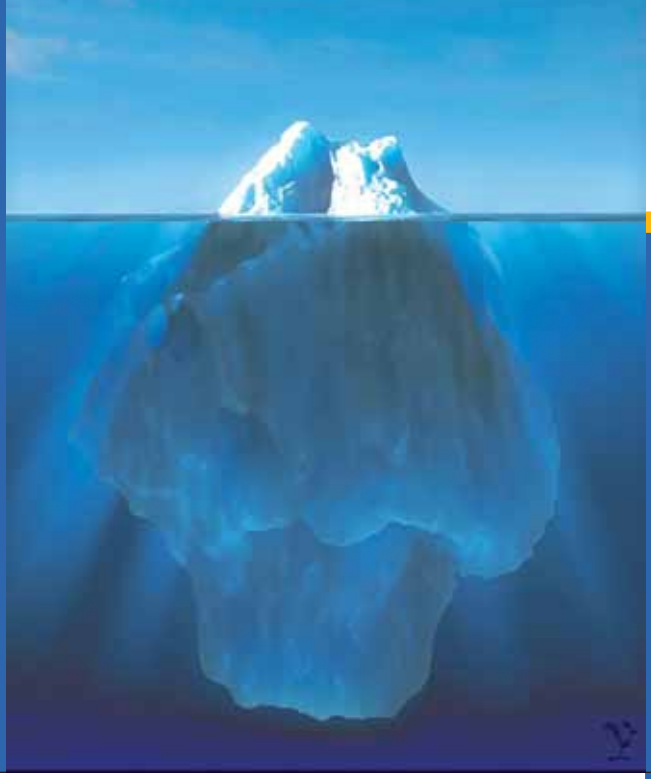

**Jaana Lindström**

# Prevention of Type 2 Diabetes with Lifestyle Intervention – Emphasis on Dietary Composition and Identification of High-Risk Individuals

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Department of Health Promotion and Chronic Disease Prevention
National Public Health Institute, Helsinki, Finland
and
Department of Public Health,
University of Helsinki, Finland

Helsinki 2006

**Jaana Lindström**

# PREVENTION OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION – EMPHASIS ON DIETARY COMPOSITION AND IDENTIFICATION OF HIGH-RISK INDIVIDUALS

A C A D E M I C  D I S S E R T A T I O N

*To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in the Small Hall, University Main Building, on November 24, 2006, at 12 o'clock noon.*

Department of Health Promotion and Chronic Disease Prevention
National Public Health Institute
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and

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*To my family*

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# ABSTRACT

Type 2 diabetes is an increasing, serious, and costly public health problem. The increase in the prevalence of the disease can mainly be attributed to changing lifestyles leading to physical inactivity, overweight, and obesity. These lifestyle-related risk factors offer also a possibility for preventive interventions. Until recently, proper evidence regarding the prevention of type 2 diabetes has been virtually missing. To be cost-effective, intensive interventions to prevent type 2 diabetes should be directed to people at an increased risk of the disease.

The aim of this series of studies was to investigate whether type 2 diabetes can be prevented by lifestyle intervention in high-risk individuals, and to develop a practical method to identify individuals who are at high risk of type 2 diabetes and would benefit from such an intervention.

To study the effect of lifestyle intervention on diabetes risk, we recruited 522 volunteer, middle-aged (aged 40 - 64 at baseline), overweight (body mass index > 25 kg/m$^2$) men (n = 172) and women (n = 350) with impaired glucose tolerance to the Diabetes Prevention Study (DPS). The participants were randomly allocated either to the intensive lifestyle intervention group or the control group. The control group received general dietary and exercise advice at baseline, and had annual physician's examination. The participants in the intervention group received, in addition, individualised dietary counselling by a nutritionist. They were also offered circuit-type resistance training sessions and were advised to increase overall physical activity. The intervention goals were to reduce body weight (5% or more reduction from baseline weight), limit dietary fat (< 30% of total energy consumed) and saturated fat (< 10% of total energy consumed), and to increase dietary fibre intake (15 g / 1000 kcal or more) and physical activity (≥ 30 minutes/day). Diabetes status was assessed annually by a repeated 75 g oral glucose tolerance testing. First analysis on end-points was completed after a mean follow-up of 3.2 years, and the intervention phase was terminated after a mean duration of 3.9 years. After that, the study participants continued to visit the study clinics for the annual examinations, for a mean of 3 years.

The intervention group showed significantly greater improvement in each intervention goal. After 1 and 3 years, mean weight reductions were 4.5 and 3.5 kg in the intervention group and 1.0 kg and 0.9 kg in the control group. Cardiovascular risk factors improved more in the intervention group. After a mean follow-up of 3.2 years, the risk of diabetes was reduced by 58% in the intervention group compared with the control group. The reduction in the incidence of diabetes was directly associated with achieved lifestyle goals.

Furthermore, those who consumed moderate-fat, high-fibre diet achieved the largest weight reduction and, even after adjustment for weight reduction, the lowest diabetes risk during the intervention period. After discontinuation of the counselling, the differences in lifestyle variables between the groups still remained favourable for the intervention group. During the post-intervention follow-up period of 3 years, the risk of diabetes was still 36% lower among the former intervention group participants, compared with the former control group participants.

To develop a simple screening tool to identify individuals who are at high risk of type 2 diabetes, follow-up data of two population-based cohorts of 35-64 year old men and women was used. The National FINRISK Study 1987 cohort (model development data) included 4435 subjects, with 182 new drug-treated cases of diabetes identified during ten years, and the FINRISK Study 1992 cohort (model validation data) included 4615 subjects, with 67 new cases of drug-treated diabetes during five years, ascertained using the Social Insurance Institution's Drug register. Baseline age, body mass index, waist circumference, history of antihypertensive drug treatment and high blood glucose, physical activity and daily consumption of fruits, berries or vegetables were selected into the risk score as categorical variables. In the 1987 cohort the optimal cut-off point of the risk score identified 78% of those who got diabetes during the follow-up (= sensitivity of the test) and 77% of those who remained free of diabetes (= specificity of the test). In the 1992 cohort the risk score performed equally well. The final Finnish Diabetes Risk Score (FINDRISC) form includes, in addition to the predictors of the model, a question about family history of diabetes and the age category of over 64 years. When applied to the DPS population, the baseline FINDRISC value was associated with diabetes risk among the control group participants only, indicating that the intensive lifestyle intervention given to the intervention group participants abolished the diabetes risk associated with baseline risk factors.

In conclusion, the intensive lifestyle intervention produced long-term beneficial changes in diet, physical activity, body weight, and cardiovascular risk factors, and reduced diabetes risk. Furthermore, the effects of the intervention were sustained after the intervention was discontinued. The FINDRISC proved to be a simple, fast, inexpensive, non-invasive, and reliable tool to identify individuals at high risk of type 2 diabetes. The use of FINDRISC to identify high-risk subjects, followed by lifestyle intervention, provides a feasible scheme in preventing type 2 diabetes, which could be implemented in the primary health care system.

Keywords: diet, dietary fat, dietary fibre, epidemiology, impaired glucose tolerance, intervention, lifestyle, obesity, physical activity, primary prevention, randomised controlled study, risk factors, screening, type 2 diabetes

Jaana Lindström, Elintapaohjaus tyypin 2 diabeteksen ehkäisyssä – ruokavalion koostumuksen merkitys sekä suuririskisten henkilöiden tunnistaminen
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# TIIVISTELMÄ

Tyypin 2 diabetes on kasvava, vakava ja kallis kansanterveysongelma. Taudin lisääntyminen johtuu pääasiassa elintapojen muutoksesta, erityisesti liikunnan vähenemisestä sekä liikapainon ja lihavuuden yleistymisestä. Elintapoihin liittyvien riskitekijöiden rooli taudin kehittymisessä tarjoaa toisaalta mahdollisuuden taudin ennaltaehkäisyyn. Viime aikoihin asti luotettavaa näyttöä tyypin 2 diabeteksen ehkäisyn toteutettavuudesta ja vaikuttavuudesta ei ole ollut olemassa. Ollakseen kustannusvaikuttavaa, tehostettu ehkäisytyö tulisi kohdistaa henkilöihin, joilla on suurentunut riski sairastua tyypin 2 diabetekseen.

Väitöskirjatyössä selvitettiin mahdollisuutta ehkäistä elintapaohjauksen avulla tyypin 2 diabeteksen puhkeamista suuren sairastumisriskin omaavilla henkilöillä, sekä kehitettiin seulontamenetelmä suuririskisten henkilöiden tunnistamiseksi. Diabeteksen ehkäisytutkimukseen (DPS) valittiin 522 vapaaehtoista, keski-ikäistä (ikä 40 - 64 vuotta tutkimuksen alussa), liikapainoista (painoindeksi > 25 kg/m$^2$) miestä (n = 172) ja naista (n = 350), joilla seulontavaiheessa todettiin heikentynyt glukoosinsieto (IGT). Henkilöt jaettiin satunnaisesti saamaan joko tavanomaista (verrokkiryhmä) tai tehostettua elintapaohjausta (interventioryhmä). Verrokeille annettiin tutkimuksen alussa yleistasoista ruokavalio- ja liikuntaneuvontaa, ja tämän jälkeen he kävivät vuosittain lääkärintarkastuksessa ja laboratoriokokeissa. Interventioryhmän jäsenet saivat lisäksi säännöllistä ravitsemusasiantuntijan (ravitsemusterapeutti tai ravitsemustieteilijä) antamaa yksilöohjausta. Heille tarjottiin myös mahdollisuus osallistua kuntosalityyppiseen voimaharjoitteluun, ja heitä ohjattiin lisäämään kaikenlaista fyysistä aktiivisuutta. Ohjauksessa tavoitteena oli laihtuminen (5 % tai enemmän lähtöpainosta), rasvan (< 30 % kokonaisenergiasta) ja erityisesti tyydyttyneen rasvan (< 10 % kokonaisenergiasta) määrän rajoittaminen ruokavaliossa, sekä kuidun saannin (vähintään 15 g / 1000 kcal) ja liikunnan (vähintään 30 minuuttia / päivä) lisääminen. Diabeteksen toteamiseksi kaikille osallistujille tehtiin vuosittain 2 tunnin glukoosirasituskoe, joka toistettiin diagnoosin varmentamiseksi. Ryhmien välinen ero diabeteksen ilmaantuvuudessa analysoitiin ensimmäisen kerran keskimäärin 3,2 vuoden seuranta-ajan jälkeen, ja varsinainen interventiojakso päätettiin keskimäärin 3,9 vuoden seuranta-ajan jälkeen. Siitä eteenpäin osallistujia seurattiin vuosittaisilla tutkimuskäynneillä keskimäärin 3 vuoden ajan.

Tehostetun ohjauksen ryhmään kuuluvat henkilöt saavuttivat verrokkeja useammin asetetut elintapatavoitteet. He laihtuivat keskimäärin 4,5 kg ensimmäisen tutkimusvuoden aikana, ja kolmen vuoden kohdalla paino oli edelleen keskimäärin 3,5 kg lähtötasoa alempana. Verrokeilla paino laski keskimäärin 1,0 kg yhden vuoden ja 0,9 kg kolmen vuoden aikana. Myös

sydän- ja verisuonitautien riskitekijät muuttuivat edulliseen suuntaan tehostettua ohjausta saaneilla. Keskimäärin 3,2 vuoden seuranta-aikana diabeteksen ilmaantuvuus oli tehostettua ohjausta saaneilla 58 % pienempi kuin verrokeilla. Diabeteksen puhkeaminen oli sitä epätodennäköisempää, mitä useamman asetetuista elintapatavoitteista henkilö saavutti. Ne henkilöt, joiden ruokavalio sisälsi enintään kohtuullisesti rasvaa mutta runsaasti kuitua, laihtuivat eniten. Heillä myös diabeteksen ilmaantuvuus oli pienin, myös sen jälkeen kun painonmuutoksen vaikutus oli huomioitu. Tehostettua ohjausta saaneet säilyttivät verrokkeja edullisemmat tavoite-elintavat myös interventiojakson päättymisen jälkeen. Keskimäärin kolmen vuoden jatkoseurannan aikana diabeteksen ilmaantuvuus oli tehostettua ohjausta saaneilla edelleen 36 % verrokkeja pienempi.

Diabeteksen sairastumisriskin arviointimenetelmän kehittämisessä käytettiin aineistona väestöstä satunnaisotoksella poimittuja FINRISKI 1987 (ennustemallin kehittäminen) ja FINRISKI 1992 (ennustemallin validointi) -tutkimuskohortteja. Perustutkimukseen osallistuneiden 35 - 64 -vuotiaiden henkilöiden diabetessairastuvuutta seurattiin Kansaneläkelaitoksen lääkekorvausrekisterin avulla vuoteen 1997. Vuoden 1987 kohortissa (n = 4435) todettiin 10 vuoden aikana 182 uutta lääkehoidettua diabetestapausta ja vuoden 1992 kohortissa (n = 4615) 67 tapausta viiden vuoden aikana. Ikä, painoindeksi, vyötärönympärys, verenpainelääkkeiden käyttö, aikaisemmin todettu korkea verensokeri, liikunnan määrä sekä hedelmien ja vihannesten käyttötiheys valikoituivat osatekijöiksi diabetesriskitestiin. Vuoden 1987 kohortissa testillä voitiin tunnistaa 78 % tulevista diabetestapauksista (testin sensitiviteetti) ja 77 % henkilöistä joilla diabetesta ei todettu seuranta-aikana (testin spesifiteetti). Vuoden 1992 kohortissa testi osoittautui yhtä luotettavaksi. Lopulliseen riskitestilomakkeeseen otettiin lisäksi kysymys diabeteksen esiintymisestä suvussa, sekä lisättiin ikäryhmä yli 64-vuotiaat. DPS-tutkimuksen osallistujien joukossa lähtötason riskitestitulos ennusti diabeteksen ilmaantumista ainoastaan henkilöillä, joille ei tarjottu tehostettua elintapaohjausta. Ohjausta saaneiden joukossa ilmaantuvuus vähentyi erityisesti henkilöillä, joilla alussa oli riskitestin perusteella suurin sairastumisriski.

Väitöskirjatyön tulokset osoittavat, että tehostetulla elintapaohjauksella on mahdollista saada aikaan pitkäaikaisia, edullisia muutoksia korkean diabetesriskin omaavien henkilöiden ruokavaliossa ja liikuntatottumuksissa sekä painossa ja sydän- ja verisuonitautien riskitekijöissä. Terveelliset elintavat puolestaan pienentävät riskiä sairastua diabetekseen, ja vaikutus säilyy myös tehostetun ohjauksen lopettamisen jälkeen. Tehostettua ohjausta tulisi tarjota erityisesti riskiryhmille. Tällaiset suuririskiset henkilöt on mahdollista tunnistaa nopeasti, pienin kustannuksin ja silti varsin luotettavasti yksinkertaisella diabetesriskitestillä.

*Avainsanat*: elintavat, epidemiologia, fyysinen aktiivisuus, heikentynyt glukoosinsieto, interventio, kontrolloitu satunnaistutkimus, lihavuus, primääripreventio, ravinnon rasva, ravintokuitu, riskitekijät, ruokavalio, seulonta, tyypin 2 diabetes

# CONTENTS

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals. Some unpublished data are also presented.

I. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Aunola S, Cepaitis Z, Moltchanov V, Hakumäki M, Mannelin M, Martikkala V, Sundvall J for the Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine 2001; 344: 1343-9.

II. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J for the Finnish Diabetes Prevention Study Group. The Finnish Diabetes Prevention Study (DPS). Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003; 26: 3230-6.

III. Lindström J, Peltonen M, Eriksson JG, Louheranta A, Fogelholm M, Uusitupa M, Tuomilehto J for the Finnish Diabetes Prevention Study Group. High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk – the Finnish Diabetes Prevention Study. Diabetologia 2006; 49:912-20.

IV. Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Rastas M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J on behalf of the Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006; 368:1673-9.

V. Lindström J, Tuomilehto J. The Diabetes Risk Score: A practical tool to predict type 2 diabetes risk. Diabetes Care 2003; 26:725-31.

# ABBREVIATIONS

| | |
|---|---|
| ADA | American Diabetes Association |
| ANCOVA | Analysis of covariance |
| AUC | Area under the receiver-operating characteristic (ROC) curve |
| BMI | Body mass index |
| DEHKO | Development Programme for the Prevention and Care of Type 2 Diabetes in Finland |
| D2D | DEHKO 2D -project; implementation project of DEHKO |
| DM | Diabetes mellitus |
| DPP | Diabetes Prevention Program |
| DPS | Diabetes Prevention Study |
| E% | Proportion of energy consumed |
| FINDRISC | Finnish Diabetes Risk Score |
| FINRISK | National risk factor survey in Finland |
| $HbA_{1c}$ | Glycosylated haemoglobin |
| HDL | High-density lipoprotein |
| HR | Hazard ratio |
| IDPP | Indian Diabetes Prevention Program |
| IFG | Impaired fasting glycaemia |
| IGT | Impaired glucose tolerance |
| LTPA | Leisure-Time Physical Activity |
| OGTT | Oral glucose tolerance test |
| PPV | Positive predictive value |
| ROC | Receiver-operating characteristic |
| UKPDS | United Kingdom Prospective Diabetes Study |
| VLCD | Very low calorie diet |
| WHO | World Health Organization |

# 1 INTRODUCTION

Type 2 diabetes develops as a result of complex multifactorial process with both lifestyle and genetic origins. It is estimated that in Caucasian populations the proportion of people with genetic predisposition to type 2 diabetes is from 20% to 50%, and in many other ethnic groups, such as some Asian populations and many native peoples, this proportion is likely to be even higher (Valle et al 1997). Currently, however, type 2 diabetes has become common all over the world and is increasing in most countries (King et al 1998); thus there seems to be no ethnic group with a particular genetic protection against the disease. Obesity and physical inactivity are considered the major environmental risk factors for type 2 diabetes, and 80 to 90% of people with diabetes are overweight or obese (CDC 2004; Sullivan et al 2005). In people genetically predisposed to the disease, the probability to develop type 2 diabetes is very high once exposed to 'obesogenic' lifestyle (Zimmet et al 2001).

Type 2 diabetes usually develops gradually and different stages can be identified (Eriksson et al 1989; Hamman 1992; Tuomilehto et al 1997). When genetically predisposed individuals become insulin resistant due to environmental exposures such as obesity or physical inactivity, they may develop post-prandial hyperglycaemia which is also called impaired glucose tolerance (IGT). Finally, when beta cell capacity is not sufficient to compensate for insulin resistance, hyperglycaemia worsens and overt diabetes will develop. It has been estimated that at the time of diagnosis of clinical type 2 diabetes only 50-60% of the pancreatic beta-cell capacity is left, due to the fact that the disease process has already existed for more than 10 years (UKPDS Group 1995). Therefore, the optimal strategy to reduce the increased burden of type 2 diabetes is the primary prevention of the disease, i.e. to tackle the worsening of glucose intolerance before harmful effects of hyperglycaemia will become permanent.

The main justification for prevention of type 2 diabetes is the supposed concurrent prevention or postponement of complications related to type 2 diabetes. This reduces human suffering and the economic burden related to diabetes in the community. Type 2 diabetes is characterised by the development of micro- and macrovascular complications which give rise to excessive rates of cardiovascular disease. These complications account for the majority of morbidity and mortality associated with diabetes. According to a Finnish study diabetes increased the risk of death in 65-74 year old men fivefold (Stengård et al 1992). It has been repeatedly shown that both symptomatic and asymptomatic diabetes patients have an increased prevalence of both microvascular and macrovascular complications already at the time of diagnosis of diabetes (Uusitupa et al 1985; Harris et al 1992; Kohner et al 1998; Haffner et al 2000). A Swedish study showed that 77% of all costs for the care of type 2 diabetes were due to late complications, mostly cardiovascular (Henriksson et al 2000). In

Finland the estimated incremental costs related to diabetes were in 1997 at least 2.8 billion Finnish marks (~ 470 million euros), and the costs were estimated to increase, at minimum, to 4.5 billion Finnish marks (~756 million euros) by year 2010 (Kangas 2002).

Primary prevention of type 2 diabetes was first proposed in the beginning of the 20th century by Dr. Joslin from the USA, who wrote: *"There are entirely too many diabetic patients in the country. Statistics for the last thirty years show so great an increase in the number that, unless this were in part explained by a better recognition of the disease, the outlook for the future would be startling. Therefore, it is proper at the present time to devote attention not alone to treatment, but still more, as in the campaign against the typhoid fever, to prevention. The results may not be quite so striking or as immediate, but they are sure to come and to be important"* (Joslin 1921). Until recently, proper evidence regarding the prevention of type 2 diabetes tested and confirmed under a randomised clinical trial setting has been virtually missing.

To be able to prevent a chronic disease, such as type 2 diabetes, certain requirements have to be met. Knowledge about its natural history with a pre-clinical phase, modifiable risk factors, effective and simple screening tool to identify high-risk individuals and effective intervention that is affordable and acceptable are necessary. In addition, the efficacy of the intervention has to be proven under a clinical trial setting (Morrison 1992; American Diabetes Association 2004a).

In this series of studies, the possibility of prevention of type 2 diabetes in high-risk individuals by comprehensive lifestyle intervention was investigated. The focus of the intervention was on the known, modifiable risk factors for type 2 diabetes: body weight, physical activity, and dietary fat, saturated fat, and fibre intake. Post-hoc analyses were completed to clarify the independent effect of dietary composition on weight change and diabetes risk during the intervention trial. Physical activity, even though an important determinant of type 2 diabetes risk, was not the focus of this thesis and is thus only briefly discussed and used as a cofactor in the analyses. Finally, a simple screening tool was developed to identify individuals who are at high risk of type 2 diabetes and thus form a feasible target group for preventive intervention.

# 2 REVIEW OF THE LITERATURE

## 2.1 Definition of type 2 diabetes and other categories of glucose intolerance

Type 2 diabetes results from a dual, continuing process of insulin resistance of liver, muscle and adipose tissue and an impairment of insulin secretion. During this process early prandial insulin secretion is blunted already in people with IGT (Kosaka et al 1977; Ward et al 1984; Bruce et al 1988; Mitrakou et al 1992; Pratley and Weyer 2002). Postprandial hyperglycaemia *per se* may contribute to the progressive deterioration of beta-cells with early insulin secretion deficiency as a vicious cycle. Half of the people with IGT will develop type 2 diabetes during a 10-year follow-up (Knowler et al 1995).

The diagnosis of type 2 diabetes and other categories of glucose intolerance is based on blood glucose values in fasting and after a glucose load (Table 1). Before the year 1979 there was enormous variation in glucose loading and diagnostic cut-off values. Then the 75 g 2-hour oral glucose tolerance test (OGTT) was proposed as a standard test for diagnosis of type 2 diabetes (National Diabetes Data Group 1979). The criteria have been revised twice by the World Health Organization (World Health Organization 1985; World Health Organization 1999). The American Diabetes Association (ADA) published its own version of the criteria in 1997, introducing a new category 'impaired fasting glycaemia' (IFG), and a slightly revised version in 2004 (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997; American Diabetes Association 2004b).

The rationale behind the cut-off points is the increase in micro- or macrovascular complications after certain thresholds. The current diagnostic criteria for fasting glucose concentration detects those at risk for microvascular diseases (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997); post-load glucose concentration predicts cardiovascular morbidity and all-cause and cardiovascular mortality even in the IGT range (The DECODE Study Group 1999; The DECODE Study Group 2001; The DECODE Study Group 2004).

**Table 1. Criteria for diagnosing type 2 diabetes based on a 75 g oral glucose tolerance test.**

| Source | | Venous plasma glucose concentration | Additional remarks |
|---|---|---|---|
| **NDDG 1979 (National Diabetes Data Group 1979):** | | | |
| IGT | Fasting value | <7.8 and | Presence of the classic symptoms of diabetes together with gross and unequivocal elevation of plasma glucose is considered diagnostic of diabetes. Otherwise, elevated glucose concentrations must be present on more than one occasion. |
| | ½, 1, or 1½ hours after glucose load | ≥11.1 and | |
| | 2 hours after glucose load | 7.8 - <11.1 | |
| DM | Fasting value | ≥7.8 or | |
| | 2 hours after glucose load | ≥11.1 | |
| **WHO 1985 (World Health Organization 1985):** | | | |
| IGT | Fasting value | <7.8 and | For epidemiological and population screening the 2-hour value may be used alone or with the fasting value. The fasting value alone is considered less reliable since true fasting cannot be assured. |
| | 2 hours after glucose load | 7.8 - <11.1 | |
| DM | Fasting value | ≥7.8 or | |
| | 2 hours after glucose load | ≥11.1 | |
| **ADA 1997 (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997):** | | | |
| IFG | Fasting value | 6.1 - <7.0 and | Symptoms of diabetes plus casual plasma glucose ≥11.1 warrant the diagnosis. In the absence of unequivocal hyperglycaemia, these criteria should be confirmed by repeat testing on a different day. OGTT is not recommended for routine clinical use. If OGTT is used, IGT warrants the diagnosis of IFG, even with fasting glucose concentration <6.1. Estimates of diabetes prevalence and incidence should be based on a fasting plasma glucose concentration ≥7.0. |
| | 2 hours after glucose load | <11.1 | |
| IGT | Fasting value | <7.0 and | |
| | 2 hours after glucose load | 7.8 - <11.1 | |
| DM | Fasting value | ≥7.0 or | |
| | 2 hours after glucose load | ≥11.1 | |
| **WHO 1999 (World Health Organization 1999):** | | | |
| IFG | Fasting value | 6.1 - <7.0 and | For epidemiological and population screening the fasting or 2-hour value may be used alone. For clinical purposes, diagnosis should be confirmed by repeat testing unless there is unequivocal hyperglycaemia with obvious symptoms. |
| | 2 hours after glucose load | <7.8 | |
| IGT | Fasting value | <7.0 and | |
| | 2 hours after glucose load | 7.8 - <11.1 | |
| DM | Fasting value | ≥7.0 or | |
| | 2 hours after glucose load | ≥11.1 | |

**ADA 2004 (American Diabetes Association 2004b):**

| | | | |
|---|---|---|---|
| IFG | Fasting value | 5.6 - <7.0 and | Patients with IFG and/or IGT are referred to as having”prediabetes“. |
| | 2 hours after glucose load | <11.1 | |
| IGT | Fasting value | <7.0 and | |
| | 2 hours after glucose load | 7.8 - <11.1 | |
| DM | Fasting value | ≥7.0 or | |
| | 2 hours after glucose load | ≥11.1 | |

IGT = impaired glucose tolerance, IFG = impaired fasting glycaemia, DM = diabetes mellitus, OGTT = oral glucose tolerance test, NDDG = National Diabetes Data group, WHO = World Health Organization, ADA = American Diabetes Association.

## 2.2 Epidemiology and pathophysiology of type 2 diabetes

The worldwide prevalence of diabetes in the year 2000 was estimated to be 2.8%, with 171 million affected people. Approximately 80% of all diabetic cases are estimated to be type 2 diabetes. Majority of people with diabetes live in the developing countries, especially in India and China, even though the absolute prevalence in these countries at the moment is lower than in the developed countries. Based solely on changes in demographic factors, most importantly the increase in the proportion of those aged 65 or over, the number of people with diabetes has been predicted to increase to 366 million in the year 2030, which probably is an underestimate, given the increasing prevalence of obesity. (Wild et al 2004)

In the year 2003 altogether 152 600 Finns were using medication for diabetes, based on the national Drug register data, with an increase from the previous year being almost 5% (Klaukka and Paldan 2004). The number increased further by 5.7% during the year 2004 (Klaukka 2005).Of the population aged 64 or over, almost 10% had diabetes in the year 2003, based solely on the medication data. The total number of known diabetes patients is clearly higher, even though the number of type 2 diabetes patients treated with diet only is difficult to estimate accurately. In the Health 2000 health examination survey 23% of the men and 38% of the women with diabetes reported that they did not have any medication for the disease (Reunanen and Kattainen 2002).

In the year 1992 a population-based sample (a subgroup of the National FINRISK Stydy) of 2087 individuals aged 45-64 had a single OGTT using WHO 1985 criteria (World Health Organization 1985) in three geographical areas in Finland. The total prevalence of diabetes was 10.2% and 7.4% in men and women, respectively (Ylihärsila et al 2005). Furthermore, 44% of these prevalent diabetes cases were previously undiagnosed. In a study completed in 2004-2005 in three hospital districts in Finland, the prevalence of known diabetes among men aged 45-74 was 7.4% and among women 4.3%, and prevalence of previously undiagnosed diabetes was 8.8% and 6.9%, respectively, using the WHO 1999 (World Health Organization 1999) criteria (Peltonen et al 2006). In all, 41.8% of men and 33.2% of women had disturbed glucose metabolism, either diabetes, IGT or IFG. Prevalence of diabetes thus seems to have markedly increased in Finland during only 12 years, even though part of the increase can be explained by the lowering of the diagnostic cut-off point for type 2 diabetes (Table 1).

The major factors behind the gradual increase in blood glucose concentrations leading to type 2 diabetes are insulin resistance and pancreatic β-cell dysfunction (Chiasson and Rabasa-Lhoret 2004). Individuals with IFG have been shown to be more insulin resistant than those with IGT, who in turn apparently have a more severe deficit in both early and late phase insulin secretion (Tripathy et al 2000; Hanefeld et al 2003). The Diabetes Epidemi-

ology: Collaborative analysis Of Diagnostic Criteria in Europe study has shown that in 40-50% of the European population blood glucose concentrations will exceed diabetes diagnostic criteria at some point (The DECODE Study Group 2003). Indeed, it has been suggested that susceptibility to type 2 diabetes in todays prosperous society is a result of so called thrifty genes which during the centuries and millennia of frequent famines were advantageous for surviving as they favoured efficient energy storage (Neel 1962).

Twin studies have suggested that the majority of monozygotic twin pairs will become concordant for type 2 diabetes after one twin develops the disease. The concordance estimates vary between 60% and 100% (Lo et al 1991). The Finnish twin study has revealed that approximately half of the liability to type 2 diabetes is related to genetic effects and a half to environmental exposure (Kaprio et al 1992).

Type 2 diabetes is a serious illness complicated by micro- and macrovascular diseases such as renal failure, retinopathy, cardiovascular diseases, and lower limb amputations (Gerstein 1997). Diabetes without any prior evidence of coronary heart disease indicates a comparable or higher myocardial infarction and mortality risk than prior coronary heart disease in non-diabetic subjects, especially in women (Juutilainen et al 2005; Pajunen et al 2005). The late complications of type 2 diabetes are related to the duration of the disease and the degree of metabolic control (Eriksson et al 1989; UK Prospective Diabetes Study Group 1998; Stratton et al 2000). Therefore it is important to postpone the clinical onset of the disease and to keep the blood glucose profile as normal as possible.

### 2.3 Risk factors for type 2 diabetes

Non-modifiable risk factors for type 2 diabetes include genes, age, sex, and low birth weight especially if followed by rapid growth in childhood (Forsen et al 2000). At the moment, the susceptibility genes for type 2 diabetes are not known, and thus genetic predisposition cannot be directly diagnosed (Hansen and Pedersen 2005). There are, however, indirect ways to identify individuals who probably have the diabetes genes: family history (Gloyn and McCarthy 2001) and (in women) manifestation of gestational diabetes during pregnancy (Dornhorst and Rossi 1998; Kim et al 2002).

Type 2 diabetes prevalence increases steeply by increasing age (Wild et al 2004), which is partly explained by concurrent increase in other risk factor levels (Geiss et al 2006). Worldwide prevalence of type 2 diabetes is slightly higher among men than among women, but because women in general have longer life expectancy, there are more affected women than men in the world (Wild et al 2004).

The metabolic syndrome is a cluster of cardiovascular risk factors (Reaven 1988; Balkau and Charles 1999; World Health Organization 1999; Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults 2001; Bloomgarden 2003; Alberti et al 2005). In addition to obesity, the other components of the metabolic syndrome such as hypertension (Kannel et al 1991; Reaven et al 1996), hypertriglyceridemia (Dotevall et al 2004), and IGT or IFG (Saad et al 1988) have been shown as being independent risk factors for type 2 diabetes. The metabolic syndrome as whole has been shown to predict type 2 diabetes, accuracy somewhat depending on what definition has been used (Hanley et al 2003; Lorenzo et al 2003; Hanley et al 2005).

### 2.3.1 Obesity

***Diagnosis and classification of overweight and obesity***

Classification of overweight in adults is based on body mass index (BMI), which is calculated dividing weight (kg) by height (m) squared. BMI less than 18.5 kg/m$^2$ denotes underweight, BMI from 18.5 to 24.9 kg/m$^2$ denotes normal weight, and BMI 25.0 kg/m$^2$ or higher denotes overweight. Category overweight is further divided into pre-obese (BMI 25.0 - 29.9 kg/m$^2$), obese class I (BMI 30.0 - 34.9 kg/m$^2$), obese class II (BMI 35.0 - 39.9 kg/m$^2$), and obese class III (BMI $\geq$ 40.0 kg/m$^2$) (World Health Organization 2000). BMI is highly correlated (coefficient of correlation from 0.7 to 0.9) with body fat percentage and is widely used as a surrogate for total body fatness (Svendsen 2003). However, classification of individuals as having either 'normal' or 'excess' weight based solely on BMI is not accurate since it does not differentiate between overweight due to fat or muscle tissue, and it does not take into account the distribution of body fat. Especially the level of physical activity may confound the association between BMI and body fatness (Janssen et al 2004c).

Accumulation of fat on the central part of the body is generally considered an independent risk factor for obesity-related metabolic disorders (Misra and Vikram 2003). The term central or abdominal fat covers different fat compartments on the abdominal area. The most generally used classification separates visceral adipose tissue, referring to the fat accumulated inside the abdominal cavity, and subcutaneous adipose tissue. Reliable methods to measure both visceral and subcutaneous adipose tissue include magnetic resonance imaging and computed tomography, but these are not suitable for large epidemiological studies. Measurement of waist circumference has been shown to be a relatively valid predictor of visceral obesity (Lemieux et al 1996b; Han et al 1997a; Han et al 1997b; Rankinen et al 1999; Chan et al 2003). The association between waist circumference and metabolic disorders seems to be linear; nevertheless attempts have been made to define a cut-off point for healthy/unhealthy waist circumference. Lean and co-workers introduced waist action levels I ($\geq$ 94 cm for men and $\geq$ 80 cm for women) and II ($\geq$ 102 cm for men and $\geq$ 88 cm for

women), to identify most individuals with BMI 25 kg/m$^2$ or higher and 30 kg/m$^2$ or higher, respectively (Han et al 1995; Lean et al 1995). In the most recent criteria for the metabolic syndrome (Alberti et al 2005) central obesity (in people with Europid origin) is defined as waist circumference 94 cm or higher for men and 80 cm or higher for women but these cut-off points are not used alone to define abdominal obesity. The current Finnish consensus (Suomalainen Lääkäriseura Duodecim ja Suomen Akatemia 2005; Suomalaisen Lääkäriseuran Duodecimin ja Suomen lihavuustutkijat ry:n asettama työryhmä 2006) rounded up these figures and stated that waist circumference 80 cm or higher in women and 90 cm or higher in men denotes mildly increased, and 90 cm or higher in women and 100 cm or higher in men substantially increased disease risk. Waist-to-hip ratio has during the earlier years been the most commonly used measurement of central adiposity. However, it does not seem to have any advantage over the simpler measurement of waist circumference in predicting central fat accumulation (Lemieux et al 1996a; Lemieux et al 1996b; Han et al 1997a; Chan et al 2003) or disease risk (Chan et al 1994; Koh-Banerjee et al 2004; Wang et al 2005).

Women in average have higher body fat percentage compared with men; however, men are, probably from hormonal reasons, more susceptible to central fat accumulation (Vague 1956; Lemieux et al 1994). Predisposition to abdominal fat accumulation is partly genetically determined (Lemieux 1997; Montague and O'Rahilly 2000; Perusse et al 2001; Rice et al 2002), but also lifestyle-related factors are important (Marti et al 1991). Smoking is known to increase central fat accumulation (Barrett-Connor and Khaw 1989; Canoy et al 2005), as are high alcohol consumption (Dallongeville et al 1998; Lukasiewicz et al 2005) and low intake of dietary fibre (Ludwig et al 1999; Koh-Banerjee et al 2003).

***Prevalence and trends of obesity***

Obesity prevalence is increasing in both developed and developing countries throughout the world (Silventoinen et al 2004). Paradoxically, in developing countries it co-exists with underweight and malnutrition (World Health Organization 2000). In Western Europe prevalence rates above 20% among working-aged people are found in the United Kingdom, Germany, Finland and Greece (International Diabetes Federation 2003). Based on the findings from the FINRISK studies with four independent cross-sectional population surveys, the mean BMI increased from 26.4 to 27.0 kg/m$^2$ in men and from 25.9 to 26.2 kg/m$^2$ in women, from 1982 to 1997. Consequently the prevalence of obesity (BMI $\geq$30 kg/m$^2$) increased from 15.4 to 19.8 in men and from 17.2 to 19.4 in women (Lahti-Koski et al 2000), and the same development seems to have continued thereafter, based on the findings from the FINRISK 2002 Study (Männistö et al 2004). Our current lifestyle seems to result in gradual, continuous weight gain during the adult years, as shown by studies from Finland (Haapanen et al 1997a) and the UK (Wannamethee and Shaper 1999). Two studies from the USA sug-

gest that while 30 years ago a slight weight loss during the late middle-age years was typical among white men and women, today the opposite is reality (Williamson 2004).

***Association of obesity with type 2 diabetes***

Observations on time trends in diabetes mortality show that on periods with food shortage and famine, diabetes prevalence and mortality have declined (Himsworth 1935; West 1978), assumably because of energy imbalance and resulting weight reduction. In 1985 WHO named obesity the single most important modifiable risk factor for type 2 diabetes (World Health Organization 1985). BMI has been shown to be even more strongly associated with several components of the metabolic syndrome than measured body fat percentage (Bosy-Westphal et al 2005).

There seems to be an exponential increase in type 2 diabetes prevalence in accordance with the increase in BMI. Type 2 diabetes is most prevalent among populations with high obesity rates, e.g. the Pima Indians of Arizona and the urbanised Micronesians of Nauru (King and Rewers 1991). In the large Nurses' Health Study (n = 114 281) women's risk of being diagnosed with diabetes during the 14 years of follow-up was five-fold in the BMI group of 24.0 - 24.9 kg/m$^2$, 40-fold in the 31.0 - 32.9 kg/m$^2$ and 93-fold in the over 35 kg/m$^2$ category compared with the BMI group of under 22.0 kg/m$^2$ (Colditz et al 1995). Among American male health professionals (n = 27 338, follow-up 5 years) the trend was similar though less steep, with 1.5-fold risk in the 24.0 - 24.9 kg/m$^2$, 12-fold risk in the 31.0 - 32.9 kg/m$^2$, and 42-fold risk in the over 35 kg/m$^2$ category compared with those with BMI under 23.0 kg/m$^2$ (Chan et al 1994). The trend has been observed also in the FINRISK populations, in which 90% of those who were diagnosed with diabetes during the mean follow-up of 9.4 years had BMI over 25 kg/m$^2$ at baseline (Hu et al 2004). Also a long duration of obesity (Sakurai 2000; Janssen et al 2004b) and body weight increase despite the baseline weight (Chan et al 1994; Colditz et al 1995; Wannamethee and Shaper 1999), have been shown to be associated with increasing type 2 diabetes risk.

The observation of the association between central fat accumulation and type 2 diabetes dates back to the 1950's (Vague 1956) and has thereafter been asserted by numerous studies (Lapidus et al 1984; Ohlson et al 1985; Lundgren et al 1989b; Van Noord et al 1990; Koh-Banerjee et al 2004). In some studies visceral adipose tissue has been a better predictor of the features of insulin resistance (Lemieux et al 1996a; Ross et al 1996; Bonora 2000; Cnop et al 2002; Lebovitz and Banerji 2005); in other studies accumulation of subcutaneous adipose tissue has been equally deleterious (Goodpaster et al 1997; Smith et al 2001). Waist circumference has been even more closely than BMI associated with insulin resistance and cardiovascular risk factors (Van Pelt et al 2001; Zhu et al 2002; Janssen et al 2004a; Racette et al 2006). In prospective epidemiological studies waist circumference has

been an independent predictor of type 2 diabetes risk (Chan et al 1994; Carey et al 1997; Koh-Banerjee et al 2004; Wang et al 2005).

Fat accumulation leads to increased insulin resistance which in turn predicts the development of type 2 diabetes (Haffner 1998; Lewis et al 2002). The pathophysiology of increased body fatness is not fully understood, even though it is today recognised that adipose tissue is not a passive energy depot, but active endocrine tissue. It serves as an important source of cytokines, including leptin, tumour necrosis factor alpha, angiotensin II and interleukin-6, which are markers of low-grade inflammation and endothelial dysfunction, as well as anti-inflammatory molecules, such as adiponectin (Sharma and Chetty 2005). Cytokines may increase hepatic production of the inflammation marker C-reactive protein, and induce insulin resistance (Bastard et al 2006). Animal models have shown that lipodystrophy (genetically-based lack of subcutaneous adipose tissue) is associated with severe insulin resistance and similar findings have been seen also in humans (Simha and Garg 2006). Insulin resistance associated with both excess and lack of adipose tissue might have a common background. It seems that adipose tissue works as a buffer for fatty acids, and at some point the buffer capacity is exceeded, either due to obesity or due to absence of adipose tissue (Yki-Järvinen 2005). This so-called lipotoxicity-theory suggests that obesity predisposes ectopic fat accumulation into cells outside the adipose tissue, followed by reduction in the insulin sensitivity of muscle cells and decrease in the pancreatic beta cells ability to react to hyperglycaemia with sufficient insulin production (Frayn 2002).

Convincing evidence on the effect of reduction of excess body fat on type 2 diabetes incidence comes from the Swedish SOS Intervention Study (Sjöström et al 1999). The 2-year incidence of diabetes in surgically treated (gastric banding, gastroplasty, or gastric bypass) obese subjects (n = 845) was reduced 30-fold compared to matched control subjects (n = 845) receiving regular care. Mean baseline BMI was 41.0 $kg/m^2$, and the corresponding mean weight losses were 28 kg vs. 0.5 kg, respectively. After 10 years, diabetes incidence was still markedly lower in the surgically treated group (Sjöström et al 2004). Due to the nature of the treatment, the treatment groups could not be assigned at random, but this apparently does not change the interpretation of the results: sustained weight reduction, achieved one way or another, is a powerful method to decrease type 2 diabetes risk.

Even though obesity is an important risk factor for type 2 diabetes, not all obese people get diabetes during their lifetime. Due to genetic background, some people are more prone to develope insulin resistance when exposed to environmental risk factors (e.g. obesity), but some are more tolerant (Herbert et al 2006). Also, some individuals, when insulin resistant, are able to augment insulin production to overcome the increased demand, but some are not (Saxena et al 2006).

***Prevention and treatment of obesity***

Observational follow-up studies offer the scientific basis for tackling risk factors that are believed to increase the risk of becoming obese. However, only few studies have actively focused on long-term prevention of weight gain in adults. In the Women's Healthy Lifestyle Project low-fat, reduced energy diet and increased physical activity prevented 5-year weight gain in postmenopausal women (Simkin-Silverman et al 2003). In some studies aiming at lifestyle modifications to reduce other health risks prevention of weight increase has been a side finding. Low-fat and/or high-fibre diet which originally aimed at inhibition of development of recurrent colorectal adenoma was associated with modestly reduced weight during 4-year follow up in the study by Schatzkin and co-workers, (Schatzkin et al 2000). In the Women's Health Initiative aiming at cancer and cardiovascular disease risk reduction through low-fat diet there was a modest weight reduction among the active intervention group women compared with the slight increase in the control group during mean follow-up of 8.1 years (Howard et al 2006b).

Sedentary lifestyle has been shown to be associated with obesity (Helmrich et al 1991; King et al 2001). However, it is not totally clear which is the cause and which is the consequence; in one study obesity predicted physical inactivity more than physical inactivity predicted obesity (Petersen et al 2004). In a Finnish follow-up study working-aged men and women who were physically inactive at baseline and still at 10-year follow-up gained weight, as did those who were physically active at baseline but no longer at 10-year follow-up, but those who either remained or become physically active did not gain weight (Haapanen et al 1997a). Similar findings have been seen in other prospective studies (Rissanen et al 1991; Williamson et al 1993; Schmitz et al 2000; Droyvold et al 2004). Physical activity may also protect against weight regain after weight loss (Fogelholm and Kukkonen-Harjula 2000; van Baak et al 2003). Physical activity directly increases energy expenditure and also through its effect on increasing muscle mass may have an effect on long-term energy balance. According to the consensus statement of the International Association for the Study of Obesity prevention of weight gain requires approximately 45 to 60 minutes per day of moderate intensity activity, and 60 to 90 minutes in formerly obese subjects (Saris et al 2003). Therefore, to achieve weight reduction or to prevent weight gain, also reduction in energy intake through dietary modification is usually necessary.

Studies with strictly controlled energy intake have shown that weight reduction can be achieved with any dietary regimen as long as energy intake is lower than energy expenditure (Luscombe et al 2003; Johnston et al 2004; Meckling et al 2004; Dansinger et al 2005). Permanently reduced energy intake, which is mandatory for weight loss maintenance unless energy expenditure by physical activity is clearly increased, is more difficult to achieve (Wing and Hill 2001; Borg et al 2004).

For several decades, the conventional approach for weight control has been reduction of fat intake. According to a review by Astrup and co-workers a 4-5 kg weight loss can be achieved with a 10 percentage unit reduction in energy proportion (E%) of dietary fat in obese individuals, shown at least in short-term (< 1 year) studies (Astrup et al 2002). Fat contains more energy per gram than other energy yielding nutrients and also makes diet palatable, but simultaneously less satiating, and therefore a high-fat diet is believed to promote weight gain (Blundell et al 1996; Bray and Popkin 1998; Hill et al 2000); however the issue is controversial (Seidell 1998; Willett 2002). In recent studies (Foster et al 2003; Samaha et al 2003) a low-carbohydrate diet resulted in more pronounced short-term weight reduction compared with conventional low-energy, low-fat dietary regimen, probably because the achieved energy deficit was larger. However, the statistically significant difference in early weight loss between the groups disappeared at 12 months (Foster et al 2003; Stern et al 2004), indicating that individuals are not able to adhere to such restricted diet. Moreover, the long-term safety of low-carbohydrate diets in weight-stable individuals is not known (Crowe 2005).

Still another popular, and evidently efficient (Johnston et al 2004; McAuley et al 2005; McAuley et al 2006) weight control approach is to increase protein intake up to 30% of total energy, with decrease in either fat or carbohydrate intake. An increase in protein intake may increase patient satisfaction during low-fat, energy restricted diet (Johnston et al 2004) and has been shown to accelerate weight loss (Eisenstein et al 2002) and prevent weight regain (Westerterp-Plantenga et al 2004). The effect is probably a consequence of increased satiety during high-protein diet. In theory protein could increase energy expenditure due to its higher thermic effect of food compared with fat or carbohydrate, but there are no human studies to support this (Schoeller and Buchholz 2005).

The intake of dietary fibre has been shown to be inversely correlated with body weight and weight change (Ludwig et al 1999; Howarth et al 2001; Liu et al 2003). High-fibre diets may cause greater satiation and thus limit energy intake directly by increasing gastric distension and feeling of fullness or indirectly through secretion of gut hormones (incretins), and increase satiety through delaying gastric emptying and nutrient absorption (Pereira and Ludwig 2001). Furthermore, fibre may decrease dietary energy intake by reducing absorption of fat and protein (Howarth et al 2001).

In contemporary food culture other signals than the need for energy seem to guide the initiation and termination of eating. Increasing food portions and package sizes have been hypothesised to lead to energy over-consumption and consequent weight increase (Nielsen and Popkin 2003). In clinical studies individuals have increased the amount they eat simply when they have been offered the food in larger portions (Diliberti et al 2004; Rolls et al

2004). Yet another recently recognised factor potentially influencing energy intake is the energy density of diet (Rolls and Bell 1999), which is calculated as energy (kcal) per weight (g) of food. People have been shown to be only partly able to compensate for changes in dietary energy density by increasing or decreasing the total amount of food consumed, at least in short-term clinical studies (Stubbs et al 1998; Bell and Rolls 2001; Devitt and Mattes 2004), and are thus prone to energy over-consumption when the energy density of diet increases (Ledikwe et al 2006). High consumption of typical modern (snack) foods that have large portion sizes, high palatability combined with high energy density (Ovaskainen et al 2006) in the form of fat and/or refined carbohydrates such as sugar may thus contribute to weight gain.

### 2.3.2 Diet composition

Table 2 lists studies that have prospectively examined the association of quality and quantity of fat, carbohydrates (quality measured as glycaemic index and glycaemic load) and fibre intakes on type 2 diabetes risk.

***Fat***

In experimental animal models high fat feeding typically results in insulin resistance (Storlien et al 1986; Storlien et al 1991) and the same effect was seen in a short-term clinical study with healthy women (Lovejoy et al 1998). Epidemiological cross-sectional studies have suggested high total fat intake to be a risk factor for insulin resistance, glucose intolerance or type 2 diabetes (Marshall et al 1991). Data from prospective studies are less consistent. In the San Luis Valley Diabetes Study high fat intake predicted conversion from IGT to type 2 diabetes (Marshall et al 1994) and hyperinsulinemia (Marshall et al 1997). In the Finnish and Dutch cohorts of the Seven Countries Study baseline intakes of total fat, saturated fat and monounsaturated fat were higher among those who were diagnosed with diabetes in the follow-up study 20 years later (Feskens et al 1995). In the Health Professionals Follow-up Study total fat intake was associated with diabetes risk during the 12-year follow-up, but the association was attenuated after adjustment for BMI (van Dam 2002).

Type of fat, rather than total fat intake, has in several studies been associated with increased type 2 diabetes risk, as reviewed by Hu and co-workers (Hu et al 2001c). Saturated fat has been associated with increased diabetes risk in some studies (Feskens et al 1995; van Dam et al 2002b). In the Nurses' Health Study (Salmeron et al 1997b; Salmeron et al 2001) no association between saturated fat and diabetes was found; however, intake of trans fatty acids was associated with increased and intake of polyunsaturated fatty acids with decreased diabetes risk (Salmeron et al 2001). In the Iowa Women's Health Study, high intake of vegetable fat and polyunsaturated fatty acids decreased diabetes risk (Meyer

et al 2001). On the other hand, the omega-3 polyunsaturated fatty acids increased and trans fatty acids decreased diabetes risk, which is in controversy with the results from other studies (Adler et al 1994; Salmeron et al 2001). The mixed findings may originate from the fact that in different food cultures, the sources of nutrients differ. In typical Western diet with low intake of olive or rapeseed oil, monounsaturated fat comes mainly from animal sources (meat, milk products) and thus is highly correlated with saturated fat intake, whereas in the Mediterranean diet the dominant source of monunsaturated fat is olive oil. Furthermore, the effect of trans fatty acids on metabolism may depend on whether the trans fat is from natural (milk and ruminant meat) or industrial (partially hydrogenated vegetable oil) origin (Chardigny et al 2006) or simply on the intake level (van de Vijver et al 2000).

In a three-month clinical study (KANWU; acronym refering to location of study centres in Kuopio, Aarhus, Naples, Wollongong, and Uppsala) substituting dietary saturated fat for monounsaturated fat impaired insulin sensitivity in healthy individuals, but the beneficial effect of monounsaturated fat was only seen at total fat intake below median intake of 37% of total energy (Vessby et al 2001). Omega-3 polyunsaturated fatty acids given as fish oil supplement did not have any effect on insulin sensitivity. In another study completed in Finland an 8-week diet enriched in monounsaturated fat (19 E%) improved glucose metabolism after a high-saturated fat (18 E%) diet in individuals with IGT (Sarkkinen et al 1996).

Several mechanisms may be behind the observed effects of quality of fat on insulin sensitivity and subsequent diabetes risk. Dietary fat composition modifies the composition of the cell membrane phospholipids, and saturated fat seems to decrease the membrane fluidity and impair insulin sensitivity (Storlien et al 1996). Polyunsaturated fat also decreases triacylglycerol accumulation into muscle and pancreatic beta-cells, compared with saturated fatty acids, and may thus modify the lipotoxisity effect (Clarke 2001). Dietary fatty acids may have an effect on the low-grade systemic inflammation and endothelian dysfunction, which in turn may induce insulin resistance. In a subgroup analysis of the Nurses' Health Study, trans fatty acid intake was directly and omega-3 fatty acid intake was inversely associated with inflammation markers C-reactive protein and interleukin-6 (Lopez-Garcia et al 2004; Lopez-Garcia et al 2005). Furthermore, fatty acid composition of diet may modulate insulin secretion, monounsaturated fat appearing to have the most beneficial effect (Rojo-Martinez et al 2006).

***Fibre***

Fibre intake, especially from cereal origin, has consistently been shown to be inversely associated with type 2 diabetes risk. The early analyses from the Nurses' Health Study I (Salmeron et al 1997b) showed an association; however, the later analyses with longer follow-up did not (Salmeron et al 2001). In the younger cohort (Nurses' Health Study II*)*

the association was apparent (Schulze et al 2004a), as also in the Health Professionals Follow-up Study (Salmeron et al 1997a), the Iowa Women's Health Study (Meyer et al 2000), the Atherosclerosis Risk in Communities Study (Stevens et al 2002) and the Finnish Mobile Clinic Health Examination Survey (Montonen et al 2003).

The protective effect may result from the ability of fibre to lower post-prandial glucose peak, which leads to decreased insulin demand and protects the pancreas from exhaustion. Fibre is known to slow down the digestion and absorption of carbohydrates, but this applies mostly on soluble fibre (Jenkins et al 1978); however, specifically unsoluble (cereal) fibre has in several studies been associated with decreased diabetes risk (Salmeron et al 1997a; Salmeron et al 1997b; Meyer et al 2000; Stevens et al 2002; Montonen et al 2003; Schulze et al 2004a). A possible mediator of the effect is the enhanced secretion of gut-hormones (glucoincretins) glucagon-like peptide-1 and gastric inhibitory peptide. They are intestinal peptides secreted in response to glucose, lipid, or non-digestible carbohydrate ingestion, and are responsible for the rapid insulin response to a meal (Burcelin 2005). In a clinical study the consumption of highly purified insoluble dietary fibres accelerated the acute gastric inhibitory peptide and insulin response, and was further associated with enhanced post-prandial carbohydrate handling the following day (Weickert et al 2005). Short-term (three days) ingestion of purified insoluble fibre has also been shown to increase whole-body insulin sensitivity in overweight women (Weickert et al 2006).

***Carbohydrates***

Total carbohydrate intake has typically not been associated with type 2 diabetes risk, when other dietary factors have been adjusted for. It is evident that the quality of carbohydrates is more important than total amount. It is well established that carbohydrates from different sources produce different glycaemic (Jenkins et al 1994; Wolever et al 1994; Wolever and Mehling 2002) or insulinogenic responses (Juntunen et al 2003a; Juntunen et al 2003b). The effect of carbohydrate on blood glucose depends on how fast it is digested. The glycaemic index refers to the ability of carbohydrate contained in a specific food item to raise blood glucose, compared with same amount of carbohydrate (typically 50g) as glucose. Dietary glycaemic load is estimated from glycaemic index by multiplying it with the amount of carbohydrates. In prospective studies dietary glycaemic index has been more consistently than glycaemic load associated with increased diabetes risk (Salmeron et al 1997a; Salmeron et al 1997b; Meyer et al 2000; Hodge et al 2004; Schulze et al 2004a). However, diet high in cereal fibre is usually also high in carbohydrates and has low glycaemic index, and this may confound the observed associations.

Intake of sucrose has in general not been associated with type 2 diabetes (Daly 2003; Hodge et al 2004). In the Nurses' Health Study II high intake of sugar-sweetened

beverages did increase diabetes risk (Schulze et al 2004b); however, in the USA beverages are typically sweetened with high-fructose corn syrup (Bray 2004), and high consumption of soft drinks can thus lead to unnaturally high intake of fructose, which in turn may disturb glucose and lipid metabolism (Basciano et al 2005; Nakagawa et al 2006). Fructose may increase diabetes risk also indirectly through weight gain (Elliott et al 2002). Fructose ingestion does not stimulate insulin or leptin secretion; as these hormones are major regulators of energy intake, high fructose consumption may lead to energy over-consumption and obesity.

***Other dietary factors***

Other dietary factors that have been proposed to have a role in progression to type 2 diabetes include vitamin C (Feskens et al 1995), vitamin D (Boucher 1998; Pittas et al 2006), vitamin E (Montonen et al 2004), several tocopherols (Montonen et al 2004), calcium (Pittas et al 2006), and most consistently magnesium (Colditz et al 1992; Salmeron et al 1997a; Salmeron et al 1997b; Lopez-Ridaura et al 2004; Song et al 2004a), all with protective effects. Intake of alcohol seems to have protective effect asociated with moderate consumption but increased risk with high consumption (Stampfer et al 1988; Holbrook et al 1990; Ajani et al 2000; Hodge et al 2006). High intake of processed meat products has been associated with higher diabetes risk (van Dam et al 2002b; Fung et al 2004; Song et al 2004b). Protective effects of high whole-grain (Meyer et al 2000; Fung et al 2002; Pereira et al 2002a; Montonen et al 2003) and fruit and vegetable intake (Sargeant et al 2001; Liu et al 2004; Montonen et al 2005a) have been reported. High dairy intake has been associated with decreased (Pereira et al 2002b; Choi et al 2005) diabetes risk. A novel finding is the association of high coffee consumption (~ 6 cups/day or more) and reduced diabetes risk (Salazar-Martinez et al 2004; Tuomilehto et al 2004; van Dam et al 2006).

During the past decade there has been a shift in the research from single nutrients or food items towards dietary patterns. In general, studies completed among different populations and food cultures have consistently shown that changing from traditional dietary patterns (typically including unrefained grains and vegetables) to a Western dietary pattern (characterized by high intakes of refined grains, high-fat foods items and sugar) has lead to increase in type 2 diabetes incidence (Hu et al 2001b; van Dam et al 2002a; Fung et al 2004; Montonen et al 2005b).

**Table 2. Epidemiologic follow-up studies on type 2 diabetes risk in relation to fat, carbohydrate, and fibre intake.**

| Data source | Follow-up time | Age Sex | n | DM cases | Dietary assessment | Reported associations |
|---|---|---|---|---|---|---|
| Gothenburg Study (Lundgren et al 1989a) | 12 years | 38-60 F | 1462 | 43 | 24-hour recall, diet records | No associations |
| Zutphen Study (Feskens and Kromhout 1989) | 25 years (median 16 years) | 40-59 M | 841 | 58 | Dietary history | No associations |
| The San Luis Valley Diabetes Study (Marshall et al 1994) | 22.6 months | 30-74 F | 134, IGT at baseline | 20 | 24-hour recall | Total fat ↑ |
| Seven Countries Study, Finnish and Dutch cohorts (Feskens et al 1995) | 20 years | 50-69 M | 338 | 26 | Dietary history | Total fat ↑, SAFA ↑, MUFA ↑, cholesterol ↑ |
| Nurses' Health Study (Colditz et al 1992) | 6 years | 30-55 F | 84360 | 702 | FFQ | Vegetable fat ↓<br>NA: Protein, sucrose, carbohydrate, fibre |
| Nurses' Health Study (Salmeron et al 1997b) | 6 years | 40-65 F | 65173 | 915 | FFQ | Glycaemic index ↑, glycaemic load ↑, total fibre ↓, cereal fibre ↓<br>NA: Vegetable fat, animal fat, SAFA, PUFA, MUFA, carbohydrates, fruit fibre, vegetable fibre |
| Nurses' Health Study (Salmeron et al 2001) | 14 years | 34-59 F | 84204 | 2507 | FFQ | PUFA ↓, vegetable fat ↓, cholesterol ↑, trans FA ↑<br>NA: Total fat, animal fat, SAFA, MUFA, carbo-hydrates, total fibre, fruit fibre, vegetable fibre |
| Nurses' Health Study II (Schulze et al 2004a) | 8 years | 24-44 F | 91249 | 741 | FFQ | Glycaemic index ↑, cereal fibre ↓, fruit fibre ↓<br>NA: Glycaemic load, total carbohydrates, total fibre, vegetable fibre |
| Health Professionals Follow-up Study (Salmeron et al 1997a) | 6 years | 40-75 M | 42759 | 523 | FFQ | Glycaemic index ↑, cereal fibre ↓<br>NA: Glycaemic load, vegetable fat, animal fat, SAFA, PUFA, MUFA, carbohydrates, total fibre, fruit fibre, vegetable fibre |

| | | | | | | |
|---|---|---|---|---|---|---|
| Health Professionals Follow-up Study (van Dam et al 2002b) | 12 years | 40-75 M | 42504 | 1321 | FFQ | Total fat ↑ (NA after adjusment with BMI), SAFA ↑ (NA after adjustment with BMI) NA: Oleic acid, linoleic acid, trans FA, α-linolenic acid, long-chain n-3 fatty acids |
| The Iowa Women's Health Study (Meyer et al 2000) | 6 years | 55-69 F | 35988 | 1141 | FFQ | Total fibre ↓, glycaemic index ↑, cereal fibre ↓, insoluble fibre ↓, glucose ↑, sucrose ↑, fructose ↑ NA: Carbohydrates, starch, lactose, maltose, glycaemic load, soluble fibre, fruit fibre, vegetable fibre, legume fibre |
| The Iowa Women's Health Study (Meyer et al 2001) | 11 years | 55-69 F | 35988 | 1890 | FFQ | Vegetable fat ↓, PUFA ↓, trans FA ↓, cholesterol ↑, long-chain n-3 PUFA ↑ |
| The Atherosclerosis Risk in Communities Study (Stevens et al 2002) | 9 years | 45-64 M, F | 12251 | 1447 | FFQ | Cereal fibre ↓ (in whites only) NA: Total fibre, fruit fibre, legume fibre, glycaemic index, glycaemic load |
| The Finnish Mobile Clinic Health Examination Survey (Montonen et al 2003) | 10 years | 40-69 M, F | 4316 | 156 | FFQ | Cereal fibre ↓, total fibre ↓, insoluble fibre ↓ NA: Soluble fibre, fruit fibre, vegetable fibre |
| The European Prospective Investigation of Cancer-Norfolk Study (Harding et al 2004) | 5 years | 40-78 M, F | 23631 | 414 | Dietary history | P/S ↓ (NA after adjusment with BMI) NA: Total fat |
| The Melbourne Collaborative Cohort Study (Hodge et al 2004) | 4 years | 40-69 M, F | 31641 | 365 | Dietary history | Carbohydrate ↓ (NA after adjusment with BMI), glycaemic index↑ (NA after adjustment with BMI), sugars ↓, starch ↑ NA: Fibre, glycaemic load |

DM = diabetes mellitus; M = males; F = females; FFQ = Food Frequency Questionnaire; NA = No association; BMI = body mass index; MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; SAFA = saturated fatty acid; trans FA = trans fatty acid;
↓ = decreased risk, ↑ = increased risk.

### 2.3.3 Physical inactivity

Physical activity protects against type 2 diabetes both through its effect on adiposity and independently, as has been consistently shown by several prospective studies (Helmrich et al 1991; Manson et al 1991; Manson et al 1992; Burchfiel et al 1995; Perry et al 1995; Lynch et al 1996; Haapanen et al 1997b; Hu et al 1999; Folsom et al 2000; Hu et al 2001a; Hu et al 2003; Kriska et al 2003; Hu et al 2004). The physiological mechanism behind the risk reduction is increased insulin sensitivity, as shown by exercise training studies (Houmard et al 1993; Cox et al 1999; Duncan et al 2003). An observational study with 1467 middle-aged men and women with either normal or impaired glucose tolerance or type 2 diabetes showed that habitual participation in physical activities is clearly associated with insulin sensitivity (Mayer-Davis et al 1998). Furthermore, the effect of training on insulin sensitivity seems to be independent of sex, age, and obesity status (Cox et al 1999) and change in body weight (Duncan et al 2003).

### 2.3.4 Other lifestyle factors

Smoking is a well-recognised health hazard (World Health Organization 2002). In addition to its effects on cardiovascular and cancer morbidity, it induces central obesity (Barrett-Connor and Khaw 1989; Marti et al 1991; Canoy et al 2005), and increases the risk of developing type 2 diabetes (Foy et al 2005; Patja et al 2005). Smoking may contribute to the development of insulin resistance, however, the mechanism behind these effects is not fully understood (Reaven and Tsao 2003).

Another feature of modern lifestyle is voluntary restriction of sleep duration. Self-reported sleep duration has decreased, and during the same time obesity and type 2 diabetes have reached epidemic proportions (Spiegel et al 2005). Both short and long sleep duration have been associated with increased diabetes risk (Ayas et al 2003; Mallon et al 2005; Yaggi et al 2006). In clinical studies even short-term sleep deprivation has modified hormonal balance and resulted in decreased insulin sensitivity and glucose tolerance, and impaired neuroendocrine regulation of appetite, which in turn may lead to weight gain (Spiegel et al 2005).

## 2.4 Previous lifestyle intervention studies to prevent type 2 diabetes

There are some natural experiments available in which ethnic groups have experienced rapid westernisation and with it a rapid increase in the rates of obesity and type 2 diabetes. Pima Indians living in Arizona have five-fold prevalence of type 2 diabetes compared with those living in the Sierra Madre mountains in Mexico (Schulz et al 2006). In the experiments by O'Dea and co-workers Australian Aboriginals changed their lifestyle back to the traditional hunter-gatherer way of life, and as a result, hyperglycaemia reversed (O'Dea

1980). Therefore it is logical to assume that by reversing the lifestyle transition it would be possible to prevent the development of the disease.

### 2.4.1 The Malmö feasibility study

The feasibility of diet and exercise intervention in 217 men with IGT was assessed in the Malmö feasibility study (Eriksson and Lindgärde 1991). The effect of exercise and diet (n = 161) was compared to a control group (n = 56) with no intervention. The groups were not assigned at randomly, since the reference group consisted of men who themselves decided not to join the intervention programme. Lifestyle intervention was delivered in group sessions, aiming at reduction in the intake of refined sugar, simple carbohydrates, fat, saturated fat, energy, and alcohol (if relevant) and increase in the intake of complex carbohydrates and vegetables. Physical activity training consisted of two weekly 60 minute sessions with various dynamic activities.

By the end of the 5-year study period 11% of the intervention group and 29% of the reference group had developed type 2 diabetes. This study is important in demonstrating the feasibility of carrying out a diet and exercise programme for 5 years among volunteers, and suggests that the incidence of type 2 diabetes might be reduced by approximately 50%. Overall, the progression to diabetes in these Swedish men was relatively low even in the reference group compared with the data from the observational studies (Knowler et al 1995). Even among the men in the control group some may have changed their lifestyle as a result of the screening programme. Thus, the results based on intention-to-treat analysis may underestimate the true effect of lifestyle changes. The intervention resulted in significant changes in lifestyle and physiological parameters. Furthermore, 12 year mortality among the IGT subjects who had participated in the intervention was comparable to that of the originally normoglycaemic men, and lower than that of the IGT control group men (Eriksson and Lindgärde 1998). While the results on diabetes risk in the Malmö feasibility study are likely to be due to the effects on diet and exercise, the non-randomised study design limits the generalisability of the results.

### 2.4.2 The Da Qing IGT and Diabetes Study

A cluster-randomised clinical trial in Da Qing, China reported promising results on the preventive effect of a diet and exercise intervention on type 2 diabetes risk (Pan et al 1997). Altogether 577 subjects (> 25 years) with IGT were assigned either to the control, exercise alone, diet alone, or exercise plus diet group. In clinics assigned to dietary intervention the participants were encouraged to reduce weight if baseline BMI was 25 $kg/m^2$ or higher (61% of all participants) aiming at 23 $kg/m^2$. Otherwise high-carbohydrate (55-65 % of energy) and moderate-fat (25-30% of energy) diet was recommended. Counselling was

done individually by physicians, and also group sessions were organised weekly for the first month, then monthly for 3 months, and every 3 months thereafter. In clinics assigned to physical exercise counselling sessions were arranged at a similar frequency. The participants were encouraged to increase their level of leisure-time physical activity by at least 1 - 2 units per day, with one unit corresponding for instance of a 30 minute slow walk, a 10 minute slow run or a 5 minute swim.

The cumulative 6-year incidence of type 2 diabetes was lower in each of the three intervention groups (41 - 46%) compared with the control group (68%). In this study the relative risk reduction was approximately 40% while the absolute risk reduction was 22 - 26% during the 6-year period.The progression rate from IGT to diabetes was high, more than 10% per year in the control group, which is more than usually reported in observational studies.

The study did not apply an individual allocation of study participants to the intervention and control groups, but the participating clinics were assigned. Furthermore, the participants were relatively lean (the mean baseline BMI 25.8 $kg/m^2$) making inferences for instance to European obese people with IGT difficult. The overall changes in risk factor patterns were relatively small. Body weight did not change in lean subjects, and there was a modest (~ 1 $kg/m^2$) weight reduction in participants with baseline BMI over 25 $kg/m^2$. Also the estimated changes in habitual dietary nutrient intakes were small and non-significant between groups. Thus, it is not easy to determine the factors responsible for the beneficial effects on the risk of type 2 diabetes. It is nevertheless obvious that weight control was not the key issue. Thus, physical activity and qualitative changes in diet that are difficult to measure on individual level probably played an important role.

## 2.5 Identification of target groups for intervention

### 2.5.1 Rationale for screening

The definition of screening, in its strict form, is "*The presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably have not"* (Wilson and Jungner 1968). The goal of screening is to reduce morbidity or mortality from the disease by early treatment of the cases discovered. Further, the term screening programme includes early detection and treatment of the disease. Screening programme should only be set for diseases that pass through a preclinical phase, and early treatment must offer some advantage over later treatment (Morrison 1992).

Type 2 diabetes develops gradually and is characterised by a lengthy preclinical phase including IGT and asymptomatic diabetes (Harris et al 1992). Correspondingly, 25-50% of affected individuals are not aware of their disease (Gregg et al 2004; Mayor 2005; Rathmann et al 2005; Thomas et al 2005; Ylihärsila et al 2005; Peltonen et al 2006). Diabetes-related microvascular lesions are common already at the time of diagnosis: in the United Kingdom Prospective Diabetes Study (UKPDS) 35-39% of new diabetes patients had clinical retinopathy (Kohner et al 1998). The same study also demonstrated that aggressive treatment of glycaemia prevents or delays diabetic complications (U.K. Prospective Diabetes Study Group 1998a; U.K. Prospective Diabetes Study Group 1998b). It is thus justifiable to argue that type 2 diabetes fulfils the criteria for screening.

The performance of screening test is usually estimated as the sensitivity (the probability of having a positive screening test given the presence of the disease), the specificity (the probability of having a negative screening test given the absence of the disease), and the positive predictive value (PPV, the proportion of individuals with the disease among those who had positive screening test), which also depends markedly on the overall prevalence of the condition. The performance of a screening test depends on the cut-off point that is chosen to define a positive test. The higher the cut-off point, the lower the sensitivity and higher the specificity, and vice versa. The receiver-operating characteristic (ROC) curve is frequently used to analyse how well a continuous variable predicts the outcome, and also to identify the cut-off value with the best combination of sensitivity and specificity. If the sensitivity increases steeply by increasing cut-off value, with only a relatively slow accumulation of false-positive results, the area under the ROC curve (AUC) will be large. The optimal cut-off point for a positive test is the 'peak' value of the curve. (Silman 1995)

**Table 3. Methods to screen for prevalent type 2 diabetes.**

| Data source | Age | n | DM diagnosis | DM cases | Predictive variables | SENS | SPEC | PPV | AUC |
|---|---|---|---|---|---|---|---|---|---|
| **'The ADA risk score'** The Second National Health and Nutrition Examination Survey (Herman et al 1995) | 20 - 74 | 3770 | OGTT (WHO 1985) | 164 | Age, sex, delivery of macrosomic infant, race, education, obesity, sedentary lifestyle, family history of DM | 79% | 65% | 10% | 0.78 |
| Model validation: Opportunistic screening of American subjects (Rolka et al 2001) | ≥20 | 1065 | | 157 | | 75% | 51% | | |
| **'Symptom-risk questionnaire'** The Hoorn Study | 50 - 74 | 2364 | OGTT (WHO 1985) | 110 | Age, sex, obesity, family history of DM, use of antihypertensive drug, frequent thirst, pain during walking, shortness of breath during walking, reluctance to use bicycle for transportation | | | | 0.80 |
| Model validation: Random sample from Hoorn population (Ruige et al 1997) | 45 - 74 | 786 | | 32 | | 72% | 56% | 6.5% | 0.69 |
| **'Routine data models'** The Rotterdam Study | 55 - 75 | 1016 | OGTT (WHO 1985) | 118 | Model 1:Age, sex, obesity, use of antihypertensive medication | | | | |
| Model validation: The Hoorn Study (Baan et al 1999) | 50 - 74 | 2364 | | 110 | Model 2: Also family history of DM, physical inactivity, BMI | M1: 78% M2: 72% | M1: 55% M2: 55% | M1: 8% M2: 7% | M1: 0.68 M2: 0.74 |
| **'The Cambridge risk score'** The Ely Study (ES; ½), The Wessex Study (WS) | 40 - 64 | 549 (ES) + 101 (WS) | ES: OGTT (WHO 1985), WS: DM diagnosed in 12 months | 25 (ES) + 101 (WS) | Age, sex, BMI, family history of DM, use of antihypertensive or steroid medication, smoking | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Model validation: The Ely Study (½) (Griffin et al 2000) | 40 - 64 | 528 | | 23 | | 77% | 72% | | 0.80 |
| The European Prospective Investigation of Cancer-Norfolk Study (Park et al 2002) | 39 - 78 | 6567 | $HbA_{1c}$ ≥7% | 84 | | 51% | 78% | | 0.74 |
| **'Multivariate predictive equation'** Diabetes in Egypt Project | ≥20 | 1032 | OGTT (ADA) | 4.9% | Age, sex, BMI, random capillary plasma glucose, time (hours) since last meal | 65% | 96% | 67% | 0.88 |
| Model validation: American subjects (Tabaei and Herman 2002) | ≥20 | 1065 | | 157 | | 62% | 96% | 63% | |
| **'Danish diabetes risk score'** Population-based sample Inter99 (½) | 30 - 60 | 3250 | OGTT (WHO 1999) | 135 | Age, sex, BMI, family history of DM, known hypertension, physical activity | 73% | 74% | 11% | 0.80 |
| Model validation: Inter99 (½) | 30 - 60 | 2874 | | 117 | | 67% | 74% | 10% | 0.76 |
| ADDITION pilot study (Glümer et al 2004) | 40 - 69 | 1028 | | 29 | | 76% | 72% | 7% | 0.80 |

DM = diabetes mellitus; SENS = sensitivity; SPEC = specificity; PPV = positive predictive value; AUC = area under the receiver-operating characteristic (ROC) curve; OGTT = oral glucose tolerance test; WHO = World Health Organization; ADA = American Diabetes Association; BMI = body mass index; $HbA_{1c}$ = glycosylated haemoglobin; ES = the Ely Study; WS = the Wessex Study; ADDITION = the Anglo-Danish-Dutch Study on Intensive Treatment in People with Screen Detected Diabetes in Primary Care. The sensitivity, specificity and positive predictive value are calculated using the cut-off point suggested by the authors.

### 2.5.2 Methods for screening

In cross-sectional setting, measuring fasting or random blood glucose concentration is commonly used for screening prevalent type 2 diabetes, even though it is questionable whether measuring fasting plasma glucose should be called screening at all since it is simultaneously part of the diagnostic test. Furthermore, it has been shown that the predictive value of a random glucose concentration depends on the age of the subject and time since last meal before the test (Engelgau et al 1995). Naturally, the outcome (especially the number of false negatives) depends also greatly on whether the WHO criteria (World Health Organization 1999) focusing on both fasting and post-load glucose concentrations or the ADA criteria (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997) which emphasise the usage of fasting glucose, are used as the diagnostic step after the screening (Mannucci et al 1999). The ADA recommends measurement of fasting plasma glucose concentration at three-year intervals for all asymptomatic individuals aged 45 or over, *particularly* if they are overweight (American Diabetes Association 2004a). Such a screening approach has been shown to have a very low yield (Modan and Harris 1994; Lawrence et al 2001); therefore, the authors recommended that screening should be targeted at subjects with multiple risk factors for type 2 diabetes.

Several screening procedures have been developed for identifying individuals with high risk for prevalent undiagnosed type 2 diabetes (Table 3). The purpose is to reduce the number of required diagnostic tests and simultaneously maintain satisfactory sensitivity. The best of the scores (Tabaei and Herman 2002) has the AUC 0.88, and requires random capillary glucose measurement (and knowledge of duration of fasting time since last meal). The model by Ruige and co-workers (Ruige et al 1997) is clearly focused on clinical symptoms of diabetes, and thus is closer to diagnosing than screening. The other risk models include mostly well-known risk factors for type 2 diabetes. The model by Griffin and co-workers (Griffin et al 2000), which was tested also in another population (Park et al 2002) was specifically developed to utilise routinely available risk factor data.

Yet, the true primary prevention of type 2 diabetes would be to identify high-risk individuals when they still are normoglycaemic (or at least in IFG or IGT state) and to treat them by interventions preventing their transition to overt diabetes. Only few studies have tested the possibility to identify subjects with the risk of getting type 2 diabetes in the future (Table 4). In a Swedish follow-up study (Rolandsson et al 2001) BMI at baseline predicted type 2 diabetes as effectively as fasting or OGTT 2-hour plasma glucose concentration. Stern and co-workers (Stern et al 2002) utilised US data (with more than half of the participants Mexican American) to develope two models to predict type 2 diabetes incidence: a ‘clinical model’ and a ‘full model’ including most of the parameters of the metabolic syndrome (Alberti et al 2005). The clinical model by Stern and co-workers has been tested in another

study population including Japanese Americans with follow-up time 5 to 6 years (n = 465) and 10 years (n = 412) (McNeely et al 2003). The clinical model appeared to be significantly better predictor of type 2 diabetes than fasting plasma glucose concentration alone in subjects aged 55 or younger, but in older subjects it did not improve the prediction. In both younger and older subjects the baseline OGTT 2-hour glucose concentration was the best predictor of future diabetes. However, large scale screening with OGTT or other laboratory tests cannot be considered very practical.

**Table 4. Methods to screen for incident type 2 diabetes.**

| Data source / follow-up time | Age | n | DM diagnosis | DM cases | Predictive variables | SENS | SPEC | PPV | AUC |
|---|---|---|---|---|---|---|---|---|---|
| **Västerbotten Intervention Project** / 8 years (median) (Rolandsson et al 2001) | 30 - 60 | 2278 | Medical records | 42 | Fasting plasma glucose (4th quartile) | | | 5.2% | 0.80 |
| | | | | | 2-hour plasma glucose (4th quartile) | | | 5.4% | 0.82 |
| | | | | | BMI (4th quartile) | | | 5.7% | 0.85 |
| **The San Antonio Heart Study** / 7.5 years (Stern et al 2002) | 25 - 64 | 2903 | OGTT (WHO 1999), medical records | 269 | Clinical model: Age, sex, ethnicity, fasting glucose, systolic blood pressure, HDL cholesterol, BMI, family history of DM | | | | 0.84 |
| | | | | | Full model: Also 2-hour glucose, diastolic blood pressure, total and LDL cholesterol, triglyceride | | | | 0.86 |
| **The Rancho Bernardo Study** (cross-sectional) | 67 ± 11 | 1549 | IGT in OGTT | 514 (IGT) | Sex, age, triglycerides, fasting glucose | | | | |
| Model validation: The Health ABC Study / 5 years (Kanaya et al 2005) | 70 - 79 | 2503 | Medical records | 143 | | | | | 0.71 |
| **The Atherosclerosis Risk in Communities Study** / 9 years (Schmidt et al 2005) | 45 - 64 | 7915 | OGTT or medical records | 1892 | Model 1: Age, ethnicity, waist, height, fasting glucose, systolic blood pressure, family history of DM | 51%<br>65%<br>75%<br>83% | 86%<br>77%<br>67%<br>56% | 41%<br>35%<br>30%<br>27% | 0.78 |
| | | | | | Model 2: Also HDL cholesterol and triglycerides | 52%<br>67%<br>77%<br>85% | 86%<br>77%<br>67%<br>57% | 42%<br>36%<br>31%<br>27% | 0.80 |

DM = diabetes mellitus; SENS = sensitivity, SPEC = specificity, PPV = positive predictive value, AUC = area under the receiver-operating characteristic (ROC) curve; OGTT = oral glucose tolerance test; WHO = World Health Organization; BMI = body mass index; IGT = impaired glucose tolerance. The sensitivity, specificity and positive predictive value are calculated using the cut-off point suggested by the authors. In the paper by Schmidt and co-workers (Schmidt et al 2005) four different cut-off points, with proportion of screen-positives 20%, 30%, 40%, or 50%, respectively, are given.

# 3 AIMS OF THE STUDY

The overall aim was to find out whether type 2 diabetes can be prevented by lifestyle intervention in high-risk individuals, and to develop a practical method to identify individuals who would benefit from such an intervention.

More specific objectives of the study were:

1. To determine the feasibility and effects of a lifestyle intervention programme designed to prevent or delay the onset of type 2 diabetes in subjects with IGT (Paper I).

2. To describe the changes in dietary habits and exercise behaviour that were achieved by the lifestyle intervention programme during the first year and the maintenance of these changes, and to assess the effect of the intervention on body weight, glycaemia, serum lipid concentrations and blood pressure (Paper II).

3. To study the association between dietary macronutrient composition, in particular dietary fat, fibre, and energy density and change in body weight, waist circumference, and type 2 diabetes risk (Paper III).

4. To assess the extent to which the originally achieved risk reduction will last after discontinuation of active counselling (Paper IV).

5. To develop a simple, practical and informative scoring system to characterise individuals according to their future risk of type 2 diabetes (Paper V).

# 4 POPULATIONS AND METHODS

## 4.1 Diabetes Prevention Study (Papers I - IV)

### 4.1.1 Population and design

The Diabetes Prevention Study (DPS) is a multicentre study with five participating centres in Finland, located in Helsinki, Kuopio, Turku, Tampere, and Oulu (Eriksson et al 1999). The original study protocol was approved by the Ethical Committee of the National Public Health Institute in Helsinki, Finland.

Based on the available prospective data from European populations the yearly incidence of type 2 diabetes among IGT subjects varies between 1% and 10% and the 6-year cumulative incidence of diabetes in this high-risk group is thus estimated to be 35% (Valle et al 1997). The DPS was designed to be large enough so that it would be possible to detect a 35% reduction in diabetes incidence with intensive diet-exercise intervention with 80% power (beta=20%) at the 2-tailed 5% significance level (alpha=5%), i.e. a reduction in cumulative incidence from 35% to 22.8%. The estimated need was 3252 person years, meaning that the study centres should recruit 650 participants to be followed for five years, or 542 participants to be followed for 6 years. The conservative estimate of a reduction in diabetes incidence by 35% was suggested by the results of earlier studies (Sartor et al 1980; Eriksson and Lindgärde 1991). The drop-out rate used in the calculations was 10%.

The recruitment period started in 1993 and was completed in 1998. The study participants were recruited through various methods, e.g. advertising in local newspapers, from epidemiological surveys and earlier clinical studies, and by opportunistic screenings. Overweight individuals (BMI > 25 kg/m$^2$) aged 40 - 64 at randomisation and with IGT according to the WHO 1985 criteria (World Health Organization 1985) i.e. OGTT 2-hour post-load plasma glucose concentration 7.8 to 11.0 mmol/L with a non-diabetic fasting plasma glucose concentration (< 7.8 mmol/L) were eligible for the study. After the first screening OGTT, a repeat OGTT was carried out in IGT subjects and the mean of the two 2-hour glucose concentrations was used as the criterion for inclusion in the study. Furthermore, willingness to participate in the study was requested and the study participants gave a written informed consent.

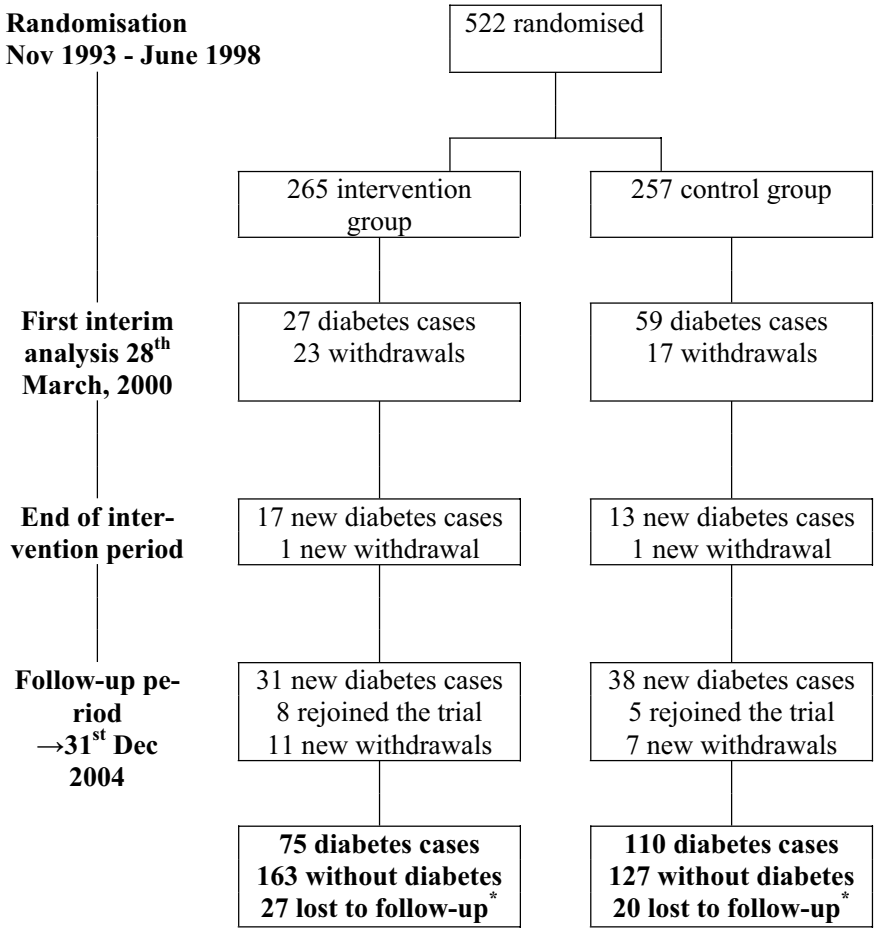
Individuals with a previous diagnosis of diabetes mellitus, other than gestational diabetes mellitus, were excluded from the study. Individuals involved regularly in a vigorous exercise programme as well as individuals receiving treatment to lower blood glucose concentration - other than routine dietary and health advice - were not included either. Individuals with any chronic disease making a 6-year survival improbable as well as other medical characteristics likely to interfere with participation in the study were excluded, as

were subjects with unbalanced clinical conditions, such as thyroid and liver diseases, which may interfere with glucose metabolism.

The study participants (n = 522) were randomly allocated to one of the two treatment modalities, the intensive diet-exercise counselling group (n = 265, the proportion of men 34.3%) or the control group (n = 257, proportion of men 31.5%). The randomisation was performed by the study physician with the use of a centrally-produced randomisation list, stratified for centre, sex, and the mean 2-hour plasma glucose concentrations (7.8 to 9.4 mmol/L or 9.5 to 11.0 mmol/L). The study nurses who scheduled the study visits did not have access to the randomisation list. The staff members involved in the intervention had to be aware of the group assignment; thus the study was only partly masked. Laboratory staff was not aware of the group assignment and the participants were not informed about their plasma glucose concentrations during the study, unless diabetes was diagnosed.

The first pre-planned interim analysis was performed in March 2000 by an independent end-point committee and an independent statistician, after a mean follow-up of 3.2 years (Paper I). After having studied the results of the analyses, the end-point committee decided that the aim of the study had been attained and it would be unnecessary to carry on the trial. The intervention period was therefore continued only until each subject's next scheduled annual clinic visit. The mean follow-up according to the original intervention protocol thus was 3.9 years (with median of 4 years) (Papers II and III).

All participants who had participated in the intervention phase of the study were invited to take part in the extended follow-up phase, also those who had withdrawn earlier (n = 24 in the intervention and 18 in the control group). The follow-up protocol was approved by the Ethical Committee of the Northern Finland Hospital District. During the follow-up all study participants had an annual visit with the study nurse but no specific counselling was offered. The visits included the same procedures for all participants regardless of their former randomisation group. Paper IV comprises of the data collected by December 31, 2004, with mean follow-up of 6.2 years (median 7 years). The study flow-chart is presented in Figure 1.




* Participants who were lost to follow-up were treated as censored observations in the analyses.

**Figure 1. Trial profile.**

### 4.1.2 Lifestyle intervention

The main goals of the lifestyle intervention were based upon available evidence on type 2 diabetes risk factors (Ohlson et al 1985; Ohlson et al 1988; Colditz et al 1990; Cassano et al 1992). They were weight reduction 5% or more; moderate intensity physical activity 30 minutes per day or more; dietary fat less than 30 E%; saturated fat less than 10 E%; and fibre 15 g / 1000 kcal (15 g / 4200 kJ) or more. Conventional unit of energy (kcal) instead of the SI unit (kJ; 1 kcal=4.186 kJ) was used while implementing the intervention because it was better known among the study participants, and consequently, it was used in the analyses of the results also.

The hypothesis of type 2 diabetes prevention by increased physical activity had already been tested in the Malmö feasibility study (Eriksson and Lindgärde 1991) with encouraging results. A non-randomised pilot study testing the effect of aerobic and resistance training exercise programmes on insulin resistance in subjects with IGT was completed before the beginning of the DPS (Eriksson et al 1998). On the basis of this pilot study, resistance training was offered to the participants of the DPS intervention.

To further increase the knowledge of a suitable diet for a long-term intervention, a dietary pilot study was completed in a subgroup of subjects prior to the start of the DPS study (Sarkkinen et al 1996). The results suggested that diet enriched with monounsaturated fat improves glucose metabolism when consumed after a diet rich in saturated fat, compared with reduced-fat diet enriched with polyunsaturated fat. Therefore, besides a moderate-fat (< 30 E%), low-saturated fat (< 10 E%) diet, also a diet with somewhat more mono-unsaturated fat (total fat not exceeding 35 E%) was considered acceptable in the DPS intervention.

***Intervention group***

*Dietary intervention*. The participants had face-to-face consultation sessions lasting for 30 minutes to1 hour with the study nutritionist at weeks 0, 1 - 2, 5 - 6, at months 3, 4, 6, and 9, i.e. altogether seven sessions during the first year, and every three months thereafter. The first year sessions had a pre-planned topic (e.g. diabetes risk factors, saturated fat, fibre, physical activity, problem solving) but the discussions were individualised focusing on specific individual problems. Printed material was used to illustrate the message and to serve as reminder at home. In addition, some of the centres arranged voluntary group sessions, expert lectures, low-fat cooking lessons, visits to local supermarkets, between-visit phone calls and letters. The goal was to equip the participants with the necessary knowledge and skills, and to achieve gradual, permanent behavioural changes. The dietary advice was based upon 3-day food records, which were completed four times yearly. Nutrient intakes were calculated and a summary of the results was given and explained to the partici-

pants. Participants were encouraged to make intermediate goals for themselves by thinking about practical things they could try to change (e.g. instead of an abstract goal of increasing fibre intake a practical goal would be to eat a slice of high-fibre rye bread on every meal). Weight was measured on every visit and a weight chart was drawn. The participants were also encouraged to measure their weight at home on a regular basis. Recommended weight loss was ½ - 1 kg per week. The spouse was invited to join the sessions, especially if she/he was the one responsible for shopping and cooking in the family. After 6 months, the use of very low calorie diet (VLCD) preparations for 2 - 5 weeks or as a substitute for 1 - 2 meals per day was considered, if preferred by the subject, to boost weight loss. Altogether 48 individuals participated in the VLCD groups arranged as part of the intensive intervention.

*Exercise intervention*. The participants were individually guided to increase their overall level of physical activity. This was done by the nutritionist during the dietary counselling sessions and highlighted by the study physicians at the annual visits. Endurance exercise was recommended to increase aerobic capacity and cardiorespiratory fitness. Supervised, progressive, individually tailored circuit-type moderate intensity resistance training sessions to improve the functional capacity and strength of the large muscle groups of the upper and lower body were also offered free of charge. As a mean of improving motivation, an exercise competition between the five study centres was organized twice during the study period. Also voluntary group-walking and hiking were organized in some of the centres.

***Control group***

At baseline the control group participants were given general information about lifestyle and diabetes risk. This was done either individually or in one group session (30 minutes to 1 hour), and some printed material was delivered. The message to reduce weight, increase physical activity, and make qualitative changes in diet was the same as for the intervention group participants, but counselling was not individualised.

### 4.1.3 Assessment of dietary intake

All study participants were asked to complete a 3-day food record at baseline (before the randomisation visit) and before every annual visit. They were requested to write down everything they eat and drink, except plain drinking water. A picture booklet of portion sizes of typical foods was used to estimate the amounts of consumed foods (Haapa et al 1985). The completeness of the food records was checked at the face-to-face session with the study nutritionist during the study visit. The nutrient intakes were calculated using a dietary analysis programme and database developed in the National Public Health Institute (Ovaskainen et al 1996). The programme allows modification of database recipes, so the changes the participants made into traditional recipes could be accounted for (e.g. the use of skimmed milk instead of regular fat milk). Energy density (kcal / 100 g) was calculated

dividing total energy with total weight of foods and beverages consumed, excluding only drinking water and mineral water.

Due to the time-consuming and therefore costly dietary data management, only data from baseline and years 1, 2, and 3 of the intervention period were included into the final database. In addition, food records from the first follow-up visit were entered and calculated using the Finnish Food Composition Database Fineli® (National Public Health Institute Nutrition Unit 2002).

### 4.1.4 Assessment of physical activity

The study participants completed the validated Kuopio Ischaemic Heart Disease Risk Factor Study 12-month Leisure-Time Physical Activity (LTPA) Questionnaire (Lakka and Salonen 1992; Lakka et al 1994) at baseline and at every annual visit. The duration (minutes per week) of total LTPA and high-intensity LTPA were calculated.

### 4.1.5 Assessment of compliance with the intervention goals

A success score from 0 to 5 was calculated as the sum of the five targeted lifestyle indicators (0 = not achieved, 1 = achieved) at year 1 and at year 3 (with mean physical activity and dietary intakes during the years 1 - 3 and last observation for body weight change) and again at the first follow-up visit (Paper IV).

### 4.1.6 Clinical examinations

A physical examination including measurements of weight (in light indoor clothes to the nearest 100 g), height (without shoes to the nearest 1 mm), waist circumference (midway between the lowest rib and iliac crest to the nearest 1 mm), blood pressure (two measurements with a standard sphygmomanometer in a sitting position, using the right arm, after 10 minutes of rest) and questionnaires regarding medical history and physical activity were collected at baseline and each annual visit. Participants were classified as having a family history of diabetes if at least one parent had diabetes. Those who smoked on 5 days per week or more often were categorised as regular smokers.

### 4.1.7 Laboratory analyses

The annually measured biochemical parameters included a 75 g OGTT after a 12 hour fast with measurements of fasting and 2-hour post-load plasma glucose concentrations. During the intervention phase plasma glucose was determined locally according to standard guidelines; during the follow-up period glucose assays were done enzymatically using hexokinase method (Thermo Electron Oy, Vantaa, Finland) in the Laboratory of Analytical

Biochemistry of the National Public Health Institute, Helsinki. The glucose measurements were standardized by measuring 60 to 80 plasma samples in duplicate from each center in the central laboratory. A linear regression equation was calculated for each center, using plasma glucose determined in Helsinki as standard. These equations were used to correct the locally measured plasma glucose values. The second screening oral glucose tolerance test was considered as the baseline for comparison with later concentrations; in some participants whose entry into the study was delayed a third oral glucose tolerance test was performed, which was considered as baseline. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by the enzymatic assay method in the central laboratory. Glycosylated haemoglobin ($HbA_{1c}$) was analysed using the Bayer DCA2000 analyser.

### 4.1.8 Assessment of the end-points

Diabetes was defined according to the WHO 1985 criteria (World Health Organization 1985) i.e. either a fasting plasma glucose concentration 7.8 mmol/L or higher or 2-hour post-load plasma glucose concentration 11.1 mmol/L or higher. The diagnosis of diabetes had to be confirmed by a repeat oral glucose tolerance test; if the diagnosis was not confirmed in the second test the subject followed the programme according to the original randomisation. The independent End-Point Committee confirmed all incident cases of diabetes. The study centres did not exchange information concerning the end-points, and the end-point data were linked to the group assignment centrally only after 80 end-points had accumulated.

### 4.1.9 Statistical methods

Analysis of variance and $\chi^2$-test were used to analyse the baseline differences between the study groups. Mean changes (with 95% confidence intervals; 95% CI) in body weight, nutrient intakes and physical activity during the intervention phase were calculated and compared between the two treatment groups with analysis of covariance (ANCOVA), adjusting for baseline level of respective variable if applicable.

Kaplan-Meier survival curves were calculated to estimate the probability of remaining free of diabetes in the two treatment groups. Participants who were lost during the follow-up were treated as censored observations. The difference between the survival curves was tested with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio for development of diabetes between the treatment groups. The proportionality assumption of the model was assessed with graphical methods (i.e. the log-log plot). All comparisons of the end-points between the treatment groups were based on the intention-to-treat principle.

The multivariate-adjusted ANCOVA, adjusting for intervention assignment, age, use of VLCD as part of the intensive intervention (adjusted to 'not used'), physical activity (minutes per week) at baseline and during the intervention period, baseline weight, and baseline intake of respective nutrient was used to analyse the associations of dietary intake during the follow-up with weight and waist circumference changes. The last-observation-carried-forward method for weight and waist circumference was used in the calculations for those who were diagnosed with diabetes (n = 53) or dropped out (n = 32) before the 3-year visit. Averaged nutrient intakes during the intervention period (years 1, 2, and 3) were used in the models. Adjustment for the baseline intake of the respective nutrient was used to control for the regression-to-the-mean effect, since those who report extreme intakes are, due to intra-individual variation, likely to report less extreme intakes at follow-up (Twisk 2003). Trends across the quartiles were analysed by adding the quartile into the model as a continuous variable.

The Cox model was used to calculate the hazard ratios for developing diabetes between quarters of dietary intake, with the lowest quarter as the reference category. These analyses were adjusted for intervention assignment, sex, age, and physical activity at baseline and during the intervention period, baseline weight, baseline nutrient intake, and the baseline 2-hour post-challenge plasma glucose, and in further analyses, with the weight change from baseline to year 3. In further analyses, the Cox model was used to analyse the relationship between diabetes and the success score.

To clarify the combined effect of dietary fat E% and fibre density, participants were divided into 'low' (below median) and 'high' (above median) intake groups. Between these categories, ANCOVA was used to analyse effects on the weight reduction and Cox model to analyse effects on diabetes risk.

Analyses were performed with the SAS statistics package (releases 6.12 and 8.2; SAS Institute Inc., Cary, North Carolina, USA) and Stata (release 8.0; STATA, College Station, Texas, USA).

### 4.1.10 Project organisation

The project was carried out in five study centres. The principal staff in each centre included a study nurse who was responsible for the screening activities and annual laboratory and other measurements, a study physician who was responsible for the inclusion (including informed consent) and randomisation of the participants and annual medical and clinical examination (including diabetes diagnosis), and a study nutritionist who was responsible for the implementation of the lifestyle intervention. Exercise counselling was arranged depending on the centres facilities; in some centres the physical activity instructor was a member of the research team, in others the service was purchased from commercial gyms.

Data were collected into the coordinating centre in Helsinki online via a web-based data entry system, with the exception of the dietary records, which were mailed to Helsinki and entered into the dietary database by nutritionists and trained nutrition students.

The principal investigators of the study were professors Jaakko Tuomilehto and Matti Uusitupa. The overall coordination of the DPS study was delegated to the author, including participation in overall planning of the practical implementation of research and intervention activities, design of study forms and, in collaboration with the data manager, the data entry system. The author worked also as the study nutritionist for the Helsinki centre, and entered and analysed a considerable proportion of the food records collected in Helsinki and also in the other centres.

## 4.2 Diabetes risk score (Paper V)

### 4.2.1 Populations and design

A random sample was drawn from the national population register in 1987 and another independent one in 1992 (the FINRISK Studies). The samples included 6.6% of population aged 25 - 64 years and were stratified so that at least 250 subjects of each sex and ten-year age-group were chosen in the areas of North Karelia, Kuopio, South-Western Finland, and in 1992 also in the Helsinki-Vantaa region. Participation rates were 82% in the 1987 survey (n = 4746) and 76% in the 1992 survey (n = 4615). Baseline surveys were carried out from January to April 1987 (model development data) and February to May 1992 (model validation data). The sampling schemes and survey procedures have been described in detail elsewhere (Salomaa et al 1990; Tuomilehto et al 1991; Vartiainen et al 1991; Tuomilehto et al 1992; Vartiainen et al 1994).

The subjects received by mail a questionnaire on medical history and health behaviour, and an invitation to a clinical examination, which included measurements of weight (in light indoor clothes to the nearest 100 g), height (without shoes to the nearest 1 mm), and waist circumference (at a level midway between the lowest rib and iliac crest to the nearest 5 mm).

### 4.2.2 Assessment of the end-points

The end-point of the follow-up was the development of drug-treated diabetes. Data were collected through a computer-based data linkage with the nationwide Social Insurance Institution's Drug register until the end of year 1997. The Drug register comprises information about all Finns who receive free-of-charge drug treatment for certain chronic diseases, including diabetes. The subjects aged 34 or under and those on antidiabetic drug treatment at the time of the baseline survey were excluded from the analyses.

### 4.2.3 Statistical methods

Logistic regression was used to compute β-coefficients for known risk factors for type 2 diabetes. First, univariate prediction models with drug-treated diabetes diagnosed during the follow-up as the dependent variable were computed. Second, based on the univariate models, the predictors for the multivariate model were selected, and the final model was computed. Coefficients (β) of the model were used to assign a score value for each variable, and the composite diabetes risk score was calculated as the sum of those scores. The sensitivity and the specificity with 95% CI were calculated for each diabetes risk score level in differentiating the subjects who developed diabetes from those who did not. Then, ROC curves were plotted for the risk score, with the sensitivity on the axis y and the false positive rate (1minus specificity) on the axis x. Analyses were performed with the statistics package SAS (release 8.2; SAS Institute Inc., Cary, North Carolina, USA).

# 5 RESULTS

## 5.1 Diabetes Prevention Study (Papers I - IV)

### 5.1.1 Baseline results

At baseline the two groups, intervention (91 men and 174 women) and control (81 men and 176 women) had virtually similar metabolic risk factor profile, indicating that the randomisation was completed successfully (Table 5). Mean BMI among the women was 31.9 kg/m$^2$ and among the men 29.9 kg/m$^2$, mean age 55 years, mean fasting plasma glucose 6.1 mmol/L and mean plasma glucose concentration 2 hours after the 75 g glucose load was 8.9 mmol/L. Of all study participants 55% had BMI over 30 kg/m$^2$. The metabolic syndrome (World Health Organization 1999) was present in 78% of the men and 72% of the women (Ilanne-Parikka et al 2004). Lipid lowering drugs were used by 5% and blood pressure lowering drugs by 29% of the participants. Family history of diabetes was common: 63% of the participants had at least one parent with diabetes.

Altogether 65% of the participants reported that they walked or did some other moderate intensity activity for at least 4 hours per week, and were thus categorised as physically active. Thus, 35% of the study participants perceived themselves as sedentary, reporting that during their spare time they mostly read, watch TV and spend time in ways, which do not restrain physically. Baseline physical activity did not differ between the groups. Dietary intake in the two groups was similar, except that saturated fat intake was slightly higher among the control group participants (Table 6).

**Table 5. Baseline characteristics of the DPS participants by intervention assignment.**

| | | Intervention group | Control group |
|---|---|---|---|
| Number (male/female) | | 265 (91/174) | 257 (81/176) |
| Age (years) | | 55 ± 7 | 55 ± 7 |
| Body weight (kg) | Male | 91 ± 13 | 91 ± 13 |
| | Female | 84 ± 14 | 83 ± 14 |
| Body mass index (kg/m$^2$) | Male | 30.1 ± 3.5 | 29.7 ± 3.6 |
| | Female | 32.1 ± 4.9 | 31.7 ± 4.7 |
| Waist circumference (cm) | Male | 104 ± 10 | 104 ± 10 |
| | Female | 101 ± 11 | 99 ± 11 |
| Fasting plasma glucose (mmol/L) | | 6.1 ± 0.8 | 6.2 ± 0.7 |
| 2-hour plasma glucose (mmol/L) | | 8.9 ± 1.5 | 8.9 ± 1.5 |
| $HbA_{1c}$ (%) | | 5.7 ± 0.6 | 5.6 ± 0.6 |
| Serum total cholesterol (mmol/L) | | 5.6 ± 1.0 | 5.6 ± 0.9 |
| Serum HDL cholesterol (mmol/L) | Male | 1.09 ± 0.29 | 1.12 ± 0.28 |
| | Female | 1.27 ± 0.30 | 1.26 ± 0.27 |
| Serum triglycerides (mmol/L) | | 1.70 ± 0.80 | 1.74 ± 0.75 |
| Systolic blood pressure (mmHg) | | 140 ± 18 | 136 ± 17 [a] |
| Diastolic blood pressure (mmHg) | | 86 ± 9 | 86 ± 10 |
| Blood pressure lowering medication (%) | | 28 | 31 |
| Lipid lowering medication (%) | | 5 | 6 |
| First degree relatives with diabetes (%) | | 66 | 61 |
| Regular smoker (%) | | 5 | 7 |
| Physically active [b] (%) | | 64 | 67 |
| Schooling in years (%) | 0 - 9 | 40 | 40 |
| | 10 - 12 | 27 | 27 |
| | >12 | 33 | 33 |
| Type of work (%) | Agricultural or industrial | 9 | 10 |
| | Office work, service, or studying | 42 | 44 |
| | Homemaker, retired, or unemployed | 49 | 46 |

Data are mean ± standard deviation, or proportion. HDL = high-density lipoprotein; $HbA_{1c}$ = glycosylated haemoglobin.

[a] p = 0.0257 for difference between the groups (Student's un-paired t-test).

[b] Individuals who reported walking, bicycling or other moderate intensity activity for at least 4 hours per week were categorised as being physically active.

**Table 6. Baseline dietary intake of the DPS participants by intervention assignment.**

| | Intervention group | Control group |
|---|---|---|
| Energy (kcal/day) | 1771 ± 520 | 1743 ± 527 |
| Carbohydrates (E%) | 44 ± 7 | 43 ± 7 |
| Fat (E%) | 36 ± 7 | 37 ± 6 |
| Saturated fat (E%) | 16 ± 4 | 17 ± 4 [a] |
| Monounsaturated fat (E%) | 13 ± 3 | 13 ± 3 |
| Polyunsaturated fat (E%) | 6 ± 2 | 6 ± 2 |
| Protein (E%) | 18 ± 3 | 18 ± 3 |
| Alcohol (E%) | 3 ± 5 | 2 ± 4 |
| Cholesterol (mg) | 312 ± 137 | 304 ± 130 |
| Fibre (g) | 20 ± 7 | 20 ± 8 |
| Fibre (g / 1000 kcal) | 12 ± 4 | 12 ± 4 |
| Energy density (kcal / 100 g) | 96 ± 21 | 96 ± 22 |

Data are mean ± standard deviation. E% = proportion of total energy consumed.

[a] p = 0.0188 for difference between the groups (Student's un-paired t-test).

### 5.1.2 Intervention results

The duration of intensive intervention varied from 0 (indicating withdrawal before first annual study visit) to 6 years (depending on the time of recruitment in relation to the closing date), with a median length of 4 years, and the number of counselling sessions per subject varied, respectively, from 1 to 28. The median number of dietary counselling sessions per intervention group participant was 20 thus indicating excellent compliance with the study protocol.

***Dietary intake***

After the first and most intensive year of intervention, total energy, E% of fat and saturated fat, cholesterol intake, and energy density of diet decreased, and E% of carbohydrates and the fibre density increased more among the participants who had been assigned to get intensive lifestyle intervention, compared with the control group (Table 7). Also E% of monounsaturated fat decreased slightly and more in the intervention group. Women in general tended to reduce their intake of fat and saturated fat and energy density more than men, but there was no significant interaction between intervention assignment and sex, indicating that the effect of intervention did not differ between men and women (data not shown).

At 2 and 3 years, the reductions in total energy, fat, saturated fat, monounsaturated fat, and cholesterol, and the increase in carbohydrates and fibre density were still statistically significantly greater in the intervention group compared with the control group.

**Table 7. Changes in dietary intake from baseline by intervention assignment.**

| | | Intervention group | | Control group | | |
|---|---|---|---|---|---|---|
| | | Mean | 95% CI | Mean | 95% CI | P* |
| Energy (kcal/day) | Year 1 | −247 | −301 - −193 | −108 | −166 - −49 | <0.001 |
| | Year 2 | −209 | −269 - −149 | −83 | −144 - −22 | 0.002 |
| | Year 3 | −204 | −268 - −140 | −97 | −161 - −33 | 0.007 |
| Carbohydrates | Year 1 | 3 | 2 - 4 | 2 | 1 - 3 | 0.002 |
| (E%) | Year 2 | 3 | 2 - 4 | 2 | 1 - 3 | 0.09 |
| | Year 3 | 3 | 2 - 4 | 2 | 1 - 3 | 0.007 |
| Fat (E%) | Year 1 | −3 | −4 - −2 | −2 | −3 - −1 | 0.002 |
| | Year 2 | −4 | −5 - −3 | −3 | −4 - −2 | <0.001 |
| | Year 3 | −5 | −6 - −4 | −3 | −4 - −2 | <0.001 |
| Saturated fat (E%) | Year 1 | −3 | −3 - −2 | −1 | −2 - −1 | <0.001 |
| | Year 2 | −3 | −3 - −2 | −2 | −2 - −1 | <0.001 |
| | Year 3 | −3 | −4 - −3 | −2 | −3 - −1 | <0.001 |
| Monounsaturated | Year 1 | −1 | −1 - 0 | −0 | −1 - 0 | 0.03 |
| fat (E%) | Year 2 | −1 | −1 - −1 | −1 | −1 - 0 | 0.09 |
| | Year 3 | −1 | −1 - 0 | −1 | −1 - 0 | 0.045 |
| Polyunsaturated | Year 1 | 0 | 0 - 0 | 0 | −1 - 0 | 0.50 |
| fat (E%) | Year 2 | 0 | 0 - 0 | −1 | −1 - 0 | 0.056 |
| | Year 3 | 0 | 0 - 0 | 0 | −1 - 0 | 0.09 |
| Protein (E%) | Year 1 | 1 | 1 - 2 | 1 | 0 - 1 | 0.052 |
| | Year 2 | 2 | 1 - 2 | 1 | 0 - 1 | 0.001 |
| | Year 3 | 1 | 1 - 2 | 1 | 1 - 2 | 0.41 |
| Alcohol (E%) | Year 1 | −1 | −2 - −1 | 0 | −1 - 0 | 0.15 |
| | Year 2 | −1 | −1 - 0 | 0 | −1 - 0 | 0.21 |
| | Year 3 | 0 | −1 - 0 | 0 | −1 - 0 | 0.68 |
| Cholesterol (mg) | Year 1 | −69 | −86 - −52 | −28 | −46 - −9 | <0.001 |
| | Year 2 | −54 | −75 - −32 | −16 | −36 - 4 | 0.01 |
| | Year 3 | −63 | −85 - −41 | −31 | −53 - −9 | 0.059 |
| Fibre (g) | Year 1 | 1 | 0 - 2 | 0 | 0 - 1 | 0.11 |
| | Year 2 | 1 | 0 - 2 | 1 | 0 - 1 | 0.22 |
| | Year 3 | 1 | 0 - 2 | 1 | 0 - 2 | 0.44 |
| Fibre (g/1000 | Year 1 | 3 | 2 - 3 | 1 | 0 - 1 | <0.001 |
| kcal) | Year 2 | 2 | 2 - 3 | 1 | 0 - 2 | 0.003 |
| | Year 3 | 2 | 2 - 3 | 1 | 1 - 2 | 0.001 |
| Energy density | Year 1 | −7 | −10 - −5 | −2 | −5 - 1 | <0.001 |
| (kcal/100 g) | Year 2 | −8 | −11 - −5 | −2 | −5 - 1 | <0.001 |
| | Year 3 | −8 | −10 - −5 | 0 | −3 - 3 | <0.001 |

Number of participants is 254 and 245 at year 1, 241 and 226 at year 2, and 227 and 197 at year 3, in the intervention and control groups, respectively. CI = confidence interval; E% = proportion of total energy consumed. *p-value for difference between the groups, adjusted for baseline intake.

The specific dietary goals of the intervention, based on the average intake during the first 3 years of the intervention period, were achieved more frequently by the intervention group participants than the control group participants (Figure 2). Among the intervention and control group participants, 50% and 71% ($p < 0.001$) did not achieve any of the specific dietary goals.

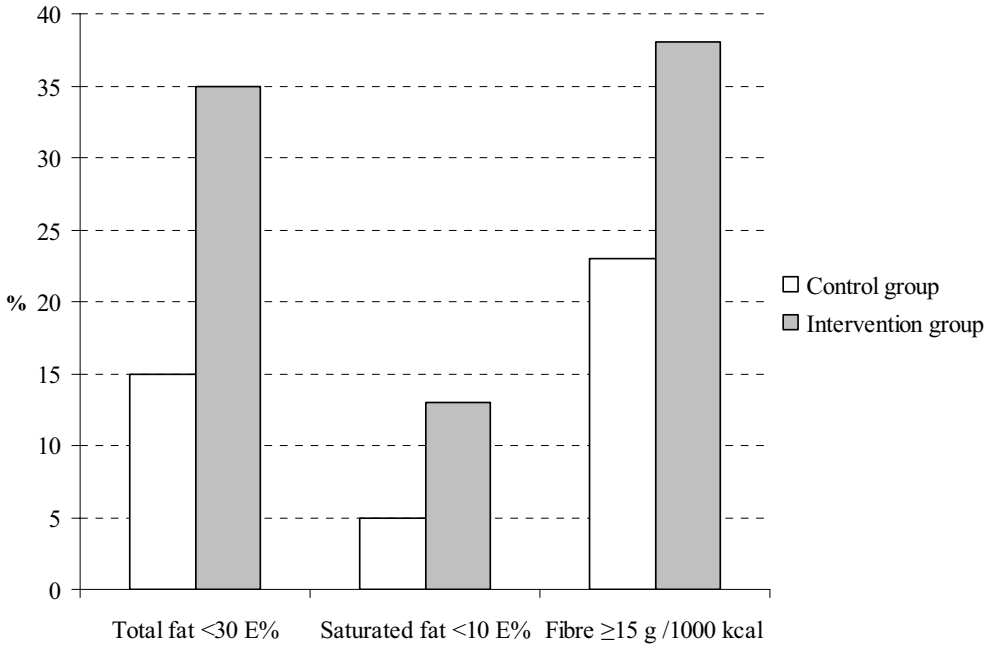



**Figure 2. Success in achieving the dietary goals by intervention assignment. E% = proportion of total energy consumed. For all differences between the groups, $p < 0.001$.**

***Physical activity***

The proportion of sedentary individuals was 14% and 31% at year 1 ($p < 0.001$ for difference between groups), 16% and 31% at year 2 ($p < 0.001$) and 17% and 29% at year 3 ($p = 0.003$) in the intervention and control groups, respectively. However, based on the LTPA Questionnaire, total amount of reported time spent physically active did not change, but moderate-to-vigorous activity increased in the intervention group compared with the control group (median increase 49 minutes per week in the intervention group and 14 minutes per week in the control group, $p = 0.007$).

***Clinical and metabolic variables***

Beneficial changes in clinical and metabolic characteristics were observed in the intervention group compared with the control group (Table 8). Mean weight reduction was 4.5 kg in the intervention group and 1.0 kg in the control group at 1 year. There was also a larger reduction in waist circumference in the intervention group compared with the control group. Some regain of weight appeared during the following two years; weight reduction was 3.8 kg and 0.9 kg after the second year and 3.5 kg and 0.9 kg after the third year ($p < 0.001$ for each comparison between the intervention and control groups). Significantly greater improvements were seen in fasting plasma glucose concentration, 2-hour plasma glucose concentration, $HbA_{1c}$, serum triglycerides, and systolic and diastolic blood pressure in the intervention group compared with the control group.

The specific goal of 5% or more weight reduction was achieved by 46% of the intervention group and 14% of the control group participants at year 1, 42% vs. 19% at year 2, and 41% vs. 21% at year 3, respectively ($p < 0.0001$ for all differences between the groups).

**Table 8. Changes in clinical and metabolic parameters from baseline by intervention assignment.**

| | | Intervention group | | Control group | | p* |
|---|---|---|---|---|---|---|
| | | Mean | 95% CI | Mean | 95% CI | |
| Body weight (kg) | Year 1 | −4.5 | −5.1 - −3.9 | −1.0 | −1.4 - −0.5 | <0.001 |
| | Year 2 | −3.8 | −4.5 - −3.1 | −0.9 | −1.5 - −0.3 | <0.001 |
| | Year 3 | −3.5 | −4.2 - −2.8 | −0.9 | −1.6 - −0.1 | <0.001 |
| Body weight (%) | Year 1 | −5.1 | −5.7 - −4.4 | −1.1 | −1.6 - −0.6 | <0.001 |
| | Year 2 | −4.3 | −5.1 - −3.6 | −1.1 | −1.8 - −0.4 | <0.001 |
| | Year 3 | −4.0 | −4.7 - −3.2 | −1.1 | −1.9 - −0.2 | <0.001 |
| Body mass index ($kg/m^2$) | Year 1 | −1.6 | −1.8 - −1.4 | −0.4 | −0.5 - −0.2 | <0.001 |
| | Year 2 | −1.4 | −1.6 - −1.1 | −0.3 | −0.5 - −0.1 | <0.001 |
| | Year 3 | −1.3 | −1.5 - −1.0 | −0.3 | −0.6 - −0.1 | <0.001 |
| Waist circumference (cm) | Year 1 | −4.4 | −5.0 - −3.7 | −1.3 | −1.9 - −0.7 | <0.001 |
| | Year 2 | −4.2 | −4.9 - −3.6 | −1.3 | −2.0 - −0.6 | <0.001 |
| | Year 3 | −3.3 | −4.0 - −2.5 | −1.2 | −2.0 - −0.4 | <0.001 |
| Fasting plasma glucose (mmol/L) | Year 1 | −0.2 | −0.3 - −0.1 | 0.0 | −0.0 - 0.1 | <0.001 |
| | Year 2 | −0.1 | −0.2 - 0.0 | 0.2 | 0.1 - 0.3 | <0.001 |
| | Year 3 | 0.0 | −0.1 - 0.0 | 0.1 | −0.1 - 0.1 | 0.07 |
| 2-hour plasma glucose (mmol/L) | Year 1 | −0.9 | −1.1 - −0.6 | −0.3 | −0.6 - 0.0 | 0.001 |
| | Year 2 | −0.8 | −1.0 - −0.5 | 0.0 | −0.3 - 0.3 | <0.001 |
| | Year 3 | −0.5 | −0.8 - −0.2 | −0.1 | −0.4 - 0.2 | 0.07 |
| $HbA_{1c}$ (%) | Year 1 | −0.1 | −0.2 - −0.1 | 0.1 | 0.0 - 0.1 | <0.001 |
| | Year 2 | −0.2 | −0.2 - −0.1 | 0.1 | 0.0 - 0.2 | <0.001 |
| | Year 3 | −0.2 | −0.2 - −0.1 | 0.0 | −0.1 - 0.1 | 0.002 |
| Serum total cholesterol (mmol/L) | Year 1 | −0.1 | −0.2 - 0.0 | −0.1 | −0.2 - 0.0 | 0.51 |
| | Year 2 | −0.1 | −0.2 - 0.0 | 0.0 | −0.1 - 0.1 | 0.13 |
| | Year 3 | −0.1 | −0.2 - 0.0 | 0.1 | −0.1 - 0.2 | 0.07 |
| Serum HDL cholesterol (mmol/L) | Year 1 | 0.05 | 0.03 - 0.07 | 0.02 | 0.00 - 0.04 | 0.07 |
| | Year 2 | 0.09 | 0.07 - 0.12 | 0.08 | 0.05 - 0.10 | 0.36 |
| | Year 3 | 0.14 | 0.12 - 0.17 | 0.11 | 0.09 - 0.14 | 0.14 |
| Serum triglycerides (mmol/L) | Year 1 | −0.19 | −0.26 - −0.13 | 0.0 | −0.10 - 0.07 | <0.001 |
| | Year 2 | −0.19 | −0.27 - −0.12 | 0.0 | −0.11- 0.11 | <0.001 |
| | Year 3 | −0.13 | −0.22 - −0.06 | 0.0 | −0.13 - 0.09 | 0.02 |
| Systolic blood pressure (mmHg) | Year 1 | −5 | −7 - −3 | −1 | −3 - 0 | 0.046 |
| | Year 2 | −5 | −6 - −3 | 0 | −2 - 2 | 0.008 |
| | Year 3 | −4 | −6 - −2 | 0 | −3 - 1 | 0.39 |
| Diastolic blood pressure (mmHg) | Year 1 | −5 | −6 - −4 | −3 | −4 - −2 | 0.005 |
| | Year 2 | −5 | −6 - −4 | −3 | −4 - −2 | 0.008 |
| | Year 3 | −4 | −6 - −3 | −3 | −4 - −2 | 0.05 |

Number of participants is 256 and 250 at year 1, 244 and 226 at year 2, and 231 and 203 at year 3, in the intervention and control groups, respectively. CI = confidence interval; HDL = high-density lipoprotein; $HbA_{1c}$ = glycosylated haemoglobin. *p-value for difference between the groups, adjusting for baseline.

*Effect of diet composition on weight change*

Weight change during the intervention period was associated with several dietary parameters, after adjustment for intervention assignment, sex, physical activity, use of VLCD, baseline weight and baseline intake of the respective nutrient (Table 9). Weight loss was related to an increase in fibre (p for trend 0.001) and decrease in fat (p for trend 0.018) and energy density (p for trend 0.001). Change in waist circumference was inversely associated with fibre density of the diet even after adjustment for weight change (p for trend=0.033), suggesting that increase in dietary fibre altered abdominal obesity independently of overall obesity.

**Table 9. Weight and waist circumference change from baseline to year 3 by quarters of dietary fibre, fat, saturated fat and energy density.***

| | | I quarter n = 125 | II quarter n = 125 | III quarter n = 125 | IV quarter n = 125 | p for trend |
|---|---|---|---|---|---|---|
| **Fibre (g / 1000 kcal)** | **Range** | **<10.85** | **10.85 - 13** | **13 -15.55** | **>15.55** | |
| Adjusted[a] weight change, kg | | −0.4 | −1.6 | −2.5 | −3.0 | 0.001 |
| Waist circumference change, cm | | −0.7 | −1.9 | −2.8 | −3.0 | |
| Adjusted[b] waist circumference change, cm | | −1.6 | −2.2 | −2.5 | −2.9 | 0.033 |
| **Fat (E%)** | **Range** | **<30** | **30 - 33.16** | **33.16 - 36.86** | **>36.86** | |
| Adjusted[a] weight change, kg | | −2.5 | −2.9 | −0.9 | −1.3 | 0.018 |
| Waist circumference change, cm | | −3.1 | −2.7 | −0.7 | −1.7 | |
| Adjusted[b] waist circumference change, cm | | −2.6 | −2.3 | −2.0 | −2.3 | 0.47 |
| **Saturated fat (E%)** | **Range** | **<12.14** | **12.14 - 14.4** | **14.4 - 16.63** | **>16.63** | |
| Adjusted[a] weight change, kg | | −2.8 | −1.5 | −2.0 | −1.2 | 0.08 |
| Waist circumference change, cm | | −3.4 | −1.8 | −2.0 | −1.1 | |
| Adjusted[b] waist circumference change, cm | | −2.6 | −2.4 | −2.2 | −2.0 | 0.27 |
| **Energy density (kcal / 100 g)** | **Range** | **<79** | **79 - 90.1** | **90.1 - 103.8** | **>103.8** | |
| Adjusted[a] weight change, kg | | −3.3 | −2.9 | −0.4 | −1.1 | 0.001 |
| Waist circumference change, cm | | −3.0 | −2.8 | −1.2 | −1.5 | |
| Adjusted[b] waist circumference change, cm | | −2.4 | −2.4 | −2.5 | −2.0 | 0.66 |

*Mean dietary intakes during the years 1-3 were used in the analyses, and last-observation-carried-forward method was used to calculate weight and waist circumference change. E% = proportion of total energy consumed. [a] Adjusted for intervention assignment, sex, age, VLCD-use, baseline weight, baseline and follow-up period physical activity, and baseline intake of respective nutrient. [b] Adjusted for intervention assignment, sex, age, VLCD-use, baseline waist circumference, baseline and follow-up period physical activity, baseline intake of respective nutrient, and weight change.

The adjusted three-year weight reduction among those whose diet was both low in fat and high in fibre was 3.1 kg (95% CI 2.3 - 3.9 kg). Among the participants with a diet of higher fat and lower fibre content, weight reduction was significantly ($p < 0.001$) less, 0.7 kg (95% CI for weight change -1.7 - +0.1 kg; Figure 3).

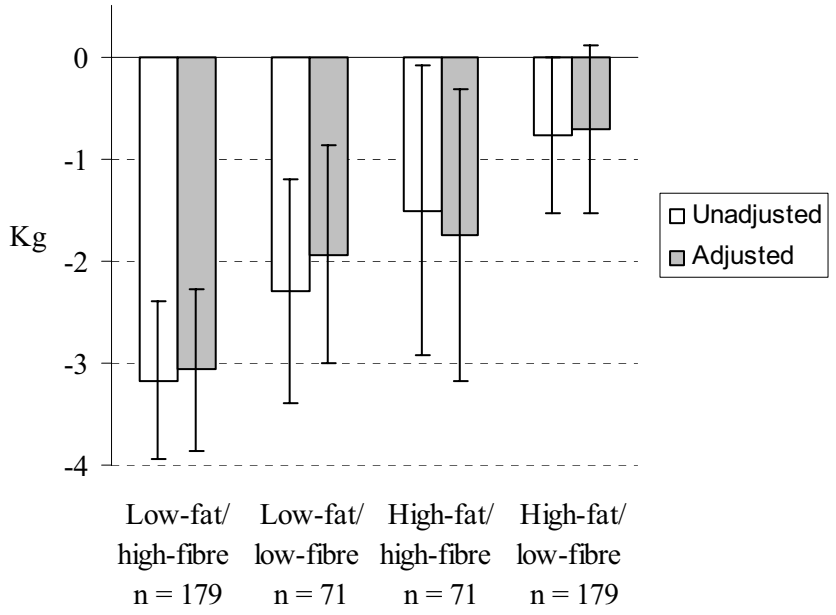



**Figure 3. Weight change (95% confidence interval) from baseline to year 3 by fibre and fat intake. Mean dietary intakes during the years 1-3 were used in the analyses, and median intakes (13.0 g / 1000 kcal for fibre and 33.15% of total energy for fat) were used as cut-off points to define low and high intake. Last-observation-carried-forward method was used to calculate weight change. Adjusted mean is calculated with analysis of covariance adjusting for intervention assignment, very low calorie diet (VLCD) use, age, sex, baseline weight, baseline fat and fibre intake, and baseline and follow-up period physical activity.**

***Diabetes incidence***

By the first interim analysis (Paper I) a total of 86 incident cases of diabetes were diagnosed; 27 in the intervention group and 59 in the control group. The average rate of change from impaired glucose tolerance to diabetes was 3% per year in the intervention group and 6% per year in the control group. The absolute risk of diabetes was 32/1000 person-years in the intervention group and 78/1000 person-years in the control group.

The probability of remaining free of diabetes was higher and, respectively, the cumulative incidence (1 minus probability of remaining free of diabetes) was lower in the intervention group than in the control group (Figure 4). The difference was statistically significant after two years: 6% in the intervention group (95% CI 3 - 9%) and 14% in the control group (95% CI 10 - 19%). At four years, the respective cumulative incidences were 11% (95% CI 6 - 15%) and 23% (95% CI 17 - 29%). Based on the Cox regression analysis using all person-years accumulated, the cumulative incidence in the intervention group was 58% lower (hazard ratio 0.42; 95% CI 27 - 67%, $p < 0.001$) than in the control group. In men the incidence of diabetes was reduced 63% (95% CI 18 - 79%, $p = 0.01$) and in women 54% (95% CI 26 - 81%, $p = 0.008$).

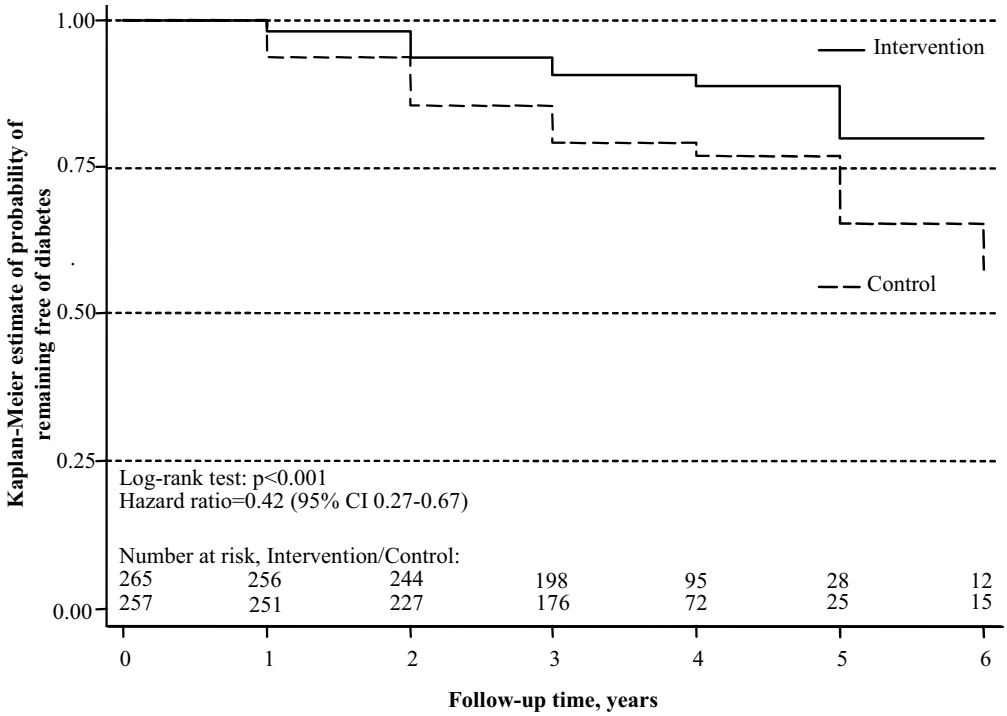



**Figure 4. Probability of remaining free of diabetes in the intervention and control groups.**

*Effect of diet composition on diabetes incidence*

Hazard ratios for diabetes during the whole intervention period by quarters of dietary intakes are given in Table 10. In the analysis adjusted for treatment assignment, sex, age, baseline weight, baseline 2-hour glucose, physical activity and baseline intake, higher fibre density (p for trend = 0.01) and lower fat intake (p for trend = 0.004) were associated with a reduced diabetes risk. Further adjustment for weight change during the trial did not affect the results notably. However, when both fat and fibre were simultaneously entered into the same adjusted prediction model neither was a significant predictor for diabetes: hazard ratio was 0.88 (95% CI 0.68 – 1.16) for increasing fibre density quarter and 1.23 (95% CI 0.95 – 1.58) for increasing fat E% quarter.

**Table 10: Hazard ratios (95% confidence intervals) for incidence of diabetes by quarters of dietary fibre, fat, saturated fat and energy density.***

| | | I quarter n = 125 | II quarter n = 125 | III quarter n = 125 | IV quarter n = 125 |
|---|---|---|---|---|---|
| **Fibre (g / 1000 kcal)** | **Range** | **<10.85** | **10.85 - 13** | **13 - 15.55** | **>15.55** |
| Hazard ratio, model 1[a] | | 1 | 0.54 (0.33-0.88) | 0.68 (0.42-1.09) | 0.34 (0.19-0.59) |
| Hazard ratio, model 2[b] | | 1 | 0.47 (0.26-0.84) | 0.60 (0.35-1.06) | 0.32 (0.16-0.66) |
| Hazard ratio, model 3[c] | | 1 | 0.50 (0.28-0.89) | 0.71 (0.40-1.23) | 0.38 (0.19-0.77) |
| **Fat (E%)** | **Range** | **<30** | **30 - 33.16** | **33.16 - 36.86** | **>36.86** |
| Hazard ratio, model 1[a] | | 1 | 0.98 (0.52-1.85) | 1.63 (0.92-2.91) | 2.85 (1.68-4.84) |
| Hazard ratio, model 2[b] | | 1 | 0.92 (0.46-1.83) | 1.44 (0.76-2.72) | 2.18 (1.17-4.04) |
| Hazard ratio, model 3[c] | | 1 | 1.07 (0.53-2.15) | 1.40 (0.74-2.64) | 2.14 (1.16-3.92) |
| **Saturated fat (E%)** | **Range** | **<12.14** | **12.14 - 14.4** | **14.4 - 16.63** | **>16.63** |
| Hazard ratio, model 1[a] | | 1 | 1.30 (0.70-2.43) | 2.10 (1.18-3.73) | 2.57 (1.47-4.52) |
| Hazard ratio, model 2[b] | | 1 | 1.34 (0.68-2.62) | 1.82 (0.98-3.38) | 1.91 (0.95-3.82) |
| Hazard ratio, model 3[c] | | 1 | 1.15 (0.58-2.29) | 1.99 (1.09-3.64) | 1.73 (0.89-3.38) |
| **Energy density (kcal/100 g)** | **Range** | **<79** | **79 - 90.1** | **90.1 - 103.8** | **>103.8** |
| Hazard ratio, model 1[a] | | 1 | 1.26 (0.74-2.15) | 1.03 (0.59-1.80) | 1.59 (0.96-2.63) |
| Hazard ratio, model 2[b] | | 1 | 1.38 (0.77-2.47) | 1.31 (0.67-2.56) | 1.70 (0.85-3.36) |
| Hazard ratio, model 3[c] | | 1 | 1.49 (0.82-2.71) | 1.04 (0.52-2.08) | 1.74 (0.89-3.37) |

*Mean dietary intakes during the years 1-3 were used in the analyses. E% = proportion of total energy consumed.

[a] Model 1: No adjustment

[b] Model 2: Adjusted for intervention assignment, sex, age, baseline weight, baseline 2-hour glucose, physical activity at baseline and during follow-up period, and baseline intake of respective nutrient

[c] Model 3: Adjusted for Model 2 and for weight change

When the participants were divided into low and high intake groups by median intakes of fat and fibre, hazard ratio for diabetes was 1.98 (95% CI 0.98 - 4.02, p = 0.06) in the low-fat/low-fibre category, 2.68 (95% CI 1.40 - 5.10, p = 0.003) in the high-fat/high-fibre category and 1.89 (95% CI 1.09 - 3.30, p = 0.024) in the high-fat/low-fibre category compared with low-fat/high-fibre diet (Figure 5).

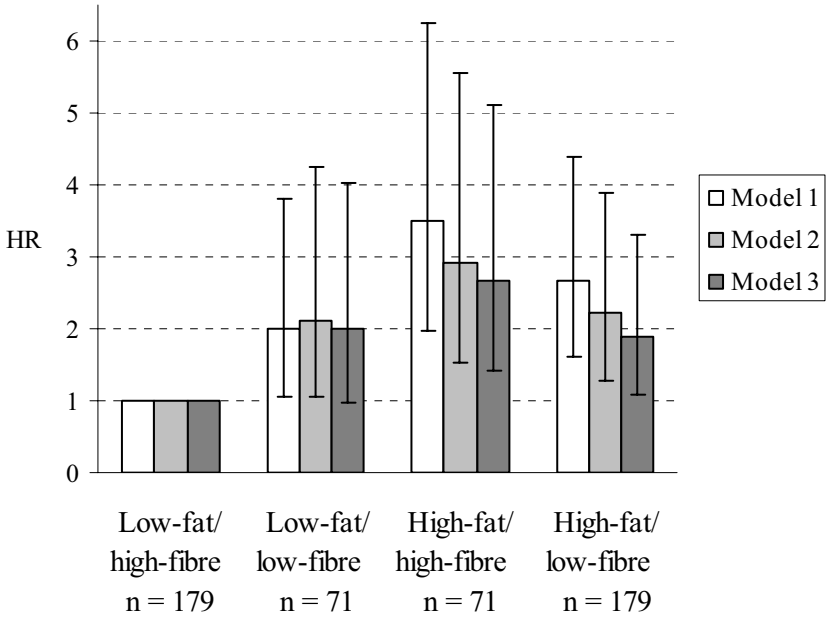



**Figure 5. Hazard ratios (95% confidence intervals) for diabetes by fibre and fat intake. Mean dietary intakes during the years 1-3 were used in the analyses, and median intakes (13.0 g / 1000 kcal for fibre and 33.15% of total energy for fat) were used as cut-off points to define low and high intake.**
**Model 1: No adjustment**
**Model 2: Adjusted for intervention assignment, sex, age, baseline weight, baseline 2-hour glucose, physical activity at baseline and during follow-up period, and baseline fat and fibre intake**
**Model 3: Adjusted for Model 2 and for weight change**

### 5.1.3 Post-intervention follow-up results

***Lifestyle***

Body weight, physical activity, and nutrient intakes at baseline, at the end of the intervention period, and at the first post-intervention visit among those without diabetes at the end of the intervention period are shown in Table 11. After the intervention period, the proportion of physically active individuals decreased in the control group. On the other hand the participants in the control group reduced their intake of saturated fat more but, since they had a higher intake to start, still maintained a higher intake than the intervention group.

**Table 11. Body weight, physical activity, and dietary intake among those participants who did not have diabetes at the end of the intervention period.**

| | Intervention group | | Control group | | | |
|---|---|---|---|---|---|---|
| | n | mean | n | mean | p* | p† |
| **Body weight (kg)** | | | | | | |
| Baseline | 190 | 84.9 | 165 | 84.0 | 0.517 | |
| The last intervention period visit | 190 | 81.8 | 165 | 83.3 | <0.001 | |
| The first post-intervention visit | 190 | 83.1 | 165 | 84.0 | 0.003 | 0.148 |
| **Proportion of physically active individuals (%)**‡ | | | | | | |
| Baseline | 184 | 70 | 164 | 70 | 0.910 | |
| The last intervention period visit | 187 | 88 | 164 | 76 | 0.003 | |
| The first post-intervention visit | 187 | 86 | 164 | 71 | <0.001 | 0.027 |
| **Fat (E%)** | | | | | | |
| Baseline | 187 | 35.9 | 159 | 36.8 | 0.188 | |
| Year 3 | 187 | 31.3 | 159 | 34.0 | <0.001 | |
| The first post-intervention visit | 187 | 31.2 | 159 | 32.9 | 0.017 | 0.199 |
| **Saturated fat (E%)** | | | | | | |
| Baseline | 187 | 16.0 | 159 | 16.9 | 0.068 | |
| Year 3 | 187 | 12.8 | 159 | 15.3 | <0.001 | |
| The first post-intervention visit | 187 | 12.3 | 159 | 14.1 | <0.001 | 0.013 |
| **Fibre (g / 1000 kcal)** | | | | | | |
| Baseline | 187 | 12 | 159 | 12 | 0.975 | |
| Year 3 | 187 | 15 | 159 | 13 | <0.001 | |
| The first post-intervention visit | 187 | 14 | 159 | 13 | 0.007 | 0.458 |

E% = proportion of total energy consumed. * p-value for test of equality between the groups, adjusting for the baseline level. † p-value for test of equal change between the groups from the last intervention period visit to the first follow-up visit, adjusting for the baseline level. ‡ Individuals who reported walking, bicycling or other moderate intensity activity for at least 4 hours per week were categorised as being physically active.

***Diabetes incidence***

The total number of cases of diabetes during the median overall follow-up time of 7 years was 75 in the intervention group and 110 in the control group. The incidence rates were 4.3 (95% CI 3.4 - 5.4) and 7.4 (95% CI 6.1 - 8.9) per 100 person-years in the intervention and control group, respectively ($p < 0.001$ log-rank test). The corresponding hazard ratio was 0.57 (95% CI 0.43 - 0.76). (Figure 6)

The cumulative incidence of diabetes at year 4 was 11% in the intervention group and 26% in the control group with an absolute risk reduction of 15%. This absolute risk reduction remained relatively constant throughout the whole follow-up period.

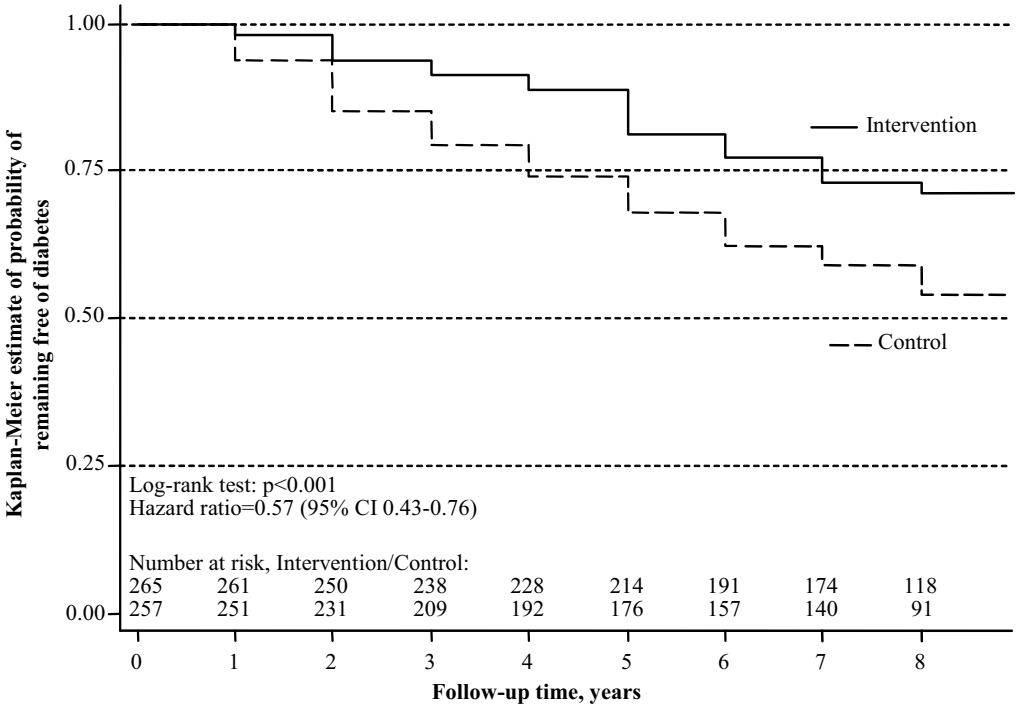



**Figure 6. Probability of remaining free of diabetes in the intervention and control groups during the total follow-up. Follow-up time shown in the figure is truncated at 8 years, as the number of participants at risk beyond this point was low, but they are included in the calculation of hazard ratios.**

To explore the extent to which the reduced long-term risk of diabetes in the intervention group could solely be attributed to a reduced risk during the actual intervention of the study, we excluded all participants who became diabetic during the intervention period (n = 116) and calculated the incidence rates and cumulative incidence exclusively for the follow-up period (Figure 7). The median post-intervention follow-up time was three years, and the number of incident cases of diabetes was 31 in the intervention group among 221 people at risk, and 38 in the control group among 185 people at risk. The corresponding incidence rates were 4.6 and 7.2 per 100 person-years, respectively (log-rank test p = 0.040), i.e. 36 percent relative risk reduction.

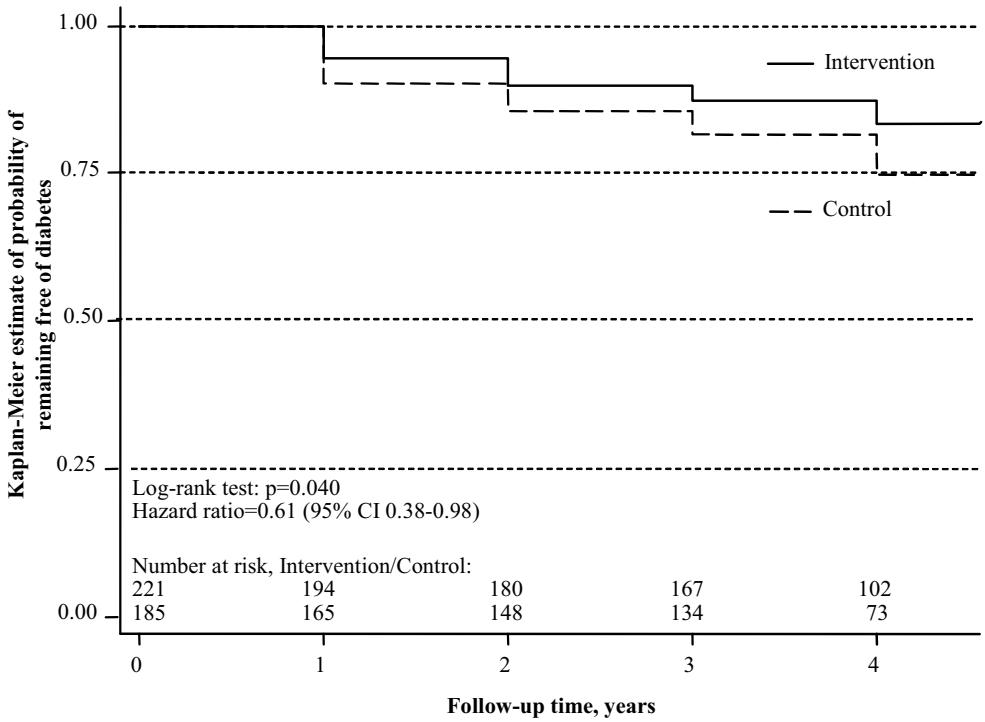



**Figure 7. Probability of remaining free of diabetes in the former intervention and control groups during the post-intervention follow-up. Follow-up time shown in the figure is truncated at 4 years, as the number of participants at risk beyond this point was low, but they are included in the calculation of hazard ratios.**

***Compliance with the intervention goals and diabetes risk: The success score***

Success in achieving the intervention goals was estimated from the food records and exercise questionnaires. The success score (from 0 to 5) was calculated as the sum of achieved lifestyle goals (Table 12).

In the intervention and the control group, respectively, 5% and 22% of the participants did not achieve any of these goals at year 1, while 21% and 5% achieved 4 or 5 goals ($p < 0.001$ for Fisher's exact test). By the 3-year examination compliance with the intervention goals had reduced slightly in both groups: 10% and 27% of the participants did not achieve any of the goals, while 14% and 6% achieved 4 or 5 goals in the intervention and the control group, respectively.

There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow-up. The hazard ratios were 1.00, 0.87, 0.67, 0.70 and 0.23, for success score from 0 to 4-5, respectively, measured at year 3 (p for trend < 0.001).

The success score analysis was repeated based on the data collected one year after the termination of the active intervention and including only participants who were free of diabetes at the end of the intervention period and had complete data for the success score variables (n = 190 in the intervention group and 165 in the control group), to analyse the effect of maintained lifestyle changes on diabetes incidence. In the intervention and the control group, respectively, 7% and 14% of the participants were not achieving any of the lifestyle goals, while 18% and 7% achieved 4 or 5 goals ($p = 0.004$ for Fisher's exact test).

In the combined group, incidence rates of type 2 diabetes were 8.0 (95% CI 4.2-15.4) among those who did not achieve any of the goals, as compared to 3.8 (95% CI 1.7-8.5) among those with 4 or 5 achieved goals. The multivariate-adjusted (adjustment for sex, age, baseline 2-hour glucose concentration and former intervention assignment) hazard ratios were 1.00, 0.90 (95% CI 0.42 - 1.94), 0.37 (95% CI 0.14 - 0.92), 0.79 (95% CI 0.32 - 1.92) and 0.50 (95% CI 0.18 - 1.37), with success score from 0, 1, 2, 3, and 4 - 5, respectively (p for trend 0.10).

**Table 12. Cox regression models for the incidence of diabetes during the total follow-up by the success score.**

| | Intervention group | | | Control group | | | Combined group | | |
|---|---|---|---|---|---|---|---|---|---|
| | % | Incidence rate* | 95% CI | % | Incidence rate* | 95% CI | % | Hazard ratio | 95% CI |
| **Success score at year 1** | | | | | | | | | |
| 0 | 5 | 9.4 | 4.2 - 20.9 | 22 | 9.1 | 6.2 - 13.3 | 13 | 1 | - |
| 1 | 27 | 5.3 | 3.5 - 7.9 | 42 | 7.0 | 5.2 - 9.4 | 34 | 0.83 | 0.53 - 1.29 |
| 2 | 32 | 3.4 | 2.1 - 5.3 | 19 | 7.2 | 4.6 - 11.1 | 26 | 0.68 | 0.39 - 1.07 |
| 3 | 15 | 4.0 | 2.2 - 7.5 | 11 | 8.6 | 5.0 - 14.7 | 13 | 0.79 | 0.47 - 1.40 |
| ≥4 | 21 | 3.8 | 2.3 - 6.5 | 5 | 2.1 | 0.5 - 8.4 | 13 | 0.50 | 0.27 - 0.92 |
| P for trend | | | | | | | | 0.042 | |
| **Success score at year 3** | | | | | | | | | |
| 0 | 10 | 5.6 | 2.9 - 10.8 | 27 | 9.7 | 6.9 - 13.5 | 18 | 1 | - |
| 1 | 31 | 6.3 | 4.4 - 8.9 | 41 | 7.0 | 5.3 - 9.4 | 36 | 0.87 | 0.59 - 1.28 |
| 2 | 24 | 2.8 | 1.6 - 5.0 | 22 | 7.2 | 4.8 - 10.8 | 23 | 0.67 | 0.41 - 1.07 |
| 3 | 21 | 3.9 | 2.4 - 6.5 | 5 | 8.6 | 3.6 - 20.7 | 13 | 0.70 | 0.40 - 1.23 |
| ≥4 | 14 | 2.5 | 1.1 - 5.6 | 6 | 1.0 | 0.1 - 6.7 | 10 | 0.23 | 0.11 - 0.52 |
| p for trend | | | | | | | | <0.001 | |

*Cases per 100 person-years. CI = confidence interval.

† Hazard models are adjusted for treatment assignment, sex, age, and baseline level of oral glucose tolerance test 2-hour glucose concentration.

## 5.2 Diabetes risk score (Paper V)

### 5.2.1 Model development

Of the 4746 subjects in the FINRISK 1987 survey 196 (4.1%) individuals developed diabetes during the follow-up of approximately 10 years. The multivariate logistic regression model to predict diabetes is presented in Table 13. Only subjects with no missing baseline risk factor data were included into the analysis (n = 4435 of whom 182 subjects developed diabetes). Statistically significant independent predictors of future diabetes were age, BMI, waist circumference, antihypertensive drug treatment (question "Have you ever used drugs for high blood pressure?" with 'no' as reference category) and history of previous high blood glucose concentration (question "Have you ever been told by a health care professional that you have diabetes or latent diabetes?" with 'no' as reference category). Also physical activity ('physical activity at least 4 hours per week' as reference category) and fruit and vegetable consumption ('roots or vegetables and/or fruits or berries on 6-7 days during the past week' as reference category) were included into the risk prediction model and to the risk score, even though these two variables were not statistically significant predictors of diabetes in the multivariate model, to emphasise the importance of physical activity and diet in the prevention of diabetes.

### 5.2.2 Model validation

Of the 4615 subjects in the 1992 survey, 67 developed diabetes during an approximately 5-year follow-up. The diabetes risk score was calculated for each subject who had complete baseline information on the selected risk factors (n = 4586). The 1987 and 1992 surveys had similar data, except for the intake of vegetables, fruits, or berries: in the 1992 survey there were 4 separate frequency questions about the use of raw and cooked vegetables, fruits and berries. If the total consumption frequency was more than 32 per month the individual was placed into the reference category. Only 15% of subjects were in the low-consumption group, compared with the 52% in the 1987 data, which may reflect a true increase in vegetable and fruit consumption during the five years between the surveys or arise from the differences in the questions.

**Table 13. Multivariate logistic regression model to predict diabetes during 10-year follow-up.**

| | Odds ratio | 95% CI | Coefficient β | Score* |
|---|---|---|---|---|
| Intercept | - | | −5.658 | |
| **Age (years)** | | | | |
| <45 | 1 | | 0 | 0 |
| 45 - 54 | 1.92 | 1.13 - 3.25 | 0.650 | 2 |
| 55 - 64 | 2.56 | 1.53 - 4.28 | 0.940 | 3 |
| **Body mass index (kg/m$^2$)** | | | | |
| ≤25 | 1 | | 0 | 0 |
| >25 - 30 | 1.02 | 0.48 - 2.15 | 0.015 | 1 |
| >30 | 2.55 | 1.10 - 5.92 | 0.938 | 3 |
| **Waist circumference (cm)** | | | | |
| men <94, women <80 | 1 | | 0 | 0 |
| men 94 - <102, women 80 - <88 | 2.78 | 1.43 - 5.40 | 1.021 | 3 |
| men ≥102, women ≥ 88 | 4.16 | 2.00 - 8.63 | 1.424 | 4 |
| **Blood pressure medication** | | | | |
| No | 1 | | 0 | 0 |
| Yes | 2.04 | 1.45 - 2.88 | 0.714 | 2 |
| **History of high blood glucose** | | | | |
| No | 1 | | 0 | 0 |
| Yes | 9.61 | 6.31 - 14.63 | 2.263 | 5 |
| **Physical activity** | | | | |
| 4 hours per week or more | 1 | | 0 | 0 |
| <4 hours per week | 1.31 | 0.88 - 1.95 | 0.268 | 2 |
| **Consumption of vegetables, fruits or berries** | | | | |
| Every day | 1 | | 0 | 0 |
| Less often than once a day | 1.18 | 0.85 - 1.64 | 0.165 | 1 |
| **Area under the ROC curve** | | | **0.860** | **0.852** |

CI = confidence interval; ROC = receiver operating characteristic.

*The diabetes risk score value was derived from the coefficient β as follows: for β from 0.01 to 0.2 the score is 1, for β from 0.21 to 0.8 the score is 2, for β from 0.81 to 1.2 the score is 3, for β from 1.21 to 2.2 the score is 4 and for β greater than 2.2 the score is 5. The total score was calculated as the sum of individual scores and varied from 0 to 20, higher value denoting higher diabetes risk.

The ROC curves (Figure 8) demonstrate that the score based on the 1987 cohort predicted diabetes very well (AUC = 0.85). The prediction was similarly good also in the 1992 cohort (AUC = 0.87). The risk score value 9 was selected as the cut-off point for increased diabetes risk, with the sensitivity of 78% and the specificity 77% in the 1987 cohort and with the sensitivity of 81% and the specificity 76% in the 1992 cohort. The positive predictive value (PPV; the probability of diabetes during the follow-up if score was 9 or higher)

was 13% for 1987 cohort (10-year follow-up) and 5% for 1992 cohort (5-year follow-up), in which the overall incidence was lower due to shorter follow-up period.

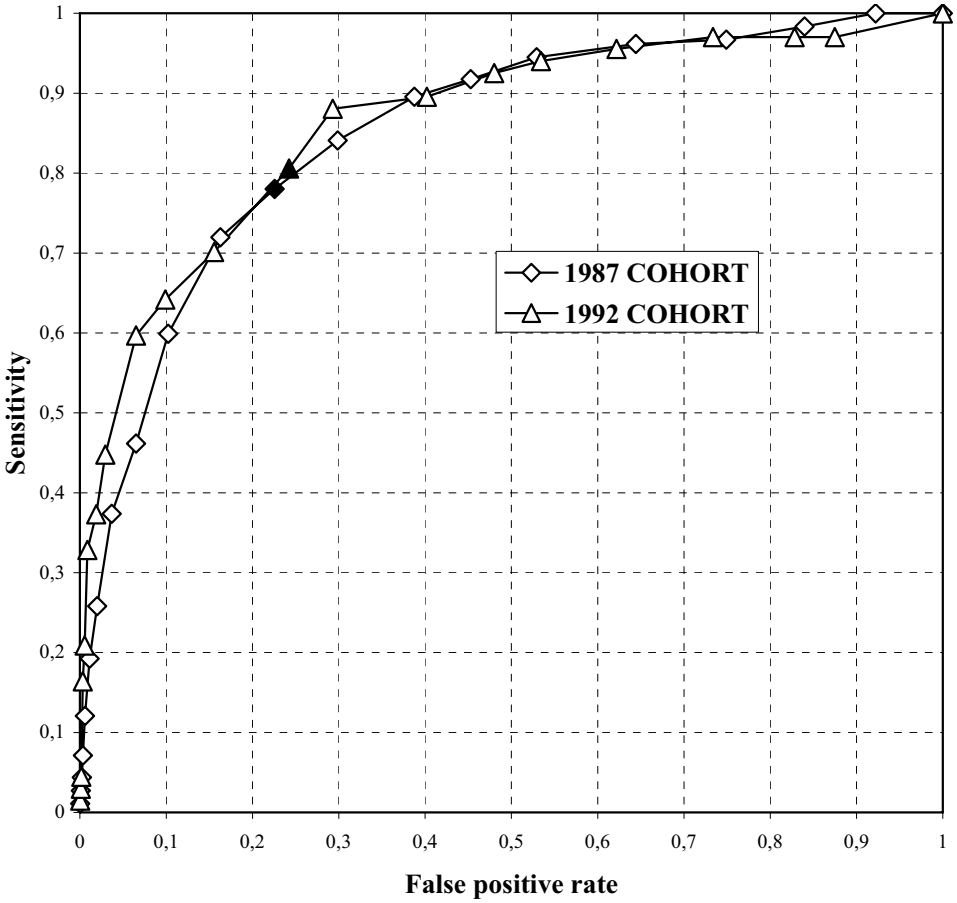



**Figure 8. Receiver operating characteristic (ROC) curves showing the performance of the risk score in predicting diabetes in the 1987 and 1992 cohorts, both cohorts with follow-up until the end of 1997. Area under the 1987 curve = 0.85 and under the 1992 curve = 0.87. For cut-off point score ≥ 9 (black marker), sensitivity (95% confidence interval) = 78% (71% - 84%) and 81% (69% - 89%), specificity = 77% (76% - 79%) and 76% (74% - 77%), positive predictive value = 13% (11% - 15%) and 5% (4% - 6%), in 1987 and 1992 cohorts, respectively.**

**Table 14. Diabetes incidence by diabetes risk score in 1987 and 1992 cohorts during the follow-up until the year 1997.**

| | 1987 cohort | | | | 1992 cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| | n | DM incidence % | n | DM incidence % | n | DM incidence % | n | DM incidence % |
| Score | | | | | | | | |
| 0 - 3 | 669 | 0.3 | 851 | 0.6 | 731 | 0.3 | 981 | 0.1 |
| 4 - 8 | 936 | 2.4 | 878 | 1.3 | 863 | 0.8 | 862 | 0.4 |
| 9 - 12 | 421 | 10.5 | 455 | 6.6 | 492 | 2.6 | 494 | 2.2 |
| 13 - 20 | 101 | 32.7 | 124 | 28.2 | 78 | 23.1 | 85 | 14.1 |
| p for trend | | 0.001 | | 0.001 | | 0.001 | | 0.001 |

DM = diabetes mellitus.

In Table 14 the men and women of both cohorts are classified into four diabetes risk score categories. The incidence of diabetes was markedly elevated in the two highest categories. In the 1987 cohort, 25% of both men and women fell into the two highest categories, and in the 1992 cohort this proportion was 26% of men and 24% of women. The risk score cut-off point 9 thus identified the high-risk quarter of the population producing 78% of the incident cases of diabetes.

### 5.2.3 The Finnish Diabetes Risk Score FINDRISC

Based on the risk score developed and validated above, the Finnish Diabetes Risk Score form (FINDRISC) was compiled. In addition to the diabetes risk factors in the regression model, there are other risk factors, about which we did not have information and therefore could not include into the model. Family history of diabetes, which reflects the genetic predisposition to the disease, is known to be an important marker for increased type 2 diabetes risk (Gloyn and McCarthy 2001). Therefore family history was included into the FINDRISC; score values 5 and 3 were estimated to be appropriate for positive history in first and second degree relatives, respectively. Furthermore, as diabetes prevalence is known to increase by age (Wild et al 2004) age category of over 64 years (with score value 4) was added into the form.

The final FINDRISC (Appendix; printed and distributed by the Finnish Diabetes Association, Tampere and retrievable also from: www.diabetes.fi/english/risktest/) thus contains 8 categorised and scored questions (age, body mass index, waist circumference,

history of antihypertensive drug treatment and high blood glucose, physical activity and daily consumption of fruits, berries or vegetables, and family history of diabetes). The maximum total score adds up to 26. Score value under 7 is estimated to represent 'low risk' (1 in 100 will develop type 2 diabetes within 10 years), value 7 - 11 'slightly elevated risk' (1 in 25), value 11 - 14 'moderate risk' (1 in 6), value 15 - 20 'high risk' (1 in 3), and value over 20 'very high risk' (1 in 2).

### 5.3 FINDRISC in the DPS population

Finally, the FINDRISC was applied to the DPS study participants, to assess whether it predicted incident type 2 diabetes also among this selected, high-risk study population. The baseline FINDRISC value was estimated retrospectively, based on the data collected at the baseline of the DPS. Accurate data had been collected on age, BMI, and waist circumference, and questions about physical activity, blood pressure medication, and high glucose concentrations had been asked. The specific question about fruit and vegetable consumption had to be omitted, but information about family history of diabetes had been collected.

A total of 509 DPS participants were classified according to their baseline FINDRISC value. The score varied from 1 to 24, with median value 13 in both intervention and control groups ($p = 0.37$ for different distributions in the two groups). Figure 9 shows the incidence rate (± 95% CI) of diabetes during the intervention period of the DPS (median follow-up time 4 years) by FINDRISC category. FINDRISC was very significantly ($p < 0.001$) associated with risk of being diagnosed with diabetes in the control group only. In the intervention group, on the other hand, there was no association. Thus it appears that the intensive lifestyle intervention given to the intervention group participants was sufficient to abolish the diabetes risk associated with baseline risk factors.

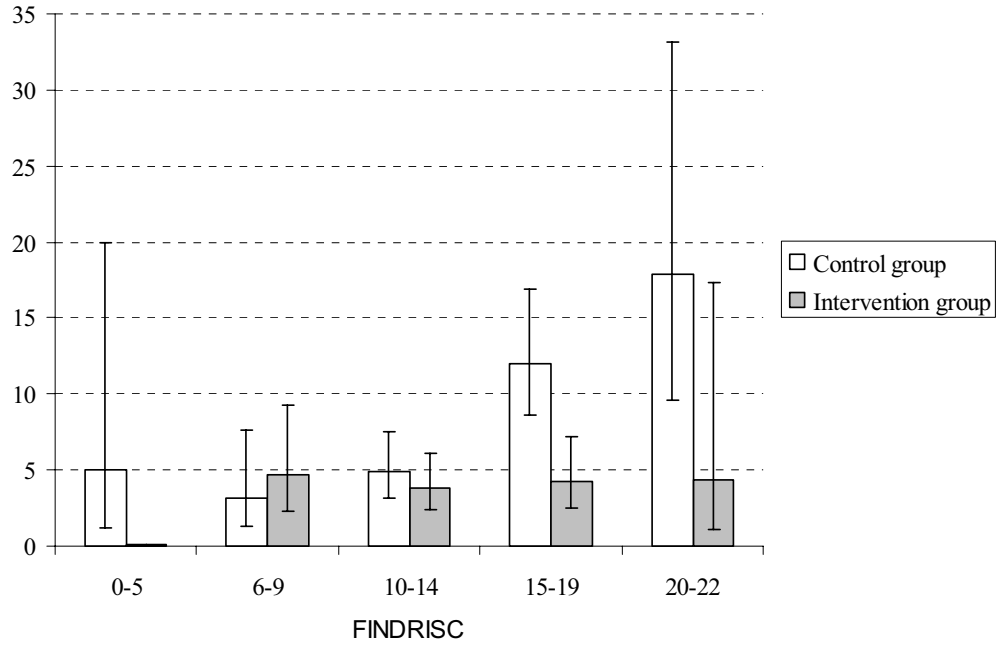



**Figure 9. Incidence rate of diabetes (cases per 100 person-years ± 95% confidence interval) during the DPS intervention period by baseline Finnish Diabetes Risk Score (FINDRISC).**

# 6 DISCUSSION

## 6.1 Prevention of type 2 diabetes

### 6.1.1 Diabetes incidence

The results from the DPS study proved, for the first time in a properly powered, controlled, individually randomised setting that type 2 diabetes is preventable with intensive lifestyle intervention in high-risk men and women. The incidence of diabetes was reduced by 58% in the group that was given intensive lifestyle counselling, compared with the control group with routine advice. The post-intervention follow-up results showed that the effect of intervention on diabetes risk was sustained at least for a median of 3 years after the discontinuation of the intervention.

The results from the Swedish Malmö feasibility study (Eriksson and Lindgärde 1991) and the Chinese Da Qing IGT and Diabetes Study (Pan et al 1997) also provide evidence that a lifestyle intervention is efficient in preventing type 2 diabetes, and the magnitude of the benefits was similar to that in our study. In these two studies the subjects were not randomly assigned to intervention and control groups, which limits the generalisability of the results. Also, the population in the Chinese study was quite different compared with the Finnish high-risk population. Their baseline BMI was relatively low, in average 25.8 $kg/m^2$, and yet the incidence of diabetes was twofold (157 per 1000 person years in the control group) compared with the DPS (78 per 1000 person years in the control group). The Chinese might be genetically more insulin resistant than European populations, including the Finnish, and thus develop diabetes at a lower risk factor level (Dhawan et al 1994).

The most important confirmation of our results comes from the US Diabetes Prevention Program (DPP) (The Diabetes Prevention Program Research Group 2002b) which was completed one year after the DPS. In the DPP 3234 individuals with impaired fasting glycaemia were randomised to receive intensive dietary and exercise counselling, metformin, or placebo. The lifestyle intervention included a 16-session (individual and/or group) core curriculum for 24 weeks and a maintenance period thereafter, with monthly contacts between the case manager and participant (The Diabetes Prevention Program Research Group 2002a). Furthermore, many different exercise activities were offered and the intervention even included ‘toolbox money’ which could be used to buy running shoes, cookbooks etc. The main aims of the intervention were 7% weight reduction and 150 minutes of moderate physical activity in a week. The relative risk reduction after 2.8 years of follow-up in the lifestyle intervention group compared with the placebo control group was exactly the same as we found in the DPS, 58%. The effect of lifestyle was higher than

the effect of metformin, which showed 35% relative risk reduction compared with the placebo control group.

The results from the DPS and the DPP have encouraged also other study groups to test the possibility of diabetes prevention by lifestyle intervention. The Indian population has high rates of insulin resistance and IGT and lower thresholds for the risk factors for type 2 diabetes (Ramachandran et al 2004). The Indian Diabetes Prevention Programme (IDPP) (Ramachandran et al 2006) recruited 531 subjects with IGT (mean age 46 years and BMI 25.8 $kg/m^2$ at baseline) who were randomised into four groups (control, lifestyle modification, metformin, and combined lifestyle modification and metformin). Lifestyle modification included advice on physical activity (30 minutes of brisk walking per day) and reduction in total calories, refined carbohydrates and fats, avoidance of sugar, and inclusion of fibre-rich foods. The intervention included personal sessions at baseline and every 6 months, and monthly telephone contacts. The intensity of the intervention was thus lower than in the DPP and DPS. After a median follow-up of 30 months, the relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin and 28.2% with lifestyle modification and metformin, as compared with the control group. Thus, there was no added benefit from combining the interventions. In the control group diabetes incidence was high (55.0% in 3 years) and comparable to the findings from the Chinese study (Pan et al 1997).

It is thus proven that lifestyle intervention of people with high diabetes risk prevents or at least postpones the onset of type 2 diabetes. Our study is the first one to show that marked difference in the cumulative incidence of diabetes between the original lifestyle intervention group and the control group still persists after the discontinuation of the active intervention. The relative risk reduction of 43% during the extended follow-up of 7 years was less than the 58% observed during the intervention period. However, the absolute difference in diabetes risk (15%) between the intervention group and the control group remained unchanged. Most importantly, diabetes incidence continued to be 36% lower among the former intervention group participants during the post-intervention follow-up. This supports the long lasting effect of the lifestyle intervention.

The relative risk reduction achieved during the total follow-up of the DPS participants was about the same compared with the Chinese study with clinics randomised either to diet (risk reduction 31%), exercise (risk reduction 46%), or diet plus exercise (risk reduction 42%) after a 6-year intervention (Pan et al 1997), even though the duration of the active intervention in the DPS was shorter. Thus, from a public health point of view there is an important message: an intensive lifestyle intervention only needs to last for a limited time period in order to yield long-term benefits in reducing the risk of type 2 diabetes in high-risk individuals.

### 6.1.2 Changes in lifestyle

The intensive, individualised lifestyle intervention brought about several beneficial lifestyle changes among the intervention group participants compared with the control group participants. Mean intake of total fat and saturated fat decreased and fibre density of the diet increased, in concordance with the focus of the counselling. There were approximately twice as many individuals in the intervention group who achieved the specific dietary goals compared with the control group; however, half of the participants in the intervention group failed to achieve any of the goals. Naturally, the intakes calculated from food records are a rough estimate of true diet composition, and should only cautiously be used to represent an individual's daily diet. Furthermore, dichotomising dietary parameters into 'adequate' and 'not adequate' intake level is a simplification: fibre density of 14 g / 1000 kcal, even though less than the goal of 15 g / 1000 kcal, is probably a marker of better dietary quality than for example 8 g / 1000 kcal.

The changes in physical activity and dietary habits made during the intervention phase seemed to be maintained among those who participated in the post-intervention follow-up. This offers encouraging evidence for the efficacy of intensive lifestyle intervention, and confirms findings from earlier studies showing that interventions can have long-term effect on lifestyle (Pereira et al 1998; Simkin-Silverman et al 2003).

It is noteworthy that also the control group participants did change their lifestyle. Mean reduction in their body weight was 1.0 kg during the first year, and they apparently also modified their diet, even though the regression-to-the-mean effect may partly account for the observed changes. It is evident that for some individuals even the low-intensity lifestyle counselling is sufficient to induce significant lifestyle modification.

### 6.1.3 Changes in body weight and clinical variables

The achieved mean weight reduction (5% at year 1 and 4% at year 3) was relatively modest but comparable to other studies on subjects with metabolic syndrome, impaired glucose tolerance or type 2 diabetes and using lifestyle approach to weight reduction (Eriksson and Lindgärde 1991; Swinburn et al 2001; Poppitt et al 2002; Mensink et al 2003). There is some evidence that weight reduction and/or maintenance is more difficult for people with type 2 diabetes than with normal glucose tolerance, mainly due to difference in dietary adherence (Guare et al 1995) and the same may be true for people with milder defects in glucose tolerance. Maintenance of the weight reduction after the first and most intensive year of the intervention period was satisfactory, and a modest difference between the intervention and control groups persisted also after the intervention had been discontinued.

The dietary intervention was individualised and allowed flexibility; the participants were not 'on a diet' but were encouraged to make gradual, permanent changes into their everyday life. A more strict, prescribed weight reduction diet would possibly have produced greater changes in diet and more substantial short-term weight reduction, but long-term results using such an approach have often been poor (Dyson et al 1997; Wing et al 1998).

These findings from the DPS are comparable to the DPP: a highly intensive lifestyle intervention (The Diabetes Prevention Program Research Group 2002a; The Diabetes Prevention Program Research Group 2003a) produced 5.6 kg (~ 6%) weight reduction during the first year of intervention, with slight, gradual regain to the end of the study at year 4 (The Diabetes Prevention Program Research Group 2002b).

Independent of weight loss, energy restriction per se results in improved glucose metabolism in subjects with type 2 diabetes (Kelley et al 1993; Wing et al 1994). It can thus be speculated that small negative energy balance sustained for a lengthy time period could be more advantageous to glucose tolerance than similar weight loss achieved with strict, short-term energy restriction. Therefore, in the long run, a lifestyle approach to weight control rather than a weight reduction diet or VLCD might be a more cost-effective way to manage overweight individuals with high type 2 diabetes risk.

Several characteristics related to the metabolic syndrome (Alberti et al 2005) were improved among the intervention group participants, which offers support for the effectiveness of lifestyle intervention in prevention of not only type 2 diabetes but also cardiovascular diseases. The intervention programme was most intensive during the first year, and consequently the changes in clinical characteristics were most prominent after the first year. The effect of intervention, e.g. the differences between the intensive intervention and the control group, was somewhat attenuated as the study continued, but this result may be biased due to the study design. The participants who developed diabetes were excluded from the study, the majority of them belonging to the control group and with the most unfavourable metabolic profile. Furthermore, also the control group participants were actually given a mini-intervention and therefore were not a true non-treatment group.

### 6.1.4 Determinants of changes in body weight and type 2 diabetes risk

In the DPS the main aim was to see if comprehensive lifestyle intervention reduces type 2 diabetes risk. We did not try to separate the effects of dietary and physical activity interventions, but tried to achieve as large lifestyle changes as possible on an individual basis. The success score analysis showed that the risk of being diagnosed with diabetes was strongly and inversely associated with the number of lifestyle goals achieved. This was especially apparent when the success in achieving the goals was assessed at year 3, which

probably reflects the importance of sustained lifestyle changes. The effect of the intervention on the incidence of diabetes was most pronounced in the participants who made comprehensive lifestyle changes; on the other hand, inability to make any changes resulted in an incidence of diabetes (9 cases per 100 person-years in the control group) that was even higher than the value of 35% in 6 years (6% per year) that was used in the power calculation. The applicability of our success score has subsequently been tested in the follow-up of the European Prospective Investigation into Cancer-Norfolk cohort (n = 24 155, ages 40 - 79) (Simmons et al 2006). Also in that population diabetes incidence was inversely associated with the number of goals achieved at baseline, and none of those who achieved all five goals at baseline (0.8% of the total population) developed diabetes during the mean follow-up of 4.6 years. The authors also estimated that if the entire population were able to meet one more goal, the total incidence of diabetes would fall by 20%. Based on these findings it is even more evident that lifestyles in general have high impact on diabetes risk; our findings on the other hand show that it is possible to change the distribution of healthy behaviours (the success score) among high-risk individuals and thus reduce the associated diabetes risk.

In the Chinese study (Pan et al 1997) an attempt to determine whether a diet or exercise intervention was more effective revealed no difference in outcome between the two interventions. Because the question about the effects of different interventions is interesting, we did complete some post-hoc analyses related to this issue, using the data collected during the DPS intervention period.

***Diet and body weight change***

Decrease in dietary fat and energy density and increase in fibre density were found to be associated with sustained weight reduction in a dose-dependent manner. Of the dietary variables investigated, energy density of diet was the most significant predictor of weight reduction. However, energy density depends mainly on fat and water content of the foods and to lesser extent on fibre content, and it is difficult to differentiate the independent effects of these factors. High energy density has been shown to be associated with passive energy overconsumption in several short-term clinical studies (Stubbs et al 1998; Bell and Rolls 2001; Devitt and Mattes 2004). Data on long-term intervention studies applying dietary energy density modification as weight management strategy are scarce. In a study by Rolls and co-workers incorporating 2 daily portions of soup with low-energy-density into a weight reduction diet resulted in a larger 12-month weight reduction compared with 2 daily portions of high-energy-density snack food of the same energy content (Rolls et al 2005). Typical high-energy-density foods are those containing fat, added sugar and/or refined grains (but not water); low-energy-density foods are those with either naturally high water content (fruits, vegetables, berries, fat-free liquid milk products) or those with high added water content (soups etc.). The former would be curtailed and the latter recom-

mended in most weight reduction regimens anyway. However, the approach to decrease energy density while maintaining the total amount of food may facilitate weight loss because it emphasises positive messages rather than negative, restrictive messages.

Our results are in line with short-term, as reviewed by Astrup and co-workers, and long-term follow-up studies showing that a reduction of E% of fat produces modest weight loss (Schatzkin et al 2000; Astrup et al 2002; Howard et al 2006a). On the other hand, also few contradictory results have been published. A study among breast cancer survivors advocating at plant-based high-fibre, low-fat diet without weight reduction goal did not produce a significant weight reduction during a 4-year follow-up even though the participants did change their diet (Thomson et al 2005). These results, however, come from a unique population of women, and may not apply for other groups.

In the DPS weight reduction among those who consumed low-fat/high-fibre diet (fat intake below median intake of 33.15 E% and fibre density above median intake of 13 g / 1000 kcal) was threefold compared with the high-fat/low-fibre group, indicating that to achieve the best results one should make extensive changes in dietary pattern, rather than focusing on any single nutrient. Our results thus support the validity of the current recommendations to moderately reduce fat and increase fibre-rich cereal and vegetable intake, to achieve sustained long-term weight reduction.

Increase in dietary protein is a novel approach to improve weight loss (Eisenstein et al 2002; Johnston et al 2004; Westerterp-Plantenga et al 2004; McAuley et al 2005; McAuley et al 2006). In our intervention we emphasised adequate protein intake (0.8 g / 1 kg body weight) but did not advise on increasing it more than that. It is impossible to say whether advocating increase in protein would have lead to a larger weight reduction than was achieved in our study. We did, however, analyse also the association of protein intake (E%) quarter with weight reduction, but did not see any significant effects (data not shown).

An increase in dietary fibre intake was associated with a reduced waist circumference, independent of weight change. A similar finding was previously seen in an observational study on American male health professionals (Koh-Banerjee et al 2003). The mechanism explaining the inverse association between abdominal fat accumulation and fibre intake is not clear. The effect of dietary fibre may be mediated by changes in insulin resistance. High fibre intake has been shown to be associated with enhanced insulin sensitivity. On the other hand, insulin resistance may, as discussed by Kahn and Flier contribute to the development of obesity (Kahn and Flier 2000). Smoking is known to be associated with central obesity (Barrett-Connor and Khaw 1989; Marti et al 1991), but smoking was uncommon among DPS participants and did not confound the association between fibre intake and waist circumference.

***Weight change and diabetes risk***

The mean weight reduction achieved by our intervention group participants was modest; yet the decrease in the incidence of diabetes was substantial. The weight reduction during the first year of the intervention was found to be a strong predictor of diabetes risk during the whole intervention period (Lindström et al 2005). The hazard ratio in the fifth with the largest weight reduction (> 7% reduction during the first year, mean reduction 10.6%) compared with those whose weight did not change was found to be 0.29 (95% CI 0.14 - 0.61) after adjustment for baseline weight, treatment group and sex. On the other hand, among those whose weight continued to increase during the first year, hazard ratio for diabetes was 1.49 (95% CI 0.89 - 2.47). This highlights the importance of even a small reduction, or at least prevention of further gain in weight, in the prevention of diabetes. Our findings are in line with those from the DPP, where the hazard ratio for a 5 kg weight reduction was 0.42 (95% CI 0.35 - 0.50) after adjustment for baseline weight and also for the other components of the lifestyle intervention (Hamman et al 2006). Weight gain of 5 - 8 kg during adulthood has been shown to be associated with twofold diabetes risk (Chan et al 1994; Colditz et al 1995; Wannamethee and Shaper 1999); based on the results from the DPS and the DPP a reduction of similar magnitude produces beneficial metabolic effects. In an average DPS male participant a 5% (4.6 kg) weight reduction means a modest decrease in BMI from 29.9 to 28.4 kg/m$^2$. Such a man, however, has approximately 15 kg excess weight, and a 5% weight reduction actually means as much as 30% reduction in this excess body weight.

In a subgroup analysis of the DPS study population there was a marked improvement in insulin sensitivity concomitantly with weight loss, whereas insulin secretion did not change significantly (Uusitupa et al 2003). These results suggest that the decline in the diabetes risk can be attributed to the persistent correction of insulin resistance, which on the other hand may preserve beta cell function. Similar findings about the effect of lifestyle intervention on insulin sensitivity in people with IGT were recently reported by a group from the UK (Oldroyd et al 2006).Thus, lifestyle intervention evidently influences the underlying pathophysiological mechanism leading to type 2 diabetes.

Weight reduction, however, apparently is not the sole important factor in diabetes prevention. In the Indian IDPP a significant reduction in diabetes risk was achieved despite that body weight was maintained within ±1 kg from the baseline level, and weight changes were not associated with changes in glucose concentrations. Therefore, other components of lifestyle modification were responsible for the risk reduction. In general the participants were more adherent to the diet than to the physical activity advice, but no further conclusions can be drawn based on the publication available at the present (Ramachandran et al 2006). In the Chinese study the diabetes risk was equally reduced in both the lean

participants without weight reduction and the overweight participants with a modest (~ 1 $kg/m^2$) weight reduction (Pan et al 1997).

***Diet and diabetes risk***

According to the present analyses the composition of diet affects diabetes risk independently of other risk factors. Low fat (defined as intake below the DPS population median intake of 33.15 E%, which actually denotes 'moderate' rather than 'low' intake) and high fibre (= above median of 13 g / 1000 kcal) intakes predicted decreased diabetes risk independently of body weight change and physical activity. The highest diabetes risk was seen among the high-fat/high-fibre and not, as would have been expected, among the high-fat/low-fibre consumers. The hazard ratios however did not statistically significantly differ and thus the effect may be coincidental, or due to confounding by unknown factors.

Several epidemiological studies have shown that low intake of total fat (Marshall et al 1994; Feskens et al 1995; van Dam et al 2002b) and saturated fat (Feskens et al 1995; van Dam et al 2002b), and high intake of cereal fibre (Salmeron et al 1997a; Salmeron et al 1997b; Meyer et al 2000; Stevens et al 2002; Montonen et al 2003; Schulze et al 2004a) and total fibre (Salmeron et al 1997b; Meyer et al 2000; Montonen et al 2003) are associated with decreased diabetes risk; however, the results have been somewhat controversial. The studies differ in relation to the dietary assessment methods, and in most of these studies diet was assessed at baseline and changes in diet during the follow-up period could not be taken into account. In our study, the participants were advised to make changes in their diet, and, to reduce intra-individual variation, dietary intake was monitored repeatedly during the intervention period.

Type of fat (namely, high saturated and trans fatty acid and low unsaturated fatty acid intake), rather than total fat intake, has in several studies been associated with increased diabetes risk (Hu et al 2001c). In clinical experiments increasing the proportion of unsaturated fat (polyunsaturated or monounsaturated fatty acids) in the diet has improved glucose tolerance compared with saturated fat either by enhancing insulin sensitivity (Storlien et al 1996; Vessby et al 2001) or increasing insulin secretion (Rojo-Martinez et al 2006). Among our study participants the total fat intake was highly correlated with saturated fat ($r = 0.81$) and monounsaturated fat ($r = 0.87$) intakes, probably because they tend to have the same dietary sources, such as meat and milk products. This might explain why total fat intake was the fat-related variable most consistently associated with diabetes risk in our analyses. Furthermore, the intake of trans fatty acids was low in our study (in average 0.7 E%; data not shown) and comparable with the intake among Finnish adult population (Männistö et al 2003); trans fatty acids thus may not be an important risk factor for type 2 diabetes in this study population nor in the Finnish population in general.

***Physical activity and diabetes risk***

Our physical activity counselling included components that improve both cardiorespiratory fitness and muscle strength. Achieving a relatively modest target of 4 hours of moderate activity per week was associated with a significant reduction in the risk of diabetes (Tuomilehto et al 2001), and an increase in moderate-to-vigorous leisure-time physical activity of 2.6 hours per week (= the highest third) was associated with 49% reduction in diabetes risk also after adjustment for weight reduction and other intervention components (Laaksonen et al 2005). In the Chinese study, which is the only one of the recent diabetes prevention studies testing the separate effects of diet and physical activity, both diet and physical activity interventions resulted in risk reduction, with no additional effect of combining the interventions (Pan et al 1997). Advocating physical activity to prevent type 2 diabetes thus evidently is of utmost importance. However, as the participants of our study reported only a modest increase in moderate-to-vigorous physical activity in the intervention group (median increase 7 minutes per day during the first year) it is implausible that increase in physical activity, even though important, was the sole explanator for the risk reduction achieved.

### 6.1.5 Limitations

***DPS study population***

The study participants were mostly volunteers who replied to newspaper advertisements etc. and thus probably were more health-conscious than the general population, as indicated also by the low number of smokers (6%) among them. They were also willing to participate in a long-lasting trial which demanded individual activity from them. It can be questioned whether similar changes in lifestyle and subsequent risk reduction could be brought about in other patient groups, e.g. screen-detected high-risk individuals. However, the same problem applies to all intervention studies following the World Medical Association's Declaration of Helsinki for the ethical conduct of trials involving human subjects. Also, the participants were selected based on results from 2 OGTTs, and were thus at very high risk; the relatively high diabetes incidence in both intervention and control groups confirms this. The selection of high-risk subjects was justifiable in order to get the results in reasonable follow-up time. Although there is no reason to assume that the same kind of intervention would not be efficient in subjects with lower initial risk, this possibility cannot be overlooked. Future studies will reveal, if the results from this clinical trial can be transposed into usual health-care settings.

Two thirds of the participants were women, even though men have at least equally high risk. A sex-specific analysis of the intervention effect (data not shown) revealed that risk reduction in the intervention group compared with the control group was similar among both sexes and therefore the results can be generalised to both men and women.

***Dietary analyses***

The dietary intervention was planned to encourage increase in dietary fibre and decrease in saturated fat intake. It is possible that the individuals receiving intensive intervention are more likely to report consuming the recommended diet (Caan et al 2004). The observed dose-dependent relationship between dietary intake and outcome, however, suggests that the associations were not entirely coincidental.

The habitual nutrient intakes of the study participants were estimated by using 3-day food records, which is a reasonably valid method in analysing dietary intakes of groups. The food records were collected annually, and in the analyses, to reduce intraindividual variability, the average intakes during the intervention period were used. The food frequency questionnaire method is widely used in epidemiological studies, since it allows large numbers of participants to be studied, once the questionnaire has been developed. The advantage of using the more laborious food record method, compared with the food frequency method, is that it does not rely on memory or assume that participants can reliably estimate the frequency they consume different food items (Schaefer et al 2000; Drewnowski 2001).

The energy intakes calculated from the food records revealed that under-reporting was common, which is a typical feature in studies assessing dietary intake (Hirvonen et al 1997). However, this may not be too problematic, because we calculated energy proportions of nutrients and not absolute amounts. Overweight and obese people are known to be even more prone to dietary under-reporting than normal weight individuals (Livingstone and Black 2003). Under-reporting has been shown to be a stable characteristic of an individual (Black and Cole 2001), and as the results were adjusted for the baseline, it may not cause a bias in our study.

Changes in specific dietary intakes were correlated: those who decreased fat intake increased consumption of carbohydrate- and fibre-containing foods, and simultaneously the energy density of the diet decreased. This real life phenomenon is problematic in statistical analyses. When the predictors entered into a model simultaneously have multicollinearity, they tend to attenuate each other. Including large number of predictors in the model also reduces the statistical power of the test. Therefore, instead of calculating a model including all dietary variables, we used separate models, and selected the most significant predictors for the combined analyses.

In addition to dietary changes, the participants were advised to increase physical activity. Therefore, the statistical models to investigate the effect of dietary composition were adjusted for physical activity at baseline and during the intervention, but some residual confounding might remain. The frequency and duration of leisure-time and lifestyle physical activity during the preceding 12 months were estimated by the study participants at each annual visit. It was not straightforward and may have been incomplete due to difficulties to recollect especially occasional activities.

## 6.2 Identification of high-risk individuals

In the past, diabetes-related screening activities have primarily been directed at detecting prevalent, undiagnosed type 2 diabetes (Herman et al 1995; Ruige et al 1997; Baan et al 1999; Griffin et al 2000; Park et al 2002; Tabaei and Herman 2002; Glümer et al 2004). The unequivocal evidence of possibility of diabetes prevention by lifestyle intervention gives a strong argument in favour of screening for subjects who have an increased risk for future type 2 diabetes.

There are two general approaches to detect future type 2 diabetes risk. One is to measure blood glucose levels to identify the so-called pre-diabetes (usually IGT or IFG) like was done in the DPS and the DPP; the other approach is to use demographic and clinical characteristics and possibly previous laboratory tests, to determine the future likelihood of incident type 2 diabetes, without measuring the present glucose concentrations. Measuring either fasting or post-load or postprandial blood glucose concentration is an invasive procedure, in large scale costly, and time consuming. Blood glucose concentration, as a whole, has a large random variation, and only gives information of the subject's current glycaemic status. The high diabetes incidence even in the intervention group of the DPS suggests that preventive actions should be targeted to all high-risk individuals – already before the IGT, which is a relatively late stage in the progress to type 2 diabetes.

The risk assessment models for incident type 2 diabetes typically include data on age, sex, ethnicity, family history of diabetes, obesity, and history of high blood pressure, glucose, or lipid concentrations (Rolandsson et al 2001; Stern et al 2002; Kanaya et al 2005; Schmidt et al 2005). Stern and co-workers (Stern et al 2002) concluded that there is no need to do the "*time-consuming, inconvenient, and expensive*" OGTT, and actually recommend instead the measurement of fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and systolic and diastolic blood pressure "*most of which are routinely gathered anyway*".

The FINDRISC is unique in that it focuses on predicting future diabetes with several factors that are fast and easy to measure with non-invasive methods, known to be associated with the risk of type 2 diabetes, easily comprehensible, and direct the person's attention to the modifiable risk factors of diabetes. The interpretation of the individual's diabetes risk is easy and can be expressed as a probability relatively accurately. People with a low FINDRISC value are unlikely to develop type 2 diabetes. Thus these people can be excluded from further medical procedures without causing a major problem of false negatives. Glucose testing after the FINDRISC is not mandatory, since people with high risk score can be assumed to benefit from lifestyle change regardless of the current glycaemic status. However, taken the high prevalence of unrecognised type 2 diabetes (Valle et al 1997; Peltonen et al 2006), and that undiagnosed diabetes is associated with increased mortality and the risk of cardiovascular disease (The DECODE Study Group 1999; The DECODE Study Group 2001) an OGTT among the subjects with high FINDRISC value is justified. Using the FINDRISC can drastically reduce the number of invasive glucose tolerance tests required at the screening phase.

Even though the FINDRISC was designed to predict future diabetes risk, it proved to be a reasonably reliable method in identifying previously unrecognised diabetes in a random population sample of 2966 men and women aged 45-74 (Saaristo et al 2005). Using the risk score cut-off value 11 to identify new diabetes resulted in sensitivity of 66% in men and 70% in women. The proportion of the population above this cut-off value was 12% of men and 15% of women. Furthermore, FINDRISC was strongly associated with the presence of cardiovascular risk factors and the metabolic syndrome. Interestingly, the risk score has been shown to be also a reasonably good predictor of coronary heart disease, stroke and total mortality (Silventoinen et al 2005) and thus lifestyle intervention for subjects with high FINDRISC is warranted.

The validity of several published screening tests to identify prevalent unknown diabetes has been tested using a population-based sample (n = 1353, age 55 to 74 years) collected in Augsburg, Germany (Rathmann et al 2005). In general, the authors found the validity of each test (Baan et al 1999; Griffin et al 2000; Stern et al 2002; Lindström and Tuomilehto 2003) to be modest and lower than in the original population. Of the scores tested, the Finnish risk score had highest sensitivity (88%) but low specificity (43%), the PPV being 12%. The authors conclude that the performance of screening questionnaires should always be assessed in the target population, due to population variation in risk factors. The validity of the Finnish risk score as an inexpensive initial screening tool for the identification of individuals with unknown diabetes or glucose intolerance has indeed been tested in Italy (Franciosi et al 2005). The performance of the risk score was assessed in the context of an opportunistic screening strategy, applied by general practitioners. The sensitivity of risk score in detecting individuals with glucose abnormalities (type 2 diabetes or IGT) was 77%

and the specificity 45%, among patients with one or more cardiovascular risk factors. A stepwise screening strategy with the risk score as an initial screening instrument, followed by the measurement of fasting blood glucose and after that by the OGTT, lead to the identification of 83% of the case subjects with type 2 diabetes and 57% of the case subjects with IGT, at a cost of an OGTT in 38% of the sample and a fasting blood glucose in 64%. The detection rate would have been the same using the fasting glucose measurement as the first screening step, but with the risk score the number of glucose measurements was reduced. Furthermore, the authors conclude that as many general practitioners in Italy do not have a possibility to measure glucose concentrations in their offices, the risk score could be a particularly useful opportunistic screening instrument. Unfortunately the authors did not use the final version of the score (the FINDRISC) which also includes question about family history of diabetes, so we do not know whether inclusion of the family history into the score would have changed the accuracy of the prediction in the Italian data.

Some limitations concerning the FINDRISC have to be addressed. We included in the model development and validation analyses all subjects who did not have antidiabetic drug treatment at baseline. Thus, patients with type 2 diabetes who were treated with diet alone were included in the prospective follow-up where the outcome was the start of antidiabetic drug treatment. The start of drug therapy indicates a deterioration of glucose homeostasis also in patients who at baseline may have been treated with diet alone. This approach decreased the possibility of bias, since during the follow-up it would not have been possible to ascertain diet-treated cases either. It is obvious that the recent incident cases, typically treated with diet, were missed in the follow-up, as were unrecognized diabetes cases. Therefore the incidence of type 2 diabetes was an underestimate of the true value. Also, the scoring of family history of diabetes was based on an educated guess, since we did not have data on that, and some other known risk factors could not be included into the model at all. Thus, in the future, after new data have accumulated, there may be need to revise the FINDRISC.

Psychological side effects of screening have been an issue under concern. Both true and false positive screening test result may cause anxiety. If the positive screening test is confirmed with diagnostic test, there may be decline in perceived health status; on the other hand, a false negative screening test may lead to false reassurance and worsening of the condition, as reviewed by Adriaanse and Snoek (Adriaanse and Snoek 2006). However, it seems that screening for diabetes does not induce anxiety (Skinner et al 2005). According to the authors, this may be explained by the fact that the general public do not perceive (type 2) diabetes as a particularly serious condition.

Finally, there are no randomised clinical trials at the moment to show the effectiveness of screening programmes for prevalent type 2 diabetes in decreasing diabetes-related mortality and morbidity. It is thus unknown whether the additional years of treatment that might be

received by individuals diagnosed through screening would result in clinically important improvements in diabetes-related outcomes (Engelgau et al 2000). However, the results from the UKPDS offer evidence in favour of early aggressive treatment of hyperglycaemia to prevent diabetic complications (U.K. Prospective Diabetes Study Group 1998a; U.K. Prospective Diabetes Study Group 1998b). When the FINDRISC form was applied in the DPS, it seemed to predict diabetes incidence in the control group, but no association was seen among the intervention group participants. This important finding clearly suggests that once when high-risk individuals have been identified with the FINDRISC and offered appropriate lifestyle counselling, type 2 diabetes can be prevented or at least postponed.

### 6.3 Practical implementation of the findings

The rapidly increasing number of patients with type 2 diabetes, the severity of the disease, its multiple and severe complications and the increasing socio-economic costs stress the importance of immediate preventive actions.

The main justification for the efforts at preventing type 2 diabetes is that it might be possible to prevent or postpone the onset and the complications of the disease and the costs of the treatment. Both asymptomatic and symptomatic diabetic patients have an increased prevalence of micro- and macrovascular complications already at the time of diagnosis of diabetes. Many also have an atherogenic serum lipid profile and hypertension (Uusitupa et al 1985; Harris 1993; Partanen et al 1995; Haffner et al 2000). The lifestyle intervention in the DPS not only improved glucose tolerance, but also reduced the levels of several other cardiovascular risk factors; whether the lifestyle intervention also reduces diabetes-related micro- and macrovascular complications is yet to be proven in the future after more cases and person-years have accumulated.

Since type 2 diabetes is a heterogeneous and multifactorial disorder preventive measures must be based upon modification of several risk factors simultaneously. Otherwise, the potential for prevention remains incomplete and insufficient. One of the advantages of using the FINDRISC form in screening is that in addition to identifying high-risk individuals, it also increases awareness of the modifiable risk factors for type 2 diabetes. The FINDRISC can be incorporated e.g. into the occupational health care check-ups, and be distributed in pharmacies, health clinic waiting rooms, health fares, newspapers, the Internet etc., and thus has a possibility to reach also those individuals who normally do not have a regular contact with health care professionals. The prerequisite is, naturally, that appropriate counselling, further testing if necessary and treatment is organised.

The need for preventive strategies for type 2 diabetes is clear. Based on the Kaplan-Meier analysis of the control group of the DPS, without intensive intervention 50% of people with

IGT will develop diabetes during the next 10 years. The observed difference in incidence between the intensive intervention and the control group indicates that the intervention needs to be individualised and continuing, to be effective. It is obvious that lifestyle intervention alone does not necessarily prevent type 2 diabetes in high-risk individuals, but it will postpone the onset of the disease in many of them. Even delaying the onset of diabetes can have a substantial impact on subsequent morbidity, and therefore on the cost-effectiveness of diabetes prevention, as was recently demonstrated with a simulation of the Diabetes Prevention Program data (Herman et al 2005).

Lifestyle changes to prevent or postpone type 2 diabetes do not have to be dramatic. As for the long-term health benefit our results strongly support the validity of the current dietary recommendations to the general population (Valtion ravitsemusneuvottelukunta 2005); reducing the intake of saturated fat, increasing whole grain cereals and fruit and vegetables, and increasing physical activity, are important, not only in terms of overall health but also for sustained weight reduction and the prevention of type 2 diabetes in overweight individuals.

The success score analysis showed that the majority of people who maintained the desired lifestyle goals at year 3 remained free of diabetes for at least 7 years. This indicates that the true effect of a healthy lifestyle would result in a considerably better outcome than that observed by the intention-to-treat analysis of the treatment effect. On the other hand, about one-third of the subjects who had participated in the intensive intervention met only one or none at all of the predefined goals one year after the intervention had stopped. These 'non-compliant' individuals clearly form a specific challenge for future prevention programmes. Oral antidiabetic drugs have in several studies been shown to prevent diabetes; however, they seem to lower blood glucose as long as they are taken, but their effect fades away as soon as the drug is discontinued (Chiasson et al 2002; The Diabetes Prevention Program Research Group 2003b; The Diabetes Prevention Program Research Group 2005). Recently published results from the large Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial showed that rosiglitazone treatment reduces diabetes risk by 60% compared with placebo among people with either IGT or IFG (Gerstein et al 2006). Drug treatment should thus be an option for those who have not responded satisfactorily to lifestyle intervention. It should be noted, though, that in the US DPP metformin treatment was estimated to be clearly less cost-effective compared with lifestyle intervention (Herman et al 2005), and thus lifestyle intervention should always be the number one choice of treatment.

It is commonly argued that it is difficult to change the lifestyle in the obese and those leading a sedentary life, but based on our results such pessimism may not be justified. The reasonably low dropout rate (10% in the intervention group and 8% in the control group) in our study also indicates that subjects with impaired glucose tolerance are willing to partici-

pate in an intervention programme if such is available. In the DPS intervention group participants had a median of 20 dietary counselling sessions per participant. In the US DPP the lifestyle intervention was much more intensive; study subjects had a 16-lesson curriculum with the personal case manager during the first 6 months of the study, and monthly individual and/or group sessions thereafter (The Diabetes Prevention Program Research Group 2002a). Both studies offered also supervised physical activity sessions. The achieved risk reduction compared with the control group was exactly the same in both the DPP and the DPS, indicating that the less intensive intervention used in the DPS was sufficient. What we do not know, however, is what would be the optimal length of intervention, from cost-effectiveness point of view. In the DPS we used one-to-one intervention to enable individualised intervention and because the recruitment and screening of study subjects was gradual. Intervention in small groups may have some benefits in the form of social support and would possibly be more cost-efficient in a clinical setting where there is no need for detailed data collection for evaluation purposes. Group intervention, however, does not suit everybody, either for personal preferences or other clinical conditions, and therefore also possibility to individual counselling should be provided.

In Finland, the current situation of type 2 diabetes can well be compared with the epidemic of coronary heart disease in the 1960's and 1970's. Primary prevention measures targeted to controlling the known modifiable risk factors of coronary heart disease have shown to be very successful (Vartiainen et al 1991). A corresponding programme to deal with the diabetes epidemic, The Development Programme for the Prevention and Care of Type 2 Diabetes in Finland 2000 - 2010 (Diabeteksen ehkäisyn ja hoidon kehittämisohjelma DEHKO), and its implementation project D2D have been launched (The Finnish Diabetes Association 2003). The Finnish Diabetes Prevention Study (DPS) intervention has formed the scientific and practical basis for the D2D, and the FINDRISC form has a central role in identifying high-risk individuals in the project. Also other activities in the field of diabetes prevention are ongoing in Finland (Uutela et al 2004). Evaluation of these national and regional diabetes prevention programmes will reveal whether the implementation of the FINDRISC form and the DPS lifestyle intervention can be performed successfully at population level.

# 7 CONCLUSIONS

The Finnish Diabetes Prevention Study (DPS) demonstrated that type 2 diabetes can be efficiently prevented by lifestyle intervention including dietary modification and physical activity in high-risk men and women. Furthermore, a simple risk score can be used to identify individuals who are at high risk of getting type 2 diabetes in the future, and who thus would be a feasible target group for intervention activities.

The conclusions related to the specific objectives are:

1. Lifestyle intervention aiming at weight reduction, increase in physical activity, and diet in line with the official dietary recommendations (moderate fat, low saturated fat and high fibre) reduced efficiently the risk of type 2 diabetes in overweight men and women with impaired glucose tolerance.

2. Intensive lifestyle intervention including frequent dietary and physical activity counselling lead to changes in dietary and physical activity behaviour. These changes were accompanied by reduction in body weight and improvements in glycaemia, blood lipids, and blood pressure. The beneficial lifestyle and clinical changes were maintained also during the less intensive maintenance period of the intervention.

3. Dietary fat and energy density were positively and dietary fibre inversely associated with change in body weight and diabetes risk. Those who consumed moderate-fat, high-fibre diet achieved the largest weight reduction and the lowest diabetes risk during the intervention period.

4. The originally achieved absolute diabetes risk reduction was maintained also 3 years after discontinuation of active counselling. During the post-intervention follow-up the diabetes incidence continued to be lower among the former intervention group participants.

5. Individual's future type 2 diabetes risk can be estimated with reasonable accuracy using a simple questionnaire (FINDRISC), with 8 questions related to diabetes risk factors. Individuals with high score value form a specific target group for lifestyle interventions to prevent the development of type 2 diabetes.

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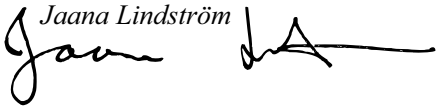
*Jaana Lindström*



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