

Pathophysiologically, T2DM is characterized by insulin resistance and/or abnormal insulin secretion from pancreas β-cells, each of which may predominate and precede the onset of clinical T2DM by many years (Harris *et al.* 1992, U.K. Prospective Diabetes Study Group 1995). Insulin resistance is an early phenomenon partly related to obesity, and β-cell function declines gradually over time before the onset of clinical hyperglycaemia (Abdul-Ghani *et al.* 2006). When insulin action decreases, as will happen in weight gain in obesity, the β-cell function increases in compensation. This will increase concentrations of blood glucose, firstly slightly but over time the increase of glucose values will be detrimental and cause glucose toxicity, which again itself exacerbates β-cell dysfunction.

2.1.3 Epidemiology of type 2 diabetes

The prevalence of diabetes has risen dramatically in Westernised societies, in developing countries and in Asia (Dunstan *et al.* 2002, Katulanda *et al.* 2008, Cowie *et al.* 2009, Chan *et al.* 2009, Yang *et al.* 2010, Shaw *et al.* 2010, Hamer *et al.* 2011). The global prevalence of diabetes at the moment is 6.6% (International Diabetes Federation 2009). Diabetes is projected to affect up to 7.8% of the world population in the near future (International Diabetes Federation 2009). The prevalence of T2DM worldwide is currently estimated to be surprisingly higher than previously suggested (King *et al.* 1998, Mainous III *et al.* 2007, International Diabetes Federation 2009).

2.1.4 Complications of diabetes

People with T2DM, IFG and IGT are at increased risk for developing long-term diabetic complications which are strongly associated with previous hyperglycaemia (Coutinho *et al.* 1999, DeVegt *et al.* 1999, Stratton *et al.* 2000). Up to 50% in patients with diabetes may have diabetic complications before the

diagnosis of diabetes (U.K. Prospective Diabetes Study Group 1995, Gerstein 1997, Kohner *et al.* 1998, DECODE Study Group 2001, Saydah *et al.* 2001, Qiao *et al.* 2003b, Ziegler *et al.* 2008). Individuals with T2DM and AGT are at higher risk for CVD; i.e. coronary artery disease, peripheral arterial disease and stroke than individuals without diabetes (Haffner *et al.* 1998, Turner *et al.* 1998, the DECODE Study Group 2003b, Selvin *et al.* 2004, Juutilainen *et al.* 2005, Pajunen *et al.* 2005, American Diabetes Association 2011). Diabetes is an equivalent of CVD in the course of time (Wannamethee *et al.* 2011).

2.2 Risk factors for type 2 diabetes

Risk factors for T2DM are common in all populations. The most important known non-modifiable risk factors are ageing, heredity, gestational diabetes, a history of CVD, and abnormal birth weight. The most important modifiable risk factors are obesity and central obesity, dietary factors, physical inactivity, metabolic syndrome, short duration of sleep, smoking, alcohol consumption, psychosocial stress and depression. People with IFG or IGT have a higher risk of developing T2DM than people with normoglycaemia (Harris 1996, Edelstein *et al.* 1997, DeVegt *et al.* 2001, Qiao *et al.* 2003a, Rasmussen *et al.* 2008). Risk is higher when IGT and IFG coexist (Unwin *et al.* 2002). The risk of diabetes in people with IGT more than doubles in the presence of other risk factors for diabetes (Lindström *et al.* 2008).

2.2.1 Non-modifiable risk factors for type 2 diabetes

Age increases the risk of T2DM (The DECODE Study Group 2005, Wild 2004), which has been explained by an increase in other risk factor levels in older age. Prevalence of T2DM is slightly higher in men than women, but T2DM affects more women than men worldwide, because women in general have longer life expectancy (Wild *et al.* 2004). Heredity is an important risk factor for the development of T2DM (Poulsen *et al.* 1999). The influence of ethnicity and familial diabetes on glucose tolerance is strong (Ferrannini *et al.* 2003). Positive family history increases the risk for T2DM 2.4 fold (Wada *et al.* 2006, Valdez *et al.* 2007).

A history of gestational diabetes predisposes women to the subsequent development of T2DM and its complications (Kaaja *et al.* 1996, Babtiste-Roberts *et al.* 2009). Conversion of gestational diabetes to T2DM varies with the length of

follow-up and cohort retention in different studies (Kim *et al.* 2002, Kaaja *et al.* 2008).

Women delivering babies weighing over 4 kg at birth are at risk for glycaemic disorders (Kramer *et al.* 2002, Wei *et al.* 2003). A slow rate of intrauterine or prenatal growth and low birth weight (< 2.5 kg) are aetiological factors in the development of T2DM in offspring (Hales *et al.* 2001, Wei *et al.* 2003, Whincup *et al.* 2008). Preterm birth before 35 weeks of gestation is associated with an increased risk of T2DM in adult life (Kajantie *et al.* 2010).

2.2.2 Modifiable risk factors for type 2 diabetes

Obesity and central obesity strongly and independently predict the risk of T2DM (Colditz *et al.* 1995, Wannamethee *et al.* 1999, Janssen *et al.* 2002, Wang *et al.* 2005, Narayan *et al.* 2007, Berghoefer *et al.* 2008). A Western dietary pattern including high intakes of refined grains and foods with high fat and sugar is supposed to be one aethiological factor behind the present diabetes epidemic (Hu *et al.* 2001, Van Dam *et al.* 2002, Montonen *et al.* 2005). Fat, carbohydrates and fibre intakes have been identified as risk factors for T2DM in prospective studies. Type of fat such as intake of saturated fat or trans fatty acids and low intake of polyunsaturated fatty acids has been associated with the risk of T2DM in many studies (Feskens *et al.* 1995, Hu *et al.* 2001, Salmeron *et al.* 2001). In prospective studies, dietary glycaemic index has been associated more consistently with the risk of T2DM than total carbohydrate intake in both sexes (Salmeron *et al.* 1997a, Salmeron *et al.* 1997b).

Obesity and overweight are strongly associated with a sedentary lifestyle and lack of physical activity (Martinez-Conzalez *et al.* 1999). Physical inactivity increases the risk of T2DM (Hu *et al.* 2003, Hu *et al.* 2004, Yates *et al.* 2007, Waller *et al.* 2010). Clustering of risk factors such as dyslipidaemia, hypertension, visceral obesity, IGT, abnormal coagulation factors and endothelial dysfunction which are part of metabolic syndrome, often correspond with hyperglycaemia (Ferrannini *et al.* 1991, Orchard *et al.* 2005). Individuals with multiple CVD risk factors are at increased risk of T2DM, which is only partially mediated by insulin resistance or central adiposity (D´Agostino *et al.* 2004).

Cigarette smoking is an independent, modifiable risk factor for T2DM (Patja *et al.* 2005, Gabrielle *et al.* 2005, Willi *et al.* 2007). Passive smoking is associated with an increased risk of diabetes (Hayashino *et al.* 2008). Moderate alcohol consumption is associated with T2DM in a U-shaped fashion compared with both

abstinence and excessive drinking in males and older women (Carlsson *et al.* 2000 and 2005, Wannamethee *et al.* 2003, Howard *et al.* 2004, Koppes *et al.* 2005, Beulens *et al.* 2005).

Difficulties maintaining sleep or short sleep duration is associated with an increased incidence of diabetes in men (Mallon *et al.* 2005, Björkelund *et al.* 2005). Psychosocial stress including symptoms of anxiety, apathy, depression, fatigue and insomnia are associated with the risk of developing T2DM (Brown *et al.* 2005, Knol *et al.* 2006, Eriksson *et al.* 2008, Mäntyselkä *et al.* 2011).

2.2.3 Factors protecting against type 2 diabetes

Some factors may protect against the development of T2DM such as exercise, use of fibre, coffee drinking, and breast feeding. Moderate and high occupational, commuting or leisure-time physical activity independently and significantly reduces the risk of T2DM among middle-aged general population (Hu *et al.* 2003, Jeon *et al.* 2007, Waller *et al.* 2010). Even a small amount of leisure-time physical activity protects against T2DM after taking familial and genetic effects into account (Waller *et al.* 2010). Better results are achieved if individuals have moderate-intensity exercise every day. Increased physical activity reduces the risk of T2DM independent of dietary or weight loss changes (Hu *et al.* 2003 and 2004, Yates *et al.* 2007, Waller *et al.* 2010).

Fibre intake has been shown to be inversely associated with the risk of type 2 diabetes (Schulze *et al.* 2004, Montonen *et al.* 2003). Coffee drinking is reported to be associated with a reduced graded inverse risk of T2DM in both men and women (Tuomilehto *et al.* 2004, Salazar-Martinez *et al.* 2004, van Dam *et al.* 2005, Pereira *et al.* 2006, Hu *et al.* 2006). Breastfeeding may be associated with protection against development of T2DM in offspring (Pettit *et al.* 1997 and 1998, Young *et al.* 2002). Moderate alcohol consumption reduces the risk of T2DM (Carlsson *et al.* 2000 and 2005, Wannamethee *et al.* 2003, Howard *et al.* 2004, Koppes *et al.* 2005).

2.3 Screening for risk of type 2 diabetes and abnormal glucose tolerance

Individuals at risk for T2DM can be identified during a preclinical period using different methods and strategies (Lindström *et al.* 2003, Engelgau *et al.* 2004 Waugh *et al.* 2007, Harding *et al.* 2006). There is a debate on whether screening

for diabetes is beneficial at population level (Griffin *et al.* 2000, Spijkerman *et al.* 2002, Christensen *et al.* 2004, Janssen *et al.* 2007, Norris *et al.* 2008), or whether screening for T2DM is feasible in asymptomatic adults (Engelgau *et al.* 1995, U.S. Preventive Task Force 2008). Data from the Ely cohort (UK) suggest that invitation to screening for T2DM and related CVD risk factors may have been associated with a reduction in mortality in the follow-up of the cohort (Simmons *et al.* 2011). There is evidence on the benefit of opportunistic screening, i.e. screening subjects visiting a health care provider for reasons unrelated to diabetes (Engelgau *et al.* 1995), but it has been reported that opportunistic screening in primary health care mainly targets middle-aged and older adults with obesity (Klein Woolthuis *et al.* 2009). Screening for T2DM and IGT, with intervention for those with IGT is estimated to be cost-effective (Waugh *et al.* 2007, Icks *et al.* 2007, Kahn *et al.* 2010).

Health care providers may use demographic data collected in patient files in searching for individuals at risk for T2DM (Greaves *et al.* 2004, Heldgaard *et al.* 2006, Simmons *et al.* 2007), even if this information usually focuses mainly on non-modifiable risk factors and data may differ between different health care centres (Buijsse *et al.* 2011).

2.3.1 Laboratory screening for type 2 diabetes and abnormal glucose tolerance

Blood glucose measurements can be used in screening for T2DM and other glucose disorders. By measuring fasting plasma glucose only, one third of individuals with T2DM may go undetected (the DECODE Study Group 1999b, Norhammar *et al.* 2002). Fasting glucose alone does not identify individuals at increased risk of death associated with hyperglycaemia (the DECODE Study Group 1999b).

OGTT identifies the stage of progression of AGT toward the onset of T2DM (WHO 1999). OGTT has been recommended by WHO and IDF as the gold standard test for diagnosing AGT and excluding undiagnosed T2DM (World Health Organization 1980, WHO 1999, World Health Organization 2003, Alberti *et al.* 2007). The two-hour value in OGTT predicts deaths from all causes and CVD better than fasting blood glucose (The DECODE Study Group 1999a and DECODE Study Group 2001). Neither A1C nor fasting glucose is effective in detecting IGT (World Health Organization 2006, Bennet *et al.* 2007). An OGTT is therefore required to diagnose IGT reliably (The DECODE Study Group 1999b).

2.4 Diabetes risk scores

2.4.1 Development of diabetes risk scores

Individuals at high-risk for T2DM can be identified by various risk equations from a simple patient questionnaire (Greaves *et al.* 2004) to multivariate risk scores (Lindström *et al.* 2003). Several risk scoring algorithms using routine collected data and combining multiple factors for estimating the risk for T2DM have been published (Tables 2–3, Buijsse *et al.* 2011). The idea of the development of a risk scoring system to identify individuals at high risk for T2DM originated in the 1990s (Herman *et al.* 1995). Almost 50 different risk scores for reporting the derivation of risk models for T2DM have been published, mostly in North American and European studies for both sexes.

2.4.2 Diabetes risk scores for prevalent and incident type 2 diabetes

Prevalent risk scores are based on data derived from cross-sectional studies to develop models that predict current AGT, mostly IGT and undiagnosed prevalent T2DM (Table 2). Incident risk scores predict the probability of developing T2DM in the future and are based on longitudinal data derived from cohorts that are free of diabetes at baseline (Table 3).

Risk scores may include noninvasive measures, biochemical measures, and measures of glucose and insulin control, models containing novel biomarkers and models involving genetic information (Tables 2–3).

Noninvasive risk scores are based on traditional risk factors of T2DM demanding anthropometric and clinical information such as age, gender, family history of diabetes and BMI, which are simple easy-to-collect parameters in the clinical setting to be ascertained by the health care provider or the person to be tested. A risk score may be very simple (Mohan *et al.* 2005, Heikes *et al.* 2008, Gao *et al.* 2010) or more complex (Talmund *et al.* 2010). Some of the easy-to-handle questionnaires have been converted into interactive www-documents (Baehring *et al.* 1997, Suomen Diabetesliitto 2009).

Adding a biochemical measure along with a noninvasively measured variable such as 2-hour glucose or lipids improves the prediction (Aekplakorn *et al.* 2006, Wilson *et al.* 2007, Sun *et al.* 2009, Schmid *et al.* 2011). Adding more sophisticated indices of glucose and insulin control such as homeostasis model assessment or the measurement of insulin secretion has not improved the

performance of a risk score and is not feasible in the primary health care setting (Kolberg *et al.* 2009).

Some diabetes risk scores include novel biomarkers such as C-reactive protein, which does not improve the performance of a risk score (Hanley *et al.* 2005, Abdul-Ghani *et al.* 2007). Adding liver enzymes with blood lipids to a risk score has been shown to improve the descrimination of a test (Schulze *et al.* 2009).

The performance of prediction models involving genetic information has improved results only marginally or been weaker than risk scores including only simple clinical variables (Meigs *et al.* 2008, 2009, Fontaine-Bisson *et al.* 2010). This reflects the importance of clinical parameters over genetic. Validated non-genetic prediction algorithms remain the most appropriate tools for predicting T2DM in the clinical setting.

Table 2. Risk scores developed to identify individuals with prevalent diabetes or abnomal glucose tolerance.

Risk score; reference	Study population. Data collection in development and validation of the score	Aim of screening	Variables	Performance Sensitivity (SENS),% Specificity (SPEF),% Positive predictive value (PPV),% Negative predictive value (NPV), % Area under the receiver-operating (ROC) curve (aROC)	Comments
ADA risk score; Herman *et al*. 1995	Development: data from 3,220 subjects in the Second National Health and Nutrition Examination Survey, U.S.A.	Undiagnosed T2DM	Age, sex, history of delivery of a macrosomic infant, obesity, sedentary lifestyle, and family history of diabetes	SENS 79 SPEF 79 PPV 10	Simple, nonivasive, and potentially cost-effective tool
Predictive Dutch Model (three models PM1–3) to identify undiagnosed diabetes; Baan *et al*. 1999	Development: data from 1,016 participants aged 55–75 years in the Rotterdam Study aged 55–75 years; Validation: a population based sample of 2,364 participants aged 50–74 years in the Hoorn Study, Netherlands	Undiagnosed T2DM	PM1: Age, sex, presence of obesity, use of antihypertensive medication, use of lipid-lowering medication, gestational diabetes, prevalence of CVD; PM2: BMI, family history of diabetes, smoking, CVD symptoms, cycling PM3: Systolic and diastolic blood pressure (BP), waist-hip ratio	For PM2: SENS 72 SPEF 55 PPV 7 aROC 0.74 aROC was higher for PM2 than for PM1 (0.68). PM2 and PM3 did not differ	Three predictive models: PM1, PM2 and PM3. PM1: Routine collected information by general practitioners; PM2: Variables obtained by additional questions; PM3: Variables from a physical examination.

Risk score; reference	Study population. Data collection in development and validation of the score	Aim of screening	Variables	Performance Sensitivity (SENS),% Specificity (SPEF),% Positive predictive value (PPV),% Negative predictive value (NPV), % Area under the receiver-operating (ROC) curve (aROC)	Comments
Cambridge Risk Score; Griffin *et al.* 2000	Development: data from 1,077 subjects aged 40–64 years in the Ely Study and prospective registration of 197 patients with newly diagnosed diabetes in 41 general practices in Wessex, UK.	Undiagnosed T2DM	Age, gender,body mass index (BMI), steroid and antihypertensive medication, family history of diabetes, and smoking history	SENS 77 SPEF 72 aROC 0.80	Also evaluated in a population-based cohort (European Prospective Investigation of Cancer-Norfolk) in 25,639 individuals followed up for a mean of 5 years for diabetes incidence. aROC 0.75. Rahman *et al.* 2008; in Danish population (Heldgaard *et al.* 2006) and in ethnic minority groups (Spijkerman *et al.* 2004)
Multivariate Logistic Regression Equation, Tabaei *et al.* 2002	Development: data from 1,032 subjects in the Diabetes in Egypt Project	Undiagnosed T2DM	Age, sex, BMI, random capillary plasma glucose, postprandial time	SENS 65 (development) 62 (validation) SPEF 96 (development) 96 (validation) PPV 67 (development), 63 (validation) aROC 0.88	Needs a handheld programmable calculator, invasive
ARIC rule to predict diabetes; Schmidt *et al.* 2003	Development: data from 7,915 participants aged 45–64 years in the Atherosclerosis Risk in Communities (ARIC) study 1987–1989 ; Validation in the ARIC study 1996–1998	Undiagnosed T2DM, IFG and IGT	Age, waist circumference, height, hypertension, BP, family history of diabetes, ethnicity, fasting glucose, triglycerides and HDL cholesterol	aROC 0.71 aROC 0.78 if including fasting glucose, and aROC 0.80 if including triglycerides and HDL cholesterol	Rules based on different approaches achieved SENS of 40–87 and SPEF of 50–86

Risk score; reference	Study population. Data collection in development and validation of the score	Aim of screening	Variables	Performance Sensitivity (SENS),% Specificity (SPEF),% Positive predictive value (PPV),% Negative predictive value (NPV), % Area under the receiver-operating (ROC) curve (aROC)	Comments
A Danish Diabetes Risk Score for targeted screening; Glümer *et al.* 2004	Development: data from 6,784 individuals aged 30–60 years in a population-based sample (Inter99 Study). Derived from the first half and validated on the second half of the study population. External validation performed based on the Danish Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION) pilot study	Identification of individuals with undiagnosed T2DM with a sensitivity of 75% and minimizing high-risk group needing subsequent testing	Age, sex, BMI, family history of diabetes, known hypertension, physical activity at leisure time	Cutoff 31: SENS 73.3 (development), 66.7 (validation), 75.9 (external validation) SPEF 74.3 (development), 73.6 (validation), 72.2 (external validation) PPV 11 (development), 9.7 (validation), 7.3 (external validation) aROC 0.804 (development), 0.761 (validation), 0.803 (external validation)	A questionnaire to be used in a stepwise screening strategy for type 2 diabetes, decreasing the numbers of subsequent tests and thereby possible minimizing the economical and personal costs of the screening strategy
Indian Diabetes Risk Score for urban Asian Indians; Ramachandran *et al.* 2005	Development: data from 4,993 men and women aged ≥ 20 years in the National Urban Diabetes Survey in India; Validation: 5,010 subjects in the same survey, and a separate survey population in Chennai (n = 2,002), and the South Asian Cohort of the 1999 Health Survey for England (n = 676).	Undiagnosed T2DM	Age, BMI, waist circumference, family history of diabetes, and sedentary physical activity	Depending on the cohort validated: SENS 72.4–76.6 SPEF 59–61 PPV 8.3–12.2 NPV 96.9–97.9 aROC 0.668–0.734	Same score can be used in Indian populations who have migrated, but population-specific cut-points would need to be used in these groups because of the different distribution of the risk factors for diabetes

Risk score; reference	Study population. Data collection in development and validation of the score	Aim of screening	Variables	Performance Sensitivity (SENS),% Specificity (SPEF),% Positive predictive value (PPV),% Negative predictive value (NPV), % Area under the receiver-operating (ROC) curve (aROC)	Comments
A simplified Indian Diabetes Risk Score (IDRS) for screening for undiagnosed diabetic subjects; Mohan *et al*. 2005	Development: data from 26,001 individuals in the Chennai Urban Rural Epidemiological Study (CURES). Every tenth subject was requested to participate in OGTT test at a later phase.	Undiagnosed T2DM	Age, abdominal obesity, age, family history of diabetes, and physical activity	SENS 72.5 SPEF 60.1 PPV 17 NPV 95.1 aROC 0.698	Simple. Internal validation on the same data. Also validated in another South Indian population with the sensitivity of 62.2 and specificity of 73.7 (Adhikari *et al*. 2010)
Omani Diabetes Risk Score; Al-Lawati *et al*. 2007	Development: data from 4,881 participants in the Oman's 1991 National Diabetes Survey; Validation: Nizwa Survey participants (n = 1,432).	Undiiagnosed T2DM	Age, BMI, family history of diabetes, current hypertension status, waist circumference	SENS 78.6 for development, 62.8 for validation; SPEF 73.4 for development, 78.2 for validation; aROC 0.83 for development, 0.76 for validation	Thai, Dutch, Finnish and Danish diabetes risk scores showed poor performance in community-based settings of Oman
Patient Self-assessment Score; Bang *et al*. 2009	Development: National Health and Nutrition Examination (NHANES) Survey 1999 to 2004 for model development and 2005 to 2006; Validation: a combined cohort of 2 community studies, Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS)	Undiagnosed T2DM	Age, sex, family history of diabetes, history of hypertension, obesity, and physical activity	SENS 79 SPEF 67 PPV 10 Positive likelihood ratio of 2.39	Easy-to implement diabetes screening score. Data during pregnancy were not available.

Risk score; reference	Study population. Data collection in development and validation of the score	Aim of screening	Variables	Performance Sensitivity (SENS),% Specificity (SPEF),% Positive predictive value (PPV),% Negative predictive value (NPV), % Area under the receiver-operating (ROC) curve (aROC)	Comments
Abnormal Glucose Risk Assessment-6 (AGRA-6) tool; He *et al*. 2010	Development: data from 1,887 adults (18 years or older) in the National Health and Nutrition Examination Survey (NHANES) 2005–2006; Validation: NHANES 2005–2006 data.	Assessment of abnormal glucose levels	Age, sex, self-reported race/ethnicity, educational attainment, smoking status, participation in any leisure-time physical activity, body mass index, history of hypertension, use of hypertension medication, high cholesterol and family history of diabetes	depending on the model SENS 0.64–0.77 SPEF 0.67–0.73 aROC 0.72–0.80	Six different models
The Leicester Risk Assessment Score; Gray *et al*. 2010	Development: data from 6,186 subjects aged 40–75 years from a multiethnic UK screening study; Validation: data from 3,171 subjects aged 40–75 years from a separate screening study	Undiagnosed T2DM	Age, ethnicity, sex, first degree family history of T2DM, antihypertensive therapy of high blood pressure, waist circumference and BMI	aROC 0.72. A cutoff point of 16: SENS 81 and SPEF 45	In the validation population 73% white European, 22% South Asian. The score is simple (seven questions) and non-invasive
A Chinese Diabetes Risk Score; Liu *et al*. 2011	Development: data from 10-year longitudinal health checkup-based population of 1,851 individuals. Validation: data from a cross-sectional sample of 699 individuals	Undiagnosed T2D and abnormal glucose tolerance	Age, hypertension, history of high blood glucose, body mass index, fasting plasma glucose, serum triglycerides and high-density lipoprotein-cholesterol	SENS 64.5 SPEF 71.6 aROC 0.734	Laboratory tests are needed

Table 3. Risk scores to identify individuals at high risk of developing type 2 diabetes (incident diabetes).

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
Diabetes Prediction Model; Stern *et al.* 2002	Development: data from 1,791 Mexican-American and 1,112 non-Hispanic white subjects aged 25–64 years at baseline in San Antonio Heart Study (prospective U.S. population-based study)	Prediction of risk for T2DM in a 7.5-year follow up	Age, sex, BMI, family history of diabetes (≥ 1 parent or sibling), fasting plasma glucose, ethnicity, systolic BP, HDL-cholesterol level and BMI	Full model with 2-h glucose: aROC 0.859, full model-no 2 h glucose: aROC 0.845, clinical model with 2-h glucose: aROC 0.843, clinical model-no 2-h glucose: aROC 0.843	Four models: Two multivariate full models with or without 2-h glucose and two clinical models with or without 2-h glucose
FINDRISC; Lindström *et al.* 2003	Development: data from 4,595 subjects aged 45–64 years in the FINRISK 1987 cohort population; Validation: data from 4,435 subjects aged 45–64 years in the FINRISK 1992 cohort population	Prediction of risk for incident T2DM	Age (2 categories), antihypertensive medication, history of high blood glucose, BMI (2 categories), vegetables, fruits, berries (daily consumption), physical activity(< 4h/week), waist circumference (2 categories)	aROC 0.87 (baseline) aROC 0.87 (validation)	Analysed also for prevalent diabetes in the 1987 and 1992 FINRISK surveys. aROC 0.80 for both surveys
A Simple Prediction Rule; Kanaya *et al.* 2005	Develoment: data from 1,549 subjects aged 67±11 years in the Rancho Bernardo Study; Validation: data from 3,075 subjects aged 74±3 years in the Health, Aging and Body Composition Study	Prediction of risk for incident T2DM	Age, female sex, fasting plasma glucose, triglycerides	aROC 0.75	
Thai Risk score; Aekplakorn *et al.* 2006	Development: data from 2,677 individuals aged 35–55 years in a Thai cohort; Validation: a different Thai cohort of 2,420 individuals resurveyed after 12 years	Prediction of high risk of T2DM in 12 years	Age, BMI, waist circumference, hypertension, and a history of diabetes in parents or siblings	SENS 77 SPEF 60 aROC 0.74	Adding IFG or IGT status to the model increased the aROC to 0.78

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
The simple clinical Framingham Offspring Study model 7; Wilson *et al*. 2007	Development: data from 3,140 middle-aged men ad women (mean age 54 years) who were participants in the 5th Framingham Offspring Study and were followed to the 7th Study examinations	Prediction of the 7-year risk of new T2DM	Simple clinical model: parental history of diabetes, obesity, hypertension, low HDL-cholesterol level, elevated triglyceride-level, IFG	Simple clinical model: aROC 0.85 Complex clinical modes: aROC 0.850–0.854	Participants: 99% white and non-Hispanic. Simple clinical model was as good as a complex clinical model
German Diabetes Risk Score; Schulze *et al*. 2007.	Development: data from 9,729 men and 15,438 women aged 35–65 years in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study; Validation: EPIC-Heidelberg, the Tübingen Family Study for T2DM, and the Metabolic Syndrome Berlin Potsdam Study	Prediction of T2DM in five years	Age, height; history of hypertension, physical activity, consumption of red meat, coffee and alcohol, smoking, waist circumference, whole-grain bread	In the EPIC-Potsdam study: aROC 0.84; In the EPIC-Heidelberg study: aROC 0.82 aROC,SENS and SPEF for undiagnosed diabetes in the Tubingen Family Study: 0.83, 83,and 72, respectively, and in the Metabolic Syndrome Berlin Potsdam Study 0.75, 94 and 43, respectively	Also evaluated in a cross-sectional setting for undiagnosed diabetes. Also related to elevated risks of myocardial infarction, stroke,specific types of cances and premature death in apparently healthy individuals (Heidemann *et al.* 2009)
Genotype score; Meigs *et al*. 2008	Development: data from 2,377 participants aged 28–62 years in the Framingham Offspring Study with the follow-up of 28 years of follow-up	To predict Incident diabetes	Single-nucleotide polymorphisms (SNPs) at 18 loci associated with diabetes	A genotype score predicted new cases of diabetes only slightly better than knowledge of common risk factors alone	Identification of adverse phenotypic characteristics remains the cornerstone of approaches to predicting the risk of T2DM

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
DESIR score; Balkau *et al.* 2006, 2008 and 2011	Development: data from 1,863 men and 1,954 women aged 30–65 years in the Epidemiological Study on the Insulin Resistance Syndrome (DESIR)	To predictit later diabetes in the follow-up of 9 years	Variables available in the clinical setting, biological variables and polymorphisms; Predictive clinical variables: waist circumference, hypertension, smoking in men, and diabetes in the family in women; Combination of clinical and biological variables: fasting glucose, waist circumference, smoking, gammaglutamyltransferase for men, and fasting glucose, BMI, triglycerides, and diabetes in family for women	aROC 0.713 for men 0.827 for women	Genetic polymorphisms studies provided little toward predicting diabetes. A large panel of SNPs may be needed to perform even simple clinical parameters. The simplest clinical parameter for identifying those at risk of diabetes is adiposity and baseline glucose is the best biological predictor
QDSCORE; Hippiesley-Cox *et al.* 2009	Development: data from 2 540,753 patients aged 25–79 years from 355 general practices in England; Validation: 1 232,832 patients from 176 separate practices	To estimate the 10- year risk of acquiring diagnosed T2DM	Age, sex, ethnicity, BMI, smoking, family history of diabetes, Townsend Deprivation Score, treated hypertension, CVD, current use of corticosteroids	aROC: 0.834 for men and 0.85 for women; In external validation (Collins *et al.* 2011) aROC 0.800 for men and 0.812 for women)	In an ethnically and socioeconomically diverse population in England and Wales, a large cohort, inclusion of both deprivation and ethnicity

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
A genetic score; Talmund *et al.* 2010	Development: data from 5,535 civil servants aged between 35 and 55 years (33% women) in the Whitehall II prospective cohort study with three 5 yearly medical screenings	To estimate the risk of T2DM in 10 years	20 common independently inherited diabetes risk alleles	aROC 0.55	Cambridge risk score and Framingham Offspring Risk score led to better discrimination of cases than did the genotype based score alone
A prediction model for T2DM risk among Chinese people, Chien *et al.* 2009	Development: data from 2,960 individuals (mean age 54 years) in the Chin-Shan Community Cardiovascular Cohort Study	To estimate the 10-year risk of T2DM	Age, elevated fasting glucose, BMI, triacylglycerol, white blood cell count, HDL-cholesterol	SENS 52 SPEF 78 aROC 0.70	Simple but invasive
Danish Type 2 Diabetes Risk Model from a panel of serum biomarkers from the Inter99 Cohort; Kolberg *et al.* 2009	Development: data from 6,600 subjects aged ≥ 39 years in the Inter99 study cohort of 6,600 subjects aged ≥ 39 years. Reinvented after 5 years (n = 4,511). A nested case-control design	To estimate the 5-year conversion to T2DM	Six biomarkers (adiponectin, C-reactive protein, ferritin, interleukin-2-receptor A, glucose, and insulin	aROC 0.78	Performs better than single risk indicators, invasive. A multimaker model also validated in a clinical laboratory setting. Urdea *et al.* 2009

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
Two ARIC risk scoring systems; Kahn *et al*. 2009	Development: data from 9,587 participants aged 45–64 years in the Atherosclerosis Risk in Communities (ARIC) study in 1987 to 1989. Validation: 3,142 participants	To estimate Incident T2DM in the follow-up of 10 years	Basic score: waist circumference, maternal diabetes, hypertension, paternal diabetes, short stature, black race, age 55 years or older, increased weight, rapid pulse, and smoking history. Enhanced score: glucose, waist circumference, maternal diabetes, triglycerides, paternal diabetes, low HDL cholesterol, short stature, high uric acid, age 55 years or older, hypertension, rapid pulse, and nonuse of alcohol.	For basic scoring system: SENS 69 SPEF 64 aROC 0.71 Enhanced scoring system: SENS 74 SPEF 71 aROC 0.79	U.S. white and black men and women, No questions regarding previous gestational diabetes. Knowledge of parental diabetes may be uncertain. Additional data from fasting blood glucose tests identified those at extreme risk better
Simple prediction model for the diagnosis of type 2 diabetes in the Brazil urban population; de Sousa *et al.* 2009	Development: data from 1,507 subjects aged over 35 years in a population-based sample of Vitoria, Brazil; Follow-up database: A subgroup of the first sample with 655 subjects; External validation: a small city population sample of individuals from 930 homes	Identification of individuals with an increased likelihood of having diabetes	Age, BMI, known hypertension	Derivation: SENS 76 SPEF 67 aROC 0.772 Validation: aROC 0.720	A simple score. Because of its low cost and feasibility, this score might optimise health care resources, mainly in developing countries such as Brazil.
Taiwan risk score; Sun *et al*. 2009	Development: data from 73,961 participants (35,987 men and 37,974 women), aged 35–74 years in the Taiwan MJ Longitudinal health-check-up-based Population Database (MJLPD). Development in a random half of the sample and validation in another half.	To estimate a 5-year risk of T2DM	Simple model: Age, sex, education level, family history, smoking, sport time, hypertension, BMI, waist circumference; Model 2: Including fasting glucose; Model 3: including triglycerides, HDL-cholesterol, liver function (ALT) and kidney function (GFR)	For model 3: aROC 0.848, For model 3 in validation: aROC 0.833	Altogether 6 different models were generated from three original models. The capability of the ARIC score was also evaluated.

Risk score; reference	Data collection in developing and validating	Aim of screening	Variables	Performance Sensitivity (SENS), % Specificity (SPEF), % Positive predictive value (PPV), % Negative predictive value (NPV), % Area under the ROC-curve (aROC)	Comments
Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK); Chen *et al.* 2010	Development: data form 600 subjects aged 25 years or older in the Australian Diabetes, Obesity and Lifestyle study (AusDiab)	To predict the risk of T2DM	Age, sex,ethnicity, parental history of diabetes, history of high blood glucose level, use of antihypertensive medications, smoking, physical inactivity, waist circumference	SENS 74 SPEF 67.7 PPV 12.7 aROC 0.66–0.79 (in two validation cohorts)	Validated in the Blue Mountains Eye Study (BMES) and in the North West Adelaide Health Study (NWAHS)
The STOP-NIDDM risk-score, Tuomilehto *et al.* 2010	Development: data from 1,368 individuals aged 40–70 years in the STOP-NIDDM study population in nine countries (Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel and Spain). Validation: 1,697 participants in the FINRISK 2002 survey and from Finnish registers	Risk of developing T2DM in subjects with IGT	Acarbose treatment, gender, serum triglyceride level, waist circumference, fasting plasma glucose, height, history of CVD and hypertension	aROC 0.64 in people with IGT in the STOP-NIDDM study, aROC 0.840 in the FINRISK population with IGT alone and aROC 0.089 in the FINRISK population with IGT and NGT combined	Identifies high-risk individuals with IGT who would benefit most from T2DM or CVD prevention strategies (lifestyle management or early acarbose treatment)
The DETECT-2 update of the FINDRISC; Alssema *et al.* 2011	Data from 18,301 participants in studies of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) project	Incident T2DM in five years	Age, sex, BMI, waist circumference, use of anti-hypertensives, history of gestational diabetes, smoking, family history of diabetes	aROC 0.766	The original FINDRISC had the aROC of 0.742 in the same population. Additional items for updated score were male sex, smoking, and family history of diabetes which improved the aROC and net reclassification

2.4.3 Validation of diabetes risk scores

Diabetes risk scores are developed in population-based specific national cohorts and generally perform well in these populations but yield a lower validity when applied to a new population due to differences in population characteristics (Rathman *et al.* 2005, Glümer *et al.* 2006). External validation is essential before implementing diabetes prediction models in clinical practice (Bleeker *et al.* 2003, Schmid *et al.* 2011). The parameters included in various models and scores are in general the same (Tables 2–3), but the cutpoints and score weights are different.

Many diabetes risk scores have been validated in populations other than where they were derived (Park *et al.* 2002, Tables 2–3). The FINDRISC has been validated in many independent cohorts (Franciosi *et al.* 2005, Balkau *et al.* 2008, Cameron *et al.* 2008, Abdul-Ghani *et al.* 2007, Makrilakis *et al.* 2011, Tankova *et al.* 2011) and in some of these chorts with some modifications of the original score (Allsema *et al.* 2011). Biochemical markers, but not genetic markers improved the identification of previously undiagnosed type 2 diabetes beyond the FINDRISC alone in a study (Wang *et al.* 2010). The Danish Risk score has been validated in a different Caucasian population (Glümer *et al.* 2005). The FINDRISC, the Danish T2DM risk score (based on Inter99 Study), the Cambdridge risk score, and two predictive Dutch models (PM1 and PM2) based on the Rotterdam study have been validated in the Whitehall II study and found that these scores perform less well in a large validation cohort compared with previous validation studies (Witte *et al.* 2010). Several risk scores were evaluated in a cross sectional Taiwanese population and it was found that they could be used to identify individuals at high risk for T2DM (Lin *et al.* 2009).

2.4.4 Performance of diabetes risk scores

The performance of a diabetes risk score is weighted in terms of accuracy, availability, practicability, and costs (Buijsse *et al.* 2011). Information on sensitivity, specificity, and predictive value is essential to decide appropriate cutoff. In a comparison of the tests, the summary measure of predictive ability of any test can be measured by plotting a Receiver-operating characteristics (ROC) curve which can be used to evaluate the discriminnatory accuracy of a risk score (De Long *et al.* 1988, Greiner *et al.* 2000). The performance varies between different risk scores (Tables 2–3).

2.4.5 Clinical use of diabetes risk scores in screening for the risk of type 2 diabetes

A diabetes risk score can be used as an initial screening step followed by a diagnostic test including an OGTT or A1C (Alberti *et al.* 2007, Chen *et al.* 2011, Balkau *et al.* 2011). Using a risk score may greatly reduce the number of individuals who would otherwise need to undergo an OGTT while achieving adequate sensitivity, specificity, and PPV (Saydah *et al.* 2002). A diabetes risk score developed in the STOP-NIDDM study population differs from the other published scores as it predicts cases who might benefit from starting the medication aiming to prevent T2DM (Tuomilehto *et al.* 2010, Table 3).

2.4.6 Diabetes risk scores in the prediction of other conditions than diabetes

Many diabetes risk scores predict other conditions than T2DM depending on the variables used in the derivation of the score. These may identify macrovascular disease, neuropathy or arterial stiffness in nondiabetic subjects (Mohan *et al.* 2010b, Mohan *et al.* 2010a), and the metabolic syndrome and CVD (Mohan *et al.* 2006). The FINDRISC is associated with insulin resistance and progression towards T2DM (Schwarz *et al.* 2009) and is a predictor of acute CHD, stroke and total mortality (Silventoinen *et al.* 2005). The Cambridge risk score predicts CVD in primary care (Chamnan *et al.* 2009). The German risk score is related to risk of myocardial infarction, stroke, specific types of cancer and mortality (Heidemann *et al.* 2009).

2.5 Prevention of type 2 diabetes

The slowly progressing development from the early stages of AGT to the onset of clinically diagnosed T2DM offers the opportunity to prevent diabetes. Over the last decades several clinical trials have tested the hypothesis that adopting a healthier lifestyle could prevent T2DM in people at risk (Jeon *et al.* 2007, Gillies *et al.* 2007). In the early studies the combined effects of lifestyle factors were largely left un-analysed. Some of these studies were controlled but not randomised and thus the results were affected by selection bias (Eriksson *et al.* 1991).

2.5.1 Randomised controlled trials to prevent type 2 diabetes

Several randomised controlled clinical trials based on randomisation by centres (Pan *et al.* 1997) or by individuals (Tuomilehto *et al.* 2001, Knowler *et al.* 2002) have shown conclusively that both lifestyle measures and pharmacological treatment may reduce the proportion of people with IGT who would otherwise develop T2DM (Table 4). Target groups have included obese individuals with AGT, mostly IGT. These studies were carried out in various populations and ethnic groups. Lifestyle interventions were based on diet and exercise. These trials prove that T2DM can be prevented or delayed quite well. The 1-year incidence of diabetes has been reduced in the lifestyle trials in medium 30–50% compared with the control group (Yamaoka *et al.* 2005). The results of the lifestyle intervention in DPS and DPP were exactly the same.

Lifestyle interventions may have a greater impact on individuals with higher baseline BMI (the Diabetes Prevention Program Research Group 2003, Gillies *et al.* 2007). Lifestyle interventions seem to be at least as effective as pharmacological interventions and their effect is long-lasting compared to that of pharmacological treatment (Gillies *et al.* 2007). Lifestyle modification is likely to have important effects on morbidity and mortality of diabetes and should be recommended to all high-risk people (Eddy *et al.* 2005). Lifestyle changes overcome the impact of known genetic and familial risk (Uusitupa *et al.* 2011a).

Interventions to reduce the risk of diabetes should primarily target weight reduction (Hamman *et al.* 2006). Physical activity has an independent effect in reducing the risk in individuals at high risk of T2DM compared with multi-component interventions (Yates *et al.* 2007). No definite conclusion can be drawn either as to the amount of physical activity needed to reduce the risk or the effectiveness of a single-component physical activity intervention compared with multi-component interventions (Yates *et al.* 2007). Lifestyle change may be more effective in people with IGT (Yates *et al.* 2007). A lifestyle intervention based on general recommendations has also been effective in reducing multiple metabolic abnormalities (Bo *et al.* 2007).

Table 4. Randomised controlled trials in prevention of type 2 diabetes.

Study; country; reference	Population; n (% men); age; BMI	Inclusion criteria; definitions of IGT and diabetes	Type of intervention	Type of exercise intervention	Type of diet intervention	Follow-up time	Relative risk reduction of T2DM versus control (*)
Da Qing IGT and Diabetes Study; China; Pan *et al.* 1997 (Ψ)	Chinese; 577 (53.4); over 25 years old	IGT; WHO 1985	DIET alone; EXE alone; EXE+DIET	Encouragement to exercise 1 unit/day (**)	Weight loss through reduced energy intake	6 years	31% 46% 42%
Diabetes Prevention Study (DPS); Finland; Tuomilehto *et al.* 2001	Finnish; 522 (33); 55 ± 7 years; 31.3 ± 6 kg/m^2	IGT; WHO 1985	EXE+DIET	Encouragement to exercise 30/min/day at moderate intensity	Weight reduction ≥ 5% throughout healthy low-energy diet	3.2 years	58%
Diabetes Prevention Program (DPP); USA; Knowler *et al.* 2002	Americans; 3,234 (32.3); 50 ± 10.7 years; 34.0 ± 6.7 kg/m^2	IGT	EXE+DIET, Metformin	Encouragement to exercise 150 min/week at moderate intensity	Weight reduction ≥ 7% through healthy low-energy diet	2.8 years	EXE + DIET 58% Metformin 31%
Kosaka Japan; Kosaka *et al.* 2005 Ψ Ψ	Japanese men; 356 (100) 30–70 years;	IGT; WHO 1980	EXE+DIET	Encouragement to exercise 30–40 min day at moderate intensity	BMI < 22kg/m^2 through healthy diet	4 years	67%
The Indian Diabetes Prevention Programme (IDPP-1); India; Ramachandran *et al.* 2006	Native Asian Indians; 531 (79); 45–46 years; 25.6 ± 3.3 kg/m^2	IGT; WHO 1999	EXE+DIET; Metformin alone; EXE+DIET + Metformin	Encouragement to exercise 30min/day at moderate intensity	Healthy dietary advice	30 months	28.5% 26.4% 28.2%

(*) Relative risk reduction of T2DM versus control: $p < 0.05$, significant differences between groups, (**) 1 unit = 30 min mild exercise, 10 min strenuous exercise, or 5 min very strenuous exercise, (Ψ) only the centres were randomised, (ΨΨ) intensive versus non-intensive lifestyle intervention groups. Abbreviations: DIET = dietary, DPP = Diabetes Prevention Programme, DPS = Diabetes Prevention Study, EXE = Exercise, IGT = Impaired glucose tolerance.

Lifestyle change studies have been shown to have long-lasting benefits (Table 5). In DPS, a relative T2DM risk reduction of 43% for 7 years after the active intervention period was reported (Lindström *et al.* 2006). A 34% reduction in diabetes incidence was shown to persist for 10 years following an intervention in the DPP (Diabetes Prevention Program Research Group 2009). A protective effect of the lifestyle intervention of about 43% in prevention of T2DM was shown in the follow-up of 20 years after the initial intervention in a Chinese study (Li *et al.* 2008). Lifestyle intervention for 6 years in this study was associated with a 47% reduction in the incidence of severe, vision-threatening retinopathy over a 20 year interval, primarily due to the reduced incidence of diabetes in the intervention group (Gong *et al.* 2011).

These long-term beneficial effects are compared to the findings in studies on the treatment of diabetes (the Writing Team for the Diabetes Control and complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group 2003, Nathan *et al.* 2005). In the UKPDS and DCCT/EDIC studies the long-term effects were explained with the hypothesis of the metabolic memory (Ihnat *et al.* 2007). Whether lifestyle intervention in individuals at high risk of T2D also is beneficial in the long run in terms of CVD morbidity and mortality has been unclear (Li *et al.* 2008). The Da Qing Diabetes Prevention Study (Li *et al.* 2008) showed sustained protection against T2DM but did not give an answer to that question. Lifestyle intervention among people with IGT in the DPS did not decrease CVD morbidity during the first 10 years of follow-up (Uusitupa *et al.* 2009). The authors concluded that the statistical power probably was not sufficient to detect small differences between the intervention and control group (Uusitupa *et al.* 2009). A lower initial CVD risk profile and regular follow-up may explain the observed lower mortality among DPS participants when compared with the population-based IGT or normoglycemic cohorts. Authors conclude that lifestyle intervention studies to prevent T2DM should be focused on individuals at high risk of T2DM and of CVD (Uusitupa *et al.* 2009).

Table 5. Follow-up studies of the major lifestyle trials in prevention of type 2 diabetes.

Study; country; reference	Population;n (% men)	Study design	Inclusion criteria	Type of intervention	Type of exercise intervention	Type of diet intervention	Follow-up time	Relative risk reduction of T2DM versus control
DPS follow-up study; Finland; Lindström *et al.* 2006	Overweight Finnish; 522 (33)	RCT Post-hoc analysis	IGT	EXE+DIET	Encouragement to increase overall physical activity + circuit exercise sessions offered	Weight reduction through a healthy diet	7 years intervention + 3-year follow-up	43%
DPP; USA; Hamman *et al.* 2006	Americans, 54.7% white; 3,234 (32.3)	RCT Cox hazard regression in intervention arm	IGT	EXE+DIET	Encouragement to exercise 150 min/ week at moderate intensity	Weight reduction > 7% through healthy low-energy, low fat diet	7 years intervention + 3-year follow-up	34%
Da Qing IGT and Diabetes Study; China; Li *et al.* 2008	Chinese; 577 (53.4)	RCT (randomized by study centres) Post-hoc analysis	IGT	EXE+DIET	Encouragement to exercise 1 unit/day (*)	Weight loss through reduced energy intake	20 years (6 years intervention + 14-year follow-up	43%

Relative risk reduction of T2DM versus control: $p < 0.05$, significant differences between groups. (*) 1 unit = 30 min mild exercise, 10 min strenuous exercise, or 5 min very strenuous exercise. Abbreviations: RCT = randomized controlled trial, DIET = dietary, DPP = Diabetes Prevention Programme, DPS = Diabetes Prevention Study, EXE = Exercise

2.5.2 Pharmacological studies to prevent type 2 diabetes

Several studies have reviewed the literature on drug therapy to either delay or prevent T2DM (Lauritzen *et al.* 2007). Many drugs including oral hypoglycaemic agents, antiobesity agents, antihypertensive agents, statins, fibrates, and estrogen replacement agents have been tested in prevention of T2DM (Table 6). Only in studies on oral hypoglycemic and antiobesity agents was diabetes a primary endpoint (Lauritzen *et al.* 2007). In studies on other agents glucose tolerance has only been a surrogate end-point. The DPP and IDPP demonstrated a 26–31% reduction in IGT conversion to DPP in individuals receiving metformin (Table 6). Part of the pharmacological effect of the hypoglycaemic agent did not persist when the drug was discontinued (The Diabetes Prevention Program Research Group 2003). Both lifestyle intervention and metformin therapy reduced the development of the metabolic syndrome (Orchard *et al.* 2005). A thiazolidinedione troglitazone reduced the incidence of T2DM by 75% in DPP even though the drug was discontinued after 10 months (Knowler *et al.* 2002, The Diabetes Prevention Program Research Group (2005). In DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial, rosiglitazone reduced conversion to T2DM by 62% (Gerstein *et al.* 2006, The DREAM Trial Investigators 2006b) but the use of ramipril for 3 years did not significantly reduce the incidence of diabetes (The DREAM Trial Investigators 2006a). Nateglinide did not decrease the incidence of T2DM in the NAVIGATOR study (the NAVIGATOR Study Group 2010). In the Xendos study, compared with lifestyle changes alone, orlistat plus lifestyle changes produced greater weight loss and a greater reduction in the incidence on T2DM over 4 years in an obese population (Torgerson *et al.* 2004).

Table 6. Trials with pharmacological intervention in prevention of type 2 diabetes.

Study; reference	Population; n	Mean age, years; (mean BMI, kg/m^2)	Inclusion criteria; definitions of IGT and diabetes by fasting the plasma glucose (FPG) value	Types of intervention	Frequency of intervention	Pharmacological agent	Years of follow-up	Effect of intervention
DPP; Knowler *et al.* 2002; The Diabetes Prevention Program Research Group 2005	3,232	51; (34)	IGT; FPG > 5.3 mmol/l	DIET, EXE	16 diet sessions in first half of year, then monthly. Twice weekly supervised exercise sessions	Metformin, troglitazone	2.8	Decreased progression to diabetes per group; DIET and EXE: 58%, 3.8 kg weight loss; Metformin: 31%,1.8 kg weight loss Troglitazone: 75% during the mean 0.9 year period of use
STOP-NIDDM; Chiasson *et al.* 2002	1,428	55; (31)	IGT; FBG 5.6 mmol/l	General advice on diet, weight loss and activity	Once a month during one year	Acarbose	6	Acarbose decreased progression to diabetes by 25%.
EDIT; Lauritzen *et al.* 2007	631	52; (28.6)	FBG 5.5–7.7 mmol/l	None	Unspecified	Metformin, acarbose or both	6	In patients with IGT at baseline, decreased progression to diabetes with acarbose, no weight loss
XENDOS, Torgerson *et al.* 2004	3,305	30–60; (> 30)	IGT; FB < 6.7 mmol/l	DIET+EXE+ orlistat	Every 3 months	Orlistat	4	Orlistat decreased 37.3% the risk of developing T2DM , mean weight loss 10.6 kg with orlistat, 6.2 kg with placebo

Study; reference	Population; n	Mean age, years; (mean BMI, kg/m^2)	Inclusion criteria; definitions of IGT and diabetes by fasting the plasma glucose (FPG) value	Types of intervention	Frequency of intervention	Pharmacological agent	Years of follow-up	Effect of intervention
DREAM; Gerstein *et al.* 2006	5,296	30 years or more (54.7)	IFG, IGT or both	lifestyle recommendations + rosiglitazone		Rosiglitazone. ramipril		8 mg rosiglitazone daily, together with lifestyle recommendations, substantialy reduces the risk of diabetes or death by 80%
IDPP; Ramachandran *et al.* 2006	531	45.9; (25.8)	FBG < 7.0 mmol/l; 2 h glucose 7.8–11.0 mmol/l	DIET + EXE + metformin	6 months interval	Metformin	3	Metformin: 26.4%; Lifestyle + metformin: 28.2%
NAVIGATOR; The NAVIGATOR Study Group 2010	9,306 (nateglinide 4,645, placebo 4,661)	63.7; (30.5)	IGT and CVD or CVD risk factors	Lifestyle modification program		Nategllinide, in a 2-by-2 factorial design with valsartan or placebo	5.0	The indicence of T2DM did not decrease

DIET = dietary, DPP = Diabetes Prevention Programme, DPS = Diabetes Prevention Study, EXE = Exercise, IGT = Impaired glucose tolerance

There are some small observational trials on the prevention of T2DM with natural products with inconclusive results. Intake of antioxidants, serum alpha-tocopherol or beeta-carotene supplementation did not affect the risk of T2DM in smoking men in a Finnish study (Kataja-Tuomola *et al.* 2011).

2.5.3 Implementation for the prevention of type 2 diabetes in primary health care

Randomised controlled trials in the prevention of T2DM were originally conducted in resource-intensive research settings with limited consideration of how the different strategies used in these trials might be implemented for population wide use (Crandall *et al.* 2008). The challenge is how to implement the evidence derived from these studies at communty level. It has been questioned whether lifestyle counselling interventions delivered by health care providers in a primary health care setting to patients at risk for T2DM are of marginal benefit only (Fleming *et al.* 2008).

There are fewer than fifty published, mainly small-scale translational lifestyle interventions in prevention of T2DM conducted in routine clinical settings by healthcare providers (Cardona-Morrel *et al.* 2010, Table 7).

Table 7. Examples of translational (*) studies on type 2 diabetes prevention (only those in real-life health care setting and with a follow-up of least one year included).

Study; country; reference	Number of participants (% pre-diabetic or AGT)	Mean age of participants, years	Percent of men, %	Mean BMI, kg/m^2, in the beginning of the study	Number of intervention sessions; (duration in weeks)	Number of sessions attended (percentage attended, %)	Follow-up in months; (loss to follow-up, %)	Mean weight loss in the intervention group (weight loss, %)	Percentage of weight loss of ≥ 5% achieved, %	Mean reduction in waist circumference, cm
Goal; Finland; Absetz *et al.* 2007 and 2009,	352	58	25	32.5	6 (32)	NA	12 (9.4)	0.8–1.0 kg	12	1.6 ± 4.8
Greater Green Triangle Diabetes Prevention Project; Australia; Laatikainen *et al.* 2007	237	56.7	27	33.5	6 (32)	(23.8)	12 (23.8)	2.5 kg	NR	3.2
DEPLOY; USA; Ackerman *et al.* 2008	92 (100)	56.5	50	31.4	16	(57)	(37/year)	5.7 kg (6)	59	NA
DPP translation; USA; Seidel *et al.* 2008	88 (42)	54	16	NR	12 (14)	6 (52)	(43)	NR	46	NA
Montana; USA; Amundson *et al.* 2009	355	53.6	20	35.9	16 (16)	13 (83)	(37/year)	6.7 (6.7)	67	NA
PREDIAS; Germany; Kulzer *et al.* 2009	182	56.3	57	31.5	12	NA	(9.3)	3.8	NA	NA
DE-PLAN; Greece; Makrilakis *et al.* 2010	191	56.3	40	32.3	6	25 (7)	(35)	1.0	NA	NA
Project HEED; USA; Parikh *et al.* 2010	99 (56)	48	8.6	31.5	8 (10)	NA	12 (23)	7.2 pounds (4.3)	34	NA

Study; country; reference	Number of participants (% pre-diabetic or AGT)	Mean age of participants, years	Percent of men, %	Mean BMI, kg/m^2, in the beginning of the study	Number of intervention sessions; (duration in weeks)	Number of sessions attended (percentage attended, %)	Follow-up in months; (loss to follow-up, %)	Mean weight loss in the intervention group (weight loss, %)	Percentage of weight loss of ≥ 5% achieved, %	Mean reduction in waist circumference, cm
TLGS (The Teheran Lipid and Glucose Study):Iran: Harati *et al.* 2009 and 2010	10,368, 3,931 in intervention group and 6,437 in control group	43	40	26.8	NA	NA	(43)	0.5 kg in men	NA	1.0 in women
FIN-D2D; Finland, the present study	10,147 (men: 68, women: 49)	54.7 for men, 53.0 for women	33	31.0	5 (NA)	2.9	(45.6)	1.2 kg	17	1.0

(*) A commonly used term for the implementation of the results and experiences on randomized controlled trials in health care aiming prevention of type 2 diabetes; NR = non registered; NA = non-available

Most of these studies were carried out in the USA based on the DPP study (The Diabetes Prevention Program Research Group 2002, Ackerman *et al.* 2008, Seidel *et al.* 2008, Amundson *et al.* 2009, Jackson 2009), or in Europe and Australia based on the DPS study (Laatikainen *et al.* 2007, Makrilakis *et al.* 2010). Some studies were RCTs with no more than 37–375 participants who were middle-aged obese people with AGT or metabolic syndrome (Bo *et al.* 2007, Barclay *et al.* 2008). Some studies had a before-after design with a control group (McTigue *et al.* 2009) or without (Absetz *et al.* 2007 and 2009, Laatikainen *et al.* 2007).

The screening of participants was usually carried out with different risk questionnaires. Lifestyle interventions included sessions on nutrition and physical activity delivered by appropriately qualified personnel but changes in dietary parameters or physical activity were generally not reported (Cardona-Morrel *et al.* 2010). Ordinary medical primary health care staffs, mainly nurses, were used (Whitemore *et al.* 2009). The DPP-based studies have generally included more intervention sessions than the DPS-based studies (Table 7). Some studies have been low-resource-intensive lifestyle modification programmes (Payne *et al.* 2008). In some studies it has been possible to achieve and maintain a clinically valuable weight loss within routine primary care by nurse-led interventions (Counterweight Project Team 2008). The participation of men has generally been lower than of women (Table 7). Drop-outs have been common in follow-up.

Most lifestyle interventions have achieved weight and waist circumference reductions after one year (Cardona-Morrel *et al.* 2010). Generally, the weight loss achieved has been better in studies including more intervention sessions than in studies with fewer interventions (Table 7). At best, more than half of the participants have achieved weight loss of 5% accompanied with some reduction of AGT and CVD risk factors (Seidel *et al.* 2008), and AGT (Payne *et al.* 2008). Predicted risk of coronary heart disease morbidity has been reported to diminish in some programmes (Lipscomb *et al.* 2009).

To summarise, implementation of the prevention of type 2 diabetes has been in its infancy. The studies published on this topic have generally been small trials and the results achieved have been modest in terms of diabetes prevention. Translational studies have been feasible, but of limited benefit one year after the intervention (Cardona-Morrel *et al.* 2010). There are only few reports on long-term follow-up (Coppel *et al.* 2009). Experiences and results on real-life translational studies to be carried out in primary health care settings by ordinary medical staff as in the present study are urgently needed.

3 Aims of the study

The overall aim was to develop tools and methods for the identification of people at high risk of T2DM in general population and primary health care, and to investigate the effectiveness of interventions on the reduction of CVD risk factor levels and the prevention of T2DM.

More specifically, the aims of the study were to address the following questions:

1. To analyse the test characteristics of the Finnish Diabetes Risk Score (FINDRISC) as a screening tool for prevalent undiagnosed type 2 diabetes and other abnormalities of glucose metabolism in middle-aged subjects in an unselected population, and to analyse the association of the FINDRISC score with the prevalence of the metabolic syndrome, and the cardiovascular risk factor levels in this population (Paper I).
2. To describe the prevalences of obesity, central obesity, abnormal glucose tolerance and the distribution of the FINDRISC score values in middle-aged individuals in an unselected population and to analyse the associations of obesity with abnormal glucose tolerance in this population (Paper II).
3. To describe the prevalence of undiagnosed type 2 diabetes, other abnormalities of glucose regulation and the cardiometabolic risk profile in individuals at high risk of T2DM identified by the FINDRISC or other methods of screening in a primary health care setting (Paper III).
4. To analyse the effect of lifestyle intervention on weight and its association with glucose tolerance in follow-up of one year in the FIN-D2D high risk cohort (Paper IV).

4 Populations and methods

The present study consists of four separate population samples: FINRISK 2002 subsample (glucose tolerance survey), FIN-D2D survey 2004–2005, FIN-D2D high-risk cohort 2004–2008, and FIN-D2D high risk cohort individuals with one-year follow-up data.

4.1 Populations and designs

4.1.1 FINRISK 2002 survey

One part of the present study is based on a subsample (glucose tolerance survey) of the national FINRISK survey performed in Finland at 5-year intervals for the surveillance of chronic non-communicable diseases and their risk factors in a random sample of the middle-aged Finnish population. Details of the FINRISK 2002 survey have been published earlier (Laatikainen *et al.* 2003b). In 2002, the survey covered six geographical areas in Finland: the provinces of Kuopio, Lapland, North Karelia, Oulu, Turku and Loimaa region and the cities of Helsinki and Vantaa.

The survey protocol closely followed the WHO MONICA protocol (WHO MONICA 1988 and 1999) and the most recent recommendations of the European Health Risk Monitoring Project (Tolonen *et al.* 2002). Six teams, with five trained nurses in each, carried out the survey (Laatikainen *et al.* 2003b). The data were collected by sending a self-administered questionnaire to a stratified sample of population and inviting participants for a health check where anthropometric measurements, blood pressure measurements and blood sampling were carried out. The participants were selected from population registers by random sampling and stratified by sex and age (45–54-, 55–64-, and 65–74- years) from six geographical areas.

In total, the sample size was 13,437 subjects (6,710 men and 6,727 women) aged mainly 25–64 years, but also including 65–74-year old subjects in North Karelia, Lapland and the cities of Helsinki and Vantaa. Of these, 8,799 participants completed the survey both by responding to a postal inquiry and by participating personally in the health check (Laatikainen *et al.* 2003a, 2003b). The response rate in the postal inquiry was 67%, and the actual participation rate was 61%. Based on the available information from the national register, the non-

attenders were young men from urban environments (Laatikainen *et al.* 2003a, Laatikainen *et al.* 2003b). The 421 men who only completed the questionnaire but did not participate in the check-up were analysed for some characteristics to evaluate the significance of dropouts. Employment status did not differ between the attenders and those who only returned the postal questionnaire.

The FINRISK 2002 glucose tolerance survey was part of the FINRISK 2002 survey and specifically monitored the prevalence of AGT and the metabolic syndrome, and the risk factors for the future development of T2DM (Paper I). A sample of FINRISK 2002 participants aged 45–74 years were invited by mail to a clinical examination including a 75-gram OGTT (WHO 1999). In total, 4,622 subjects were invited (Figure 1).

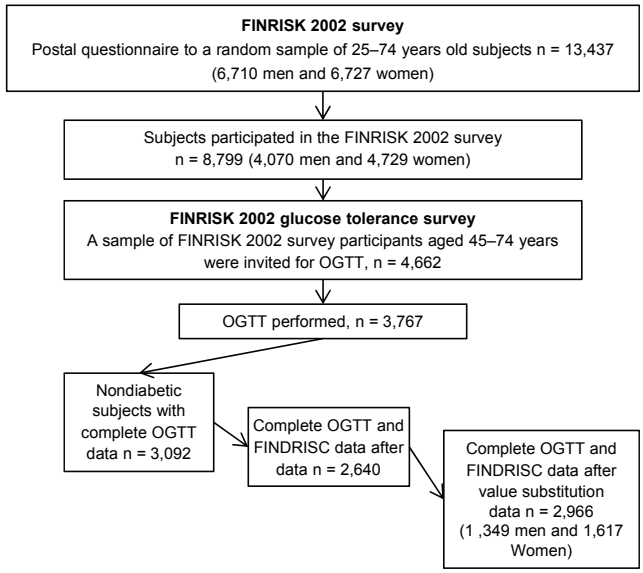

Fig. 1. FINRISK 2002 glucose tolerance survey population.

Of these, the OGTT was carried out in 3,767 subjects, and data on glucose tolerance status was obtained for 3,092 subjects without a prior history of diabetes. Of the 3,092 subjects with OGTT data, a total of 2,640 subjects completed the diabetes risk score. The most commonly missed data on the form were those on BMI (n = 271 (9%) missing) and waist circumference (n = 286 (9%) missing). In the study missing values for BMI and waist were substituted using corresponding values from the health examination, giving 2,966 subjects with complete data.

The participation rates in the FINRISK 2002 glucose tolerance survey were lowest in the youngest age groups of both sexes (61% in the age group 45–54 years, 71% in the age group 55–64 years, and 72% in the age group 65–74 years respectively) (Unpublished data). Those who did not participate did not differ from the participants in respect to their educational status, history of CVD or prevalence of self-reported chronic diseases. A significant difference between non-participants and participants was reported in smoking status (35% vs. 25%, $p < 0.001$), self-reported history of high serum cholesterol (47% vs. 50%, $p = 0.039$), use of antihypertensive medication (58% vs. 53%, $p = 0.035$), and self-reported history of diabetes (8% vs. 3%, $p < 0.001$). In non-participants there were slightly more individuals taking prescribed medication.

4.1.2 FIN-D2D 2004–2005 survey

One part of the present study is based on a sample of the FIN-D2D survey 2004–2005 performed in three Finnish hospital districts of Pirkanmaa, South Ostrobothnia and Central Finland. The survey was connected to the evaluation of the implementation programme (FIN-D2D) for the national T2DM prevention programme. The study monitored the prevalence of obesity, central obesity and AGT and the distribution of the FINDRISC values in the middle-aged Finnish population, and analysed the associations between AGT, normal weight, overweight, obesity and central obesity in this population (Paper II).

The survey protocol closely followed the WHO MONICA protocol (WHO MONICA 1988 and 1999) and the most recent recommendations of the European Health Risk Monitoring Project (Tolonen *et al.* 2002). Three teams with five nurses in each specially trained for the survey procedures carried out the survey. The survey included a self-administered questionnaire and a health check with anthropometric measurements, BP measurements, and blood sampling including a 75-gram oral OGTT (WHO 1999).

The data were collected by sending a postal questionnaire to a total of 4,500 subjects (2,250 men and 2,250 women) aged 45–74 years, stratified according to sex, 10-year age groups (45–54, 55–64, and 65–74- years) and the three geographical areas of Pirkanmaa, South Ostrobothnia and Central Finland during October 2004 and January 2005 (Figure 2). The response rate was 62% for men and 67% for women (Paper II, Table 1).

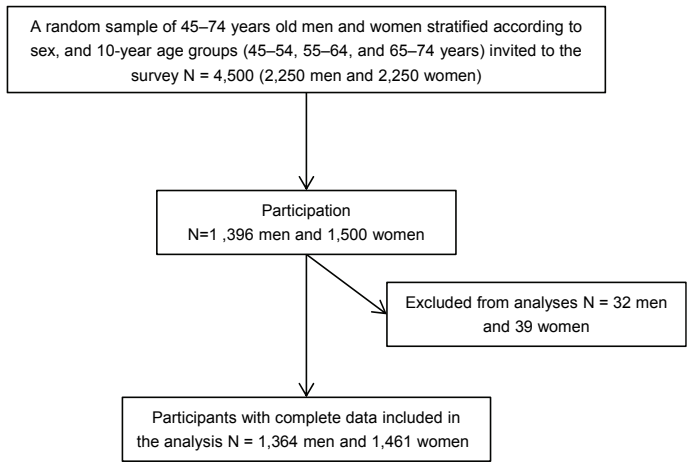

Fig. 2. FIN-D2D 2004–2005 survey population.

4.1.3 FIN-D2D high risk cohort

One part of the present study is based on the FIN-D2D high risk cohort consisting of individuals identified for being at high risk for T2DM in the implementation project (FIN-D2D) for the national T2DM prevention programme in primary health care settings in Finland between 2003 and 2008. The study described the prevalence of T2DM and other abnormalities of glucose regulation in this cohort and assessed the cardiometabolic risk profile of individuals identified as high risk subjects of T2DM for lifestyle intervention (Paper III).

The data were collected by identifying subjects at high risk for developing diabetes using the modified Finnish diabetes risk score (FINDRISC), which included a question on family history of diabetes in addition to the original seven questions (Lindström *et al.* 2003). The FINDRISC was used for opportunistic screening in primary health care centres and pharmacies and at public events as well as in a nationwide advertising campaign (Saaristo *et al.* 2007). Screening was done by local nurses and pharmacy personnel. Subjects could also complete the FINDRISC test in the Internet. Those with FINDRISC scores ≥ 15 were considered to be at high risk of T2DM, and they were referred to the FIN-D2D for lifestyle interventions. The other methods of identification for high risk of T2DM were past medical history of myocardial infarction or other ischaemic CVD event, history of IFG or IGT, and in women a history of gestational diabetes.

In total, 10,149 high-risk subjects (3,379 men and 6,770 women) aged 18–87 years (53.6 ± 10.9 years) were initially identified (Figure 3).

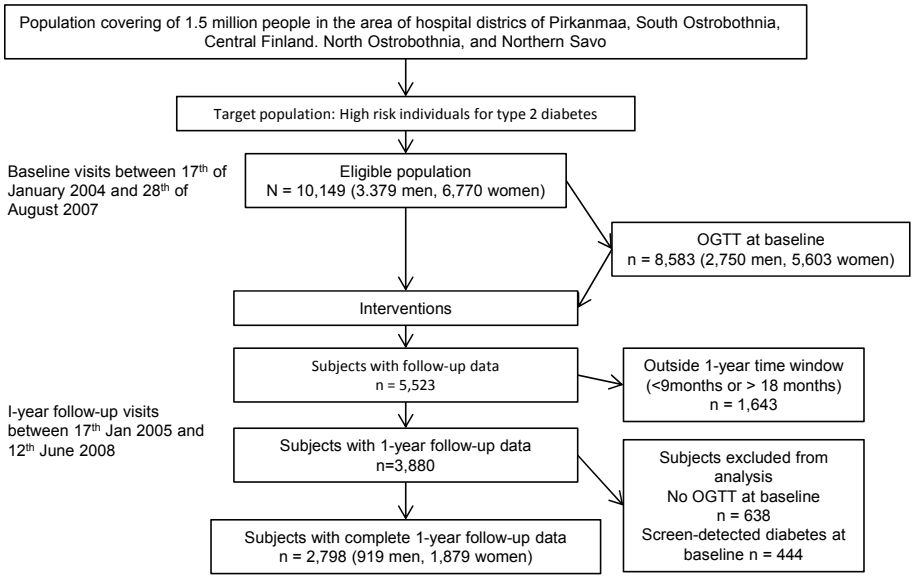

Fig. 3. The FIN-D2D high risk cohort 2004–2008 study population and the subjects with 1-year follow-up data.

Of these, 8,353 had an OGTT at baseline. In total 51% of men and 57% of women were referred to the FIN-D2D based on the high (≥ 15) FINDRISC score, 34% of men and 21% of women because of a history of IFG or IGT, 8% of men and 2% of women due to a history of ischaemic CVD and 13% of women because of a the history of gestational diabetes mellitus.

The baseline visits occurred between 17 January 2004 and 28 August 2007. Each of the 400 participating primary health care centres and occupational health care clinics locally developed flowcharts for the implementation of prevention of diabetes programmes using existing resources. The flowcharts were based on the FIN-D2D project plan (Suomen Diabetesliitto 2004, Finnish Diabetes Association 2006).

4.1.4 FIN-D2D high risk cohort individuals with one-year follow-up data

One part of the present study is based on subjects selected from 10,149 subjects identified as being at high risk for T2DM in the FIN-D2D, and who were non-diabetic at the beginning of the project and had any 1-year follow-up data (n = 5,523) (Figure 3). The subjects (n = 1,643) outside the set time window of 9–18 months for a one year visit were excluded from the analyses. One-year follow-up data were available for 3,880 (70.3%) participants. Of these 638 individuals did not have an OGTT at baseline and 444 individuals had screen-detected type 2 diabetes (ST2DM) at baseline and were excluded from the study. Thus a sample of 2,798 subjects (919 men and 1,879 women) who were nondiabetic at baseline and had 1-year follow-up data were included in the analyses (Paper IV). The 1-year visits occurred between 17 January 2005 and 12 June 2008. The mean follow-up time was 14 months (Paper IV).

4.2 Methods

Questionnaires, clinical interviews, clinical examinations, and laboratory measurements were used in data collection.

In the FINRISK 2002 glucose tolerance survey (Paper I) information on socioeconomic background, health behaviour and medical history was collected sending a standardised, self-administered questionnaire to those who were invited to participate in the study. In addition to the socioeconomic background the postal questionnaire included questions about health habits including smoking, consumption of alcohol, chronic diseases and medical treatments. Chronic diseases were identified by asking if the subjects had suffered any medical conditions (myocardial infarction, angina pectoris, stroke, cerebral haemorrhage, cerebral vascular thrombosis, elevated BP or manifest or latent diabetes) diagnosed by a physician during the past 12 months, or whether they had undergone a coronary bypass operation or angioplasty or used antihypertensive, antidiabetic or cholesterol-lowering drugs (Laatikainen *et al.* 2003b).

In the FIN-D2D 2004–2005 survey (Paper II), the contents and structure of the postal questionnaire was very similar to that in the FINRISK 2002 survey. The FIN-D2D high risk cohort data (Papers III and IV) were collected with the FIN-D2D basic questionnaire and three different FIN-D2D forms; the FIN-D2D data

collection form, the FIN-D2D doctor visit collection form, and the FIN-D2D intervention form.

The FIN-D2D basic questionnaire elicited information about medical history, smoking, nutrition, exercise, other physical activity, and general well-being. The contents and structure of the FIN-D2D basic questionnaire were modified from the postal questionnaire used in FINRISK 2002 and the FIN-D2D survey 2004–2005 so that it could be used not only for assessing an individual's total risk for T2DM and CVD risk factors but also in the practical planning of lifestyle intervention measures. The health status section included questions about respondents' history and family history of diabetes. The history of previous diseases and abnormalities, as well as the medications used, based on self-report. Smoking habits were also ascertained. The FIN-D2D high risk cohort participants were asked to complete the FIN-D2D basic questionnaire prior to the clinical examination.

The FIN-D2D data collection form included information about type and date of visit, health care professional receiving the visit, the total count of the diabetes risk test score, the reason for referral to the FIN-D2D project, earlier prescribed medication, information on the results of the clinical examination during the visit, the results of the laboratory measurements and the selected mode of lifestyle intervention agreed together with the health care provider and the subject at high risk of diabetes.

The FIN-D2D data collection form also elicited information on the reasons other than the FINDRISC score value for referral to the FIN-D2D project, such as coronary artery disease or other CVD, earlier diagnosis of IFG or IGT, and gestational diabetes. The FIN-D2D data collection form was completed in by health care professionals.

The form included information about the date of visit to the doctor, classification of glucose metabolism based on the results of the OGTT, diabetes complications diagnosed previously or during the current visit, and new prescriptions during the current visit. The FIN-D2D doctor visit collection form was completed by the physician.

The FIN-D2D intervention form included information about the date of the visit, mode of intervention (group or individual counselling), advisors (public primary health care nurse, occupational health nurse, other nurse, diabetes nurse, physician, physiotherapist, dietitian, psychologist or other) and mapping and follow-up form for lifestyle changes including the three main goals according to the stages of change (Prochaska *et al.* 1983). The FIN-D2D intervention visit

form was used during the interventions and completed filled by the intervention advisors.

The modified Finnish Diabetes Risk Score (FINDRISC) was used to predict the risk of T2DM (Lindström *et al.* 2003). The questionnaire form contains eight questions with categorised answers on age, BMI, waist circumference, physical activity, consumption of fruits, berries or vegetables, history of antihypertensive medication, history of high blood glucose, and family history of diabetes. The threshold for high risk of diabetes (Papers III and IV) was 15 or above. The one-page FINDRISC form was completed during the examination visit if not done earlier, at which time the completion was checked by the nurse and the result of the test was discussed together with the participant.

4.3 Clinical interviews and examinations

In the FINRISK 2002 survey according to the FINRISK survey protocol (Laatikainen *et al.* 2003b) BP was measured three times at one-minute intervals from the right arm of the sitting subject after five minutes' rest using a standard mercury sphygmomanometer with a cuff size of 14 cm x 40 cm. The mean of the measurements was used in the analysis. SBP was recorded at the first sound heard and DBP at Korotkoff's fifth sound (Paper I).

Height, body weight, BP, and waist circumference were measured by trained nurses. For the measurement of body weight and height the subjects wore light clothing and no shoes. Waist circumference was measured midway between the lowest ribs and the iliac crest during expiration. Additional measure was BMI (Paper I).

In the FIN-D2D 2004–2005 survey (Paper II) the content of the clinical examination was similar to that in the FINRISK 2002 survey. All measurements were performed by trained nurses.

In the FIN-D2D high risk cohort (Papers III and IV) the measurements were instructed to be carried out according to the working instructions in the Project Plan (Suomen Diabetesliitto 2004, Finnish Diabetes Association 2006) by local nurses. BP was instructed to be measured according to the current Finnish guidelines on hypertension (Suomen Verenpaineyhdistys ry:n asettama työryhmä 2002). BP was instructed to be measured two times at one-minute interval from the right arm of the sitting subject after five minutes' rest using a standard mercury sphygmomanometer or electronic BP measurement device with the recommended cuff size (minimum width 40% and minimum length 80% of the

upper arm circumference). The mean of two measurements was used in the analysis. Height was instructed to be measured to the nearest centimetre in standing position the feet of the subject together on a firm base using a fixed measure of length. For the measurement of body weight the subjects were instructed to wear light clothing and no shoes. Weight was instructed to be measured to the nearest 0.1 centimetre. Waist circumference was instructed to be measured to the nearest centimetre on bare skin midway between the lowest ribs and the iliac crest during expiration.

An integrative model of stages of change by Prochaska and DiClemente (Prochaska *et al.* 1983) for readiness for lifestyle changes was used during the interviews with the participant to predict the subject's response to lifestyle counselling before the start of lifestyle interventions. During the interviews the high-risk subject and the advisor together agreed on the form of lifestyle intervention needed for risk reduction.

4.4 Laboratory measurements

In the FINRISK 2002 survey OGTT was carried out according to the WHO recommendations (WHO 1999). A 300 ml test solution containing 75 g anhydrous glucose and 1.6 g citric acid was used. The test started after 12-hour fast, and the two-hour blood sample was obtained 120 minutes after ingestion of the solution. Fasting and two-hour samples for plasma glucose determination were drawn into fluoridated tubes and centrifuged within 30 minutes.

Plasma glucose was determined with a dehydrogenase method (ABX Diagnostics, Montpellier, France). The serum insulin concentration was measured by a microparticle enzyme immunoassay (Axsym, Abbot Diagnostics Division, Wiesbaden, Germany). Serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by enzymatic assay (Thermo Electron Corporation, Vantaa, Finland). All assays were performed at the Laboratory of Analytical Biochemistry in the National Public Health Institute, Helsinki. The concentration of Low-Density Lipoprotein (LDL) cholesterol was calculated by the Friedewald formula (Friedewald *et al.* 1972). In the FIN-D2D 2004–2005 survey the laboratory examinations were performed very similarly as in the FINRISK 2002 survey.

In the FIN-D2D, the examination included an OGTT with a glucose load of 75 g and fasting and 2-hour plasma samples (WHO 1999) performed in the local health care centre or occupational health care centre laboratories. The subjects

received written instructions on preparing for the test (Suomen Diabetesliitto 2004). OGTT started in the morning after overnight fasting. Glucose tolerance was classified according to the WHO 1999 criteria (WHO 1999). Appropriate threshold values were used by sample source (plasma or whole blood) as well by sampling location (venous or capillary). The values for the test interpretation were given in the Project Plan (Suomen Diabetesliitto 2004). In total 20% of the tests used capillary and 80% venous plasma samples at baseline, and 15% and 85% respectively at 1-year follow-up.

For lipid determinations fasting venous blood samples were drawn. Serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were determined in the local health care centre or occupational health care centre laboratories using enzymatic methods. (LDL) cholesterol was calculated according to Friedewalds formula (Friedewald *et al.* 1972). All laboratories participated in the national External Quality Assessment Schemes organised by Labquality Ltd. (www. labquality.fi), and the measurements met the national primary health care standards.

4.5 Definitions and formation of variables

Body mass index (BMI) was calculated as weight (kg) divided by height^2 (m^2). Central obesity was defined with the WHO criteria (WHO 2000); waist circumference ≥ 102 cm and ≥ 88 cm in men and women respectively. In addition, the waist criteria for central obesity of ≥ 94 cm in men and ≥ 80 cm in women used in the IDF-definition of metabolic syndrome was also used (Alberti *et al.* 2006).

Glucose tolerance was classified according to the WHO 1999 criteria (WHO 1999). Individuals who did not have T2DM, and had fasting glucose ≥ 7.0 mmol/L or 2-hour plasma glucose ≥ 11.1 mmol/L were classified as having ST2DM. Those with 2-hour plasma glucose ≥ 7.8 and < 11.1 mmol/L, and fasting plasma glucose < 7.0 mmol/L were classified as having IGT. IFG was defined as fasting plasma glucose ≥ 6.1 mmol/L but < 7.0 mmol/L, and 2 hour plasma glucose < 7.8 mmol/L. Individuals with ST2DM, IGT or IFG were classified as AGT. The classification of glucose tolerance in the present study was based on one OGTT.

Metabolic syndrome was defined according to the American National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria (U.S. Department of Health and Human Services 2002) and by the American National

Cholesterol Education Program (NCEP) modified criteria (Grundy *et al.* 2005), and the International Diabetes Federation (IDF) 2005 criteria (Alberti *et al.* 2006).

Individuals fulfilling at least three of the following conditions were classified as having metabolic syndrome by the NCEP criteria: waist circumference > 102 cm in men and > 88 cm in women; triglycerides ≥ 1.7 mmol/L; HDL-cholesterol < 1.04 mmol/L in men and < 1.29 mmol/L in women; systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or medication for high blood pressure; fasting plasma glucose ≥ 6.1 mmol/l.

Individuals were classified as having metabolic syndrome by the IDF criteria (Alberti *et al.* 2006) if the following criteria were fulfilled: Central obesity defined as a waist circumference ≥ 94 cm for men and ≥ 80 cm for women plus any two of the following four factors: 1) Elevated triglyceride level: > 7 mmol/L, or specific treatment for this abnormality 2) Reduced HDL-cholesterol < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality 3) Elevated BP: systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension 4) Elevated fasting glucose ≥ 5.6 mmo/L, or previously diagnosed T2DM.

The risk of CVD morbidity was predicted by the Framingham Study risk equation (Anderson *et al.* 1991). The cutoff point of 20% or over in a ten-year period was used for definition of high risk. The risk of the CVD mortality was predicted by the Systematic Coronary Risk Evaluation (SCORE) formula (Conroy *et al.* 2003). A cutoff point of 5% or over in the course of ten years was used for the definition of high risk.

4.6 Intervention visits

All individuals screened for being at high risk for type 2 diabetes in the FIN-D2D were offered lifestyle counselling interventions. The options were participation in the group sessions, individual counselling visits, self-administered lifestyle change or other type of intervention (Suomen Diabetesliitto 2004, Finnish Diabetes Association 2006).

Basic lifestyle counselling for high-risk individuals was planned to be carried out primarily in groups of several (8–10) individuals four times at intervals of 1–2 weeks. The fifth follow-up visit was planned to take place one month after the last intervention visit. The frequency of intervention visits varied among health centres depending on local circumstances and resources. The agenda and methods used in the sessions were planned and agreed together with participants and a

multiprofessional team (nurse, physican, dietitian, physiotherapist, and psychologist, the composition depending on local resources).

The methods used depended on the experience of the healthcare providers and tools available. Counselling was tailormade and based on the idea of empowerment. Different topics in type 2 diabetes, such as weight control, exercise, and psychosocial factors were addressed during the sessions. The focus of the visits was on weight, meal frequency, fat intake, quality of fat, use of salt, fibre intake, consumption of alcohol, exercise, and smoking, depending on which topic the individual at risk preferred. The emphasis in the groups varied from weight maintenance to exercise groups. The programme might include lectures on diabetes and lifestyle changes.

Nurses lead these groups. For every participant, an individual intervention plan was tailored for which the application of different stages of change in behaviour was recommended (Prochaska 1983). Groups were real peer groups where experiences could be exchanged and support and positive feedback received. The ultimate target was to lose weight by small changes.

In individual counselling groups the methods and agenda were generally the same but were carried out in more confidential sessions between a client and a health care provider. Some high-risk individuals wanted to start lifestyle changes in their own way by self-acting and they were only given instructions on services available in the area. Interventions were also carried out in the third sector outside healthcare.

4.7 Ethical questions

The Ethics Committee for Research in Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa approved the study protocols of the FINRISK 2002 survey and the FIN-D2D survey 2004−2005. All participants gave their written consent prior participation to the study.

FIN-D2D was an incentive measure in public health undertaken as part of normal daily practice in primary health care. The participating hospital districts established the FIN-D2D data collection system as part of the normal patient records in primary health care. As participating in the FIN-D2D was voluntary and diabetes prevention an essential part of the regular health care, the participants were not asked to provide any written consent but they were given the written information on the FIN-D2D and ways to prevent diabetes. The Ministry of Health and Welfare (currently the Ministry of Social Affairs and

Health) granted the National Health Institute (currently the National Institute of Health and Welfare) to collect health information in participating FIN-D2D centres for project evaluation.

4.8 Statistical methods

In the analyses the statistical methods established as relevant for the study designs and variables were used. New methods were not developed. Mean values and standard deviations (SD) were calculated for the baseline characteristics.

To assess the FINDRISC test characteristics, sensitivity, false-positive rate, positive and negative predictive values were calculated. Confidence intervals for these measures were calculated using exact methods, and from these constructed receiver operating characteristics (ROC) curves were generated. Continuous variables were presented as means and class variables as percentages. Confidence intervals were stated. Analyses were performed using the statistics package Stata, Release 8.0 (Stata Corp. 2003).

Differences in glucose regulation by age group, and in different obesity and central obesity classes were analysed by stepwise logistic regression analysis. Odds ratios for abnormal glucose regulation were calculated using the lowest obesity or central obesity category as the reference group. Analyses were done separately for both sexes, and adjusted for age and geographical area of residence. The estimates of total prevalences in the whole study population were calculated taking into account the stratified sampling design used in the study and standardizing the result to the age distribution of the whole population. Analyses were performed with the statistics package Stata, Release 9.0 (Stata Corp. 2005).

One-way analysis of variance (ANOVA) and Chi-square test were used for comparison of grouped data. The Cochran-Armitage test for trend (Armitage 1955) was used to examine the predicted CVD morbidity and mortality (linear trend) against different glucose tolerance categories and age groups. SAS (version 9.2) for Windows was used for all statistical analyses.

Analysis of covariance (ANCOVA) was used to compare means of risk factor levels at follow-up with means at baseline adjusting for age. Mixed models of repeated analyses were used to analyse changes during follow-up in risk factor levels according to weight loss groups (weight loss ≥ 5%, weight loss 2.5–4.9%, stable weight, and gained ≥ 2.5%), adjusting for age: stable weight was used as the control group. The likelihood ratio test was used to compare differences of probabilities of incident diabetes according to weight loss. Risk ratios with 95%

CI were calculated by log-binominal regression analysis to examine the association between incident diabetes and weight loss.

5 Results

5.1 The Finnish Diabetes Risk Score (FINDRISC) as a screening tool for prevalent undiagnosed type 2 diabetes and other abnormalities of glucose metabolism (Paper I)

The FINDRISC was evaluated in the FINRISK 2002 glucose tolerance survey for undiagnosed T2DM and AGT. The formation of FINRISK 2002 glucose tolerance survey population is presented in Figure 1. Basic characteristics of the participants are presented in Paper I in Table 1. The prevalence of ST2DM and AGT increased parallel with the increasing score value (Figure 4). The increase in prevalence of ST2DM was curvilinear and that of AGT more linear, especially in men. The prevalence of ST2DM in men was two times higher than in women (11.5% vs. 6.4%) and the prevalence of AGT also higher in men (50.6% vs 33.3%).

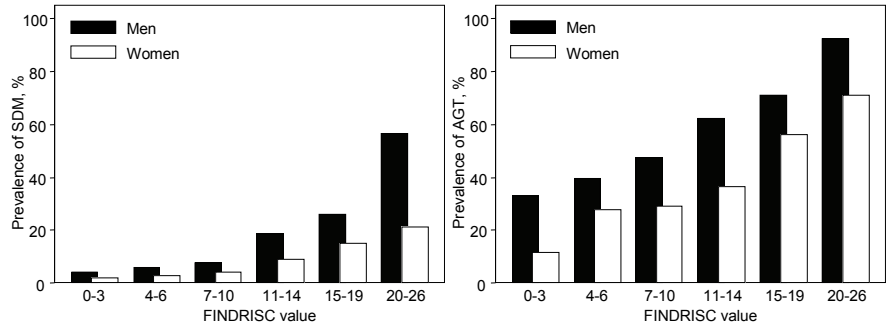

Fig. 4. Prevalence of screen-detected type 2 diabetes (SDM) and abnormal glucose tolerance (AGT) by gender and FINDRISC values in the FINRISK-2002 survey. Data are age-standardised to the population of 45–74-year-olds in Finland.

Basic test characteristics of the FINDRISC as a screening tool for prevalent T2DM and AGT are presented in Table 8.

In the study sample one third of men and 40% of women had FINDRISC scores of 11 or above whereas only one tenth of men and one eighth of women had a FINDRISC score of 15 or over. Sensitivity, false-positive rate, positive predictive value, and negative predictive value were calculated for ST2DM and AGT with the three cutoff values of 11, 13, and 15, and for both sexes. With a cutoff value of 11 the sensitivity of FINDRISC was better for ST2DM than AGT and better for women than men. With increasing cutoff values of up to 13 and 15

the sensitivity for ST2DM and AGT decreased but was still better for ST2DM than AGT, and better for women than men. Correspondingly, negative predictive value (NPV) was highest with a cutoff value of 11 and highest in women. Positive predictive value (PPV) was lowest with a cutoff value of 11 and lowest for women.

Table 8. Characteristics of FINDRISC using different cutoff values for screen-detected type 2 diabetes and abnormal glucose tolerance. The FINRISK-2002 survey.

Glucose tolerance	Sensitivity	False-positive rate	PPV	NPV	% of study sample[a]	% of population[b]
SDM						
cutoff = 11						
Men	66.1 (58.3–73.8)	30.9 (28.2–33.5)	21.7 (17.8–25.5)	94.0 (92.4–95.6)	34.8	12.4
Women	70.0 (60.6–79.5)	38.6 (36.1–41.1)	11.4 (8.9–13.8)	96.0 (94.7–97.4)	40.5	14.6
cutoff = 13						
Men	44.6 (36.5–52.7)	17.3 (15.2–19.5)	25.3 (19.8–30.8)	92.1 (90.4–93.7)	20.5	7.3
Women	54.5 (44.3–64.7)	24.6 (22.4–26.7)	14.0 (10.5–17.5)	95.5 (94.3–96.8)	26.5	9.5
cutoff = 15						
Men	29.8 (22.2–37.3)	9.3 (7.7–11.0)	29.6 (22.0–37.2)	90.8 (89.1–92.5)	11.7	4.2
Women	37.7 (27.9–47.6)	14.9 (13.1–16.7	15.5 (10.8–20.2)	94.6 (93.4–95.9)	16.3	5.9
AGT	Sensitivity	False-positive rate	PPV	NPV		
cutoff = 11						
Men	45.6 (41.7–49.5)	24.6 (21.3–27.9)	65.9 (61.5–70.4)	57.7 (54.4–61.0)		
Women	53.4 (49.1–57.7)	34.2 (31.3–37.1)	45.2 (41.3–49.1)	72.4 (69.6–75.3)		
cutoff = 13						
Men	27.8 (24.4–31.3)	13.4 (10.8–16.0)	69.7 (63.9–75.5)	54.4 (51.4–57.4)		
Women	39.4 (35.3–43.6)	19.9 (17.4–22.4)	52.1 (47.0–57.3)	71.4 (68.8–74.0)		
cutoff = 15						
Men	16.9 (14.0–19.8)	6.6 (4.7–8.6)	74.2 (67.0–81.4)	52.8 (49.9–55.6)		
Women	26.7 (22.9–30.4)	11.9 (9.9–14.0)	57.3 (50.7–63.8)	69.7 (67.2–72.1)		

Data are percentages (95% CI).

PPV = positive predictive value; NPV = negative predictive value; [a] = Proportion of the study sample with risk score above the cutoff value; [b] = Proportion of the population with risk score above the cutoff value

The area under the receiver-operating (ROC) curve (aROC) for ST2DM was 0.72 in men and 0.73 in women, and aROC for AGT was 0.65 in men and 0.66 in women respectively (Figure 5).

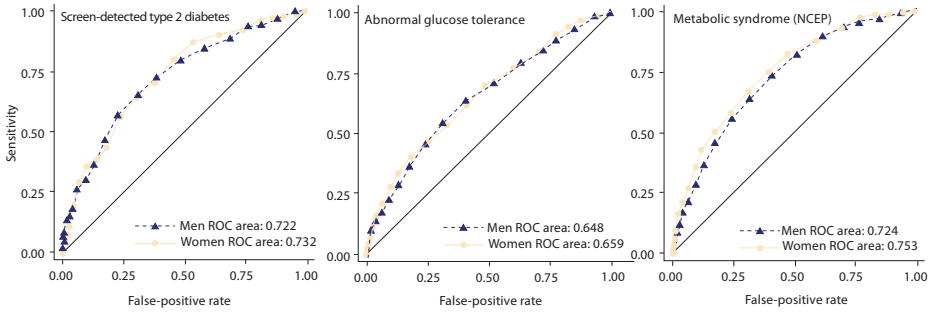

Fig. 5. Receiver operating characteristics (ROC) curves for the prevalence of screen-detected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome (NCEP criteria) by gender and FINDRISC values. Data are taken from the FINRISK-2002 survey.

5.2 Association of the FINDRISC score with the prevalence of metabolic syndrome and cardiovascular risk factors (Paper I)

In men, the proportion of individuals classified to have metabolic syndrome according to the NCEP criteria increased from 10% in the lowest FINDRISC category of 0–3 points to 83% in the highest category of 20–26 points (Table 9).

Table 9. Cardiovascular risk factor profile by gender and FINDRISC values. Data are taken from the FINRISK-2002 survey.

Risk factors	FINDRISC value						p value[a]
	0–3	4–6	7–10	11–14	15–19	20–26	
Men							
Age, years	52.2	57.3	58.0	58.8	59.8	61.0	< 0.001
BMI, kg/m^2	24.2	25.6	27.6	29.4	30.6	33.5	< 0.001
Waist circumference, cm	87.3	91.9	98.0	102.6	106.3	110.9	< 0.001
Plasma glucose, 0h, mmol/l	5.8	5.9	6.0	6.3	6.4	7.3	< 0.001
Plasma glucose, 2h, mmol/l	5.6	6.3	6.6	7.6	8.5	10.8	< 0.001
Serum Insulin, 0h, mmol/l	5.9	7.8	8.8	11.3	14.0	15.8	< 0.001
Total cholesterol, mmol/l	5.7	5.8	5.8	5.8	5.7	5.5	0.959
HDL cholesterol, mmol/L	1.47	1.43	1.35	1.27	1.27	1.20	< 0.001
Triglycerides, mmol/L	1.35	1.45	1.68	1.93	1.89	2.27	< 0.001
Systolic BP, mmHg	134.4	140.3	141.1	144.5	146.4	149.9	< 0.001
Diastolic BP, mmHg	80.3	81.2	83.2	85.3	85.3	85.0	< 0.001
MBS (NCEP), %	9.7	13.3	32.2	50.6	56.9	82.6	< 0.001
Women							
Age, years	53.4	55.5	56.7	57.3	58.8	60.3	< 0.001
BMI, kg/m^2	23.2	24.5	26.9	29.3	31.6	34.2	< 0.001
Waist, circumference, cm	75.5	79.1	84.5	91.2	97.8	102.1	< 0.001
Plasma glucose, 0h, mmol/l	5.4	5.6	5.6	5.7	6.0	6.3	< 0.001
Plasma glucose, 2h, mmol/l	5.7	6.3	6.5	6.9	8.1	8.8	< 0.001
Serum insulin, 0h, mmol/l	5.6	6.6	8.0	9.7	11.9	12.5	< 0.001
Total cholesterol, mmol/l	5.7	5.7	5.8	5.8	5.9	5.6	0.138
HDL cholesterol, mmol/L	1.81	1.77	1.66	1.63	1.57	1.60	< 0.001
Triglycerides, mmol/L	1.12	1.11	1.28	1.40	1.54	1.56	< 0.001
Systolic BP, mmHg	126.0	135.0	138.6	140.5	144.8	148.6	< 0.001
Diastolic BP, mmHg	75.7	78.5	80.1	80.9	82.4	83.2	< 0.001
MBS (NCEP), %	2.8	8.4	1736	31.4	51.1	73.5	< 0.001

Data are means except where noted otherwise. MBS = metabolic syndrome; [a] = p-values for test of linear trend; adjusted for age; BMI = body mass index; HDL = high-density lipoprotein; NCEP = National Cholesterol Education Program; BP = blood pressure

The aROC of the FINDRISC for the metabolic syndrome was 0.72 in men and 0.75 in women (Figure 5). All CVD risk factors apart from total cholesterol had a strong direct association with the FINDRISC value (Table 9).

5.3 Prevalence of obesity, central obesity, abnormal glucose tolerance, and the distribution of FINDRISC values in middle-aged Finnish population (Paper II)

The formation of the FIN-D2D 2004–2005 survey population is presented in Figure 2. The prevalence of obesity (BMI ≥ 30 kg/m^2) was 24% in men, and 28% in women in this population aged 45–74 years. Obesity and central obesity increased with age in both sexes (Table 11). The distribution of the FINDRISC values according to age group and sex are presented in Table 11. The percentage of individuals with FINDRISC value of ≥ 15 was 12% and 15% in the age group of 45–54-year-old men and women respectively, and was 26% and 33% in the age-group of 65–74 years respectively (Table 1).

Prevalence of total type 2 diabetes including diagnosed and undiagnosed diabetes was 16.4% in men and 11.2% in women (Table 10). Prevalence of total type 2 diabetes increased from 9% in the youngest age-group to 25% in the oldest age-group of men, and from 5% to 20% in the respective age groups of women. (Table 10). Screen-detected diabetes accounted for 57% in men and 65% in women of all prevalent cases of T2DM. AGT was observed in 42% of men and in 33% of women. Accordingly, the prevalence of AGT including diabetes, increased with age in both sexes.

Table 10. Prevalence (95% confidence interval, CI) of type 2 diabetes (T2D), screen-detected type 2 diabetes (ST2D), total type 2 diabetes (TT2D), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), abnormal glucose tolerance (AGT = TT2D, IGT, or IFG) in the study sample according to sex and age groups.

Abnormal	Men					Women				
glucose tolerance	45–54	55–64	65–74	Total	p*	45–54	55–64	65–74	Total	p*
n	405	485	474	1364		479	511	471	1461	
T2D, %	2.7	8.2	12.2	7.1	< 0.001	2.3	3.5	8.3	3.9	< 0.001
95% CI	(1.4–4.8)	(6.0–11.1)	(9.4–15.5)	(5.7–8.5)		(1.2–4.1)	(2.1–5.5)	(6.0–11.1)	(2.9–4.9)	
ST2D, %	5.9	8.7	12.7	9.3	0.002	2.5	8.0	12.1	7.3	< 0.001
95% CI	(3.8–8.7)	(6.3–11.5)	(9.8–16.0)	(7.7–11.0)		(1.3–4.3)	(5.8–10.7)	(9.3–15.4)	(5.9–8.7)	
TT2D, %	8.6	16.9	24.9	16.4	< 0.001	4.8	11.5	20.4	11.2	< 0.001
95% CI	(6.1–11.8)	(13.7–20.5)	(21.1–29.0)	(14.3–18.5)		(3.1–7.1)	(8.9–14.6)	(16.8–24.3)	(9.6–12.8)	
IGT, %	7.9	15.1	23.8	15.5	< 0.001	10.4	15.1	25.1	17.0	< 0.001
95% CI	(5.5–11.0)	(12.0–18.5)	(20.1–27.9)	(13.5–17.6)		(7.8–13.5)	(12.1–18.5)	(21.2–29.2)	(15.0–19.1)	
IFG, %	9.9	12.4	5.9	10.0	0.002	5.2	5.1	4.2	5.2	0.746
95% CI	(7.2–13.2)	(9.6–15.6)	(4.0–8.4)	(8.2–11.8)		(3.4–7.6)	(3.4–7.4)	(2.6–6.5)	(3.9–6.5)	
AGT, %	26.4	44.3	54.6	42.0	< 0.001	20.5	31.7	49.7	33.4	< 0.001
95% CI	(22.2–31.0)	(39.9–48.9)	(50.0–59.2)	(39.2–44.8)		(16.9–24.4)	(27.7–35.9)	(45.1–54.3)	(30.9–36.0)	

*p-values are for test of equivalence (likelihood-ratio test) between the three age-groups

Total is an estimate of the population prevalence in the age group 45–74 years, taking into account the stratified sampling used in the study.

5.4 Associations of obesity with abnormal glucose tolerance (Paper II)

The associations of BMI with abnormal glucose tolerance are presented in Figure 6. Men and women classified as obese (BMI ≥ 30 kg/m^2) had a 5-fold increased risk for T2DM compared with normal weight people.

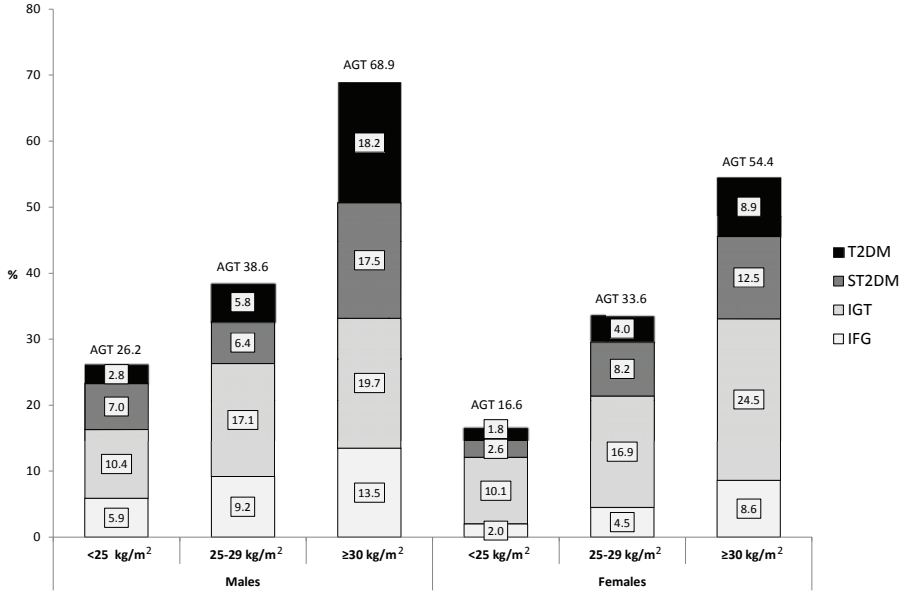

Fig. 6. Prevalence of previously known type 2 diabetes (T2DM), screen-detected type 2 diabetes (ST2DM), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and abnormal glucose tolerance (AGT) of the study sample to BMI category (< 25 kg/m^2, 25–29 kg/m^2, ≥ 30 kg/m^2) and gender.

Central obesity, measured by large waist circumference, was associated with AGT in overweight and obese categories (Figure 7).

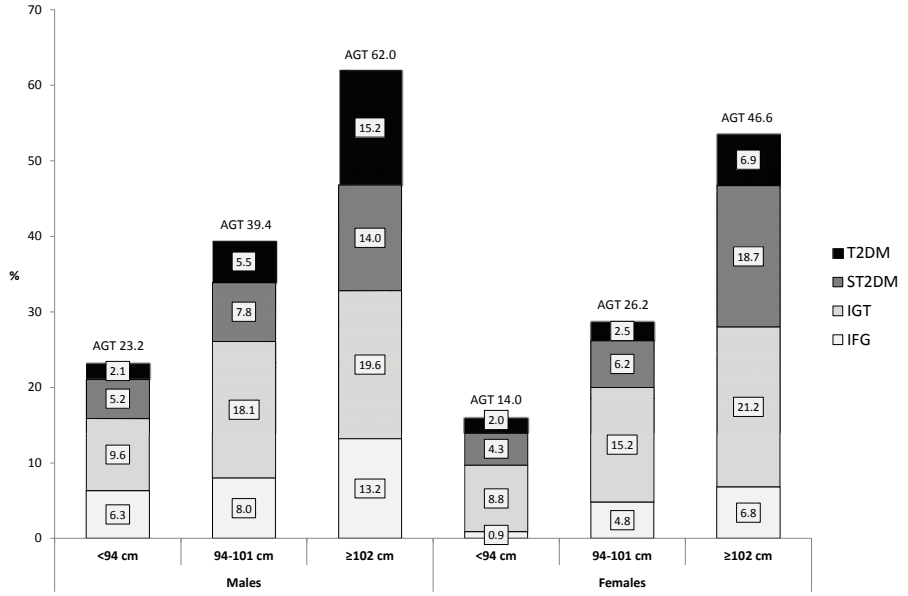

Fig. 7. Prevalence of previously known type 2 diabetes (T2DM), screen-detected type 2 diabetes (ST2DM), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and abnormal glucose tolerance (AGT) of the study sample to waist circumference (< 94 cm, 94–101 cm, ≥ 102 cm) and gender.

Table 11. Characteristics of the FIN-D2D Survey 2004–2005 participants according to sex and age group.

Age groups	Men				Women			
	45–54	55–64	65–74	Total	45–54	55–64	65–74	Total
Participants, n	405	485	474	1,364	479	511	471	1,461
Age, years (SD)	50.2 (2.8)	59.6 (2.8)	69.5 (2.9)	60.3 (8.3)	50.2 (2.9)	59.5 (2.8)	70.1 (2.8)	59.8 (8.5)
Weight, kg (SD)	86.2(14.8)	86.8 (14.9)	83.5 (13.6)	85.8(14.5)	72.3 (13.8)	73.4(13.8)	72.6(13.8)	72.7 (13.8)
BMI, kg/m^2 (SD)	27.3 (4.2)	27.9 (4.2)	27.7 (4.0)	27.6 (4.1)	27.0 (5.0)	27.8 (5.1)	28.4 (5.2)	27.6 (5.2)
BMI < 25 kg/m^2, %	31.1	23.3	24.5	26.8	40.5	34.4	26.3	34.7
BMI 25–29 kg/m^2, %	48.1	51.5	50.4	49.7	35.9	36.6	40.6	37.3
BMI > 30 kg/m^2, %	20.7	25.2	25.1	23.5	23.6	29.0	33.1	28.0
Waist, cm (SD)	97.3(11.9)	100.3 (12.0)	99.9 (11.4)	99.3(11.8)	87.6 (12.9)	90.3(13.3)	91.5(13.7)	89.6 (13.4)
FINDRISC score (*) mean (SD)	8.7 (4.7)	10.8 (5.0)	11.5 (5.0)	10.4 (5.1)	9.7 (4.6)	11.4 (5.0)	12.5 (4.7)	11.2 (4.9)
FINDRISC score 0–6, %	34.4	17.5	16.2	22.2	23.4	16.2	8.8	16.2
FINDRISC score 7–4, %	53.4	58.7	58.2	56.9	61.2	56.9	58.2	58.7
FINDRISC score ≥ 15, %	12.2	23.8	25.6	21.0	15.5	27.0	33.0	25.1

(*) previous unpublished data

5.5 Prevalence of type 2 diabetes and other abnormalities of glucose tolerance in the FIN-D2D high risk cohort (Paper III)

The formation of the FIN-D2D high risk cohort is presented in Figure 3. In total 51% of men and 57% of women entered the diabetes prevention project due to a FINDRISC score of ≥ 15. Altogether 8% of men and 2% of women were included in the high risk cohort due to a history of coronary artery disease or other CVD, 13% of women on the basis of gestational diabetes and 34% of men and 21% of women because of a history of IFG or IGT.

Altogether 35% of men and 29% of women of the cohort were overweight (BMI 25–29.9 kg/m^2), 40% of men and 35% of women obese (BMI 30–34.9 kg/m^2 (Obese class I, WHO 2000), 15% of men and 18% of women severely obese (BMI 35–39.9 kg/m^2) (Obese class II, WHO 2000), and 5% of men and 9% of women morbidly obese (BMI ≥ 40 kg/m^2) (Obese class III, WHO 2000) (unpublished data). Up to 66% of men and 82% of women were centrally obese due to waist circumference criteria of > 102 cm and > 88 cm respectively.

The prevalence for ST2DM was 19% for men and 12% for women. Total prevalence of AGT (including IFG, IGT, T2DM and ST2DM) was 68% for men and 49% for women.

5.6 Cardiometabolic profile in the FIN-D2D high risk cohort (Paper III)

Over half of men (55%) and women (58%) had elevated measured cholesterol values (≥ 5 mmol/l) and two-thirds (78% of men and 67% of women) elevated BP of > 135/85 mmHg. The proportion of regular smokers was 17% among men and 10% among women. Altogether 17% of men and 12% of women were taking cholesterol-lowering medication, and 5% of men and 3% of women had medication for coronary artery disease. One in four was taking antihypertensive medication.

At least half of the individuals in the high risk cohort had elevated levels of traditional CVD risk factors, which were partly untreated. Those included in the cohort due to CVD criteria had lower CVD risk factor levels compared with those included due to high FINDRISC score or IFG/IGT criteria (Table 12).

Table 12. Past self-reported medical history, prevalence of cardiovascular risk factors and regular medication in the high risk cohort by reason for referral to FIN-D2D (Data on women with a history of gestational diabetes not shown).

Medical history, CVD risk factors and medication	FINDRISC		CVD		IFG/IGT		Chi-Square test
	n	n (%)	n	n (%)	n	n (%)	p-value
Men							
Past medical history							
Elevated blood pressure, hypertension	1480	952 (64.3%)	218	132 (60.6%)	1004	589 (58.7%)	0.016
Heart failure/Cardiac insufficiency	1480	41 (2.8%)	218	22 (10.1%)	1004	39 (3.9%)	< 0.001
Coronary artery disease	1480	71 (4.8%)	218	121 (55.5%)	1004	56 (5.6%)	< 0.001
Stroke or TIA	1480	34 (2.3%)	218	30 (13.8%)	1004	30 (3.0%)	< 0.001
Intermittent claudication	1480	13 (0.9%)	218	8 (3.7%)	1004	12 (1.2%)	0.002
High or elevated cholesterol or other dyslipidaemia	1480	562 (38.0%)	218	130 (59.6%)	1004	429 (42.7%)	< 0.001
Depression or other psychiatric illness	1480	151 (10.2%)	218	16 (7.3%)	1004	105 (10.5%)	0.370
Reduced mobility	1480	158 (10.7%)	218	25 (11.5%)	1004	105 (10.5%)	0.908
Other chronic disease	1480	121 (8.2%)	218	20 (9.2%)	1004	98 (9.8%)	0.388
Prevalence of cardiovascular risk factor							
Current smoking	1474	259 (17.6%)	217	29 (13.4%)	995	174 (17.5%)	0.295
Serum total cholesterol ≥ 5mmol/L	1583	927 (58.6%)	239	59 (24.7%)	1119	629 (56.2%)	< 0.001
LDL cholesterol ≥ 2.5mmol/L	1503	1144 (76.1%)	233	104 (44.6%)	1058	789 (74.6%)	< 0.001
Serum triglycerides ≥ 1.7 mmol/L	1567	679 (43.3%)	236	89 (37.7%)	1100	500 (45.5%)	0.086
Blood pressure ≥ 135/85 mmHg	1680	1334 (79.4%)	252	159 (63.1%)	1147	908 (79.2%)	< 0.001
Regular medication							
Acetylsalicylic Acid	1709	158 (9.2%)	259	78 (30.1%)	1163	122 (10.5%)	< 0.001
Cholesterol-lowering medication	1709	265 (15.5%)	259	120 (46.3%)	1163	177 (15.2%)	< 0.001
Antihypertensive medication	1709	497 (29.1%)	259	68 (26.3%)	1163	264 (22.7%)	< 0.001
Coronary artery disease medication	1709	60 (3.5%)	259	64 (24.7%)	1163	28 (2.4%)	< 0.001

Medical history, CVD risk factors and medication	FINDRISC		CVD		IFG/IGT		Chi-Square test
	n	n (%)	n	n (%)	n	n (%)	p-value
Women							
Past medical history							
Elevated blood pressure, hypertension	3316	2021 (60.9%)	112	75 (67.0%)	1240	774 (62.4%)	0.320
Heart failure/Cardiac insufficiency	3316	44 (1.3%)	112	12 (10.7%)	1240	29 (2.3%)	< 0.001
Coronary artery disease	3316	96 (2.9%)	112	50 (44.6%)	1240	54 (4.4%)	< 0.001
Stroke or TIA	3316	93 (2.8%)	112	23 (20.5%)	1240	35 (2.8%)	< 0.001
Intermittent claudication	3316	13 (0.4%)	112	2 (1.8%)	1240	8 (0.6%)	0.078
High or elevated cholesterol or other dyslipidaemia	3316	1256 (37.9%)	112	64 (57.1%)	1240	543 (43.8%)	< 0.001
Depression or other psychiatric illness	3316	501 (15.1%)	112	13 (11.6%)	1240	218 (17.6%)	0.060
Reduced mobility	3316	435 (13.1%)	112	9 (8.0%)	1240	162 (13.1%)	0.288
Other chronic disease	3316	413 (12.5%)	112	15 (13.4%)	1240	120 (9.7%)	0.030
Prevalence of cardiovascular risk factor							
Current smoking	3301	314 (9.5%)	112	2 (1.8%)	1234	150 (12.2%)	< 0.001
Serum total cholesterol ≥ 5mmol/L	3571	2221 (62.2%)	123	41 (33.3%)	1351	780 (57.7%)	< 0.001
LDL cholesterol ≥ 2.5mmol/L	3509	2634 (75.1%)	122	54 (44.3%)	1314	929 (70.7%)	< 0.001
Serum triglycerides ≥ 1.7 mmol/L	3533	1027 (29.1%)	123	30 (24.4%)	1333	477 (35.8%)	< 0.001
Blood pressure ≥ 135/85 mmHg	3796	2749 (72.4%)	127	81 (63.8%)	1396	1009 (72.3%)	0.101
Regular medication							
Acetylsalicylic Acid	3860	280 (7.3%)	129	29 (22.5%)	1419	110 (7.8%)	< 0.001
Cholesterol-lowering medication	3860	463 (12.0%)	129	53 (41.1%)	1419	201 (14.2%)	< 0.001
Antihypertensive medication	3860	993 (25.7%)	129	29 (22.5%)	1419	332 (23.4%)	0.178
Coronary artery disease medication	3860	85 (2.2%)	129	28 (21.7%)	1419	40 (2.8%)	< 0.001
Antidepressive medication	3860	244 (6.3%)	129	7 (5.4%)	1419	88 (6.2%)	0.912

FINDRISC = Finnish Diabetes Risk Score. CVD = Previous myocardial infarction or other artery disease.

IFG/IGT = Diagnosed earlier with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

In total 43% of men were at high predicted risk of morbidity and 42% at high predicted risk of mortality for CVD. The proportion of women at high predicted risk of CVD morbidity or mortality was significantly lower; 13% and 11% respectively. Age increased the predicted risk of CVD morbidity and mortality in all glucose tolerance categories (p for trend < 0.001) (Figure 8). The presence of screen-detected diabetes markedly increased the predicted risk of CVD morbidity.

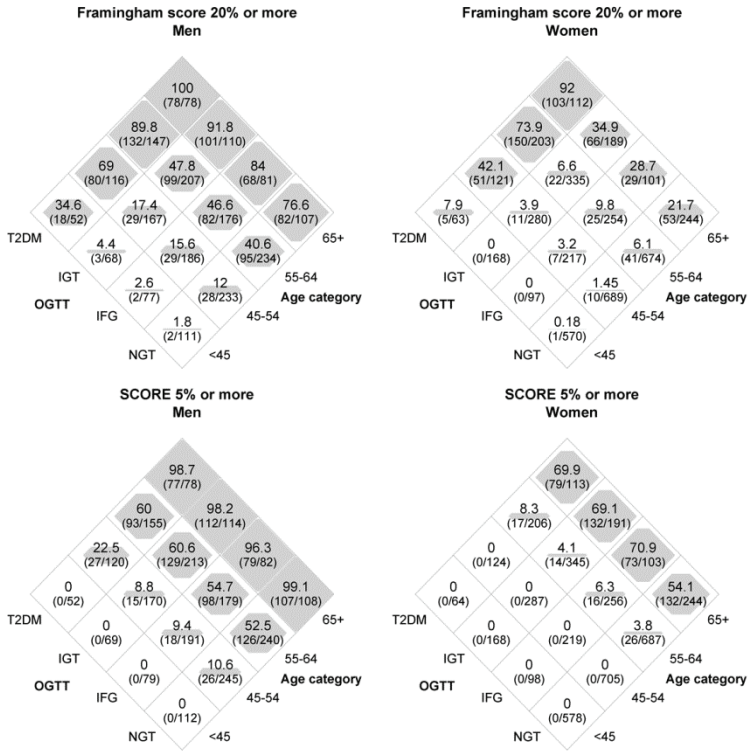

Fig. 8. Proportion of men and women with high predicted 10-year risk of CVD event (Framingham score 20% or more) and fatal CVD (SCORE 5% or more) by age category and glucose tolerance. NGT = normal glucose tolerance, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, ST2DM = screen-detected diabetes. In parenthesis number of individuals at high CVD risk versus total number of individuals in each age and glucose tolerance category.

5.7 Effect of lifestyle intervention on weight and its association with glucose tolerance at one-year follow-up in the FIN-D2D high risk cohort (Paper IV).

The formation of the FIN-D2D high risk cohort is presented in Figure 3. Non-participants did not differ from participants included in the cohort. The baseline characteristics of men and women at high risk for T2DM are presented in Table 13. The mean baseline weight was 96 kg for men and 84 kg for women. The mean baseline BMI was 31 kg/m^2 for men and 32 kg/m^2 for women. The mean FINDRISC score was 17.

Table 13. Baseline characteristics and changes in risk factors from baseline to one-year visit in men and women.

Characteristics and risk factors	Baseline		Change from baseline to one-year follow-up	
	N	Mean (SD)	Mean (SD)	p-value[1]
Men				
Age (years)	919	55.95 (9.88)	0.00 (0.00)	
FINDRISK Score	536	16.64 (3.66)		
Weight (kg)	919	95.77 (15.87)	−1.18 (5.30)	< 0.0001
BMI (kg/m^2)	914	30.95 (4.58)	−0.41 (1.55)	< 0.0001
Waist (cm)	888	107.32 (11.36)	−1.28 (4.94)	< 0.0001
Systolic BP (mmHg)	903	140.99 (16.15)	−0.83 (14.81)	0.0932
Diastolic BP (mmHg)	903	87.19 (9.61)	−1.52 (8.85)	< 0.0001
Total cholesterol (mmol/l)	822	5.06 (1.01)	−0.25 (0.86)	< 0.0001
HDL cholesterol (mmol/l)	814	1.25 (0.33)	0.02 (0.22)	0.0030
LDL cholesterol (mmol/l)	779	3.03 (0.87)	−0.23 (0.76)	< 0.0001
Triglycerides (mmol/l)	811	1.80 (1.19)	−0.11 (1.12)	0.0050
Women				
Age (years)	1,879	53.95 (10.66)	0.00 (0.00)	
FINDRISK Score	1,259	17.15 (2.99)		
Weight (kg)	1,879	83.76 (15.43)	−1.12 (5.77)	< 0.0001
BMI (kg/m^2)	1,872	31.63 (5.44)	−0.43 (2.11)	< 0.0001
Waist (cm)	1,821	99.37 (12.36)	−1.30 (5.86)	< 0.0001
Systolic BP (mmHg)	1,845	138.36 (17.77)	−1.89 (14.83)	< 0.0001
Diastolic BP (mmHg)	1,845	85.25 (9.22)	−1.58 (8.39)	< 0.0001
Total cholesterol (mmol/l)	1,658	5.24 (0.95)	−0.14 (0.79)	< 0.0001
HDL cholesterol (mmol/l)	1,639	1.50 (0.43)	0.04 (0.31)	< 0.0001
LDL cholesterol (mmol/l)	1,616	3.07 (0.86)	−0.16 (0.76)	< 0.0001
Triglycerides (mmol/l)	1,632	1.48 (0.77)	−0.03 (0.64)	0.0769

[1]p-value for ANCOVA comparing mean at follow-up to mean at baseline; analyses were adjusted for age.

Deterioration of glucose status to diabetic category in the participants at high risk of type 2 diabetes during a mean follow-up of 14 months was 2% among men and 1% among women with normoglycaemia at baseline, The corresponding figures in men and women who had IFG at baseline were 14% and 7%, and in men and women who had IGT at baseline 16% and 11%.

The mean weight loss in high risk individuals at 1-year follow-up was 1.3 kg in men and 1.1 kg in women. Altogether 17.5% of the participants lost ≥ 5% weight (Table 14).

Table 14. Changes in risk factors from baseline to one-year visit according to weight loss.

Risk factors	Weigt loss 5% or more		Weight loss 2.5–4.9%		Stable weight*		Gained 2.5% or more		Ancova p-value†
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	
Weight (kg)	490	−8.48 (6.48)‡§	471	−3.14 (0.90)‡§	1,290	−0.11 (1.20)	546	4.54 (3.70)‡§	< 0.001
BMI (kg/m^2)	489	−3.03 (2.25)‡§	470	−1.13 (0.33)‡§	1,285	−0.04 (0.46)	541	1.59 (0.99)‡§	< 0.001
Waist (cm)	477	−6.56 (6.08)‡§	449	−2.69 (4.19)‡§	1,258	−0.43 (4.18)	525	2.62 (5.08)‡§	< 0.001
sBP (mmHg)	480	−4.45 (14.42)‡§	464	−3.13 (15.35)‡§	1,267	−0.72 (14.45)	536	0.52 (15.12)‡	< 0.001
dBP (mmHg)	480	−3.78 (8.36)‡§	464	−2.16 (8.33)	1,267	−1.12 (8.41)	536	−0.06 (8.73)	< 0.001
Lipids (mmol/l)									
Cholesterol	438	−0.35 (0.78)	411	−0.23 (0.92)	1,148	−0.15 (0.78)	482	−0.02 (0.81)‡§	< 0.001
HDL cholesterol	430	0.10 (0.25)‡§	408	0.05 (0.29)	1,138	0.02 (0.27)	476	−0.01 (0.31)	< 0.001
LDL cholesterol	420	−0.33 (0.71)‡§	400	−0.22 (0.89)	1,111	−0.17 (0.72)	463	−0.07 (0.74)‡	< 0.001
Triglycerides	430	−0.29 (0.66)‡§	406	−0.15 (0.95)‡§	1,133	−0.01 (0.76)	473	0.12 (0.95)‡§	< 0.001

*Weight loss < 2.5% or weight gain <2.5%. †ANCOVA for overall and pairwise comparisons of mean changes between the groups; analyses were adjusted for age (‡) or for age and sex (§). ‡Pairwise comparisons between groups, P < 0.05 (stable weight served as the reference group). §Pairwise comparisons between groups, P < 0.05 (stable weight served as the reference group).

A total of 17% of the participants lost 2.5–4.9% weight and 46% maintained their weight. Only 20% of the participants gained weight ≥ 2.5%. The incidence of diabetes was linked to weight loss (Figure 9). The relative risk for diabetes was 0.31 in the group that lost 5% weight or more compared with the group that maintained weight. The relative risk for diabetes was 0.72 in the group that lost 2.5–4.9% weight and 1.10 in those who gained weight.

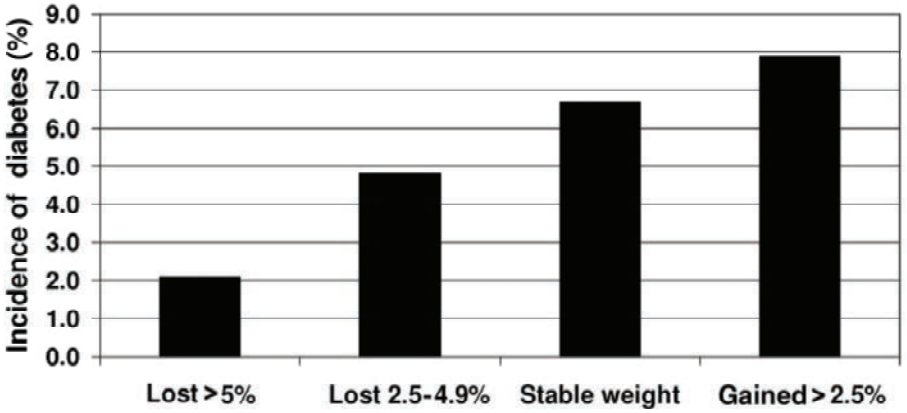

Fig. 9. Incidence of type 2 diabetes during the 1-year follow-up according to weight loss. Data are adjusted to age 50 years. P < 0.001 for the likelihood ratio test for the difference of probabilities according to weight loss.

Beneficial changes in risk factors for CVD were seen in individuals who lost weight. Their BP decreased, and the lipid and lipoprotein profile changed in a less atherogenetic direction. This was mainly seen in the group with the greatest weight loss (Table 14). The most beneficial change in the lipid and lipoprotein levels was seen in the group which lost 5% or more weight. Triglycerides reduced significantly even in the group with a weight loss of 2.5–4.9%. The decrease in systolic BP was more marked in women than in men, whereas the decrease in the diastolic BP was of similar magnitude in both sexes. There were no differences by sex in changes in lipid and lipoprotein levels.

Participants had on average 3 intervention visits during the 1-year follow-up, and 68% had at least one intervention visit. Among participants who had intervention visits, 51% had individual counselling visits only, 13% attended group sessions only, and 10% participated in both individual and group visits. In 26% of the participants information on the type of intervention was not available. The shares of individuals who had three or more, two, and one intervention visit were 29%, 13% and 26% respectively. Individuals in the group who lost ≥ 5%

weight had on average 4 intervention visits, whereas those who maintained weight had 3 intervention visits during follow-up.

In the present study most of the men and women participated in individual intervention sessions (88.7% and 77.8%, $p < 0.001$). Men with a low education and men who were not working participated more often in the lifestyle interventions than men with more education or men who were working (67.6% vs. 59.2%, $p = 0.009$) (unpublished data). A greater proportion of men who were not working had three or more intervention visits compared to men who were working (46.8% vs. 36.8%, $p = 0.004$) (unpublished data).

6 Discussion

The study presented here addresses the FINDRISC as a screening tool for prevalent undiagnosed T2DM, AGT and metabolic syndrome. The prevalence of AGT and obesity in the middle-aged population was analysed. The present study moreover describes the use of the FINDRISC in screening for individuals at high risk of T2DM in health care and at the community level and analyses the effect of lifestyle counselling offered in primary health care for people at high risk of T2DM aiming to prevent diabetes. Together the results build a solid base for the prevention of T2DM in the Finnish population.

6.1 Finnish Diabetes Risk Score (FINDRISC) as a screening tool for undiagnosed type 2 diabetes, the metabolic syndrome and abnormal glucose tolerance

The present study is the first evaluation of the FINDRISC in a cross-sectional setting. It shows that the FINDRISC has a good ability to predict undiagnosed prevalent T2DM, metabolic syndrome, and sligthly lower ability to predict AGT. FINDRISC can be used for screening for these conditions in addition to screening for incident T2DM, for which the score was originally developed. The ability of the FINDRISC to predict incident T2DM (aROCs 0.87) is known to be among the highest published (Lindström *et al.* 2003, Table 3).

The ability of the FINDRISC to predict prevalent T2DM is in line with the ability of other risk scores for prevalent T2DM (Table 2). The aROCs for the most prevalent and incident risk scores including nonivasive measures range from 0.7 to 0.85. A few studies have reported aROCS of less than 0.7 with risk models involving 3–4 variables. Recently the FINDRISC was updated using clinically diagnosed and screen-detected T2DM instead of drug-treated diabetes as an endpoint and by considering additional predictors to improve the accuracy (Alssema *et al.* 2011).

The ability of the FINDRISC to identify metabolic syndrome as defined by the NCEP criteria was as good as its ability to predict prevalent T2DM. For prevalent AGT the performance was weaker. The ability of the FINDRISC to identify undiagnosed T2DM depends on the cutoff value used and it is best with a cut-off value of 11.

If a cutoff point of ≥ 15 is used, as was used in the FIN-D2D in screening for individuals at high risk of T2DM, at least one third of men and one fifth of

women may have ST2DM. However, it also must be noted that the risk for having undiagnosed prevalent T2DM is also elevated by lower cut-off points and is rather high if the FINDRISC score exceeds 11. Thus, FINDRISC cannot be used for the diagnosis of T2DM but a diagnostic test such as OGTT is needed to confirm the presence or absence of any current glucose disorder.

To summarise, the prevalence of AGT is common and increases linearly with increasing FINDRISC score. The performance of the FINDRISC for prevalent T2DM is comparable to other published diabetes risk scores. FINDRISC can be used as a first step tool for prediction of prevalent T2DM and metabolic syndrome. The higher the cutoff value for high risk of diabetes in the FINDRISC is used, the higher is the prevalence of T2DM and AGT found in a diagnostic test.

6.2 Prevalence of abnormal glucose tolerance, obesity and the risk of type 2 diabetes in middle-aged Finnish population

In the present study every fourth middle-aged man and almost every third middle-aged woman was obese. This concurs with another recent population-based survey made in Finland which indicates that one in five Finnish adults is defined as obese (Lahti-Koski *et al.* 2007). In the FINRISK 2002 survey 25% of 45–64-year-old men and women were obese and 49% of men and 39% of women were overweight (Laatikainen 2003a).

Obesity increases the risk of type 2 diabetes. The present study shows clearly that glucose disorders are very common in Finnish middle-aged population, over 40% of men and over 30% of women having a glucose disorder. Such high prevalence numbers have not previously been reported in the Finnish population in this age-group.

The prevalence of AGT varies between populations (Must *et al.* 1999, The DECODE Study Group 2003a, International Diabetes Federation 2009) and comparison is challenging, because no entirely comparable population surveys exist. In European populations 40% of individuals aged 55 to 74 years have AGT and 15–26% of men and 15% of women have IFG or IGT (Rathman *et al.* 2003, The DECODE Study Group 2003a).

The total prevalence of diabetes reported here including both diagnosed and undiagnosed type 2 diabetes of 16% for men and 11% for women is high. On the basis of results of the present study and previous FINRISK surveys it has been calculated that in Finland there were already half a million people with diabetes in 2008 giving a prevalence of 10% (Klaukka *et al.* 2008).

The prevalence of undiagnosed type 2 diabetes in the present study was higher than that of diagnosed diabetes. The high prevalence of undiagnosed vs. diagnosed diabetes, 9% vs. 7% in men and 12% vs. 8% in women, respectively, is in line with other studies, that up to over half of all individuals with T2DM are undiagnosed (Dunstan *et al.* 2002, Cowie *et al.* 2009, Ylihärsilä *et al.* 2005). Thus the correct prevalence of diabetes in the population is markedly higher than recognised (The DECODE Study Group 2003a). In the Inter99 study two of the three individuals with T2DM were undiagnosed (Glümer *et al.* 2003). In the southern German population half of the total cases with diabetes were undiagnosed in the age group of 55 to 74 years (Rathmann *et al.* 2003). In China the majority of cases of T2DM are undiagnosed (Yang *et al.* 2010).

Both BMI and waist circumference have been shown to have similar associations with risk of incident T2DM (Janssen *et al.* 2002, Vazquez *et al.* 2007). The present study concurs with those studies, which show that central obesity as defined on the basis of waist circumference is an independent predictor of diabetes regardless of BMI (Carey *et al.* 1997, Folsom *et al.* 2000, Snijder *et al.* 2003, Wang *et al.* 2005). Waist circumference was not in the present study a better predictor of diabetes for women as estimated elsewhere (Wannamethee *et al.* 2010).

6.3 Cardiometabolic profile in the FIN-D2D high risk cohort

Most individuals in the FIN-D2D high risk cohort were obese and every fifth man and every third woman were severely (Obese class II) (WHO 2000) or morbidly (Obese class III obese) (WHO 2000). According to the present guidelines individuals in Obese Class II with diabetes and individuals in Obese Class III fullfill the criteria for bariatric surgery (Dixon *et al.* 2011, Suomalaisen Lääkäriseuran Duodecimin ja Suomen Lihavuustutkijat ry:n asettama työryhmä 2011).

In total 60% of men and 50% of women in the FIN-D2D high risk cohort had a glucose disorder. Every fifth man had screen-detected diabetes. The proportion of ST2DM in this high risk cohort was higher compared to middle-aged Finnish general population (9.3% of men and 12% of women).

The proportion of smokers (17% of men, 10% of women) was only sligthly lower than in Finnish general population (24% for men and of 16% for women) (Laatikainen *et al.* 2003a, Peltonen *et al.* 2008, Suomen virallinen tilasto 2009), but higher than in the DPS study (mean 7%) (Uusitupa *et al.* 2009). The

proportion of smokers was lower in the group included in the cohort due to previous coronary artery disease or other CVD compared with other high risk groups. Because CVD is the most common cause of death among people with AGT, stopping smoking should always be one of the main goals in the prevention of T2DM and CVD.

The present study showed that individuals' levels of traditional risk factors were high and mostly untreated in the FIN-D2D high risk cohort. In line with this finding, the proportion of men at high predicted risk for CVD morbidity and mortality was also really high. This is in line with findings from other studies where population screening with OGTT identifies a significant burden of modifiable CVD risk (Spijkerman *et al.* 2002, Sandbaek *et al.* 2008, Webb *et al.* 2011, Chamnan *et al.* 2011). This emphasises the need to treat these high risk individuals effectively through lifestyle changes and medication is probably also needed. Significant CVD risk reduction may be possible once a glucose abnormality is identified (Webb *et al.* 2011). Furthermore, individuals who have many CVD risk factors are not only at risk of CVD but also at high risk of T2DM (Norhammar *et al.* 2002, D'Agostino *et al.* 2004, Hu *et al.* 2005, Bartnik *et al.* 2007).

The present study describes the real risk profile of individuals screened in primary health care for being at high risk of type 2 diabetes. Their risk reduction is possible once a glucose disorder is identified. The finding in the present study is in line with previous studies (Heldgaard *et al.* 2011) supporting the need for early diagnosis.

6.4 Effect of lifestyle intervention on weight and its association with glucose tolerance in one year follow-up in the FIN-D2D high risk cohort

This study shows that with a very modest lifestyle intervention effort an average weight reduction of 1.3 kg in men and 1.1 kg in women at high risk of type 2 diabetes was achieved. The result is in line with other published real-life translational studies in the prevention of type 2 diabetes, where similar weight reduction has been achieved in a primary health care setting (Absetz *et al.* 2007 and 2009, Harati *et al.* 2009 and 2010). In some smaller translational studies with better resources and more intensive interventions (Ackermann *et al.* 2008, Amundson *et al.* 2009), and in trials for prevention of type 2 diabetes or obesity

greater weight loss has been achieved (Tuomilehto *et al.* 2001, Sjöström *et al.* 1998).

In 18% of individuals at high risk of type 2 diabetes weight decreased by 5% or more. Weight loss increased with increasing numbers of intervention visits, indicating that for effective lifestyle counselling at least several intervention visits are needed which is in line with previous studies (Venditti *et al.* 2008). In 46% of participants weight did not change. However, a stable weight in individuals at high risk for diabetes is still a good result as a continuous weight gain is a rule in the Finnish population (Lahti-Koski *et al.* 2007).

Deterioration of glucose values to diabetic category decreased with weight loss. This is in line with the evidence that weight loss decreases the risk factors for T2DM (Tuomilehto *et al.* 2001). In the present study this was demonstrated for the very first time in real life in a large population sample in a primary health care setting. Weight loss also reduced risk factors for CVD except cholesterol. It has been shown earlier that lifestyle intervention improves the CVD risk (Goldberg *et al.* 2009). The lifestyle interventions in the present study were undertaken in the normal daily circumstances of primary health care providers. The intensity of the interventions was modest, but included individual tailored lifestyle counselling, which was agreed together between a health care provider and an individual at high risk of diabetes.

It has been known that diet associated with exercise results in significant and clinically meaningful initial weight loss (Curioni *et al.* 2005). In the present study population, a conversion rate of up to 16% from glucose abnormalities towards diabetes was regardless of lifestyle interventions much higher than reported in observational population-based studies where the progression from IGT to diabetes has varied between 5% and 6% per year. (Qiao *et al.* 2003b, Nichols *et al.* 2007, Rasmussen *et al.* 2008, Engberg *et al.* 2009). DPP demonstrated a conversion rate of 11% per year (Knowler *et al.* 2002). The annualized relative risk of a person with IGT progressing to diabetes has been reported to increase 6-fold compared to people with NGT and 12-fold with both IFG and IGT (McMaster University Evidence Based Practice Center). In the Dutch Hoorn study, the 6-year progression rate to diabetes was 9%, 33% and 65% for persons with IFG, IGT or both respectively (De Vegt *et al.* 2001). The reasons for the at least two times higher conversion rate found in the present study compared to other studies are unclear. One explanation may be that the participants of the FIN-D2D high risk cohort were really high risk individuals having both diabetes and CVD risk factors and being very obese.

The present study shows that a significant weight loss can be achieved in primary health care with relatively modest lifestyle interventions and without excessive use of personnel resources. This weight loss reduces risk factors for type 2 diabetes and CVD and promotes individuals' health in general. If the results of the FIN-D2D are translated to the whole of Finland, at least 4,000 new cases of T2DM diabetes could be prevented nationwide each year (Pietiläinen *et al.* 2011). The results achieved in the present study are important as interventions to delay or prevent T2DM have the potential to improve the health of the entire population and to reduce the burden of healthcare costs (Gillies *et al.* 2007).

6.5 Methodological considerations

6.5.1 Study population

The present study utilized two population-based samples of Finnish men and women. Two samples were obtained from the National Population Registry of Finland; the FINRISK 2002 survey and the FIN-D2D 2004–2005 survey. The FINRISK surveys are carried out every five years using independent, random and representative population samples from different parts of Finland. The FIN-D2D 2004–2005 survey was carried out as a single separate study in the FIN-D2D areas of three hospital districts and was as representative as the catchment of FINRISK surveys. Both surveys had a moderate and acceptable particiption rate; in the FINRISK 2002 survey of 61% and in the FIN-D2D 2004–2005 survey of 62%. This, combined with a large sample size and the stratification of data by age and sex, allows fairly good generalization to Finnish population. These representative population samples give the study the relevance of an epidemiological survey.

The FIN-D2D high-risk cohort was a cross-sectional sample of Finnish middle-aged population collected mainly by opportunistic screening in primary health care. A smaller cohort was formed from the high risk cohort individuals, who took part in the one-year follow-up and had data available. Neither of these cohorts was collected systematically, but because of the large sample sizes they can be assessed to be representative for Finnish people.

6.5.2 Participation rates and drop-out

In the FINRISK 2002 study nothing specific is known about the reasons for non-participation. In general, younger men who not participate are commonly healthier than older men. Due to the method of sampling by stratifying according to sex, younger age groups were relatively overrepresented in the study sample, but not in the participation compared with the other age groups in Finland.

In the FIN-D2D 2004–2005 survey only 56% of the youngest age group participated. The reasons for the low participation remain unknown in the present study, but may be due to time constraints since both surveys require an attendance of at least two hours, which may be difficult for working people in day-time. Some non-participants may already have had diabetes, and thus considered it unnecessary to take part in the survey. Thus the prevalence of known T2DM may have been underestimated (Tolonen *et al.* 2005).

In the FIN-D2D high risk cohort men were underrepresented (33%). Based on epidemiological data from population surveys, glucose disorders in Finland are more common in men (Peltonen *et al.* 2008) but in the present study women were still overrepresented.

Nothing is known about men's reasons for non-participation in the present study, but the same phenomenon has been observed in other translational studies of diabetes prevention (Venditti *et al.* 2008).

6.5.3 Assessment of methods and measurements

The measurements in Papers I and II were performed by a trained and experienced staff. All measurements in Papers III and IV were performed according to the guidelines and working instructions given in the Project Plan (Suomen Diabetesliitto 2004). Whether these instructions were properly followed by all health care providers in the 400 participating health centres was not monitored.

In the FINRISK 2002 and FIN-D2D 2004–2005 studies (Papers I and II), the central laboratory of the Public Health Institute in Helsinki examined all specimens. In Papers III and IV, all samples were examined in the local health care centre laboratories, which were under laboratory quality control and followed national international guidelines and recommendations. The OGTT was performed and lipid and lipoprotein values measured in fasting state according to

the existing guidelines. Plasma glucose values were used to determine an individual's glucose tolerance (Colagiuri *et al.* 2003).

The OGTT was performed once at baseline and once at the follow-up visit. The 2-hour OGTT has known to have relatively wide intraindividual variety among middle-aged and elderly populations (Feskens *et al.* 1991, Stolk *et al.* 1995).The reasons for this variability may be many, such as diet or exercise even days before the test (Stolk *et al.* 1995). In the present study the fasting time before the test was standardised for at least 8 hours but no strict regimen of diet or exercise before the test was given or monitored.

The predicted risk of CVD morbidity and mortality in the present study was calculated by two CVD risk engines. The SCORE is currently recommended to be used in Finnish primary health care (Conroy *et al.* 2003, De Backer *et al.* 2004). The Framingham risk engine was previously used in Finland. Both of these risk engines were originally developed in general population; the original Framingham 1991 version (Anderson *et al.* 1991) in a population of 5,573 men and women aged 30–74 years. The SCORE project is based on a large European population of 205,178 men and women aged 35–74 years but the definition or prevalence of diabetes was not applicable (Conroy *et al.* 2003). The prevalence of diabetes in both cohorts was 6% (428 individuals). The Framingham risk equation and other non-diabetes-specific risk calculators have been shown to underestimate CVD risk in diabetic cohorts (Price *et al.* 2009).

In the present study no CVD risk score derived from population with diabetes was used (Chamnan *et al.* 2009). It is unclear which risk scores should be used in individuals with diabetes for the prediction of the CVD risk (Chamnan *et al.* 2009). The UKPDS risk engine, specifically designed for T2DM patients (Stevens *et al.* 2001), appears to predict the occurrence of cardiac events better than the Framingham risk engine, but it has been observed that the UKPDS risk engine overestimates CDV risk (van Dieren *et al.* 2011). The UKPDS risk engine was not used here because it has not been used in Finnish primary health care. The Finnish FINRISK calculator (Vartiainen *et al.* 2010b) was not used in the present study as there was no information available on the family history of diabetes.

6.6 Strengths

In the present study large populations were analysed. Papers I and II covered large geographical areas in Finland and included an OGTT. Papers III and IV analysed the results of the largest real-life translational study so far on the

prevention of T2DM among high-risk individuals in a primary health care setting. All studies used well-known research methods. In Paper I an important tool in screening for people at high risk of T2DM was validated in the cross-sectional setting.

In the present study, risk factors for T2DM, screening tools and methods for screening people at high risk for T2DM at the population level and in primary health care were examined. The screening of people at high risk of diabetes was carried out opportunistically. By using opportunistic screening methods it was possible to gather a large sample of individuals at high risk for diabetes and to initiate lifestyle interventions in the daily routines of primary health care. It has been shown that the strategies in which screening is done opportunistically in combination with other clinical routine procedures such as BP measurement and lipid testing have the lowest cost per quality-adjusted life-year (Kahn *et al.* 2010).

Lifestyle interventions were feasible to carry out in the routine primary health care. This real-life implementation of prevention of T2DM was extensively investigated. Participation rates were reasonable and methods were validated. A large study with 400 participating centres made it possible to standardise practical clinical procedures in the prevention ofT2DM.

In the present study it was shown for the very first time that it is possible to translate the results of the landmark RCTs in the prevention of T2DM into practical measures aiming at primary prevention of diabetes.

6.7 Limitations

The FINRISK 2002 and FIN-D2D 2004–2005 population surveys included two one-hour health checks and an OGTT which took over two hours in the laboratory. This may have prevented working aged people from participating. Although not all the precision requirements of the clinical study could be taken into account in Papers III and IV in the daily circumstances of primary health care, the finding in the present study probably reflects the real situation.

In Paper IV only one-year results were analysed. A longer follow-up is needed to analyse any long-term results. Those with a FINDRISC score less than 15 were excluded from the FIN-D2D unless recruited on the basis of other inclusion criteria. In these individuals with moderate risk for diabetes, the prevalence of AGT and undiagnosed T2DM could be high but this was not analysed in the present study. The present study investigated middle-aged Finnish people and the findings cannot be generalized to younger or older age-groups.

The participation rate in the interventions and during follow-up was lower than expected. Only half the individuals in the high risk cohort had any data available in one year the follow-up. One fifth of the subjects attending the first follow-up visit did not have a baseline OGTT which according to protocol, should have been performed for all. This shows how difficult it is to follow-up patients in a real life setting.

6.8 General discussion and practical implications

The present study was the first large-scale real-life implementation project in T2DM prevention. It showed that it is indeed possible to reduce the risk factors for T2DM by modest lifestyle intervention efforts in a primary health care setting. The present study was part of the implementation project (FIN-D2D) for the Finnish National Programme for the Prevention of Type 2 Diabetes (Finnish Diabetes Association 2006). The FIN-D2D tested the effectiveness and feasibility of the Diabetes Prevention Programme. The rationale behind the Finnish diabetes prevention programme and the FIN-D2D was the Finnish Diabetes Prevention Study, and the design of the project was based on experiences in the DPS. In the FIN-D2D new clinical tools, methods and strategies were developed. Some of them were analysed in the present study.

It has been reported earlier that the FINDRISC is a feasible tool that can be used in health care and at community level in opportunistic and targeted screening for incident T2DM (Lindström *et al.* 2003) and it has been recommended to be used in detection of people at high risk for diabetes (Ryden *et al.* 2007). Without the FIN-D2D the launch of the FINDRISC on large scale would not have been possible in Finland or elsewhere (Lindström *et al.* 2010). According to the present study the FINDRISC can also be used as a risk score for prevalent undiagnosed T2DM. The cutoff point of 15 or over used in the FIN-D2D as an indication for high risk of T2DM identifies individuals who may already be in a late stage of developing T2DM, as the present study shows. By lowering the threshold for high risk of diabetes, people with milder glucose disorders could be screened and prevention measures could be initiated earlier aiming at real true primary prevention of diabetes. On the other hand, using a lower cutoff point a larger population sample should be tested.

People scoring less than 15 on the FINDRISC were excluded from the FIN-D2D because it was believed that by using a lower cutoff point, primary health care providers with limited resources would not have been able to arrange

prevention measures for an anticipated large number of individuals screening positive (Suomen Diabetesliitto 2004). Furthermore, the resources in primary health care might also have been a limiting factor for OGTT testing and lifestyle interventions. The people at moderate risk for T2DM were only offered written information on the prevention of diabetes. Lifestyle interventions based on general recommendations have been reported to be effective in reducing multiple metabolic or inflammatory abnormalities (Bo *et al.* 2007).

OGTT is necessary after screening to accurately detect undiagnosed T2DM and other classes of AGT for motivational and health care priority purposes (Schmidt *et al.* 2003). Lifestyle interventions in high risk individuals can be initiated on the basis of a high FINDRISC score alone but OGTT reveals the presence of AGT. For at-risk individuals this information may be a motivational factor to start lifestyle changes and for a medical professional an indication to initiate medical treatment. The effectiveness of prevention or treatment can be monitored through repeated OGTTs. The current guidelines recommend starting treatment for new cases of T2DM without delay (American Diabetes Association 2011, Gaede *et al.* 2008). The missing information on accurate glucose tolerance status may cause a treatment delay.

The screening methods for risk factors of T2DM and for AGT used in the FIN-D2D are in line with recommendations that prevention of T2DM should be a systematic and continuous process and an integral part of primary health care (Simmons *et al.* 2010 and 2011). As shown in the present study, opportunistic or targeted screening in primary health care will mainly target middle-aged and older adults with obesity (Klein Woolthuis *et al.* 2009). Occupational health care providers can effectively identify the risk of type 2 diabetes through the FINDRISC, also in younger age groups (Viitasalo *et al.* 2010).

People screened for being at high risk for T2DM should be treated for their risks aiming at diabetes prevention as screening only impacts sligthly and inconsistently on lifestyle (Mai *et al.* 2007). In primary health care it is important to pay attention to central obesity by measuring waist circumference in overweight people besides focusing on weight only. Weight loss was effective in reducing the risk of diabetes and CVD risk factors during one-year follow-up even if it is not yet known whether this will reduce CVD events in people with AGT or diabetes (The Look AHEAD Research Group 2006).

Calculated on the basis of the known prevalence of diagnosed T2DM, on the basis of prevalence of T2DM in middle-aged population reported in the present study, and on earlier population-based surveys, it has been estimated that in

Finland there are approximately 200,000 individuals with undiagnosed T2DM (Reunanen *et al.* 2008) and in addition, the prevalence of AGT and of risk factors for T2DM is high. This estimation should lead to urgent prevention activities in health care. A remarkable part of the middle-aged Finnish population should change their lifestyle. There is an urgent need to continue large-scale T2DM prevention in the population.

A novel finding in the present study is that it is possible to achieve a moderate weight loss in individuals at high risk for T2DM in a routine primary health care setting and that this weight loss significantly decreases the conversion of AGT to the diabetic category. How to translate research findings into practical health promotion and if these promotion efforts be effective and sustainable has been largely unknown (Dzewaltowski *et al.* 2004). Studies on prevention of T2DM have mostly been conducted in hospital research settings in populations with IGT (Lauritzen *et al.* 2007, Rasmussen *et al.* 2008). The problem with these studies is that they assume that the programmes would be equally effective in different populations (Yates *et al.* 2007). The prevention of T2DM can be organised by using low-resource models and methods as in the FIN-D2D. A protocol-driven, nurse-led method with open clinical algorithm as used in the FIN-D2D has previously been used effectively to manage CVD risk reduction in T2DM (Woodward *et al.* 2006).

The findings of the present study indicate that primary health care has a special emphasis to get men involved in T2DM prevention, and to improve high-risk individuals' participation and follow-up in general (Icks *et al.* 2007, Ealovega *et al.* 2004).

The results of the present study can be generalized and implemented in primary health care nationwide. Individuals at high risk of T2DM and the entire population should be targeted simultaneously with lifestyle modification through a stepwise approach (Alberti *et al.* 2007). This would probably modify risk factor levels in the population, promote primary prevention of T2DM and CVD, and target people at high risk for developing diabetes. The FIN-D2D has influenced the creation of European evidence-based guidelines (Paulweber *et al.* 2010, Lindström *et al.* 2010, Pajunen *et al.* 2010) and very similar modifications of the Finnish programme are going on elsewhere (Qiao *et al.* 2010).

The prevalence of risk factors for T2DM and of AGT reported in the present study are so high that the diabetes epidemic probably cannot be controlled by health care alone by targeting only people at high risk for T2DM, but focusing on risk factors in the entire population simultaneously (Alberti *et al.* 2007, Vartiainen

et al. 2010a, Simmons *et al.* 2010). Diabetes prevention should be the challenge of other organizations as well (Colagiuri *et al.* 2010).

The present study is the first large-scale real-life implementation project of T2DM prevention. It shows that it really is in the routine primary health care setting possible to reduce risk factors for type 2 diabetes by modest lifestyle intervention efforts.

7 Conclusions

The Finnish Diabetes Risk Score (FINDRISC) can be used as a screening tool for detecting undiagnosed type 2 diabetes in an unselected middle-aged population. With an optimal cutoff point of 11, the performance of the score to detect undiagnosed diabetes is good. Using a higher than optimal cut-off point, the prevalence of screen-detected diabetes is high in screening-positive individuals. FINDRISC is associated with cardiovascular risk factor levels and their clusters.

Obesity, central obesity, abnormal glucose tolerance, and the risk of type 2 diabetes are common in the middle-aged population and more common in men than in women. Obesity and central obesity are associated with abnormal glucose tolerance. Central obesity is associated with abnormal glucose tolerance in all categories of obesity.

In the population screened for being at high risk for type 2 diabetes glucose disorders are very common. Every fifth high-risk individual has screen-detected diabetes. Elevated cardiovascular risk factor levels are common in this population and the risk factors are partly untreated. Almost half of the men are at high predicted risk for cardiovascular morbidity and mortality.

It is possible to achieve a significant weight loss by lifestyle counselling in the primary health care setting in individuals at high risk for type 2 diabetes. This weight loss is associated with a reduction in deterioration towards diabetes in one year follow-up.

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Appendix

Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age

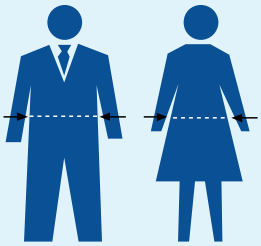
0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)

0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm



4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?

0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?

0 p. Every day
1 p. Not every day

6. Have you ever taken medication for high blood pressure on regular basis?

0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?

0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score ☐

The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki, and Jaana Lindström, MFS, National Public Health Institute.

Finnish Diabetes Association

WHAT CAN YOU DO TO LOWER YOUR RISK OF DEVELOPING TYPE 2 DIABETES?

You can't do anything about your age or your genetic predisposition. On the other hand, the rest of the factors predisposing to diabetes, such as overweightness, abdominal obesity, sedentary lifestyle, eating habits and smoking, are up to you. Your lifestyle choices can completely prevent type 2 diabetes or at least delay its onset until a much greater age.

If there is diabetes in your family, you should be careful not to put on weight over the years. Growth of the waistline, in particular, increases the risk of diabetes, whereas regular moderate physical activity will lower the risk. You should also pay attention to your diet: take care to eat plenty of fibre-rich cereal products and vegetables every day. Omit excess hard fats from your diet and favour soft vegetable fats.

Early stages of type 2 diabetes seldom cause any symptoms. If you scored 12–14 points in the Risk Test, you would be well advised to seriously consider your physical activity and eating habits and pay attention to your weight, to prevent yourself from developing diabetes. Please contact a public-health nurse or your own doctor for further guidance and tests.

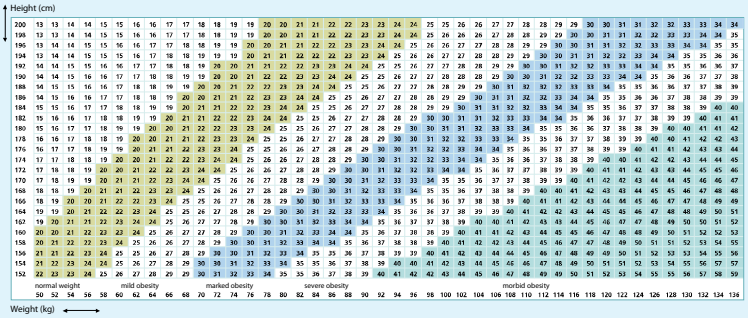
If you scored 15 points or more in the Risk Test, you should have your blood glucose measured (both fasting value and value after a dose of glucose or a meal) to determine if you have diabetes without symptoms.

BODY-MASS INDEX

The body-mass index is used to assess whether a person is normal weight or not. The index is calculated by dividing body weight (kg) by the square of body height (m). For example, if your height is 165 cm and your weight 70 kg, your body-mass index will be 70/(1.65 x 1.65), or 25.7.

If your body-mass index is 25–30, you will benefit from losing weight; at least you should take care that your weight doesn't increase beyond this. If your body-mass index is higher than 30, the adverse health effects of obesity will start to show, and it will be essential to lose weight.

BODY-MASS INDEX CHART



Original publications

I Saaristo T, Peltonen M, Lindström J, Saarikoski L, Sundvall J, Eriksson J & Tuomilehto J (2005) Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. Diabetes and Vascular Disease Research 2: 67–72.

II Saaristo T, Barengo N, Korpi-Hyövälti E, Oksa H, Puolijoki H, Saltevo J, Vanhala M, Sundvall J, Saarikoski L, Peltonen M & Tuomilehto J (2008) High prevalence of obesity, central obesity and abnormal glucose tolerance in the middle-aged Finnish population. BMC Public Health 8: 423. DOI: 10.1186/1471-2458-8-423.

III Saaristo T, Moilanen L, Jokelainen J, Korpi-Hyövälti E, Vanhala M, Saltevo J, Niskanen L, Peltonen M, Oksa H, Cederberg H, Tuomilehto J, Uusitupa M & Keinänen-Kiukaanniemi S (2010) Cardiometabolic profile of people screened for high risk of type 2 diabetes in a national diabetes prevention programme (FIN-D2D). Primary Care Diabetes 4: 231–239. DOI: 10.1016/j.pcd.2010.05.005.

IV Saaristo T, Moilanen L, Korpi-Hyövälti E, Vanhala M, Saltevo J, Niskanen L, Jokelainen J, Peltonen M, Oksa H, Tuomilehto J, Uusitupa M & Keinänen-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: 2146–2151.

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1128. Thevenot, Jérôme (2011) Biomechanical assessment of hip fracture : development of finite element models to predict fractures

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1130. Haapsamo, Mervi (2011) Low-dose aspirin therapy in IVF and ICSI patients

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1134. Kaustinen, Teija (2011) Oulu-hoitoisuusluokitus ja hoitohenkilökunnan ajankäyttö hoitotyön laatuvaatimusten näkökulmasta

1135. Liukkonen, Timo (2011) Low-grade inflammation in depression, anxiety and sleep disturbances

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