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Metabolic Syndrome

Lifestyle intervention in subjects with impaired glucose tolerance

ACADEMIC DISSERTATION
To be presented, with the permission of
the board of the School of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building B,
School of Medicine of the University of Tampere,
Medisiinarinkatu 3, Tampere, on November 11th, 2011, at 12 o'clock.

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ACADEMIC DISSERTATION
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www.uta.fi/taju
http://granum.uta.fi

Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 1658
ISBN 978-951-44-8575-6 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1120
ISBN 978-951-44-8576-3 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2011

Contents

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original articles. In addition, some unpublished data are also presented.

1. Ilanne-Parikka P, Eriksson JG, Lindström J, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Rastas M, Salminen V, Aunola S, Sundvall J, Valle T, Lahtela J, Uusitupa M and Tuomilehto J on behalf of the Finnish Diabetes Prevention Study Group. Prevalence of the metabolic syndrome and its components – findings from a Finnish general population sample and the Diabetes Prevention Study (DPS) cohort. Diabetes Care 2004; 27: 2135–2140.

2. Ilanne-Parikka, P, Eriksson JG, Lindström J, Peltonen M, Aunola S, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Lahtela J, Uusitupa M and Tuomilehto J on behalf of the Finnish Diabetes Prevention Study Group. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. Diabetes Care 2008; 31: 805–807.

3. Ilanne-Parikka P, Laaksonen DE, Eriksson JG, Lakka TA, Lindström J, Peltonen M, Aunola S, Keinänen-Kiukaanniemi S, Uusitupa M, Tuomilehto J on behalf of the Finnish Diabetes Prevention Study Group. Leisure-time physical activity and the metabolic syndrome in the Finnish Diabetes Prevention Study. Diabetes Care 2010; 33: 1610–1617.

4. Lindstöm 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, Paturi M, Sundvall J, Valle TT, Uusitupa M and Tuomilehto J. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006; 368: 1673–1679.

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* P.Ilanne-Parikka and J Lindström share the primary authorship of the 4th publication. It has been used in the PhD thesis of J. Lindström.

ABBREVIATIONS

AHA	American Heart Association
BMI	Body mass index (kg/m^2)
CI	Confidence interval
CVD(s)	Cardiovascular disease(s)
DPP	Diabetes Prevention Program Trial
DPS	Diabetes Prevention Study
E%	Proportion of total daily energy intake
HbA1c	Hemoglobin A1c; glycosylated hemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
IASO	International Association for the Study of Obesity
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low-density lipoprotein
LTPA	Leisure-time physical activity
MetS	Metabolic syndrome
NCEP	National Cholesterol Education Program
NGT	Normal glucose tolerance
NHLBI	National Heart, Lung and Blood Institute
MUFA	Monounsaturated fatty acid
OGTT	Oral glucose tolerance test
PUFA	Polyunsaturated fatty acid
SAFA	Saturated fatty acid
VLDL	Very low-density lipoprotein
WHO	World Health Organization

ABSTRACT

Metabolic syndrome (MetS) is characterized by insulin resistance and a clustering of risk factors for both type 2 diabetes and cardiovascular diseases (CVDs). MetS and type 2 diabetes show rising prevalence worldwide. The most important modifiable risk factors for MetS and type 2 diabetes are overweight, abdominal obesity and physical inactivity, as well as dietary factors.

The aim of this work was to assess 1) the prevalence of MetS and its components, 2) the effects of a lifestyle counseling program and weight change on MetS and its components, 3) the effects of leisure-time physical activity (LTPA) on the prevention and treatment of MetS, and 4) the long-term effects of lifestyle intervention on the development of type 2 diabetes.

The study population consisted of middle-aged (mean age 55 years), overweight (mean BMI 31 kg/m^2) men (n = 172) and women (n = 350) with impaired glucose tolerance (IGT) taking part in the Diabetes Prevention Study (DPS) in Finland. They were randomized to an intensive, individualized lifestyle-counseling group or a standard care control group. In addition, a population-based cross-sectional subsample of individuals from the FINRISK 1992 cohort with ages ranging from 45 to 64 years was studied.

In the FINRISK 1992 population, about one fourth of the men and women had a BMI over 30 kg/m^2 and nearly 80% of the men and 20% of the women had abdominal obesity. MetS was found in 39% of the men and in 22% of the women. The prevalence of MetS increased with age and worsening glucose metabolism; approximately 75% of those with IGT had MetS.

In DPS, lifestyle counseling reduced the occurrence of MetS, abdominal obesity and elevated fasting glucose after the first year of intervention. Abdominal obesity and the overall prevalence of MetS were also reduced in the long term (median intervention of four years) in the intervention group compared to the control group.

Among the 386 DPS participants with MetS at baseline, the intervention resulted in significant improvement in all the MetS components at the first annual visit. By the end of the study fasting and 2-hour insulin concentration, HOMA-IR index and HDL-cholesterol were significantly improved in the intervention group compared to

the control group. Nearly 50% of the individuals with MetS in the intervention group succeeded in losing ≥ 5% of their weight by the first annual follow-up visit. The long-term results were encouraging: over 30% of the intervention group participants still had a weight loss ≥ 5% at the end of the study. The participants in the intervention group showed a resolution of MetS over two times more often. Weight loss was the most powerful predictor of MetS resolution, as was weight gain for MetS development.

Increased participation in moderate-to-vigorous physical activity and regular long-term participation in resistance training increased the likelihood of MetS resolution and decreased the likelihood of MetS development in the DPS participants. Physical activity, and resistance training more specifically, had benefits with respect to elevated plasma glucose and dyslipidemia, but improvements in abdominal obesity and blood pressure were not observed.

The DPS participants were re-examined during follow-up visits for up to three years without specific intervention in this study. The median intervention and follow-up time together was 7 years. The total diabetes incidence rate was reduced by 43% in the intervention group compared to the control group.

In conclusion, a lifestyle intervention program with a comprehensive approach resulted in lifestyle changes that reduced weight and abdominal obesity and the prevalence of MetS. Long-term follow-up showed that the progression to type 2 diabetes diminished up to three years after the discontinuation of active intervention.

TIIVISTELMÄ

Metabolista oireyhtymää luonnehtii elimistön alentunut insuliiniherkkyys eli insuliiniresistenssi ja tyypin 2 diabetekselle sekä sydän- ja verisuonisairauksille altistava riskitekijöiden kasauma. Tärkeimmät ja vaikutettavissa olevat metabolisen oireyhtymän ja tyypin 2 diabeteksen riskitekijät ovat ylipaino, vyötärölihavuus, liikkumattomuus ja epäterveelliset ruokailutottumukset. Elintapojen muuttaminen on ensisijaista metabolisen oireyhtymän ehkäisyssä ja hoidossa.

Tämän tutkimuksen tavoitteena oli selvittää 1) metabolisen oireyhtymän ja sen osatekijöiden esiintyvyyttä, 2) tehostetun elintapaohjauksen ja painonmuutoksen vaikutusta metaboliseen oireyhtymään ja sen osatekijöihin, 3) vapaa-ajan liikunnan merkitystä metabolisen oireyhtymän ehkäisyssä ja hoidossa ja 4) elintapaohjauksen pitkäaikaisvaikutusta tyypin 2 kehittymiseen suuren sairastumisvaaran henkilöillä.

Tutkimusaineisto koostui keskimäärin 55-vuotiaista, ylipainoisista (painoindeksi 31kg/m^2) miehistä (n = 172) ja naisista (n = 350), jotka osallistuivat tyypin 2 diabeteksen ehkäisytutkimukseen (Diabetes Prevention Study; DPS) vuosina 1993–2000 viidellä paikkakunnalla Suomessa. Tutkittavat satunnaistettiin intensiivisen ja yksilöllisen elintapaohjauksen interventioryhmään ja tavanomaisen ohjauksen kontrolliryhmään. Metabolisen oireyhtymän esiintyvyyttä selvitettiin lisäksi väestöpohjaisessa FINRISK 1992 -poikkileikkaustutkimuksessa 45–64 -vuotiailla henkilöillä.

FINRISK 1992 -tutkimukseen osallistuneista miehistä ja naisista joka neljännen painoindeksi ylitti 30 kg/m^2 ja lähes 80%:lla miehistä ja 20%:lla naisista todettiin vyötärölihavuus. Metabolinen oireyhtymä todettiin miehistä 39%:lla ja naisista 22%:lla. Metabolisen oireyhtymän esiintyvyys lisääntyi iän ja glukoosi-aineenvaihdunnan häiriön etenemisen myötä.

Tehostettu elintapaohjaus vähensi metabolisen oireyhtymän, vyötärölihavuuden ja kohonneen paastoglukoosin esiintyvyyttä DPS tutkimuksen ensimmäisen vuoden aikana. DPS-tutkimuksen päättyessä, mediaaniltaan 4 vuoden intervention jälkeen, vyötärölihavuuden ja metabolisen oireyhtymän esiintyvyys oli tehostetun ohjauksen ryhmässä edelleen merkitsevästi pienempi kuin kontrolliryhmässä.

DPS-tutkimukseen osallistui 386 henkilöä, joilla jo alkututkimuksessa todettiin heikentyneen glukoosinsiedon ohella metabolinen oireyhtymä. Interventioryhmään kuuluneilla henkilöillä kaikki metabolisen oireyhtymän osatekijät korjaantuivat

ensimmäisen tutkimusvuoden aikana merkittävästi useammin kuin kontrolliryhmään kuuluneilla. Tutkimuksen lopussa paasto ja kahden tunnin insuliinipitoisuus, insuliiniresistenssiä kuvaava HOMA-IR-indeksi ja HDL-kolesteroli olivat merkittävästi parantuneet interventioryhmässä kontrolliryhmään verrattuna. Interventioryhmään kuuluneilla metabolinen oireyhtymä korjaantui kaksi kertaa useammin. Interventioryhmään osallistuneista lähes 50% onnistui laihduttamaan ≥ 5% painostaan ensimmäisen vuoden aikana verrattuna 14%:iin kontrolliryhmässä. Myös pitkäaikaistulokset olivat rohkaisevia: interventioryhmässä yli 30%:lla paino oli tutkimuksen lopussa edelleen ≥ 5% pienempi kuin tutkimuksen alussa. Laihtuminen ennusti parhaiten metabolisen oireyhtymän korjautumista ja lihominen metabolisen oireyhtymän kehittymistä.

Kohtuu- tai voimakaskuormitteinen kestävyysliikunta ja lihasvoimaharjoittelu edistivät metabolisen oireyhtymän korjaantumista ja vähensivät metabolisen oireyhtymän kehittymistä. Liikunta, erityisesti lihasvoimaharjoittelu, korjasi kohonnutta glukoosipitoisuutta ja rasva-aineenvaihdunnan häiriötä, mutta vyötärölihavuudessa ja kohonneessa verenpaineessa ei tapahtunut merkittävää korjaantumista pelkästään liikunnan avulla.

DPS-interventioryhmään osallistuneet saavuttivat elintapoihin liittyneet tavoitteet useammin kuin kontrolliryhmään osallistuneet. Pitkäaikaisseurannassa interventio ja seuranta-ajan mediaani oli yhteensä seitsemän vuotta. Diabeteksen ilmaantuvuus oli seurannan päättyessä 43% pienempi interventioryhmässä kuin kontrolliryhmässä.

Tutkimuksen perusteella kokonaisvaltainen ja intensiivinen elintapaohjaus aikaansai muutoksia ruokailutottumuksissa ja liikunnassa, mikä johti laihtumiseen ja vyötärölihavuuden sekä metabolisen oireyhtymän vähentymiseen. DPS-tutkimukseen osallistuneiden seuranta kolme vuotta intervention päättymisen jälkeen osoitti, että heikentyneen sokerinsiedon eteneminen diabetekseksi oli edelleen vähäisempää interventioryhmän henkilöillä verrattuna kontrolliryhmän henkilöihin.

1. INTRODUCTION

A syndrome is a clustering of factors that occur together more often than by chance alone and for which the underlying cause is often unknown. The concept of clustering of metabolic disorders and cardiovascular disease (CVD) risk factors has a long history that dates back to the 17th century, when Nicolaes Tulp reported a case of the hypertriglyceridemia syndrome (Crepaldi 2005). In the 18th century Morgagni described the association between visceral obesity, hypertension, hyperuricemia, atherosclerosis and obstructive sleep apnea syndrome (Kylin 1923; Enzi et al. 2003; Crepaldi 2005). Kylin (1923) documented a connection between hypertension, hyperglycemia, and gout, and Vague (1956) identified the importance of upper body adiposity as a condition often associated with "diabetes, atherosclerosis, gout and uric calculous disease."

The metabolic syndrome (MetS) or syndrome X, as introduced by Reaven (1988), is characterized by insulin resistance and a clustering of risk factors for both type 2 diabetes and CVD. These risk factors include abdominal obesity, insulin resistance and/or elevated plasma glucose, elevated blood pressure, dyslipidemia with elevated triglycerides and/or lowered HDL-cholesterol, as well as proinflammatory and prothrombotic state (Alberti et al. 2006). Individuals with MetS are at twofold risk of CVDs and at three- to fivefold risk of type 2 diabetes over the next 5 to 10 years, compared to individuals without MetS (Ford et al. 2008b; Alberti et al. 2009).

The prevalence of type 2 diabetes has constantly been increasing worldwide. This is primarily due to the global increase in obesity as a result of sedentary lifestyle, unhealthy eating, and positive energy balance, as well as due to urbanization and an increase in the proportion of people over 65 years of age (Wild et al. 2004). The total number of people with diabetes is projected to rise from 285 million in 2010 to 438 million in 2030, and the number of people with impaired glucose tolerance (IGT) from 344 million to 472 million (IDF 2010).

Prevention, early identification, and treatment of MetS serve for the primary and secondary prevention of type 2 diabetes and CVDs. Besides being a major challenge for health care, prevention and treatment of MetS is also a challenge for predisposed individuals. Recent recommendations promote lifestyle changes, e.g., increased physical activity, a healthy diet, and weight loss (Grundy et al. 2005; Alberti et al. 2006; Eckel et al. 2010).

There are now several studies supporting the possibility of preventing type 2 diabetes through changes in lifestyle (Tuomilehto et al. 2001; Knowler et al. 2002), but only a few studies on the treatment of MetS have been published. The series of studies included in this work focused on the prevalence of MetS in a population-based cohort of middle-aged Finns from FINRISK 1992, as well as the participants of the Diabetes Prevention Study (DPS) in Finland. Post hoc analyses of the DPS data of the effects of intensive and individual lifestyle counseling, weight loss, and exercise on MetS were performed. Furthermore, the post-intervention follow-up examinations of the DPS participants, which lasted for a median total of 7 years, were studied.

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2. REVIEW OF LITERATURE

2.1 The concept and development of MetS

The term ‘metabolic syndrome’ (MetS) refers to a clustering of cardiovascular disease (CVD) risk factors, including abdominal obesity, impaired glucose regulation, hyperinsulinemia, elevated triglycerides, decreased HDL-cholesterol and elevated blood pressure. These risk factors occur simultaneously more often than would be expected by chance alone, supporting the existence of a discrete disorder, MetS. Syndrome X, as MetS was originally introduced by Reaven, was a pathophysiological construct attempting to explain the clustering of CVD risk factors in non-diabetic individuals (Reaven 1988; Reaven 2010). This pathophysiological concept was not intended for clinical or epidemiological use, in contrast to subsequent definitions created in order to aid the diagnosis of MetS.

Insulin resistance explains most, if not all, of MetS (Eckel et al. 2010). Ectopic fat accumulation in several organs, activation of the immune system with low-grade inflammation, cellular processes such as mitochondrial dysfunction and endoplasmic reticulum stress, as well as alterations of the hypothalamic-pituitary-adrenal axis may be involved in the pathogenesis of insulin resistance (Cornier et al. 2008; Kolb and Mandrup-Poulsen 2009; Eckel et al. 2011). Some evidence suggest that chronic psychosocial stress (Vitaliano et al. 2002; Pyykkönen et al. 2010) and alterations in circadian systems and sleep deprivation (Maury et al. 2010) may contribute to the development of MetS.

Obesity, sedentary lifestyle, and dietary and genetic factors are known to contribute to and interact with the development of MetS (Reaven 1988; Liese et al. 1998). Studies investigating genetic factors that predispose to MetS have revealed inconsistent results. Povel et al. (2011) described the most studied single nucleotide polymorphisms (SNPs) in relation to MetS. They found evidence for an association with MetS for eight SNPs, suggesting that lipid metabolism plays a central role in MetS development.

The availability of highly palatable, low-price, and energy-dense food, combined with increased portion sizes and sedentary lifestyles, results in a positive energy balance and weight gain. Besides being a storage for energy, adipose tissue is regarded as an endocrine organ that secretes adipocytokines and vasoactive substances (Wajchenberg 2000). The contribution of adipokines, including proinflammatory cytokines, hormones, and growth factors produced by adipocytes and/or fat tissue macrophages to the development of MetS is under active investigation.

In 2005 the American Diabetes Association and the European Association for the Study of Diabetes called for critical reappraisal of Mets. The associations stated that there is a lack of certainty regarding the pathogenesis of Mets and its value as a CVD risk marker (Kahn et al. 2005b; Reaven 2010). A position statement of the American Association for Clinical Endocrinology pointed out that MetS should not be used as a disease unto itself (Mechanick et al. 2005). A recent WHO report by Simmons et al. (2010) came to a conclusion that MetS has a limited use as diagnostic or management tool. MetS is rather a concept that focuses attention on complex multifactorial health problems and should be considered a pre-morbid condition excluding individuals with diagnosed diabetes or CVD (Simmons et al. 2010).

The pathogenesis of MetS is complex and no single unifying pathophysiological mechanism has been agreed. Positive energy balance is followed with excess and ectopic fat accumulation with low grade inflammation resulting in insulin resistance. Even though the concept of MetS has been critically discussed it offers an understandable framework both for patients and care provides, of the development and comprehensive treatment of clustered risk factors for type 2 diabetes and CVDs.

2.2 Definitions of MetS

There have been several definitions of MetS (Table 1). Some of the definitions have been used for epidemiological or clinical studies, while others are more suitable for clinical practice. The latest consensus definition is a joint statement by the International Diabetes Federation (IDF), the National Heart, Lung and Blood Institute (NHLBI), the American Heart Association (AHA), the World Health

Foundation, the International Atherosclerosis Society (IAS) and International Association for the Study of Obesity (IASO) from 2009 (Alberti et al. 2009). It incorporates earlier IDF and AHA/NHLBI criteria. It is an initiative that develops a unified global definition of the clinical criteria of MetS. According to this initiative, MetS is defined by at least three of the five following risk factors occurring simultaneously: 1) elevated waist circumference, 2) elevated triglycerides or specific drug treatment, 3) reduced HDL-cholesterol or specific drug treatment, 4) elevated blood pressure or blood pressure lowering medication, and 5) elevated fasting plasma glucose or specific drug treatment (Alberti et al. 2009). While the relationship between waist circumference and CVD differs globally, national or regional cut points for waist circumference are used (Eckel et al. 2010).

Table 1. Different definitions of MetS.

World Health Organization (WHO 1998) (Alberti and Zimmet 1998; World Health Organization 1999)

Insulin resistance or impaired glucose regulation or diabetes together with two or more of the following:

- Waist-to-hip ratio > 0.9 in men and > 0.85 in women and/or BMI $\geq$ 30 kg/m^2
- Systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg
- Fasting plasma triglycerides $\geq$ 1.7 mmol/l and/or HDL-cholesterol < 0.9 mmol/l in men and < 1.0 mmol/l in women
- Urinary albumin excretion rate $\geq$ 20 µg/min or albumin/creatinine ratio $\geq$ 30 mg/g

European Group for the Study of Insulin Resistance (EGIR 1999) (Balkau and Charles 1999)

Insulin resistance or fasting hyperinsulinemia (above the highest quartile of the population) in non-diabetic population with two or more of the following:

- Waist circumference $\geq$ 94 cm in men and $\geq$ 80 cm in women
- Systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg or blood pressure lowering medication
- Fasting plasma triglycerides > 2.0 mmol/l and/or HDL-cholesterol < 1.0 mmol/l or specific drug treatment
- Fasting plasma glucose 6.1– 6.9 mmol/l

National Cholesterol Education Program (NCEP 2001) (The National Cholesterol Education Program 2001)

Three or more of the following:

- Waist circumference ≥ 102 cm in men and ≥ 88 cm in women
- Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or blood pressure lowering medication
- Fasting plasma triglycerides ≥ 1.7 mmol/l
- Fasting plasma HDL-cholesterol < 1.03 mmol/l in men and < 1.3 mmol/l in women
- Fasting plasma glucose ≥ 6.1 mmol/l (In 2003, the American Diabetes Association changed the criteria for IFG from 6.1 mmol/l to 5.6 mmol/l)

American Association for Clinical Endocrinologist (AACE 2003) (American College of Endocrinology Task Force in the Insulin Resistance Syndrome 2003)

BMI > 25 kg/m^2 or waist circumference > 40 inches (~100cm) in men, > 35 inches (~90cm) in women identifies individuals at increased risk of insulin resistance syndrome.

Identifying abnormalities of MetS:

- Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or blood pressure lowering medication
- Fasting plasma triglycerides ≥ 1.7 mmol/l
- Fasting plasma HDL-cholesterol < 1.03 mmol/l in men and < 1.3 mmol/l in women
- Fasting plasma glucose 6.1−6.9 mmol/l or 2-hour post load plasma glucose 7.8–11.0 mmol/l

International Diabetes Federation (IDF 2005) (Alberti et al. 2006)

Central obesity as defined by ethnic specific waist circumference (European men ≥ 94 cm and women ≥ 80 cm or BMI > 30kg/m^2

with two or more of the following :

- Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or blood pressure lowering medication
- Fasting plasma triglycerides ≥ 1.7 mmol/l or specific drug treatment
- Fasting plasma HDL-cholesterol < 1.03 mmol/l in men and < 1.3 mmol/l in women or specific drug treatment
- Fasting plasma glucose ≥ 5.6 mmol/l or glucose lowering medication

American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI 2005) (Grundy et al. 2005)
As the original National Cholesterol Education Program 2001 criteria, but cut-off for elevated fasting plasma glucose lowered to ≥ 5.6 mmol/l.

IDF, NHLBI, AHA, WHF, IAS, IASO 2009 (Alberti et al. 2009)
Presence of any three of the following five risk factors:

- Waist circumference ≥ 94 cm in men and ≥ 80 cm in women (population and country specific)
- Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or lipid lowering medication
- Fasting plasma triglycerides > 1.7 mmol/l or specific drug treatment
- Fasting plasma HDL-cholesterol < 1.0 mmol/l in men and < 1.3 mmol/l in women or specific drug treatment
- Fasting plasma glucose ≥ 5.6 mmol/l or glucose lowering medication

2.3 Components of MetS

2.3.1 Abdominal obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a health risk. Obesity is traditionally measured by the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in meters) (World Health Organization 2011). Overweight is defined by a BMI 25.0−29.9 kg/m^2 and obesity by a BMI ≥ 30 kg/m^2.

Waist circumference provides an easily available measure of abdominal obesity (Wahrenberg et al. 2005). It is measured with a person in standing position at the level midway between the lowest rib and iliac crest. The cut-off values for waist circumference defining high-risk groups for both type 2 diabetes and CVD vary between populations. The IDF 2005 MetS criteria cut-off for abdominal obesity is defined as waist circumference ≥ 94 cm for European men and ≥ 80 cm for

European women, with ethnicity-specific values for other population (Alberti et al. 2009). In addition, waist-to-hip ratio has been used for the assessment of abdominal obesity.

The amount of excess fat, its distribution within the body, and the associated health consequences vary considerably between obese individuals (World Health Organization 2004). Waist circumference is a measure of both subcutaneous abdominal adipose tissue and visceral adipose tissue. Visceral adipose tissue refers to the fat accumulated inside the abdominal cavity (Fox et al. 2007). Excess visceral adipose tissue is associated with an adverse metabolic risk profile, and also influences the risk of developing MetS (Fox et al. 2007; Matsushita et al. 2010). Elevated fasting plasma triglycerides may be a useful indicator of the possibility that increased waist circumference is due to visceral fat accumulation (Després et al. 2001).

Although waist circumference may be a powerful predictor of clinical outcome linked to insulin resistance, there is also considerable evidence that overall obesity, as estimated by BMI, not only contributes to insulin resistance, but also increases the likelihood that an individual will develop the clinical condition associated with insulin resistance (Reaven 2008).

2.3.2 Insulin resistance

The normal effects of insulin on glucose and lipid metabolism are predominantly directed to the liver, muscle, and fat tissue (Barrett et al. 2010). In the liver, insulin reduces glucose output and increases protein and lipid synthesis. In muscle, insulin increases glucose uptake, storage, and use, as well as amino acid uptake and protein synthesis. In adipose tissue, insulin increases glucose uptake, fatty acid synthesis, and triglyceride deposition.

Insulin resistance can be defined as the inability of insulin to produce its usual biologic actions at normal circulating concentrations (Yki-Järvinen 2010). Insulin resistance can be measured by a variety of methods. Euglycemic insulin clamp is a golden standard technique for quantification of whole-body insulin sensitivity (DeFronzo et al. 1979). Homeostasis model assessment of insulin resistance (HOMA-IR) index, defined by Matthews (1985), has been used in clinical and

cross-sectional epidemiological studies. This model is based on fasting plasma insulin and glucose concentrations (fasting insulin (μU/ml) x fasting glucose (mmol/l) / 22.5).

Insulin resistance associates with a number of other MetS components, and correlates with the risk of type 2 diabetes and CVDs (Alberti et al. 2005). The follow-up of over 15 000 individuals in the AusDiab and Mauritius surveys suggests that MetS begins with excess abdominal adiposity followed by insulin resistance (Cameron et al. 2008), which explains most of MetS and its components (Cameron et al. 2008; Eckel et al. 2010). Kolb and Mandrup-Poulsen (2009) summarize that lifestyle factors cause insulin resistance and β-cell failure via systemic and local low-grade inflammation and metabolic stress. They become pathogenic if genetically controlled anti-inflammatory counter-regulatory mechanisms fail (Kolb and Mandrup-Poulsen 2009).

2.3.3 Abnormal glucose tolerance

In the pancreas, insulin resistance results in an increase in ß-cell mass and/or an increase in insulin secretory capacity, resulting in hyperinsulinemia. Fasting and postprandial glucose values remain normal for years. Those individuals who are genetically predisposed or have defects in their insulin secretion, develop abnormal glucose tolerance (Eckel et al. 2010).

In the WHO 1998 (World Health Organization 1999) MetS criteria, high fasting plasma insulin levels and either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) were requisite criteria for MetS. Different categories of glucose tolerance were updated by WHO in 1999 as follows: Normal glucose tolerance (**NGT**): fasting plasma glucose < 6.1 mmol/l and 2-hour plasma glucose < 7.8 mmol/l, **IFG**: fasting plasma glucose 6.1–6.9 mmol/l and 2-hour plasma glucose < 7.8 mmol/l, **IGT**: fasting plasma glucose < 7.0 mmol/l and 2-hour PG 7.8–11.0 mmol/l, **diabetes**: fasting plasma glucose $\geq$ 7.0 mmol/l or 2-hour plasma glucose $\geq$ 11.1 mmol/l, or current use of diabetes medication. In the NCEP (2001) criteria, abnormal glucose tolerance was simplified first to a fasting plasma glucose $\geq$ 6.1 mmol/l, but in 2005 the cut-off value was lowered to a fasting plasma glucose $\geq$ 5.6

mmol/l. This is the same definition used in the recent consensus criteria (Alberti et al. 2009).

2.3.4 Atherogenic lipid profile

Resistance to the ability of insulin to suppress very low-density lipoprotein (VLDL) cholesterol production increases serum triglycerides. Insulin resistance in adipose tissue increases the flux of non-esterified fatty acid (NEFA) both to the liver and skeletal muscle, and impairs the action of insulin on glucose metabolism in these tissues (Yki-Järvinen 2010).

Dyslipidemia in MetS is characterized by a combination of elevated serum triglycerides, low concentration of HDL-cholesterol together with elevated apolipoprotein B, small dense LDL-cholesterol and small HDL-cholesterol particles (The International Diabetes Federation 2006), as well as postprandial accumulation of triglyceride-rich remnant lipoproteins (Reaven 2008), all of which are independently atherogenic (Stern et al. 2004).

The latest definition of MetS specifies the cut-off point for elevated triglycerides as ≥ 1.7 mmol/l and reduced HDL-cholesterol as < 1.0 mmol/l for men and < 1.3 mmol/l for women (Alberti et al. 2009) .

2.3.5 Elevated blood pressure

Of the MetS components, hypertension has the weakest association with insulin resistance (Alberti et al. 2005). Despite insulin resistance, the effects of insulin on sodium reabsorbtion and sympathetic nervous system activation are maintained, and increases in angiotensinogen, resistin and leptin secretion from adipose tissue have been implicated in the pathophysiology of hypertension in MetS (Cornier et al. 2008), as well as functional and structural changes in endothelium.

The WHO 1998 MetS criteria listed cut-off points for systolic blood pressure of 140 mmHg and for diastolic blood pressure of 90 mmHg. In the ADA/NHLB and IDF criteria, the cut-off values were lowered to 130 mmHg for systolic and to 85 mmHg for diastolic blood pressure.

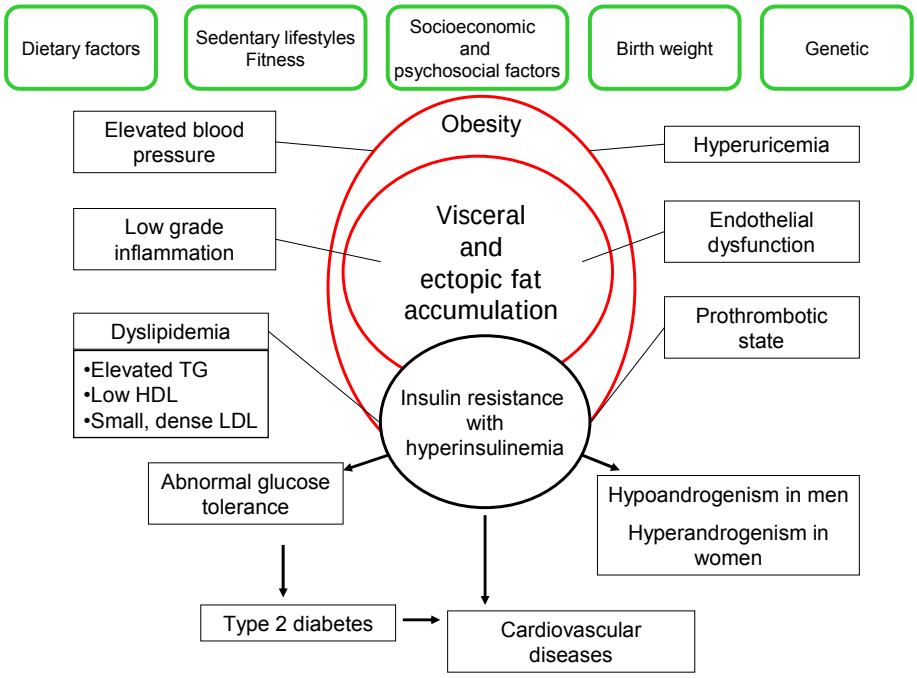

Figure 1. Schematic representation of MetS. Environmental and genetic factors predispose to the development of MetS. Together with excess/ectopic fat accumulation, they result in insulin resistance associated with several risk factors for type 2 diabetes and CVD. Modified after Laaksonen and Niskanen (2006).

2.3.6 Other features of MetS

Individuals with MetS commonly manifest prothrombotic state with elevated levels of plasminogen activation inhibitor (Alberti et al. 2005) and low-grade inflammation with elevated levels of inflammatory markers (Alberti et al. 2009). Non-alcoholic fatty liver disease refers to excess fat accumulated in the liver causing elevated liver enzymes in circulation and abnormal liver histology (e.g. steatosis, steatohepatitis, fibrosis, and cirrhosis) (Yki-Järvinen 2010). Elevated levels of uric acid (Vuorinen-Markkola and Yki-Järvinen 1994) and obstructive sleep apnea (Alam et al. 2007) associate with obesity and MetS. The characteristics of polycystic ovary syndrome include insulin resistance, polycystic ovaries, elevated testosterone, and chronic anovulation (Bray 2007; von Elm et al. 2007). Microalbuminuria, an increase in the urinary albumin excretion rate, was a part of

the WHO 1998 MetS definition (Table 1). The subsequent definitions did not include microalbuminuria.

2.4 Epidemiology of obesity, MetS and type 2 diabetes

2.4.1 Trends in obesity

Worldwide obesity rates have more than doubled since 1980. In 2008, 200 million men and nearly 300 million women were reported as being obese (World Health Organization 2011).

In the U.S., the prevalence of obesity increased from 12% to 33% in men and from 17% to 37% in women, as reported by the National Health and Nutrition Examination Studies from years 1971–1975 and 2005–2006 (Austin et al. 2011). Flegal et al. (2010) investigated the prevalence and trends in obesity among U.S. adults from 1999 to 2008. They concluded that the increase in the prevalence of obesity previously observed did not appear to be continuing at the same rate over the past 10 years (Flegal et al. 2010).

In Finland, Lahti-Koski et al. (2010) found that the prevalence of obesity increased from 11% to 21% in men and from 18% to 24% in women during a 20-year period from 1980 to 2000. The latest population-based, cross-sectional FINRISK study from year 2007 showed that the mean BMI was 27.0 ± 4.1 kg/m^2 and 26.5 ± 5.4 kg/m^2 and obesity rates were 19.3% and 21.1% in men and in women aged 25–74 years, respectively (Peltonen et al. 2008a). A random postal survey with 2826 respondents (response rate 57%) aged 15 to 64 years from 2010 showed that 15.7% of the men and 15.5% of the women had BMI ≥ 30 kg/m^2.

The FIN-D2D surveys, population based cross-sectional samples of subjects aged 45–74, did not show any significant increase in mean BMI (~28 kg/m^2 both in men and women) or obesity rates from 2004 to 2007. The FIN-D2D surveys also focused on abdominal obesity. Between the two studies, mean waist circumference increased slightly from 99.3 ± 11.8 cm to 101 ± 11.9 cm in men and from 89.8 ± 13.4 cm to 90.5 ± 13.3 cm in women. The prevalence rates in obesity are presented in Table 2.

Table 2. Prevalence rates (%) of obesity (BMI ≥ 30kg/m^2) among adult population in U.S. and in Finland.

Authors **Area**	**Year(s)**	**Population**	**Age (years)**	**Prevalence of obesity (%)**	
				Men	***Women***
Austin et al. 2011	1971–1975	13 106	20–74	11.9	16.6
U.S.	2005–2006	4381		33.4	36.5
Flegal et al. 2010	2007–2008	5555	> 20	32.2	35.5
U.S.					
Lahti-Koski et al. 2010	1978–1980	7178	≥ 30	11.3	17.9
Finland	2000–2001	6666		20.7	24.1
Laatikainen et al. 2003	2002	7829	25–64	20.4	17.5
FINRISK, Finland					
Peltonen et al. 2006	2004	2896	45–74	23.7	28.6
Saaristo et al. 2008					
FIN-D2D, Finland					
Peltonen et al. 2008b	2007	2862	45–74	21.9	27.4
FIN-D2D, Finland					
Peltonen et al. 2008a	2007	6257	25–74	19.3	21.1
FINRISK, Finland					

2.4.2 MetS in the general population

MetS is generally observed in 15−30% of middle-aged people (Reaven 1988; DeFronzo and Ferrannini 1991; Isomaa et al. 2001a; Balkau et al. 2002; Ford et al. 2002; Hu et al. 2004; Malik et al. 2004; Cameron et al. 2008). In the DECODE

study, based on 11 prospective cohort studies with 6156 non-diabetic men and 5356 non-diabetic women aged 30 to 89 years, the age-specific prevalence of MetS was 15.7% in men and 14.2% in women (Hu et al. 2004). In the third National Health and Nutrition Examination Survey (NHANES III) ~44% of the U.S. population over 50 years of age met the NCEP-MetS criteria (Alexander et al. 2003).

The 10-year change in the prevalence of MetS was assessed in two cross-sectional population surveys in 1992 and 2002 in Finland (Hu et al. 2008). In both surveys, MetS was found to be more common among men than among women. In men, the prevalence of MetS tended to increase slightly between 1992 and 2002, from 49% to 53% based on the NCEP definition and from 51% to 56% based on the IDF definition. In women, the prevalence of MetS increased significantly from 32% to 39% based on the NCEP definition, and from 38% to 45% based on the IDF definition (Hu et al. 2008).

2.4.3 MetS in different categories of glucose tolerance

In a study by Isomaa et al. (2001a), MetS was present in 10% and 15% of women and men in Finland with normal glucose tolerance, in 42% and 64% of those with IFG/IGT, and in 78% and 94% of those with type 2 diabetes. Among the FIN-D2D intervention program participants, a high-risk group for type 2 diabetes, MetS was found in 63% and 75% of the men and in 59% and 67% of the women by NCEP 2005 and IDF 2006 criteria, respectively (Saaristo et al. 2010). In general, roughly 70% of subjects with IGT and around 80 to 90% of subjects with type 2 diabetes have MetS (Rodriguez et al. 1996; Laakso and Lehto 1998; Isomaa et al. 2001a; Liao et al. 2001).

2.4.4 Trends in type 2 diabetes

The prevalence of type 2 diabetes has constantly increased worldwide (Amos et al. 1997; King et al. 1998; Wild et al. 2004). Fueled by rapid urbanization, nutrition transition, and increasingly sedentary lifestyle, the diabetes epidemic has grown in parallel with the rise in obesity (Hu 2011). The worldwide prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and 4.4% in 2030 (Wild et al.

2004). The total number of people with diabetes is projected to rise from 285 million in 2010 to 438 million in 2030 and the number of people with IGT from 344 million to 472 million (IDF 2010). In the U.S. over 11% of people aged ≥ 20 years have diabetes (Centers for Disease Control and Prevention 2011).

The FinDM II study is a register-based measurement of the prevalence and incidence of diabetes and its long-term complications in Finland. According to the FinDM II study, the number of people with type 2 diabetes has increased from 138 337 in 1997 to 245 257 in year 2007 (Sund and Koski 2009), and it is estimated that over 10% of the adult population in Finland has diabetes (Koski 2011). The first FIN-D2D survey in 2004 reported that the prevalence of previously diagnosed type 2 diabetes was 7.4% in men and 4.3% in women aged 45−74 years (Peltonen et al. 2006). It has been estimated that half of the people with diabetes are undiagnosed. In FIN-D2D, the total prevalence of type 2 diabetes including both previously diagnosed and screen detected diabetes, was 16% in men and 11% in women. The prevalence of abnormal glucose regulation was 42% in men and 33% in women (Peltonen et al. 2006). The most recent statistics from the Social Insurance Institution in Finland showed that 307 762 individuals used diabetes medication in 2010 (Statistical Database Kelasto 2011).

2.5 MetS and the risk of type 2 diabetes and CVD

MetS is clinically important because of its association with the subsequent development of type 2 diabetes (Laaksonen et al. 2002a; Lorenzo et al. 2003; Wang et al. 2004; Wang et al. 2007; Ford et al. 2008a; Ford et al. 2008b). Prospective studies have shown that MetS, regardless of how it is defined, is a significant predictor of type 2 diabetes with the average estimated summary risk ratio of 3−5 in many different populations (Ford et al. 2008b; Gupta et al. 2008).

MetS has been associated with an increased risk of CVD morbidity and mortality in case control studies (Mente et al. 2010), population based cohort studies (Lakka et al. 2002; Ford 2004; Malik et al. 2004; Wilson et al. 2005; Jeppesen et al. 2007; Ärnlöv et al. 2010), and prospective cohort studies (Isomaa et al. 2001a; Sattar et al. 2003; Hu et al. 2004; Hunt et al. 2004; Broekhuizen et al. 2011). In a systematic review and meta-analysis of longitudinal studies, Gami et al. (2007) found 37

eligible studies including 43 cohorts with 172 573 individuals showing that individuals with MetS had a risk ratio of cardiovascular events and death of 1.78. This increased risk ratio remained significant after adjusting for traditional CVD risk factors.

In recent years some controversy has emerged surrounding the clinical significance of MetS compared to other tools that identify individuals at elevated risk of CVDs (Kahn et al. 2005a; Reaven 2006). A review of prospective studies by Ford (2005b) concluded that the predictive value of MetS for all-cause mortality was unremarkable with an estimated summary relative risk of ~1.2 to ~1.4, and that MetS has a modest predictive value for CVDs with an estimated summary relative risk of ~1.7 to ~1.9, depending on the definition of MetS (Ford 2005b).

In conclusion, MetS has been most widely promoted for the identification of individuals at risk of CVDs. The traditional risk scores, such as the Framingham or the FINRISK risk scores, may be more accurate for the prediction of future risk of CVDs. However, MetS is an understandable and useful tool in clinical work. After recognition of a person at risk, awareness and lifestyle counseling and/or specific treatment for different features of MetS can be offered.

2.6 Management of MetS

Clinical management of MetS involves the modification of risk factors to prevent or delay the onset of CVDs. If not already present, the prevention and delay of the onset of type 2 diabetes is a concomitant goal. Lifestyle modification is the primary intervention, but the possible residual risk of CVD may require drug treatment (Eckel et al. 2010). Weight control, weight reduction and/or prevention of further weight gain, deserves first priority in individuals with abdominal obesity and MetS (Grundy et al. 2005).

2.6.1 Dietary considerations in the prevention and treatment of MetS

The optimal fat, protein, and carbohydrate composition for weight loss and for prevention and treatment of MetS and type 2 diabetes has been debated (Nordmann

et al. 2006; Accurso et al. 2008; Feinglos and Totten 2008; Sacks et al. 2009). Excessive caloric intake is a major driving force, but the quality of fats and carbohydrates have important and independent effects. Higher glycemic load and trans-fats are associated with increased diabetes risk, whereas greater consumption of cereal fiber and polyunsaturated fats is associated with decreased risk (Hu 2011).

2.6.1.1 Fat

In a review article on studies addressing the association between dietary fat intake and obesity, MetS, and diabetes, Melanson et al. (2009) concluded that the data on the association between total fat intake and/or saturated fat intake and body weight remains inconclusive. However, the study further concluded that there are a sufficient number of studies suggesting that total fat and saturated fat intake increases the risk of having the components of MetS, and that higher intake of MUFA and PUFA has a beneficial effect in reducing the risk (Melanson et al. 2009).

On the role of reducing intake of saturated fat in the prevention of CVDs, a panel of dietary experts (Astrup et al. 2011) reached the following conclusions: "The evidence from epidemiological, clinical, and mechanistic studies is consistent in finding that the risk of coronary heart disease is reduced when SAFAs are replaced with PUFAs. No clear benefit of substituting carbohydrates for SAFA has been shown, although there might be a benefit if the carbohydrate is unrefined and has a low glycemic index".

2.6.1.2 Carbohydrates

In obese individuals, low-carbohydrate diets result in greater initial weight loss and improvements in CVD risk factors for up to one year, as compared to conventional low-fat diets (Hession et al. 2009). There have been only a few long-term trials, and none of them is primarily intended to treat MetS or prevent type 2 diabetes. After either one year (Foster et al. 2003) or two years (Foster et al. 2010) of treatment, no significant differences in weight loss were found between low-carbohydrate and conventional low-fat diets. However, Shai et al. (2008) found that a dietary regimen

lower in carbohydrates (~40 E%) resulted in greater weight loss (4.7 kg) than a Mediterranean-diet (4.4 kg) or calorie-restricted low-fat diet (2.9 kg), after a 2-year period.

The effects of low-carbohydrate diet on CVD risk factors and MetS have been inconclusive. There are studies showing more improvements with a low-carbohydrate diet (Foster et al. 2003; Shai et al. 2008; Frisch et al. 2009), while others do not show any significant associations (Sacks et al. 2009; Goldstein et al. 2011), especially when weight loss was taken into account. Sacks et al. (2009) reported similar reduction in the prevalence of MetS in all dietary groups, from 32% to 18−22% among 811 overweight adults randomized to four different diet modalities.

Dietary glycemic load is estimated form glycemic index by multiplying it by the amount of carbohydrates. A high glycemic load diet, which increases insulin demand and may lead to pancreatic ß-cell exhaustion in the long run, has been implicated in increased risk of type 2 diabetes and CVD (Hu and Willett 2002). In a meta-analysis of 37 prospective studies, Barclay et al. (2008) found that diets with high glycemic index and/or glycemic load increased the risk of type 2 diabetes and heart disease.

2.6.1.3 Dietary patterns

The role of a single nutrient, food item or lifestyle factor does not seem to be as important as dietary patterns or the combined effects of lifestyle change and dietary factors in the prevention and treatment of MetS and type 2 diabetes. Hu et al. (2001) followed 84 941 women from 1980 to 1996 in the Nurses Health Study. They defined a low-risk group for type 2 diabetes according to five variables: 1) BMI < 25 kg/m^2, 2) a diet high in cereal fiber and PUFAs and low in trans-fat, 3) moderate-to-vigorous physical activity for at least half an hour/day, 4) no current smoking; and 5) an average intake of a half-serving of an alcoholic beverage/day.

With regard to CVD risk factors, several epidemiological and intervention studies support the benefits of Mediterranean diet low in SAFAs and high in MUFAs (Sofi et al. 2010; Astrup et al. 2011). A meta-analysis by Kastorini et al. (2011) of prospective epidemiological studies and clinical trials assessing the effect

of Mediterranean diet on MetS and its components showed that adherence to diet associated with reduced risk of MetS, and the results from clinical studies revealed a protective effect against the components of MetS.

Several diet-quality scores have been developed (de Koning et al. 2011) to provide healthy dietary guidelines targeting major chronic diseases (McCullough et al. 2002). De Koning et al. (2011) compared associations of different scores with incidence of type 2 diabetes among men from the Health Professionals Follow-up study. They concluded that several diet-quality scores, especially Alternative Healthy Eating Index (AHEI) and Dietary Approaches to Stop Hypertension (DASH), were associated with lower risk of type 2 diabetes. These scores reflect a dietary pattern characterized by high intakes of plant-based foods such as whole grains; moderate alcohol; low intakes of red and processed meat, sodium, sugar-sweetened beverages, and trans fat (de Koning et al. 2011). High scores of AHEI have earlier been shown to associate with decreased risk of CVD (Fung et al. 2007) and type 2 diabetes (McCullough et al. 2002) and higher odds of MetS resolution (Akbaraly et al. 2010). A recent population-based cross-sectional study among elderly Finns showed that a healthy diet (vegetables ≥ 400 g/day, fish ≥ 2 servings/week, fiber ≥ 14 g/1000 kcal, saturated fat < 10 E%/day) is associated with a reduced risk of having MetS (Kouki et al. 2011).

2.6.1.4 Dietary recommendations for the treatment of MetS

For an overall healthy diet, the 2010 U.S. dietary guidelines emphasize three major goals: 1) balance calories with physical activity to manage weight, 2) consume more fruits, vegetables, whole grains, fat-free and low-fat dairy products and seafood, and 3) consume fewer foods with sodium, saturated fats, trans-fats, cholesterol, added sugars, and refined grains (U.S. Department of Agriculture and U.S. Department of Health and Human Services 2010). New dietary recommendations for the Scandinavian countries are under revision.

Current care guidelines for adult obesity in Finland emphasize individualized approach, but support regular meals with avoidance of “empty” calories. Energy deficit of ~600 kcal/day can be achieved by reducing (saturated) fats, sugar, sweets, pastry, white cereal and alcohol as well as portion sizes of pasta, rice and potatoes

and increasing consumption of vegetables, berries and fruits (Adult obesity: Current Care Summary 2011).

2.6.2 Exercise and MetS

Increased time spent engaging in sedentary behaviors and decreased time spent engaging in moderate-to-vigorous physical activity has been reported to independently correlate with the risk of MetS and its components in cross sectional studies (Bertrais et al. 2005; Dunstan et al. 2005; Ford et al. 2005; Healy et al. 2006; Dunstan et al. 2007; Li et al. 2007; Balkau et al. 2008).

In a meta-analysis of 10 prospective cohort studies, Jeon et al. (2007) found a substantial inverse correlation between physical activity of moderate intensity and risk of type 2 diabetes. Those who were regularly engaged in physical activity of moderate intensity had ～30% lower risk of type 2 diabetes as compared with sedentary individuals. A similar decrease in diabetes risk was observed when they specifically examined regular walking. After adjustment for BMI, the reduction in diabetes risk remained substantial for both regular moderately-intense activity and walking (Jeon et al. 2007).

2.6.2.1 Leisure time physical activity

Data on the role of leisure time physical activity (LTPA) in the treatment of MetS is limited. More is known about the effect of exercise on insulin resistance and the MetS components, especially obesity, in cross-sectional and prospective cohorts.

Borodulin et al. (2006) found in the FINRISK 2002 cross-sectional cohort study that higher levels of LTPA were associated with lower 2-hour plasma glucose and fasting insulin levels and reduced risk of having IGT and type 2 diabetes, independent of the level of abdominal obesity. A 16-year follow-up of 18 414 women in the Nurses Health Study II showed that bicycling, when of an intensity similar to that of brisk walking, was associated with less weight gain with an inverse dose-response relationship, especially among overweight and obese women (Lusk et al. 2010). Ekelund et al. (2011) followed 84 511 men and 203 097 women in a prospective cohort study for 5 years and found that a higher level of physical

activity reduced abdominal adiposity, independent of body weight and weight and changes. Ekelund et al. (2007) also found that an increase in physical activity energy expenditure lowered plasma triglycerides, fasting insulin, and 2-hour glucose even in the absence of improved aerobic fitness and weight loss among 393 individuals followed for 5.6 years. On the other hand, cardiorespiratory fitness, even without weight loss, has been shown to prevent MetS (LaMonte et al. 2005). Hassinen et al. (2010) found that higher cardiorespiratory fitness at baseline, measured by maximum VO_2 uptake, protected against MetS development and was associated with higher MetS resolution rate in 2 years of follow-up of elderly Finns.

There are some intervention trials that examine the role of LTPA on insulin resistance, abdominal obesity and MetS. Boule et al. (2005) studied the effect of a 20-week endurance training program in 596 healthy but sedentary individuals. They found that insulin sensitivity, measured by an intravenous glucose tolerance test, increased by 10% following the intervention, although the variability was high. In this study, improvements in fasting insulin were transitory and disappeared within 72 hours after the last bout of exercise. They concluded that in the absence of substantial weight loss, regular exercise is required for sustained improvement in glucose homeostasis. Lee et al. (2005) found that regular exercise for 60 minutes five times per week was associated with reduction in total and visceral fat and muscle lipids among 24 men participating in 13 weeks of supervised aerobic exercise. Johnson et al. (2007) used a MetS score and found that, compared to the inactive controls, moderate intensity exercise – at an amount calorically equivalent to walking approximately 17 km over an average of 170 minutes per week – resulted in a significant improvement in calculated MetS scores.

2.6.2.2 Resistance training

Physical inactivity and ageing reduce muscle mass and contribute to obesity, insulin resistance, type 2 diabetes, dyslipidemia, and hypertension (Williams et al. 2007). Increase in muscle mass may reduce multiple CVD risk factors (Braith and Stewart 2006). Cross-sectional studies have demonstrated that muscular strength is inversely associated with the prevalence of MetS (Jurca et al. 2005), and resistance training improves the components of MetS (Strasser et al. 2010).

2.6.2.3 Sedentary lifestyle

In the Nurses Health Study, independent of exercise levels, sedentary behaviors were found to be correlated with elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with substantially lower risk (Hu et al. 2003). In a cross-sectional cohort of 4864 subjects in the AusDiab study, sitting time, independent of central adiposity, and TV viewing time were deleteriously associated with CVD risk markers (Thorp et al. 2010).

Healy et al. (2007) examined the associations of objectively measured sedentary time, light-intensity physical activity, and moderate-to-vigorous intensity activity with fasting and 2-hour plasma glucose in a cross-sectional cohort. Physical activity was measured by accelerometers worn by participants during waking hours for seven consecutive days. Light-intensity physical activity was shown to be beneficially associated and sedentary time unfavorably associated with plasma glucose levels. They also found that independent of time spent in moderate-to-vigorous physical activity, there were significant associations of sedentary time, light intensity time, and mean activity intensity with waist circumference and clustered metabolic risk. Independent of waist circumference, moderate-to-vigorous physical activity time was significantly associated with triglycerides (Healy et al. 2008).

In a cross-sectional analysis with 4757 participants from the NHANES study, Healy et al. (2011) found associations between prolonged sedentary time and CVD and inflammatory biomarkers such as waist circumference, HDL-cholesterol, C-reactive protein, triglycerides, and insulin.

2.6.2.4 Exercise recommendation for the prevention of type 2 diabetes and for the treatment of MetS

The American College of Sport Medicine and the American Diabetes Association published a joint statement on exercise and type 2 diabetes in 2010 (Colberg et al. 2010). It recommends at least 2.5 hours/week of moderate-to-vigorous physical activity as part of lifestyle changes to prevent the onset of type 2 diabetes in high-risk adults. The current care guidelines for health-related physical activity in Finland recommends at least 30 minutes of any moderate-intensity physical activity,

consisting of one or several shorter bouts at least five days a week, or vigorous exercise for 1 hour 15 minutes once per week for the treatment of MetS (Physical activity and exercise training: Current Care Summary 2010). Additionally, muscle-strengthening activity like push-ups, sit-ups, and lifting weight at least twice weekly, and a personal exercise program is recommended.

2.6.3 Lifestyle trials in type 2 diabetes prevention

The best evidence for the benefit of lifestyle intervention to reduce weight and insulin resistance comes from intervention studies that were designed to investigate the possibility of preventing or delaying type 2 diabetes in high-risk groups via intensive lifestyle intervention (Table 3). These studies have recruited overweight or obese individuals with abnormal glucose tolerance, mainly IGT. They have mostly aimed at achieving weight loss through a combination of dietary changes and physical activity. Only one of the studies, the Diabetes Prevention Program (DPP), reports the prevalence of MetS among the participants or the effects of the intervention on MetS development or resolution. It is, however, not clear how the results of these trials apply to a non-IGT population with MetS.

Table 3. Lifestyle intervention trials for the prevention of type 2 diabetes in high risk individuals with impaired glucose tolerance.

Authors(s), year **Name of the study**	**Area**	**Study population**			**Duration** (years)	**RR** (%)
		N	**Age** (years)	**Glucose tolerance**		
Eriksson and Lindgärde 1991 Malmö -study	Sweden	181	47–49	IGT	6	63
Pan et al. 1997 DaQing	China	577	~45	IGT	6	31 / 46 / 42 [a]
Tuomilehto et al. 2001 DPS	Finland	522	40–64	IGT	3.2	58
Knowler et al. 2002 DPP	U.S.	3234	≥ 25	IGT+IFG	2.8	58
Kosaka et al. 2005 Toranomon Study	Japan	458	~55	IGT	4	67
Ramachandran et al. 2006 Indian DPP	India	531	35–55	IGT	3	28
Roumen et al. 2008 SLIM -study	Netherlands	147	> 40	IGT	3	58

DPS, Diabetes Prevention Study; DPP, Diabetes Prevention Program; SLIM, Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht; IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose; RR, Relative risk reduction; [a] DaQing had three intervention groups: diet/exercise/diet+exercise.

2.6.3.1 Diabetes Prevention Study

The Diabetes Prevention Study (DPS) in Finland was a multicentre, randomized, prospective and controlled lifestyle intervention trial with the main aim of assessing prevention of type 2 diabetes in subjects with IGT (Uusitupa et al. 2000; Tuomilehto et al. 2001). The participants were randomized to an intensive and individually-tailored diet and exercise counseling group and to a usual care control group. In addition, the effects of the intervention on insulin sensitivity and CVD risk factors were assessed (Eriksson et al. 1999; Lindström et al. 2003). The details of DPS are presented in the Methods section of the present study.

The primary results of DPS showed that lifestyle changes can prevent the progression from IGT to type 2 diabetes in middle aged (mean age 55 years) and overweight (mean BMI 31 kg/m^2) men (n = 172) and women (n = 350). The cumulative incidence of diabetes after the intervention period of a median of four years was 11% in the intervention group and 23% in the control group with a relative risk reduction of 58% (Tuomilehto et al. 2001).

In a substudy of 81 participants, Uusitupa et al. (2003) showed that a sustained weight reduction at year 4 resulted in a substantial improvement in insulin sensitivity index measured by frequently-sampled intravenous glucose tolerance test.

Significantly greater improvements were seen at year 3 in waist circumference, serum total cholesterol-to-HDL-cholesterol ratio, and serum triglycerides in the intervention group compared with the control group (Lindström et al. 2003).

2.6.3.2 Diabetes Prevention Program in the U.S.

There were 1043 men and 2191 women with BMI > 24 kg/m^2, age > 25 years, and both IGT and elevated fasting plasma glucose that participated in the Diabetes Prevention Program (DPP) in the U.S.. During the average intervention and follow-up of 2.8 years, lifestyle intervention reduced the incidence of diabetes by 58% and metformin by 31%, as compared with placebo (Knowler et al. 2002). The DPP researchers also reported that the intensive lifestyle intervention improved CVD risk

factor status (including hypertension, high triglyceride levels, low HDL levels, and small dense LDL) compared with placebo and metformin therapy (The Diabetes Prevention Program Research Group 2005).

The DPP researchers conducted post hoc analyses to evaluate changes in the resolution and incidence of MetS. By the third year the prevalence of MetS increased from 55% to 61% in the placebo group, from 54% to 55% in the metformin group, and decreased from 51% to 43% in the lifestyle group (Orchard et al. 2005). Of those having MetS at baseline, 18% of the placebo group, 23% of the metformin group, and 38% of the lifestyle group had recovered from MetS by the third study-year. Among those without MetS at baseline, 53% of the placebo group, 47% of the metformin group, and 38% of the lifestyle group had developed MetS by the third year. The incidence of MetS was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with placebo (Orchard et al. 2005). Lifestyle intervention reduced the incidence of all components of MetS except HDL-cholesterol level, while metformin was effective only in reducing the incidence of elevated waist circumference and fasting glucose (Orchard et al. 2005).

2.6.3.3 Diabetes Prevention Program Outcome Study

The Diabetes Prevention Program Outcomes Study showed that after about 7 years of follow up and 10 years after DPP randomization, cumulative incidence of diabetes remained lower in the lifestyle and metformin groups than in the placebo group (The Diabetes Prevention Program Research Group 2009). Type 2 diabetes incidence in the original lifestyle group was reduced by 34% compared with the control group. Average systolic and diastolic blood pressure and triglycerides were lower in the lifestyle group than in the others, although use of blood pressure lowering medication was less frequent. However, these differences were not maintained by the end of the follow-up period.

2.6.4 Medical treatment and MetS

The medical treatment of MetS largely requires separate agents, each designed to take care of its different features. Clinical trials have mainly focused on the

treatment of obesity or the prevention of type 2 diabetes in high-risk groups (Table 4).

A number of glucose lowering drugs have been shown to be effective in delaying the onset of type 2 diabetes in subjects with IGT. Thiazolidinediones alone (Buchanan et al. 2002; Knowler et al. 2005; The DREAM Trial Investigators 2006) or in combination with metformin (Zinman B et al. 2010) are the most effective, reducing incident diabetes by up to 80%. However, longer follow-up after drug withdrawal suggests that they do not have a sustained effect on the underlying pathophysiology (The DREAM Trial Investigators 2011). DeFronzo et al. (2011) found that, compared with placebo, pioglitazone reduced the risk of conversion from IGT to type 2 diabetes by 72%. Unfortunately, pioglitazone resulted in significant weight gain and edema (DeFronzo et al. 2011).

Metformin (Knowler et al. 2002; Ramachandran et al. 2006), orlistat (Torgerson et al. 2004), and acarbose (Chiasson et al. 2002) also reduce incident diabetes, but their efficacy is lower than that of thiatzolinediones. On the other hand, taking nateglinide for five years did not reduce the incidence of diabetes or the composite cardiovascular outcomes (The Navigator Study Group 2010). Rimonabant, a selective cannabinoid 1-receptor blocker, reduces weight and waist circumference and improves several cardiovascular risk factors in overweight or obese persons with atherogenic dyslipidemia (Després et al. 2005). Due to adverse psychiatric effects, rimonabant is no longer available for clinical use. Incretin based therapies have also been studied in the prevention of type 2 diabetes.

Table 4. Medical treatment trials for the prevention of type 2 diabetes in high-risk subjects with impaired glucose tolerance.

Author(s), Year Name of the study	Area	Study population			Duration (years)	Intervention (daily dose)	RR (%)
		N	Mean age (years)	Glucose tolerance			
Buchanan et al.2002 TRIPOD	**U.S.**	266	34	IGT	2.5	Troglitazone 400mg	55
Knowler et al. 2002 DPP	U.S.	2155	51	IGT+IFG	2.8	Metformin 1700 mg	31
Chiasson et al. 2002 STOP-NIDDM	International	1419	54	IGT+IFG	3.2	Acarbose 300 mg	25
Ramachandran et al. 2006 Indian DPP	India	269	46	IGT	2.5	Metformin 500 mg	26
Torgerson et al. 2004 XENDOS	Sweden	3277	43	NGT or IGT	4	Orlistat 360 mg	37
The DREAM Trial Investigators 2006 DREAM	International	5269	55	IGT or IFG	3	Rosiglitazone 8 mg	60
DeFronzo et al. 2011 ACT NOW	U.S.	602	52	IGT	2.4	Pioglitazone 45 mg	72

DPP, Diabetes Prevention program; STOP-NIDDM, Study to Prevent Non-Insulin Dependent Diabetes; XENDOS, Xenical in the prevention of Diabetes in Obese Subjects; DREAM, Diabetes Reduction Assessement with Ramipril and Rosiglitazone; NGT, Normal glucose tolerance; IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose

3. AIMS OF THE STUDY

The purpose of this series of studies was to investigate the prevalence and treatment of the metabolic syndrome (MetS) in middle-aged Finns at high risk of type 2 diabetes. In addition, the long-term effect of lifestyle intervention on the development of type 2 diabetes was investigated.

The specific aims of these studies were:

1. To investigate the prevalence of MetS and its components in a population-based sample of middle-aged Finns from the FINRISK 1992 study and among participants of the Diabetes Prevention Study (DPS) in Finland **(Study 1).**

2. To assess the effects of lifestyle intervention and weight change on MetS and its components in middle-aged, overweight men and women with impaired glucose tolerance (IGT) participating in DPS **(Study 2)**.

3. To assess the effects of lifestyle counseling on leisure-time physical activity and to study the role of physical activity in the prevention and treatment of MetS in DPS **(Study 3).**

4. To assess the long-term results of lifestyle counseling on the development of type 2 diabetes in individuals with IGT in DPS **(Study 4).**

4. SUBJECTS AND METHODS

4.1 Study populations

In study 1 two cohorts of middle-aged Finnish men and women from FINRISK 1992 and from the Diabetes Prevention Study (DPS) were studied. **Study 2** included all the participants of DPS (n = 522). Those having MetS by NCEP 2005 criteria at baseline (n = 386) were separately studied. **In study 3**, those participants of DPS who had completed a questionnaire quantifying leisure-time physical activity at baseline as well as during follow-up visits (n = 486) were included. In addition, a subgroup of 137 participants taking part in supervised resistance training sessions was analyzed separately in study 3. All individuals who had participated in the DPS were invited to take part in the post-intervention follow up and were analyzed in **study 4**.

4.1.1 The FINRISK 1992 population

The FINRISK survey, a national cardiovascular risk factor monitoring study, is performed every fifth year by the National Institute for Health and Welfare (former National Public Health Institute). The methods follow the WHO Monitoring trends and determinants in cardiovascular disease (MONICA) protocol (Tuomilehto et al. 1992; World Health Organization 2003).

FINRISK 1992 was a cross-sectional population-based sample of 8000 men and women aged 25–74 years from four regions in Finland (North Karelia, Kuopio, South-Western Finland and Helsinki-Vantaa region). The sample was drawn at random after stratification by sex and by four equally large 10-year age groups. A subsample of 3300 individuals, aged 45–64 years, was formed in order to assess glucose metabolism. Initially, after filling a questionnaire on medical history and health behaviors, 3201 of those 3300 individuals participated in clinical and laboratory examination, and 2087 attended the second visit with an OGTT. Glucose tolerance status was classified in 2061 subjects. After excluding individuals with type 1 diabetes (n = 12), 2049 subjects

were included in the final analysis of glucose tolerance and components of MetS, representing 62% of the original subsample of 3300 subjects (Figure 2).

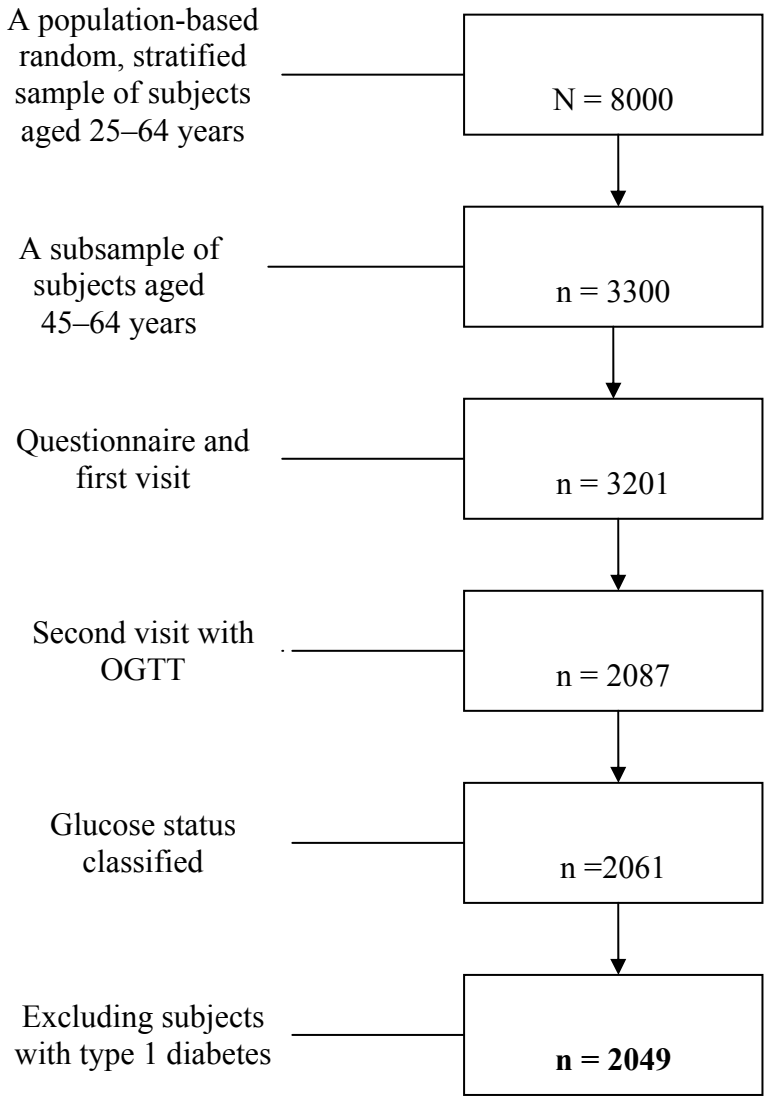

Figure 2. FINRISK 1992 sample flow. A subsample of 3300 subjects aged 45–64 years was formed and invited to a clinical visit with oral glucose tolerance test (OGTT).

4.1.2 The DPS subjects

There were five participating centers in DPS, located in Helsinki, Kuopio, Turku, Tampere, and Oulu, with about 100 participants from each center. The study

participants were recruited between 1993 and 1998 through various methods, e.g. advertising in local newspapers, from epidemiological surveys and earlier clinical studies, and by opportunistic screenings (Eriksson et al. 1999).

Overweight (BMI $\geq$ 25 kg/m^2) and middle-aged (40–64 years) individuals without previous diagnosis of diabetes other than gestational diabetes were eligible for DPS. Persons who were already participating in regular vigorous exercise programs or had a chronic disease that would make a 6-year survival unlikely were excluded from the study. After the first screening OGTT, a repeat OGTT was done in those within the IGT range, i.e., 2-hour plasma glucose 7.8–11.0 mmol/l and fasting plasma glucose less than 7.8 mmol/l at the first visit. The mean of the two 2-hour glucose concentrations was used as the criterion for inclusion.

The participants were randomly allocated to one of the two treatment modalities: the intensive and individualized diet-exercise counseling group (intervention group; n = 265, the proportion of men 34.3%), or the standard care group (control group; n = 257, proportion of men 31.5%) (Lindström 2006). The primary end point of DPS was the diagnosis of type 2 diabetes by WHO 1985 criteria (World Health Organization 1985) with a repeated plasma glucose value in the diabetes range, i.e., a fasting plasma glucose $\geq$ 7.8 mmol/l or 2-hour value $\geq$ 11.1 mmol/l during OGTT (75g).

4.2 Measurements

FINRISK 1992 and DPS involved self-administered questionnaires on medical history, physical activity, and dietary factors. Those taking medication for elevated blood pressure or dyslipidemia during the past week were recorded as being on medication. Trained study personnel completed the clinical and laboratory examinations, including OGTT.

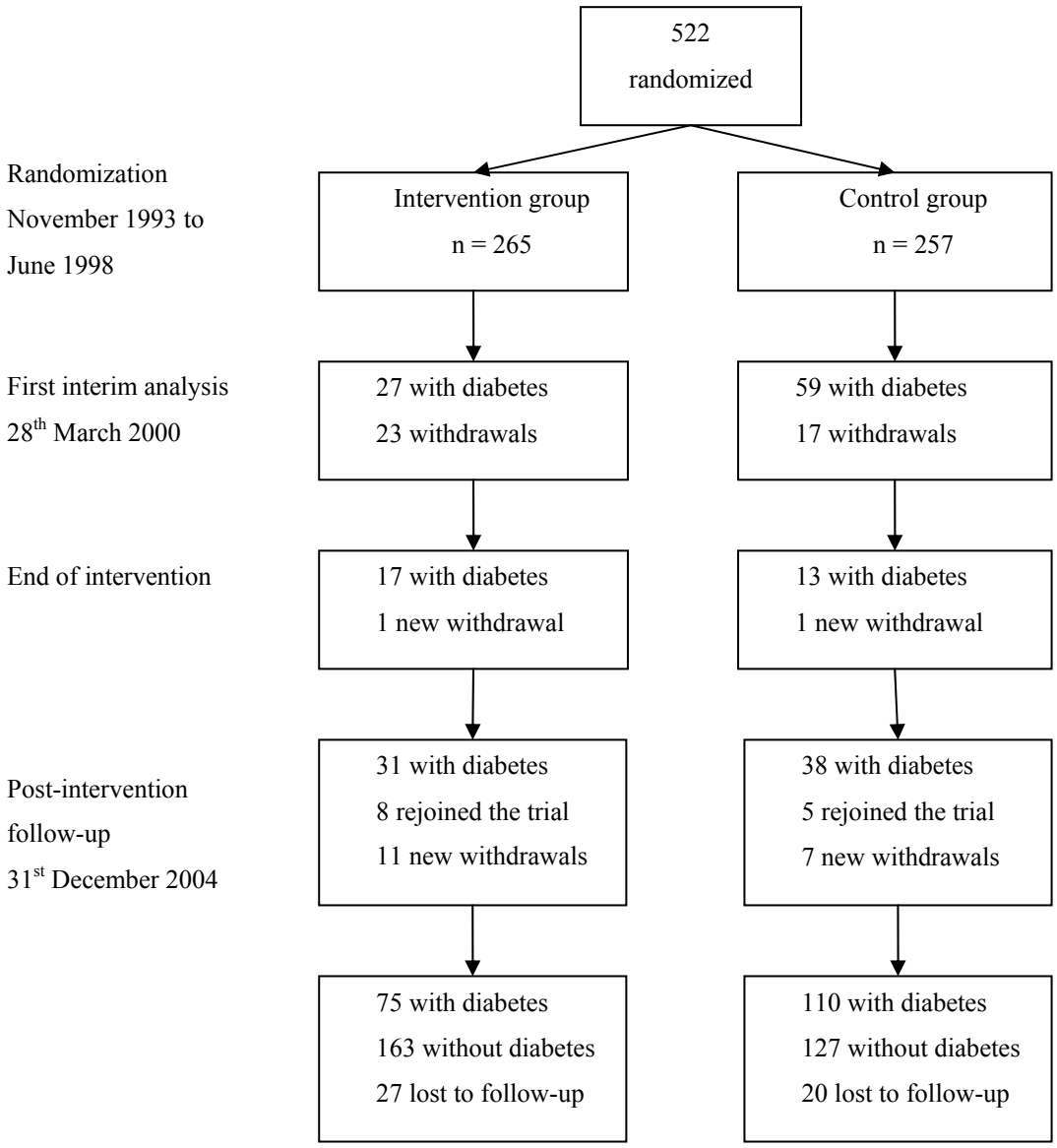

Figure 3. The DPS profile. 522 participants with IGT were randomized into an intervention and a control group. After the decision to end the study, the intervention was continued until each participants´ next scheduled yearly clinical visit. The end date of DPS thus varied from March 2000 to December 2001. All participants were invited to take part in the post-intervention follow-up.

4.2.1 Anthropometric measurements

Height (without shoes to the nearest 1 mm), weight (in light indoor clothes to the nearest 100 g), and waist circumference (midway between the lowest rib and iliac crest

to the nearest 1 mm with the subjects in a standing position) were measured by a trained study nurse at baseline and at yearly visits using standardized equipment. Body mass index (BMI) was calculated from measured weight and height as kg/m^2.

4.2.2 Blood pressure

Blood pressure was measured at baseline and annually from the right arm of the subject seated for 10 min before measurement using a standard sphygmomanometer. Systolic and diastolic blood pressure values were recorded as the mean of two measurements.

4.2.3 Laboratory examinations

In the FINRISK 1992 study, plasma glucose was measured at the local laboratory by a hexokinase method. The OGTT (75g) was done after fasting for 12 hours according to the WHO 1985 criteria (World Health Organization 1985). In the DPS study, plasma, serum, or capillary glucose was determined locally according to standard guidelines during the OGTT. The results were confirmed and corrected by linear regression equation, using values measured in the National Public Health Institute central laboratory. During the post-intervention follow-up, glucose assays were made centrally in Helsinki with the hexokinase method. All other blood samples in both studies were analyzed in the same central laboratory (National Public Health Institute, Helsinki). Cholesterol and triglyceride levels were determined by enzymatic assays (Boehringer Mannheim, Germany). HDL-cholesterol was measured after the completion of a dextran sulfate magnesium chloride precipitation of apoB-containing lipoproteins. Serum insulin was determined by a radioimmunoassay (Pharmacia, Uppsala, Sweden). The intra-assay coefficient of variation for serum insulin was 5.3%, and the interassay coefficient of variation was 7.6%. The HOMA-IR index (fasting insulin (μU/ml) x fasting glucose (mmol/l)/22.5) was calculated.

4.3 Dietary assessment in DPS

All study participants completed a 3-day food diary with a picture booklet of portion sizes of typical foods (Haapa et al. 1985). Average intake of energy (kcal/day), carbohydrates (E%), total fat (E%), saturated fat (E%) and dietary fiber (g/1000 kcal) were calculated at baseline and at 1-year, 2-year, and 3-year visits of the intervention period using a dietary analysis program and the Finnish Food Composition Database (Ovaskainen et al. 1996). The dietary changes were calculated by subtracting the average intake from years 1 to 3 from the corresponding baseline value. The dietary analyses were repeated at the first post-intervention follow-up visit.

4.4 Assessment of physical activity in DPS

At baseline and at each annual visit the participants completed the validated Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) 12-month leisure time physical activity (LTPA) questionnaire (Lakka and Salonen 1992; Lakka et al. 1994; Laaksonen et al. 2005). They estimated the frequency (times per month), average duration (minutes), and intensity (0, recreational; 1, conditioning exercise; 2, brisk conditioning exercise; and 3, competitive, strenuous exercise) of their common lifestyle and structured LTPA during the past 12 months.

Metabolic equivalent task (MET) was used to assess the physical activity. One MET is defined as the energy expenditure for sitting quietly, and is equivalent to 3.5 ml oxygen uptake per kilogram of body weight per minute. Based on the reported intensity of different activities and their corresponding MET values, total LTPA was divided into groups of low and moderate-to-vigorous intensity LTPA (Laaksonen et al. 2005). Low intensity LTPA included activities such as casual walking, bicycling at recreational intensity, gardening and yard work, and picking berries and mushrooms with light intensity. Moderate-to-vigorous intensity LTPA included activities such as brisk walking, jogging, bicycling, skiing, swimming, rowing, forest work, gymnastics, resistance training, ball games (if reported intensity ≥ 1), and lifestyle activities such as snow shoveling, gardening, hunting and picking berries (if reported intensity ≥ 2), and fishing, housework and repairs (if reported intensity = 3).

The KIHD questionnaire was originally designed for younger and leaner men participating in the population-based KIHD cohort study. While a sample of DPS participants showed ~30% lower maximal oxygen uptake during a bicycle exercise, the MET values assigned to different subjective intensities for given forms of physical activity were decreased by 30% (Laaksonen et al. 2005).

The duration of total LTPA, low-intensity LTPA, and moderate-to-vigorous intensity LTPA were calculated as hours/week. The changes were calculated by subtracting averaged values during the study from the corresponding baseline value.

Participation in the resistance training program was offered in three of the five study centers for those in the intervention group. The number of visits the participants made to the training facilities was recorded as the participation rate (session / year).

In addition to the KIHD questionnaire, participants who reported in the annual questionnaire that they "mostly read, watch TV, and spend time in other ways that are not physically demanding" during their leisure time were categorized as sedentary. Those who reported "walking, bicycling, or other exercise for at least 4 hours per week" were categorized as achieving the physical activity goal.

4.5 Goals and success score

The main goals of the intensive intervention in DPS were: 1) weight reduction of ≥ 5%, 2) < 30% of the daily energy intake from fat, 3) < 10% of the daily energy intake from saturated fat, 4) fiber intake ≥ 15 g per 1000 kcal, and 5) moderately intense physical activity ≥ 30 minutes per day.

The study participants were categorized according to their success in achieving these five predefined intervention goals (0 = not achieved, 1 = achieved) by the third year visit (mean LTPA and nutrient intake during the years 1, 2, and 3). A **success score** from 0 to 5 was calculated as the sum of the achieved goals.

4.6 Definition of MetS and its components

In **study 1**, the modified WHO 1998 definition of MetS (Table 1) was used. Insulin resistance was defined by the top quartile distribution of fasting insulin among subjects

without diabetes (Balkau and Charles 1999). Top quartile cut-off points were 9.42 and 9.80 mU/l for men, and 8.20 and 9.75 mU/l for women in age groups of 45–54 and 55–64 years, respectively. A subject was considered to have MetS if she/he had either normal glucose tolerance with insulin resistance, IFG, IGT, or type 2 diabetes and two or more of the following features: obesity, hypertension, or dyslipidemia.

Different categories of glucose tolerance were defined by applying the WHO 1999 criteria (World Health Organization 1999). Subjects were considered obese if waist-to-hip-ratio was > 0.90 in men and > 0.85 in women and/or BMI was $\geq$ 30 kg/m^2. Subjects were considered to have hypertension if blood pressure was $\geq$ 140/90 mmHg or if they were taking antihypertensive medication. The criteria for having dyslipidemia included plasma triglyceride concentration $\geq$ 1.7 mmol/l and/or HDL-cholesterol < 0.9 mmol/l in men and < 1.0 mmol/l in women, or if lipid-lowering medication was used.

In studies 2 and 3 we updated the criteria for MetS to match those of the NCEP 2005 criteria (Grundy et al. 2005), as described in Table 1.

4.7 Intervention and follow-up in DPS

The participants were not informed about their OGTT results during the study unless they were in the diabetic range. Other laboratory results and their targets, as well as the anthropometric measurements, were discussed at annual visits with the study physician.

Medication for blood pressure and/or dyslipidemia was initiated if necessary. The use of blood pressure lowering medications increased during the study in both groups: 34.5% vs. 35.4% (p = 0.822 between the groups) used antihypertensive medication at baseline and 40.7% vs. 42.9% (p = 0.521 between the groups) used antihypertensive medication at the end of the study in the intervention group and in the control group, respectively. The same trend was seen for the lipid lowering medication: 4.6% vs. 5.8% (p = 0.623 between the groups) used lipid lowering medication at baseline, whereas the corresponding figures were 14.4% vs. 13.8% (p = 0.382 between the groups) for the intervention and control groups at the end of the study

4.7.1 Intensive lifestyle counseling in the intervention group

The aim of the intensive lifestyle counseling was to encourage people to make informed healthy lifestyle choices to achieve the goals with the help of a detailed and individualized dietary and exercise counseling program.

The participants in the intervention group had seven personal counseling sessions with the study nutritionist during the first year and every 3 months thereafter. The median number of dietary counseling sessions per participant was 20, which indicated excellent adherence to the protocol. The methods used for the implementation of the program have been published and described in detail elsewhere (Lindström et al. 2003; Lindström et al. 2005).

The participants were advised to increase their overall level of physical activity, and endurance exercise was recommended in order to increase aerobic capacity and cardiorespiratory fitness. This was promoted by the study nurses and the nutritionist during the counseling sessions and highlighted by the study physicians. Sessions for supervised, individually-tailored and progressive circuit-type resistance training with moderate intensity were recommended twice a week. Sessions were offered free of charge in three of the study centers with the aim to improve functional capacity and strength of large muscle groups of the upper and lower body.

4.7.2 Standard care in the control group

The participants in the standard care control group were given general verbal and written health behavior information about food choices, physical activity, and weight loss at baseline, but no individualized counseling was offered. Control group participants filled out the same annual questionnaires and food diaries. The participants visited the study center once a year for measurements and met the study nurse, nutritionist, and physician.

4.7.3 Post-intervention follow-up

After the decision to end DPS, the intervention was continued until each participant's next scheduled annual clinic visit. All participants were given a summary of their

laboratory test results during the intervention period, including the plasma glucose values.

All DPS participants were invited to take part in the post-intervention follow-up. There were 27 and 20 participants lost to follow-up in the intervention and control groups, respectively, resulting in 238 participants in the intervention and 237 in the control group taking part in the follow-up. All participants had an annual visit with the study nurse, which included the same measurements as during the intervention period. The study physician evaluated the results and made a written summary for the participants. If needed, the participants were advised to contact their own physician. No specific diet or exercise counseling was provided. The trial flow is given in Figure 3.

4.8 Ethical aspects

The participants of DPS all willingly volunteered to take part in a lifestyle counseling program. After the screening OGTT the results were discussed with the participants. Those with IGT were informed about glucose intolerance and the need of dietary and physical activity change in order to prevent progression to type 2 diabetes. The purpose of DPS and the procedures involved were explained to participants at the beginning by the study nurse and the physician. All participants gave a written informed consent. The voluntary participation and the right to withdraw from the study at any time were outlined in the consent form.

General verbal and written information of healthy lifestyles and weight loss was given to the individuals in the control group. The information given was similar to what one could have expected to receive from primary health care at that time.

The participants were not informed about their OGTT results during the study unless they were in the diabetic range. Those who progressed to diabetes or developed a medical condition needing treatment were seen by the study physician. The diagnosis of diabetes was explained and the individual was directed to his / her own physician for the treatment.

The data were stored on the server of the Institute for Health and Welfare and without individual identification on the researcher's personal computer.

The DPS protocol was approved by the ethics committee of the National Public Health Institute in Helsinki, Finland (intervention phase) and the ethics committee of the North Ostrobothnia Hospital District (follow-up period).

4.9 Statistical methods

The data were analyzed using SPSS statistical software (version 11.5, SPSS Inc, Chicago, IL, USA; study 1–3) and the Stata statistics package (release 8.0; STATA, College Station, TX, USA; study 4).

The baseline values are given as mean ± SD, as medians with 0.25–0.75 interquartile range, or as percentages. The Student's two-tailed t-test was used for normally distributed variables and the nonparametric Mann-Whitney U-test for skewed distributed variables (serum fasting and 2-hour serum insulin, $HOMA_{IR}$, triglyceride, GT, and LTPA) to compare the differences between the intervention and the control group at baseline (studies 1–3). The χ^2 test was used to analyze the differences in categorical variables in study 1 and 2. P values ≤ 0.05 were considered statistically significant.

In **study 2,** the changes in the prevalence of MetS within the group from baseline to the end of the study were analyzed by Wilcoxon´s nonparametric test. The change in MetS prevalence between the groups was analyzed by regression analyses adjusted for sex, age, and respective baseline value. The analyses for elevated blood pressure were further adjusted for blood pressure medication, and elevated triglycerides, as well as low HDL-cholesterol for lipid medication. Repeated-measures ANOVA for normally distributed variables and the Cochrane test for binominal variables were applied in order to compare the change within a group.

For participants who dropped out or developed diabetes during the intervention, the measurements at the last observation year were used as the end value. There were nine drop-outs during the first year (6 in the intervention group and 3 in the control group) and another 16 subjects before the 3-year follow-up (8 in the intervention group and 8 in the control group).

In **study 3,** the primary outcome measure was the change in MetS status in the combined intervention and control group from baseline to the end, i.e., resolution of MetS from the baseline, development of MetS, or no change with LTPA changes as

explanatory variables. Secondary outcome measures were the changes in the MetS components. These post hoc analyses were not included in the power calculations of DPS. The original intervention and control groups were pooled together, and the change of different LTPAs was categorized into thirds. The association with the change in MetS status and its components was analyzed with multinomial regression analysis. The models were adjusted for age, sex, intervention group, and DPS study years (model 1) with further adjustments for changes in diet (intake of total fat, saturated fat, fiber, and energy) (model 2) and BMI (model 3). The change in low intensity LTPA was also adjusted for the change in moderate-to-vigorous LTPA and vice versa.

In **study 4,** Kaplan-Meier survival curves were calculated to estimate the probability of participants in the two groups remaining free of diabetes. 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. All comparisons of the end points were based on the intention-to-treat principle. The analyses were adjusted for treatment group, study centre, sex, age, and the baseline 2-hour post-challenge plasma glucose concentration. Mean levels of body weight, nutrient intake, and physical activity during the follow-up examinations were compared between the groups with analysis of covariance, adjusting for baseline level of the respective variable. In further analysis with the groups pooled, the Cox model was used to analyze the relationship between diabetes and the success score.

5. RESULTS

5.1 Prevalence of MetS and its components in FINRISK 1992 study

The clinical and metabolic characteristics of the 2049 individuals from FINRISK 1992 who had their glucose and insulin values measured during OGTT are given in Table 5.

Insulin resistance was found in 10.8% of the men and in 15.1% of the women with NGT (n = 1482). Abnormal glucose tolerance, either IFG (n = 177), IGT (n = 218) or type 2 diabetes (n = 172), was found in 34.9% of the men and 21.3% of the women, respectively. OGTT values in a diabetic range were found in 10.1% and 6.8% of the men and women, respectively. According to the questionnaires, 37.2% of the 172 participants with diabetic values were aware of the condition.

The prevalence rates of MetS, obesity, hypertension, and dyslipidemia by gender are shown in Table 6. Even though men had higher BMI, the obesity rate measured by BMI was not significantly higher in men than in women as opposed to the abdominal obesity measured by waist-to-hip ratio. MetS was observed in 12.3% of the subjects with NGT, in 63.1% of those with IFG, in 75.1% of those with IGT, and in 87.1% in subjects with diabetes. The prevalence rates of MetS and its components in men and women by glucose tolerance status are given in Table 7. In all categories, men had a higher prevalence of obesity and dyslipidemia than women did.

Table 5. Clinical and metabolic characteristics of the FINRISK 1992 subsample of 2049 individuals.

	Men	Women	*p*
BMI (kg/m^2)	27.8 ± 3.8	27.3 ± 4.8	*0.008*
Waist (cm)	98.3 ± 10.7	84.0 ± 11.6	*<0.001*
Waist-to-hip ratio	0.95 ± 0.66	0.80 ± 0.66	*<0.001*
Systolic blood pressure (mmHg)	144 ± 20	141 ± 20	*0.001*
Diastolic blood pressure (mmHg)	88 ± 11	83 ± 10	*<0.001*
Fasting plasma glucose (mmol/l)	5.8 ± 1.3	5.4 ± 1.0	*<0.001*
2-hour plasma glucose (mmol/l)	6.4 ± 2.5	6.2 ± 2.0	*0.048*
Fasting serum insulin (mU/l)	8.3 ± 5.6	7.6 ± 5.1	*<0.001*
2-hour serum insulin (mU/l)	36.0 ± 35.9	39.3 ± 39.4	*<0.001*
HOMA-IR -index	2.27 ± 1.89	1.92 ± 1.57	*<0.001*
Total cholesterol (mmol/l)	6.0 ± 1.0	6.0 ± 1.1	*0.363*
LDL-cholesterol (mmol/l)	3.9 ± 1.0	3.8 ± 1.0	*0.061*
HDL-cholesterol (mmol/l)	1.24 ± 0.32	1.50 ± 0.39	*<0.001*
Triglycerides (mmol/l)	1.94 ± 1.24	1.44 ± 0.95	*<0.001*

Data are mean ± SD or percentages. N varied between 820 and 936 in men and between 1014 and 1113 in women. BMI, Body Mass Index; HOMA-IR, Homeostasis model assessment for insulin resistance; LDL, Low-density lipoprotein; HDL, High-density lipoprotein

Table 6. Prevalence of MetS and its components in FINRISK 1992 subsample of 2049 individuals.

	Men	Women	*p*
MetS	**38.8**	**22.2**	*<0.001*
Obesity	**79.8**	**33.2**	*<0.001*
BMI ≥ 30kg/m^2	26.5	24.7	*0.335*
Waist-to-hip ratio			
> 0.90 in men and > 0.85 in women	79.1	21.8	*<0.001*
Hypertension	**66.1**	**54.9**	*<0.001*
Systolic blood pressure ≥ 140 mmHg	55.1	47.3	*<0.001*
Diastolic blood pressure ≥ 90 mmHg	43.1	25.7	*<0.001*
Use of blood pressure medication	18.2	16.3	*0.255*
Dyslipidemia	**52.4**	**29.0**	*<0.001*
Triglycerides ≥ 1.7 mmol/l	45.2	22.9	*<0.001*
HDL-cholesterol			
< 0.9 in men and < 1.0 in women	34.3	34.5	*<0.001*
Use of lipid medication	7.3	5.8	*0.046*

Data are percentages. BMI, Body Mass Index; HDL, High-density lipoprotein. N varied between 892 and 924 in men and between 1106 and 1113 in women.

Table 7. Prevalence of the components of MetS (WHO 1998 definition) in the FINRISK 1992 subgroup of 45−64 year old men and women by glucose tolerance status.

	NGT			IFG			IGT			Diabetes		
	Men	**Women**	*p*	**Men**	**Women**	*p*	**Men**	**Women**	*p*	**Men**	**Women**	*p*
N	607	875		125	52		108	110		96	76	
MetS	14.4	10.1	*0.019*	74.0	52.2	*0.007*	84.8	65.4	*<0.001*	91.5	82.7	*0.084*
Obesity	75.4	25.5	*<0.001*	80.8	46.2	*<0.001*	92.6	57.3	*<0.001*	93.1	81.6	*0.013*
Hypertension	61.9	49.9	*<0.001*	72.0	69.2	*0.711*	75.9	76.4	*0.940*	78.1	76.4	*0.778*
Dyslipidemia	44.7	22.0	*<0.001*	55.3	39.0	*0.074*	69.0	52.6	*0.018*	76.9	69.4	*0.282*

Data are percentages. NGT, Normal glucose tolerance;; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance.
Obesity: BMI $\geq$ 30 kg/m^2 or waist-to-hip ratio > 0.90 in men and > 0.85 in women.
Hypertension: Systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or use of oral antihypertensive medication.
Dyslipidemia: Serum triglycerides $\geq$ 1.7 mmol/l or HDL-cholesterol < 0.9 mmol/l in men and < 1.0 mmol/l in women or use of lipid lowering medication.

5.2 Prevalence of MetS and its components in DPS

Altogether 78.4% of the men and 72.2% of the women in the DPS fulfilled the modified WHO 1998 criteria for MetS. The prevalence's of obesity, hypertension and dyslipidemia in men and women is shown in Table 8.

Table 8. Prevalence of MetS and its components in DPS by gender.

	Men	Women	*p*
MetS	**78.4**	**72.2**	*0.082*
Obesity	**96.5**	**86.3**	*<0.001*
BMI ≥ 30 kg/m^2	45.3	59.1	*0.004*
Waist-to-hip ratio > 0.90 men, > 0.85 women	96.5	75.3	*<0.001*
Hypertension	**62.9**	**60.9**	*0.647*
Systolic blood pressure ≥ 140 mmHg	38.2	44.0	*0.181*
Diastolic blood pressure ≥ 90 mmHg	39.4	33.1	*0.161*
Use of blood pressure medication	29.1	29.2	*0.745*
Dyslipidemia	**51.2**	**48.6**	*0.599*
Triglycerides ≥ 1.7 mmol/l	44.8	39.0	*0.205*
HDL-cholesterol < 0.9 in men and < 1.0 mmol/l in women	22.7	17.8	*0.183*
Use of lipid medication	5.8	5.4	*0.857*

Data are percentages. Obesity: BMI ≥ 30 kg/m^2 or waist-to-hip ratio > 0.90 in men and > 0.85 in women. Hypertension: Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of oral antihypertensive medication. Dyslipidemia: HDL-cholesterol < 0.9 mmol/l in men and < 1.0 mmol/l in women or triglycerides ≥ 1.7 mmol/l or use of lipid lowering medication.

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5.3 Effects of the lifestyle intervention on MetS in DPS

The MetS status of the DPS participants was reassessed by the NCEP 2005 definition for study 2. Table 9 shows the baseline clinical and metabolic characteristics, dietary intake, and LTPA of the DPS participants by presence (MetS +) or absence (MetS −) of MetS. There were no significant differences in these variables between the intervention group and control group, except for slightly lower saturated fat intake in the intervention group. Reported dietary intakes did not differ between those with MetS

and those without MetS at baseline. On the other hand, those with MetS exercised significantly less than those without MetS at baseline.

Table 9. Baseline clinical and metabolic characteristics of the DPS participants by the presence or absence of MetS.

	Intervention group			**Control group**		
	MetS +	MetS –	*p*	MetS +	MetS –	*p*
N	196	69		190	67	
Age (years)	55 ± 7	56 ± 7	*0.531*	55 ± 7	55 ± 7	*0.811*
Weight (kg)	88. 8 ±14.7	81.0 ± 10.0	*<0.001*	87.7 ± 14.8	79.3 ± 10.9	*<0.001*
BMI (kg/m^2)	32.1 ± 4.6	29.4 ± 3.8	*<0.001*	32.1 ± 4.5	28.2 ± 3.0	*<0.001*
Waist (cm)	103. 9 ± 11.2	96.7 ± 8.3	*<0.001*	103.1 ± 10.9	93.0 ± 8.3	*<0.001*
Fasting plasma glucose (mmol/l)	6.3 ± 0.7	5.6 ± 0.8	*<0.001*	6.3 ± 0.7	5.9 ± 0.7	*0.001*
2-hour plasma glucose (mmol/l)	9.0 ± 1.6	8.5 ± 1.3	*0.011*	9.0 ± 1.4	8.7 ± 1.6	*0.126*
Fasting insulin (mU/l)	14 (11 – 19)	11 (8 − 14)	*<0.001*	15 (11 − 20)	10 (7 − 11)	*<0.001*
2-hour insulin (mU/l)	90 (61 – 134)	62 (38 − 92)	*0.028*	88 (65 − 135)	59 (37 − 73)	*<0.001*
HOMA-IR	4.1 (2.9 – 5.4)	2.5 (1.7 − 3.5)	*<0.001*	4.0 (3.1 − 5.6)	2.4 (1.9 − 3.0)	*<0.001*
Total cholesterol (mmol/l)	5. 6 ± 1.0	5. 7 ± 0.9	*0.220*	5.6 ± 0.9	5.7 ± 0.8	*0.327*
HDL-cholesterol (mmol/l)	1.14 ± 0.30	1.40 ± 0.25	*<0.001*	1.16 ± 0.26	1.37 ± 0.26	*<0.001*
Triglycerides (mmol/l)	1.68 (1.29 – 2.26)	1.20 (0.98 − 1.45)	*<0.001*	1.79 (1.40 − 2.35)	1.11 (0.87 − 1.42)	*<0.001*
Lipidi lowering medication (%)	4.6	4.3	*0.854*	7.4	1.5	*0.208*
Systolic blood pressure (mmHg)	141 ± 16	137 ± 16	*0.155*	139 ± 17	136 ± 17	*<0.001*
Diastolic blood pressure (mmHg)	87 ± 9	83 ± 11	*<0.001*	87 ± 10	82 ± 10	*<0.001*
Blood pressure medication (%)	40.0	18.8	*<0.001*	42.4	14.9	*<0.001*
Energy (kcal/day)	1763 ± 350	1791 ± 495	*0.704*	1725 ± 500	1796 ± 597	*0.346*
Fat (E%)	35.8 ± 6.6	36.7 ± 7.0	*0.337*	37.4 ± 6.7	36.3 ± 6.0	*0.260*
Saturated fat (E%)	16.0 ± 3.8	16.5 ± 4.6	*0.452*	17.3 ± 4.4	16.3 ± 3.7	*0.130*
Carbohydrate (E%)	43.7 ± 7.6	43.2 ± 7.3	*0.650*	42.8 ± 6.8	44.1 ± 6.5	*0.346*
Fiber (g/1000kcal)	11. 6 ± 3.9	12.0 ± 4.4	*0.509*	11.7 ± 3.9	11.8 ± 4.2	*0.761*
Total LTPA (hours/week)	5.3 (3.0 − 9.0)	7.0 (4.3 − 9.1)	*0.014*	5.1 (2.6 − 9.1)	6.6 (3.8 − 11.4)	*0.022*

Data are mean + SD or median with 0.25−0.75 interquartile range or percentages; p for the difference in those with MetS and those without MetS.
BMI, Body mass index; HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, High-density lipoprotein;
LTPA, Leisure time physical activity.

5.3.1 Changes in dietary intakes and physical activity

The weight, dietary intakes, and physical activity of the participants at baseline, year 1, and year 3 are shown in Table 10. Weight and intake of total fat and saturated fat were lower, while intake of carbohydrates and fibers and the proportion of physical activity were higher in the intervention group than in the control group during the intervention.

All five of the predefined goals were met by year 3 more often in the intervention group than in the control group. Three or more goals were fulfilled by 30.3% of the participants in the intervention group and by 13.1% in control group. The percentage of those with dietary fat intake ≤ 30E% was 38.2% vs. 23.6% ($p < 0.001$), the percentage of those with saturated fat intake ≦ 10E% was 21.3% vs. 10.6% ($p = 0.001$), and the percentage of those with fiber intake ≧ 15 g/1000kcal was 32.6% vs. 26.0% ($p = 0.014$) in the intervention group and in the control group, respectively. Weight reduction of ≥ 5% was achieved by 39.1% in the intervention group and in 18.7% in the control group ($p < 0.001$), and 51.0% in the intervention group exercised at least 2.5 hours per week with moderate-to-vigorous intensity compared to 41.3 % in the control croup ($p = 0.030$). In a logistic regression analysis adjusted for age, sex, and baseline MetS lower BMI and BMI change was shown to be associated with MetS prevalence. No goals other than achieving weight loss of ≥ 5% associated alone with MetS prevalence. However, the number of the predefined goals (0−5) that were met at year 3, analyzed as a continuous variable, associated with MetS prevalence ($p = 0.047$ adjusted for sex, age and baseline MetS).

5.3.1 Changes in the prevalence of MetS

The prevalence of MetS decreased during the first year with the most intensive dietary intervention − from 74.0% to 58.0% and from 73.9% to 67.7% ($p = 0.018$) in the intervention group and control group, respectively. At the end of the study, with a mean intervention time of 3.9 years, 62.6% of the subjects in the intervention group and 71.2% of the subjects in the control group ($p = 0.025$) had MetS (Figure 4), which corresponds to 38% relative risk reduction (Odds Ratio 0.62 with 95% CI 0.40–95; adjusted for age, sex and baseline value) in the intervention group.

Table 10. Mean weight, mean dietary intakes and proportion (%) of physical active at baseline, at year 1 and at year 3 in the intervention group and in the control group.

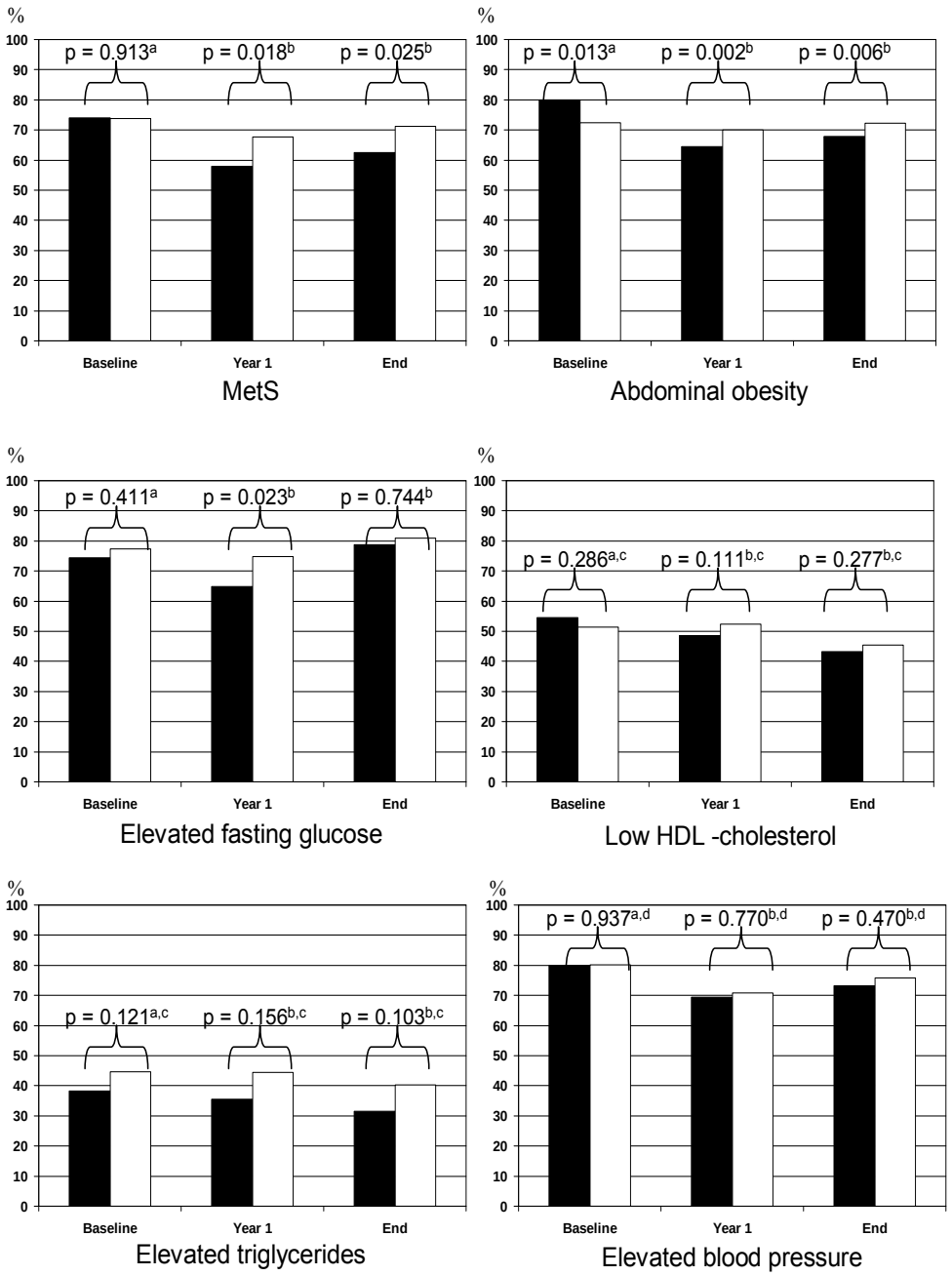
	Intervention group	Control group	*p*
Weight			
Baseline	86.7 ± 14.0	85.5 ± 14.4	*0.327*
Year 1	82.2 ± 13.6	84.8 ± 14.6	*<0.001*
Year 3[a]	83.4 ± 14.1	85.1 ± 15.5	*<0.001*
Fat (E%)			
Baseline	36.0 ± 6.7	37.1 ± 6.5	*0.067*
Year 1	32.6 ± 6.7	35.0 ± 6.2	*<0.001*
Year 3[a]	31.6 ± 6.2	34.4 ± 6.1	*<0.001*
Saturated fat (E%)			
Baseline	16.2 ± 4.0	17.0 ± 4.3	*0.019*
Year 1	13.5 ± 3.8	15.8 ± 4.1	*<0.001*
Year 3[a]	13.0 ± 3.8	15.4 ± 4.1	*<0.001*
Carbohydrate (E%)			
Baseline	43.6 ± 7.5	43.2 ± 6.7	*0.506*
Year 1	47.0 ± 7.5	44.9 ± 7.0	*0.002*
Year 3[a]	47.2 ± 7.4	45.0 ± 7.1	*0.001*
Fiber (g/1000kcal)			
Baseline	11.7 ± 4.0	11.7 ± 3.9	*0.943*
Year 1	14.2 ± 4.6	12.5 ± 3.7	*<0.001*
Year 3[a]	14.0 ± 4.7	12.6 ± 4.1	*<0.001*
Proportion of physically active (%)			
Baseline	64	67	*0.519*
Year 1	86	69	*<0.001*
Year 3[a]	82	71	*<0.001*

[a] Last observation carried forward for individuals who dropped out or developed diabetes during the study. [b] p for test of equality between groups adjusted for baseline level. N varied between 252 and 265 in the intervention group and between 245 and 257 in the control group.

5.3.2 Changes in the MetS components

The prevalence rates of the different components of MetS at year 1 and at the end of the DPS intervention are shown in Figure 4. During the study, there were significant improvements in all of the components except fasting glucose in the intervention group, but there were only improvements in HDL-cholesterol in the control group. Significant differences between the groups were seen in abdominal obesity and fasting glucose after the first year. By the end of the study only abdominal obesity and the overall prevalence of MetS were significantly different between the groups. The risk reduction for abdominal obesity was 52% (Odds Ratio 0.48; 95% CI 0.2–0.81 adjusted

for age, sex, and baseline value) in the intervention group from baseline to the end of the study.



p = difference between intervention group and control group; a, adjusted for age and sex; b, adjusted for age, sex and baseline value; c, adjusted for lipid medication at baseline and end; d, adjusted for blood pressure medication at baseline and at end.
Abdominal obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women;
Elevated fasting glucose: fasting plasma glucose ≥ 5.6 mmol/l; Elevated blood pressure: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or blood pressure lowering medication; Low HDL-cholesterol: HDL cholesterol < 1.03 mmol/l in men and < 1.3 mmol/l in women;
Elevated triglycerides: serum fasting triglycerides ≥ 1.7 mmol/l

Figure 4. Prevalence rates (%) of MetS and its components in the intervention group ■ and in the control group □ at baseline, at year 1 and at the end of DPS.

5.4 Effects of lifestyle changes in those with MetS at baseline

Among those 386 participants with MetS at baseline the mean weight loss was 4.8 ± 5.1 kg vs. 0.9 ± 3.4 kg ($p < 0.001$) after the first year and 2.4 ± 5.3 kg vs. 0.4 ± 5.1 kg ($p < 0.001$) at the end of the intervention period in the intervention group and control group, respectively.

Table 11. Clinical measurements of those with MetS at baseline, taken at baseline, at year 1, and at the end of DPS.

	Intervention group	**Control group**	***p*[e]**
N	196	190	
Weight (kg)			
Baseline	88.8 ± 14.7	87.7 ± 14.8	*0.693* [a]
Year 1	84.0 ± 14.0	87.0 ± 15.1	*<0.001* [b]
End	86.5 ± 15.5	87.3 ± 16.3	*<0.001* [b]
p[d] for change within group	*<0.001*	*0.311*	
Waist (cm)			
Baseline	103.9 ± 11.2	103.1 ± 10.5	*0.648* [a]
Year 1	99.0 ± 11.4	101.6 ± 11.6	*<0.001* [b]
End	101.6 ± 11.8	102.4 ± 11.8	*0.003* [b]
p[d] for change within group	*<0.001*	*0.176*	
Systolic blood pressure (mmHg)			
Baseline	141 ± 16	139 ± 17	*0.223* [a,c]
Year 1	135 ± 17	138 ± 16	*0.021* [b,c]
End	138 ± 17	138 ± 19	*0.409* [b,c]
p[d] for change within group	*0.006*	*0.444*	
Diastolic blood pressure (mmHg)			
Baseline	87 ± 9	87 ± 10	*0.714* [a,c]
Year 1	81 ± 9	84 ± 9	*0.027* [b,c]
End	82 ± 9	84 ± 10	*0.068* [b,c]
p[d] for change within group	*<0.001*	*<0.001*	

Data are mean ± SD.
[a] Adjusted for age and sex; [b] adjusted for age, sex and baseline value; [c] adjusted for blood pressure lowering medication; [d] p for change within group from baseline to end, paired samples t-test; [e] p for difference between groups, general linear model ANCOVA.

Comparisons within the groups showed that indicators for obesity or insulin resistance, i.e., fasting and 2-hour plasma insulin, HOMA-IR index, dyslipidemia, and hypertension, improved significantly in the intervention group from baseline to the end of the study, whereas only HDL-cholesterol, triglycerides, and diastolic blood pressure improved in the control group. Fasting and 2-hour plasma glucose were significantly lower within the intervention group after the first year compared to baseline, but the glucose values increased significantly within both of the groups during the study.

Table 11 and 12 give mean (or median) values of these indicators at the first annual visit and at the end of DPS.

Table 12. Laboratory measurements of those with MetS at baseline, taken at baseline, at year 1, and at the end of DPS.

	Intervention group	Control group	p^e	
Fasting plasma glucose (mmol/l)				
Baseline	6.3 ± 0.7	6.3 ± 0.7	*0.739*	[a]
Year 1	6.0 ± 0.7	6.3 ± 0.8	*<0.001*	[b]
End	6.5 ± 1.0	6.6 ± 0.9	*0.155*	[b]
p^d for change within group	*0.001*	*<0.001*		
2-hour plasma glucose (mmol/l)				
Baseline	9.0 ± 1.6	9.0 ± 1.4	*0.706*	[a]
Year 1	8.2 ± 1.9	8.9 ± 2.1	*<0.001*	[b]
End	9.5 ± 2.8	9.9 ± 2.6	*0.064*	[b]
p^d for change within group	*0.030*	*<0.001*		
Fasting insulin (mU/l)				
Baseline	14 (11 − 19)	15 (11 − 20)	*0.185*	[a]
Year 1	12 (9 − 15)	14 (11 − 19)	*<0.001*	[b]
End	12 (9 − 17)	15 (11 − 21)	*<0.001*	[b]
p^d for change within group	*<0.001*	*0.488*		
2-hour insulin (mU/l)				
Baseline	90 (61 − 134)	88 (65 − 135)	*0.665*	[a]
Year 1	58 (37 − 108)	78 (50 − 123)	*<0.001*	[b]
End	61 (43 − 108)	90 (56 − 128)	*<0.001*	[b]
p^d for change within group	*<0.001*	*0.370*		
HOMA-IR				
Baseline	4.1 (2.9 − 5.4)	4.0 (3.1 − 5.6)	*0.264*	[a]
Year 1	3.2 (2.3 − 4.1)	4.0 (2.8 − 5.4)	*<0.001*	[b]
End	3.5 (2.4 − 5.0)	4.4 (3.1 − 6.4)	*<0.001*	[b]
p^d for change within group	*0.001*	*0.268*		
HDL-cholesterol (mmol/l)				
Baseline	1.14 ± 0.3	1.16 ± 0.26	*0.527*	[a,c]
Year 1	1.19 ± 0.27	1.17 ± 0.29	*0.015*	[b,c]
End	1.25 ± 0.33	1.23 ± 0.33	*0.007*	[b,c]
p^d for change within group	*<0.001*	*<0.001*		
Triglycerides				
Baseline	1.68 (1.29 − 2.26)	1.79 (1.40 − 2.35)	*0.108*	[a,c]
Year 1	1.50 (1.10 − 1.95)	1.75 (1.33 − 2.39)	*<0.001*	[b,c]
End	1.47 (1.13 − 2.02)	1.65 (1.21 − 2.30)	*0.075*	[b,c]
p^d for change within group	*<0.001*	*0.013*		

Data are mean ± SD or median (with 0.2−0.75 interquartile range).
[a] Adjusted for age and sex; [b] adjusted for age, sex and baseline value; [c] adjusted for lipid lowering medication; [d] p for change within group from baseline to end; [e] p for difference between groups; general linear model.

Comparison between the groups at the first annual visit showed significantly more improvements in all parameters studied in the intervention group. At the end of the

study, significant differences were still seen in the markers of insulin resistance, except in glucose values and systolic and diastolic blood pressure.

Fasting plasma glucose and 2-hour post challenge glucose increased in both of the groups during the study, but 2-hour values tended to be lower in the intervention group (9.5 ± 2.8 mmol/l vs. 9.9 ± 2.6 mmol/l; p = 0.064, Table 12). Specifically, when men and women were analyzed separately, a significant difference between the groups at the end of the study was observed. Mean 2-hour glucose at the end of the study was 9.2 ± 2.8 mmol/l vs. 10.4 ± 2.7 mmol/l (p = 0.032) in men and 9.6 ± 2.8 mmol/l vs. 9.8 ± 2.6 mmol/l (p = 0.437) in women in the intervention group vs. control group, respectively.´

5.4.1 Resolution of MetS

Resolution of MetS was seen in 76 out of 386 (19.7%) subjects during the course of the study, and more often among the participants in the intervention group (25.5% in the intervention group vs. 13.7% in the control group; p = 0.005).

Resolution of MetS was most strongly associated with weight loss. In a logistic regression analysis where weight gain was given reference value 1, a weight loss of 0–5% resulted two times more often in resolution, and a weight loss over 5% resulted nearly five times more often in resolution (Table 13). Resolution of MetS was associated with participation in the intervention group and also to the success score calculated by the third annual visit. Participants in the intervention group recovered from MetS over two times more often than the participants in the control group, and further adjustments with baseline BMI and BMI change did not have a marked effect on these results (Odds ratio 1.81; 95% CI 1.02−3.23).

Table 13. Odds ratios for the effects of group, weight change, and success score by year 3 on MetS resolution during the study.

Variable	n (%)	Odds ratio[a]	95% CI
Group			
Control group		1	
Intervention group		2.11	(1.25−3.59)
Weight change by year 3			
Weight gain		1	
Weight loss 0 to 5%		2.10	(1.02−4.37)
Weight loss > 5%		4.89	(2.44−9.79)
Success score by year 3			
0 goal achieved	89 (24.2)	1	
1 goal achieved	121 (32.9)	2.46	(1.09−5.55)
2 goals achieved	73 (19.8)	2.31	(0.95−5.63)
≥ 3 goals achieved	85 (23.1)	3.10	(1.33−7.21)

[a] Adjusted for age and sex.

5.4.2 Success score

The progress of achieving the predefined five intervention goals was assessed by the third annual visit and a success score calculated. The effect of success score on MetS resolution, as well as on the indicators of insulin resistance and glucose tolerance, were analyzed in the combined cohort. By year 3, 24.2% of participants did not meet any goals (16.5% in intervention group vs. 32.2% in control group), 52.7% met 1 to 2 goals (50.0% in intervention group vs. 55.6% in control group) and 23.1% met 3 to 5 goals (33.5% in intervention group vs. 12.2% control group). MetS resolution was seen in 30.7% of participants who met 3 to 5 goals and in 12.0% of those who did no meet any of the goals. The odds ratios for the effect of success score on MetS resolution are shown in Table 13.

5.5 Weight change and MetS

Weight loss is the most important target in the treatment of MetS. Some weight regain occurred after the first year, but a difference between the groups remained throughout the study. Mean BMI was 32.1 ± 4.6 kg/m^2 vs. 32.1 ± 4.5 kg/m^2 (p = 0.839, adjusted

for age and sex) at baseline, 30.3 ± 4.5 kg/m^2 vs. 31.8 ± 4.7 kg/m^2 ($p < 0.001$ additionally adjusted for baseline value) at year 1, and 30.7 ± 4.7 kg/m^2 vs. 31.9 ± 5.0 kg/m^2 ($p < 0.001$) at the end in the intervention group vs. in the control group participants, respectively. Those in the intervention group showed ≥ 5% weight loss over three times more often than those in the control group after the first year and nearly twice as often at the end of the study. A weight loss of ≥ 5% was seen in 47.9% in the intervention group and in 14.0% in the control group at year one and in 35.2% in the intervention group and 18.4% in the control group at the end. Weight gain was observed in 14.2% in the intervention group and 43.5% in the control group at year one and in 31.6% in the intervention group and 49.5% in the control group at the end of the study.

The effects of weight change on indicators of insulin resistance and glucose tolerance were analyzed in the combined cohort (Table 14). Both fasting and 2-hour plasma glucose, as well as insulin and HOMA-IR index, improved significantly in those with a weight loss. Significant improvements were also seen in blood pressure and lipid values.

Resolution of MetS was observed in 39.4% of those with weight loss of ≥ 5% and in 7.1% of those with weight gain. In a logistic regression model for the resolution of MetS (age, sex, group, baseline weight, and percentage of weight change by the year 3 as explanatory variables), the odds ratio for weight change was 0.89 (95% CI 0.84−0.93), conferring to 10% relative odds for MetS resolution for one percentage of weight loss.

Table 14. Clinical and metabolic characteristics at baseline and at the end of the study according to the weight change category during the study.

	Weight loss ≥ 5%	Weight loss 0%–5%	Weight gain	*p*
N	139	180	203	
Weight (kg)				
Baseline	87.1 ± 13.4	87.5 ± 16.3	89.7 ± 14.3	
End	79.0 ± 12.9	85.7 ± 15.9	93.1 ± 15.1	*<0.001*
Waist (cm)				
Baseline	103.2 ± 9.9	102.6 ± 11.6	103.2 ± 10.9	
End	96.3 ± 9.8	100.8 ± 11.7	106.8 ± 11.2	*<0.001*
Fasting glucose (mmol/l)				
Baseline	6.2 ± 0.7	6.3 ± 0.7	6.3 ± 0.7	
End	6.1 ± 0.7	6.5 ± 0.8	6.9 ± 1.0	*<0.001*
2 h glucose (mmol/l)				
Baseline	9.0 ± 1.6	9.2 ± 1.4	8.9 ± 1.5	
End	8.2 ± 2.2	10.0 ± 2.4	10.4 ± 2.9	*<0.001*
Fasting insulin (mU/l)				
Baseline	15 (10 − 19)	15 (11 − 19)	15 (11 − 20)	
End	10 (8 − 13)	13 (10 − 17)	18 (13 − 24)	*<0.001*
2 h insulin (mU/l)				
Baseline	85 (59 − 134)	92 (65 − 136)	89 (63 − 130)	
End	54 (36 − 87)	82 (54 − 116)	93 (59 − 146)	*<0.001*
HOMA-IR-index				
Baseline	4.2 (2.7 − 5.4)	3.8 (3.0 − 5.6)	4.2 (3.1 − 5.6)	
End	2.7 (2.1 − 3.7)	3.8 (3.0 − 5.6)	5.2 (3.5 − 7.7)	*<0.001*
HDL-cholesterol (mmol/l)				
Baseline	1.15 ± 0.31	1.16 ± 0.29	1.13 ± 0.25	
End	1.32 ± 0.37	1.24 ± 0.34	1.18 ± 0.26	*<0.001*[a]
Triglycerides (mmol/l)				
Baseline	1.84 (1.41 − 2.47)	1.64 (1.24 − 2.12)	1.74 (131 − 2.30)	
End	1.37 (1.05 − 2.07)	1.53 (1.13 − 2.05)	1.70 (1.29 − 2.31)	*<0.001*[a]
Systolic BP (mmHg)				
Baseline	141 ± 17	140 ± 17	139 ± 16	
End	135 ± 18	138 ± 17	140 ± 19	*0.003*[b]
Diastolic BP (mmHg)				
Baseline	87 ± 8	86 ± 9	87 ± 10	
End	80 ± 9	82 ± 9	85 ± 10	*<0.001*[b]

Data are mean ± SD or median (with 0.25–0.75 interquartile range). HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, High-density lipoprotein; BP, Blood pressure; p for difference between weight change groups adjusted for age, sex, respective baseline and [a] lipid medications; [b] blood pressure medications; general linear model.

5.6 MetS development

Of the 136 DPS participants who did not meet the MetS criteria at baseline, 39 (28.7%) developed MetS during the study. There were no differences in the MetS development

between the groups; 29.0% of those in intervention group and 28.4% of those in control group developed MetS during the study. The development of MetS was associated with weight gain ($p < 0.001$ for weight change) and lower total LTPA ($p = 0.043$ for total LTPA change).

Development of MetS was observed in 14.3% of those with weight loss of ≥ 5% and in 55.3% of those with weight gain. The mean weight gain among those who developed MetS was 3.0 ± 6.3 kg during the study (0.63 ± 5.8 kg in the intervention group vs. 5.5 ± 5.8 kg in the control group), while those who did not develop MetS had a mean weight loss of 2.6 ± 4.7 kg (3.7 ± 4.5 kg in intervention group vs. 1.4 ± 3.9 kg in control group). The change in total LTPA was −1.1 ± 2.3 hours per week vs. 0.4 ± 5.3 hours per week ($p = 0.043$) in those who developed, compared with those who did not develop MetS, respectively.

5.7 LTPA and its changes and MetS

5.7.1 Baseline LTPA and it changes

The 486 participants who had completed the questionnaire quantifying LTPA during the previous 12 months at baseline and at least once during the follow up were included in the assessment of LTPA and its effects on MetS in the combined cohort of DPS participants in study 3. The mean time of follow-up in this cohort was 4.1 ± 1.3 years.

In general, men exercised more and with a higher intensity than women did. Men exercised with moderate-to-vigorous intensity for 2.3 (0.9−4.8) hours per week, in comparison to 1.4 (0.3−3.9) hours per week in women. The baseline LTPA in all participants and arranged according to the presence or absence of MetS is shown in Table 15. Those, especially women, who had MetS at baseline, reported less low intensity LTPA in the previous 12 months.

The median (with interquartile range) for total LTPA increased from 7.2 (3.6–10.8) at baseline to an average of 7.7 (4.8–11.7) hours per week ($p = 0.061$) in men and from 5.3 (2.8–8.6) to 5.8 (3.2–9.0) hours per week ($p = 0.016$) in women during the intervention. The median for moderate-to-vigorous intensity LTPA increased from 2.3 (0.9–4.8) to 3.1 (1.8–4.9) ($p = 0.005$) hours per week in men and from 1.4 (0.3–3.5) to 2.5 (1.1–4.1) ($p \leq 0.001$) hours per week in women. There was also a slight, albeit

statistically insignificant, increase in low intensity LTPA in men; the median for low intensity LTPA increased from 3.2 (1.3–6.9) hours per week at baseline to average 4.1 (1.8–6.7) hours per week (p = 0.328) in men and decreased from 2.9 (1.2–5.6) hours per week to 2.8 (1.3–4.8) hours per week (p = 0.669) in women.

Table 15. Baseline LTPA (hours/week) of the participants according to the absence (MetS −) or presence (MetS +) of MetS.

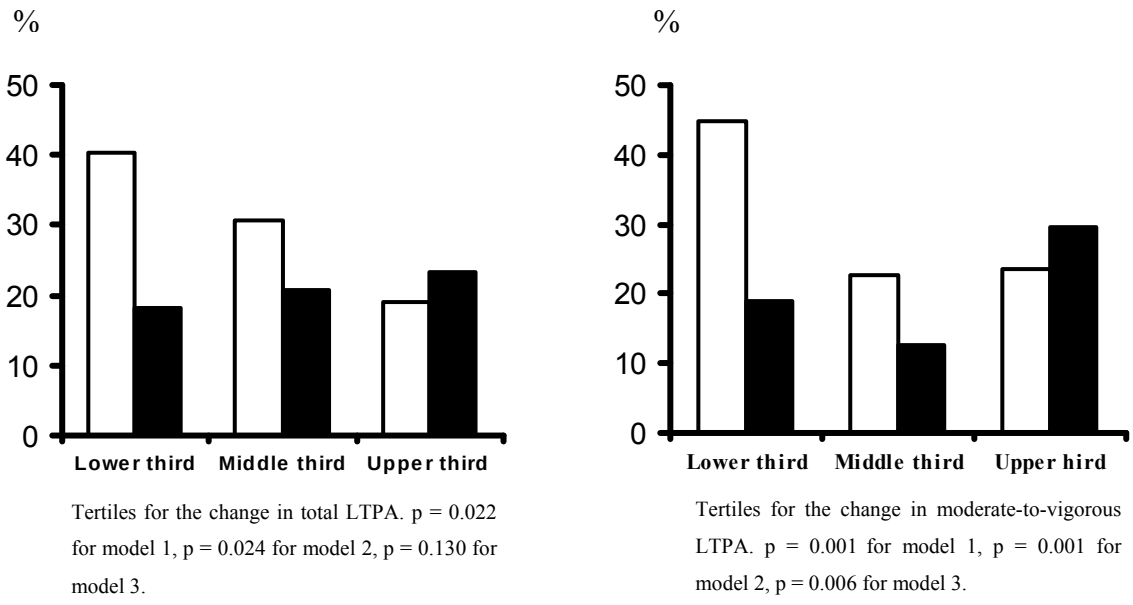
	All	**MetS −**	**MetS +**	***p***
N	486	125	361	
Total LTPA	5.7(3.1 − 9.3)	6.9(4.3 − 10.1)	5.1(2.8 − 9.1)	*0.001*
Men	7.2(3.6 − 10.8)	7.5(3.8 − 10.4)	6.9 3.4 − 10.9)	*0.503*
Women	5.3(2.8 − 8.6)	6.7(4.3 − 9.8)	4.9(2.6 − 8.2)	*0.002*
Moderate-to-vigorous LTPA	1.7(0.5 − 4.0)	1.9(0.6 − 4.4)	1.6(0.4 − 3.8)	*0.165*
Men	2.3(0.9 − 4.8)	2.1(1.1 − 4.7)	2.4(0.7 − 4.9)	*0.725*
Women	1.4(0.3 − 3.5)	1.7(0.4 − 4.2)	1.3(0.3 − 3.5)	*0.481*
Low-intensity LTPA	3.0(1.2 − 5.9)	4.1(1.9 − 7.2)	2.9(1.1 − 5.3)	*0.004*
Men	3.0(1.4 − 6.9)	3.7(1.9 − 7.2)	3.0(1.2 − 6.9)	*0.268*
Women	2.9(1.2 − 5.6)	4.4(1.5 − 7.2)	2.8(1.1 − 4.6)	*0.011*

Data are medians (interquartile range), hours/week; LTPA, Leisure time physical activity
p indicates the difference between those with MetS− and MetS+ in combined cohort.

5.7.2 LTPA changes and MetS resolution and development

The averaged total, low, and moderate-to-vigorous intensity LTPA change during the study years were categorized into thirds and the association with MetS status change (MetS resolution, MetS development, and unchanged status) during the study was examined. Change in **total LTPA** was associated with change in MetS status after adjustments for age, sex, intervention group, DPS study years (model 1), and dietary intakes (model 2), but the association was no more significant after adjustments for BMI change (model 3; Figure 5, left panel). However, the association of **moderate-to-vigorous LTPA** change with MetS status change was significant even after adjustments for dietary intakes and weight change (Figure 5, right panel). The resolution of MetS was seen in 29.7% vs. 19.1% (p = 0.004) of those with MetS at baseline and the development of MetS was seen in 23.5% vs. 44.7% (p = 0.041) of

those without MetS at baseline in the upper vs. lower third of change in moderate-to-vigorous LTPA. The change in **low-intensity LTPA** did not associate with MetS status change.



Tertiles for the change in total LTPA. p = 0.022 for model 1, p = 0.024 for model 2, p = 0.130 for model 3.

Tertiles for the change in moderate-to-vigorous LTPA. p = 0.001 for model 1, p = 0.001 for model 2, p = 0.006 for model 3.

Figure 5. Incidences (%) of the development □ and the resolution ■ of MetS according to tertiles for total (left panel) and for moderate-to-vigorous intensity LTPA (right panel) change. Model 1: Adjustments for age, sex, group and DPS study years. The change in moderate-to-vigorous intensity LTPA was also adjusted for change in low intensity LTPA. Model 2: Model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber and energy. Model 3: Model 2 and change in BMI.

5.7.3 LTPA changes and components of MetS

The prevalence of different MetS components and the percentage of individuals who developed or recovered from a MetS component by the end of the study are shown in Table 16. There was a significant association between the total LTPA change (adjusted for age, sex, intervention group and DPS study years; model 1) and elevated fasting plasma glucose (p = 0.003), low HDL-cholesterol (p = 0.018), and elevated triglycerides (p = 0.002). However, the association remained significant only for

elevated triglycerides (p = 0.003) when the analysis was adjusted for dietary changes (model 2) and further for BMI change (model 3).

The change in moderate-to-vigorous intensity LTPA was correlated with change in elevated fasting glucose (p = 0.003; model 1), and the correlation remained significant (p = 0.011; model 2) with further adjustments for dietary intakes of total fat, saturated fat, fiber, and energy, as well as with adjustment of BMI change (p = 0.018; model 3).

5.7.4 Resistance training

In a subgroup of 137 participants in the intervention group who were offered progressive circuit-type resistance training, the median (with 0.25−0.75 interquartile range) attendance rate was 27.0 (13.4−42.9) sessions per year during the 4.1 years. The attendance rate was associated with improvements in fasting plasma glucose (model 1, 2, 3), triglycerides (model 1), and HDL-cholesterol (model 1, 2, 3), but not with blood pressure or abdominal obesity (Table 17).

Table 16. Prevalence and incidence rates (%) of development and resolution of MetS and its components at the end of the study according to tertiles of total and moderate-to-vigorous intensity LTPA change.

		Tertiles for total LTPA change median (0.25 − 0.75)			**Tertiles for moderate-to-vigorous intensity LTPA change** median (0.25 − 0.75)		
	All	Lower	Middle	Upper	Lower	Middle	Upper
	%	-3.2 (-5.5 − -1.6)	0.6 (-0.1 − 1.2)	3.8 (2.4 − 5.9)	−1.5 (-3.1 − -0.5)	0.5 (0.2 − 0.8)	2.6 (1.8 −3.8)
Abdominal obesity	**69.5**	**70.4**	**72.8**	**65.4**	**72.2**	**74.7**	**61.7**
Development	4.3	7.4	2.5	3.1	6.2	2.5	4.3
Resolution	11.1	8.6	12.3	12.3	9.3	6.8	4.3
		p=0.119 for model 1; p=0.184 for model 2;p=0.408 for model 3			*p=0.065 for model 1; p=0.083 for model 2;p=0.181 for model 3*		
Elevated fasting glucose	**80.0**	**82.0**	**78.4**	**79.6**	**80.9**	**82.7**	**76.4**
Development	12.4	17.4	13.0	6.8	19.1	11.7	6.2
Resolution	8.9	8.1	10.5	8.0	8.6	8.0	9.9
		p=0.020 for model 1; p=0.033 for model 2;p=0.053 for model 3			*p=0.003 for model 1; p=0.011 for model 2;p=0.018 for model 3*		
Elevated triglycerides	**36.7**	**40.4**	**37.0**	**32.7**	**40.1**	**37.9**	**32.1**
Development	9.3	11.1	6.8	9.9	12.3	8.0	7.4
Resolution	14.4	6.2	20.4	16.7	14.9	12.4	16.0
		p=0.002 for model 1; p=0.002 for model 2;p=0.003 for model 3			*p=0.491 for model 1; p=0.526 for model 2;p=0.672 for model 3*		
Low HDL-cholesterol	**44.0**	**46.9**	**46.9**	**38.3**	**45.1**	**47.5**	**39.5**
Development	7.8	12.3	6.8	4.3	11.7	6.2	5.6
Resolution	16.5	13.6	13.6	22.6	14.8	13.6	21.3
		p=0.018 for model 1; p=0.013 for model 2;p=0.057 for model 3			*p=0.098 for model 1; p=0.086 for model 2;p=0.232 for model 3*		
Elevated blood pressure	**75.1**	**74.7**	**75.3**	**75.2**	**79.6**	**73.5**	**72.0**
Development	4.7	5.6	5.6	3.1	7.4	4.3	2.3
Resolution	9.7	8.0	9.3	11.8	6.8	8.0	14.8
		p=0.661 for model 1; p=0.643 for model 2;p=0.800 for model 3			*p=0.068 for model 1; p=0.066 for model 2;p=0.151 for model 3*		

LTPA, Leisure time physical activity; HDL, High-density lipoprotein

Model 1: Adjustments for age, sex, group and DPS study years. The change in low intensity LTPA was also adjusted for change in moderate- to-vigorous LTPA and vice versa. Model 2: Model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber and energy. Model 3: Model 2 and change in BMI.

Table 17. Prevalence and incidence rates (%) of the development and resolution of MetS and its components at the end of the study according to tertiles of resistance training attendance rate (median with 0.25–0.75 interquartile range).

	Tertiles of average yearly attendance rate for resistance training			
	All	Lower	Middle	Upper
	27.0 (13.3−42.9)	8.5 (5.5−13.4)	27.9 (21.9−32.7)	50.7(42.3−67.2)
N	**137**	**45**	**46**	**46**
MetS	**88 (64.2)**	**33 (73.3)**	**30 (65.2)**	**25 (54.2)**
Development	15 (10.9)	6 (13.3)	7 (15.2)	2 (4.3)
Resolution	27 (19.7)	7 (15.6)	7 (15.2)	13 (28.3)
Abdominal obesity	**101 (73.7)**	**40 (88.9)**	**32 (69.6)**	**29 (63.0)**
Development	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resolution	14 (10.2)	2 (4.4)	6 (13.0)	6 (13.0)
	p = 0.438 for model 1; 0.537 for model 2; 0.549 for model 3			
Elevated fasting plasma glucose	**113 (82.5)**	**36 (80.8)**	**41 (89.1)**	**36 (78.3)**
Development	23(16.8)	6(13.3)	12 (26.1)	5 (10.9)
Resolution	7(5.1)	3 (6.7)	1 (2.2)	3 (6.5)
	p = 0.127 for model 1; 0.157 for model 2; 0.029 for model 3			
Elevated triglycerides	**43 (31.4)**	**19(42.2)**	**15 (32.6)**	**9 (19.6)**
Development	14 (10.2)	5 (11.1)	8 (17.4)	1 (2.2)
Resolution	29 (21.2)	5 (11.1)	10 (21.7)	14 (30.4)
	p = 0.046 for model 1; 0.067 for model 2; 0.081 for model 3			
Low HDL-cholesterol	**62 (45.3)**	**24 (53.3)**	**20 (43.5)**	**18 (39.1)**
Development	15 (10.9)	7 (15.6)	7 (15.2)	1 (2.2)
Resolution	25 (18.2)	3 (6.7)	12 (26.1)	10 (21.7)
	p < 0.000 for model 1; 0.001 for model 2; 0.002 for model 3			
Elevated blood pressure	**98 (71.5)**	**32 (71.1)**	**32 (69.6)**	**34 (73.9)**
Development	5 (3.6)	2 (4.4)	1 (2.2)	2 (4.3)
Resolution	14 (10.2)	4 (8.9)	5(10.9)	5 (10.9)
	p = 0.982 for model 1; 0.967 for model 2; 0.957 for model 3			

Data are N (percentage).
p value for the trend across tertiles of resistance training attendance rate and MetS components change (no change, development, resolution).
Model 1: Adjustments for age, sex, DPS study years and low intensity LTPA.
Model 2: Model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber and energy.
Model 3: Model 2 and change in BMI.

5.8 Long-term results of lifestyle intervention in diabetes prevention

5.8.1 Diabetes incidence

The total number of individuals with diabetes diagnosed during the intervention and post-intervention follow-up, with an overall median duration of 7 years, was 75 in the intervention group and 110 in the control group. The corresponding incidence rates were 4.3 (95% CI 3.4–5.4) and 7.4 (6.1–9.9) per 100 person-years in the intervention group and in the control group, respectively ($p < 0.001$) with a hazard ratio of 0.57 (95% CI 0.43–0.76) (Figure 6). The cumulative incidence of diabetes at year 6 was 23% in the intervention group and 38% in the control group. The number needed to treat to prevent one case of type 2 diabetes by lifestyle intervention was 22 for 1 year.

In the intervention group and in the control group, respectively, 14% and 6% ($p < 0.001$) achieved 4 to 5 of the predefined goals by the 3-year examination, and 30% and 13% ($p < 0.001$) achieved at least 3. There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow up. The hazard ratios for success score from 0, 1, 2, 3, to 4–5 were 1.00, 0.85 (0.57–1.28), 0.66 (0.40–1.09), 0.69 (0.38–26), and 0.23 (0.10–0.52) (p for trend < 0.001), compared to reference value 1 for 0 goals achieved.

5.8.2 Lifestyles

Lifestyle-related variables during the intervention time are shown in Table 10. Mean body weight and intake of total and saturated fat were lower in the intervention group compared with that of the control group during the intervention period. Further, intake of dietary fiber and physical activity were higher in the intervention group than in the control group.

The Cox model was used to assess independent effects of achieving different lifestyle goals. The univariate and multivariate-adjusted hazard ratios for diabetes with 95% CI are given in Table 18. Weight change was significantly associated with the achievement of each of the four other lifestyle goals, and consequently, success score was strongly and inversely correlated with weight reduction. The 3-year weight

reduction was 0.5%, 2.1%, 4.3%, 4.5%, and 8.7% for the success scores 0, 1, 2, 3, and 4–5, respectively ($p < 0.001$).

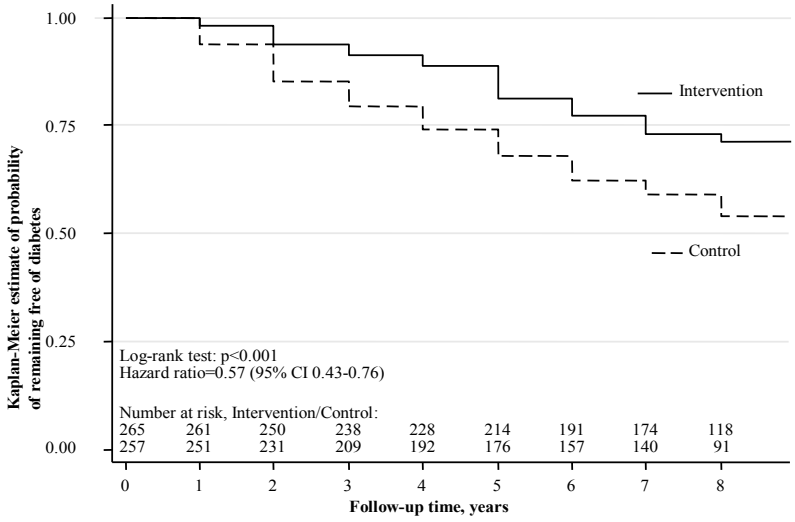


Figure 6. Diabetes by group during a total follow-up for a median of 7 years.

Table 18. Hazard ratios for diabetes incidence during the total follow-up by achieved treatment goals at the 3-year examination in the DPS follow-up.

Goal	Univariate hazard ratio	95% CI	Adjusted hazard ratio[1]	95% CI
Weight reduction ≥ 5%	0.45	0.31−0.64	0.43	0.30−0.61
Intake of fat < 30E%	0.65	0.45−0.95	0.80	0.48−1.34
Intake of saturated fat < 10E%	0.59	0.31−1.13	0.55	0.26−1.16
Intake of fiber ≥ 15g/1000kcal	0.69	0.49−0.96	0.97	0.63−1.51
Physical activity > 0.5 hours/day	0.62	0.46−0.84	0.80	0.57−1.12

[1] Adjusted for other goals in the table.

6. DISCUSSION

The Finnish Diabetes Prevention Study (DPS) was the first randomized and controlled trial that showed primary prevention of type 2 diabetes by lifestyle changes to be possible in high-risk individuals (Tuomilehto et al. 2001). The results have since been confirmed by others (Knowler et al. 2002; Ramachandran et al. 2006; Roumen et al. 2008) and also in a primary care setting (Absetz et al. 2007; Saaristo et al. 2011), and practical guidelines have been developed (Tuomilehto et al. 2011).

The DPS participants, recruited during the years 1993 to 1998, were volunteers with IGT according to the WHO 1985 definition. One aim of the present study was to determine whether the DPS participants differed from individuals with IGT in the general population. Therefore, the glucose tolerance status among the FINRISK 1992 participants, as well as the prevalence of MetS in both of the cohorts, was assessed in study 1. MetS is clinically important because of its association with CVDs and the development of type 2 diabetes. It has also been shown to increase the risk of microvascular complications in those with established diabetes (Isomaa et al. 2001b). Therefore, it is important to intervene with all known risk factors, not only plasma glucose. The effects of the lifestyle counseling used in DPS and the role of weight change on the prevalence, resolution, and development of MetS and its components was assessed in study 2. The effects of LTPA of differed intensity on the overall MetS status and MetS components were assessed in study 3. In order to study the long-term effects of the lifestyle changes on type 2 diabetes prevention, the DPS participants were followed up to three years after the end of the active intervention and the data was analyzed in study 4.

6.1 Obesity

The prevalence of obesity in different categories of glucose tolerance was studied in a cross-sectional and population-based cohort of middle-aged subjects from the

FINRISK 1992 study, as well as among the DPS participants with IGT. Among the FINRISK 1992 participants the mean BMI was 27.6 kg/m^2 and 27.4 kg/m^2 and the mean waist circumference was 97.9 cm and 84.2 cm in men and women aged 45–64 years, respectively. The percentage of those with BMI $\geq$ 30 kg/m^2 was 25.0% and 26.3% in men and women, respectively, indicating that already in the early 90's every fourth middle-aged man and women was obese.

All of the DPS participants had IGT, and the proportion of those who were obese, especially with abdominal obesity, was high in both men (96.5%) and women (86.3%), in accordance with the DPS inclusion criteria. Among the FINRISK 1992 participants with IGT, especially among women, the obesity rate was lower than among the DPS participants: 92.6% in men and 57.3% in women.

The FINRISK studies are conducted every five years and Lahti-Koski (2010) showed that in a broader age group (over 30 years) the prevalence of obesity had increased from 11% to 21% in men and from 18% to 24% in women during a 20 year period from 1978–1980 to 2000–2001. However, the latest FINRISK study from 2007 showed that mean BMI among participants in the age group of 45–74 years was 27.0 kg/m^2 in men and 26.5 kg/m^2 in women, and the proportion of those who were obese was 19% and 21% in men and women, respectively (Peltonen et al., 2008a). This indicates that the rate of obesity has stabilized. Comparison between the FIN-D2D surveys, from 2004 and 2007, points to the same direction. The proportion of obesity decreased from 24% to 22% in men and from 29% to 27% in women (Peltonen et al. 2008b; Saaristo et al. 2008).

The obesity rate is higher in the U.S. than in Finland, but there is also a similar trend in the U.S.. Flegal et al. (2010) studied the National Health and Nutrition Examination Studies (NHANES) data and found that in 2007–2008, the prevalence of obesity was 32% among adult men and 36% among adult women in the U.S.. The increasing prevalence of obesity that has been previously observed does not appear to have occurred at the same rate over the past 10 years, particularly for women and possibly also for men. The reported NHANES data suggests that the U.S. obesity prevalence, though very high, appears to have stabilized over the past 5 to 10 years (Yanovski and Yanovski 2011).

The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change with regard to diabetes prevalence across the world appears to be the increase in the proportion of people > 65 years of

age. These findings indicate that the "diabetes epidemic" will continue even if levels of obesity remain constant. Given the increasing prevalence of obesity, it is likely that these figures provide an underestimate of future diabetes prevalence (Wild et al. 2004).

6.2 Prevalence of MetS and its components

In the FINRISK 1992 cohort of people aged 45–64 years, ~40% of the men and ~20% of the women fulfilled the modified WHO 1998 criteria for MetS. The prevalence of MetS increased with established abnormalities in glucose metabolism, from 12% in subjects with NGT to 87% in those with manifest diabetes. It was similar in both study cohorts among those with IGT: 75% in the FINRISK and 73% in the DPS. Although comprised of volunteers for an interventional study, the DPS participants were rather similar to the general Finnish population.

The prevalence of MetS was higher among men in all categories of glucose tolerance and also increased with age, which is in accordance with previous studies (Bonora et al. 1998; Isomaa et al. 2001a; Balkau et al. 2002). In another Finnish cohort, the prevalence of MetS by WHO definition was 15% and 10% in subjects with normal glucose tolerance, 64% and 42% in those with IFG or IGT, and 84% and 78% in those with type 2 diabetes among men and women, respectively (Isomaa et al. 2001a).

The prevalence of MetS reported from different studies has varied widely, mainly because of the application of different criteria and in part due to the differences in the populations studied (e.g. age, ethnicity, prevalence of hypertension) (Ford et al. 2002; Hu et al. 2004; Ford 2005a; Ford et al. 2008b). It is estimated that about 20–25% of the world's adult population has MetS (Alberti et al. 2006).

The results of studies examining the trend in the prevalence of MetS are inconsistent (Ford et al. 2004; Lorenzo et al. 2005; Lorenzo et al. 2006; Park et al. 2007). Hu et al. (2008) studied the same FINRISK 1992 population as in study 1 and assessed the 10-year change in the prevalence of MetS defined by the newer criteria, i.e. by the updated NCEP (Grundy et al. 2005) and IDF 2005 (Alberti et al. 2005) definitions. In both years, MetS was more common among men than among women. In men, the prevalence of MetS tended to increase slightly between 1992 and 2002, from 49% to 53% according to the NCEP 2005 definition and from 51% to 56% according to the IDF 2005 definition. In women, the prevalence of MetS increased significantly from

32% to 39% according to the NCEP 2005 definition, and from 38% to 45% according to the IDF definition (Hu et al. 2008). The increase was significant only in women. They concluded that the prevalence of MetS in Finland is relatively high in international comparisons.

The MetS prevalence rates presented by Hu et al. (2008) were higher than in the present study. The main differences between the WHO 1999 definition and the newer IDF criteria are the lower threshold for elevated blood pressure, higher threshold for HDL-cholesterol, and the change of the definition of abdominal obesity from WHR to waist circumference. The older WHO criteria were more suitable for epidemiological studies and the IDF criteria are more suitable for clinical work.

Of the CVD risk factors, elevated blood pressure was more common than dyslipidemia in both the FINRISK 1992 and the DPS populations. The prevalence of hypertension was significantly higher among men with normal glucose tolerance, but the sex difference disappeared with abnormal glucose tolerance in both of the cohorts. The parallel difference between the two sexes was also seen in dyslipidemia rate, which was twofold in men compared to women with normal glucose tolerance. With worsening glucose tolerance, the prevalence of dyslipidemia increased among women.

Hu et al. (2008) further found a trend in FINRISK 1992 and 2002 showing that mean blood pressure and triglyceride levels decreased, whereas the prevalence of glucose abnormalities increased significantly in both genders, as did the waist circumference and the prevalence of abdominal obesity in women but not in men (Hu et al. 2008).

The Diabetes Prevention Program in the U.S. confirmed the effectiveness of intensive lifestyle intervention for the prevention of type 2 diabetes in a population of 3234 overweight individuals aged 25−82 years with IGT (Knowler et al. 2002). In that population with heterogeneous ethnicity, the prevalence of MetS (by NCEP 2001 criteria) was 55%, but if they had used the NCEP 2005 criteria, as was used in study 2, the prevalence would have been higher, i.e., 69% (Orchard et al. 2005).

6.3 Effects of lifestyle intervention on MetS and its components

Among all DPS participants, a significant difference was found in the prevalence of overall MetS, abdominal obesity, and elevated fasting glucose between the two groups after the first year of intensive intervention. In addition, the proportion of those with elevated blood pressure, elevated triglycerides, and low HDL-cholesterol decreased in the intervention group. During the subsequent years, there were some relapses, as expected. However, at the end of the study, a significant difference between the groups still existed in the prevalence of MetS and abdominal obesity. The proportion of those with elevated fasting glucose increased slightly from baseline in both of the groups.

Among the 386 participants with MetS at baseline, a significant difference in the resolution of MetS between the groups was found. The participants in the intervention group were over two times more likely to recover from MetS than those in the control group. Aside from belonging to the intervention group, the resolution of MetS was associated with weight loss and the success score.

Subjects in the intervention group compared to subjects in the control group had a significant improvement in all of the insulin resistance markers, i.e., waist circumference, fasting and 2-hour plasma glucose and insulin concentrations, HOMA-IR index, systolic and diastolic blood pressure, HDL-cholesterol and triglycerides, after the first year. By the end of the study a significant difference still existed in waist circumference, fasting and 2-hour insulin, HOMA-IR index, and HDL-cholesterol.

The intervention resulted in a significant decrease in plasma glucose values after the first year. However, during the subsequent years of the maintenance phase, these results deteriorated and glucose values increased in both of the groups, although the intervention group showed a tendency for lower 2-hour glucose values. The increase in glucose values is not surprising because all of the individuals in this analysis had both MetS and IGT, and the mean fasting glucose among them was 6.3 mmol/l at baseline. This emphasizes the importance to find and treat people with MetS earlier, before IGT has developed.

Among the 136 participants in DPS without MetS at baseline, there was no difference in the development of MetS between the groups. Around 30% in both of the groups developed MetS by the end of the study. In the DPP study a similar trend was reported (Orchard et al. 2005), i.e., 27% in the lifestyle intervention group developed

MetS (by NCEP 2005 criteria) within three years, but for the control group the incidence rate was even higher, 40%. The differences compared to our results may partly be due to the population studied. The DPS participants were individuals with high risk of type 2 diabetes. During the 4.1-year follow-up, 22% developed type 2 diabetes (Laaksonen et al. 2005). While the development of MetS was associated with weight gain and less LTPA, those individuals who developed MetS appeared not to adhere with the intervention.

6.4 Dietary factors and MetS

The dietary counseling used in DPS is effective in the prevention of type 2 diabetes (Tuomilehto et al. 2001). The results of DPS also show that a high-fiber, low-fat diet predicted long-term weight loss and decreased the risk of type 2 diabetes, independent of changes in body weight and physical activity (Lindström et al. 2006).

Excessive caloric intake is a major factor behind obesity, MetS, and type 2 diabetes, but the quality of diet also has independent effects (Hu et al. 2001; Hu 2011). The optimal fat, protein, and carbohydrate composition for weight loss and treatment of MetS in individuals with different genetic, metabolic, and lifestyle background have been discussed. Long-term studies, where the effects of macronutrients could be isolated, are difficult and maybe even impossible to perform. The interpretation of dietary studies is also difficult, because there are various definitions, assessment and counseling methods, and formats in which the results are presented. Most of the dietary studies are cross-sectional or prospective cohort studies exploring predictive or explanatory dietary factors for weight loss or change in CVD risk factors. Dietary trials are usually of short duration and have a high drop out rate – adherence to new dietary restrictions that change daily lifestyle patterns are difficult to maintain over longer periods.

It seems obvious that change from traditional dietary patterns to a Western style dietary pattern has led to an increase in obesity and type 2 diabetes incidence in many countries. There are no long-lasting dietary trials that study the prevention or treatment of MetS. DPS was not designed or powered to study different dietary factors in detail or in subgroups, like those with MetS. The experience from diabetes prevention trials supports the recommendations to achieve long-term weight reduction by reducing

energy density, total fat, saturated fat, and glycemic load, and by increasing fiber-rich carbohydrate intake. The present analysis regarding MetS resolution and decrease in insulin resistance markers points to the same direction of healthy diet.

6.5 Weight change and MetS

Abdominal obesity and insulin resistance are the main elements of MetS (Eckel et al. 2005; Alberti et al. 2006), and lifestyle changes aiming at weight loss are therefore the primary treatment for people with MetS. The mean BMI of those with MetS at baseline in DPS was 32 kg/m^2. Weight loss was the most important predictor for MetS resolution; those with at least 5% weight loss recovered nearly five times more often from MetS compared to those with weight gain. One percent weight loss corresponded to 10% higher odds for MetS resolution.

After the first year of intensive dietary intervention, almost half of the participants with MetS in the intervention group lost over 5% of their weight. However, weight maintenance after the initial weight loss period is a challenge in most studies, as in real life. Nevertheless, among those DPS participants with MetS at baseline, about 35% of those in the intervention group still had $\geq$ 5% weight loss at the end of the study.

The analysis with both groups pooled together showed that long-term weight loss $\geq$ 5% resulted in the resolution of MetS in ~40% of the participants with MetS at baseline. In turn, weight gain resulted in the development of MetS in ~50% of the participants without MetS at baseline. Body weight alone may not be the only critical issue, but it may work as a summary indicator of several dietary and activity factors (Tuomilehto et al. 2011). However, this study shows the importance and priority of long-term concordance in obesity treatment.

6.6 LTPA and MetS

Strong and mostly linear dose-response associations between the change in **total LTPA** and the development and resolution of MetS were found when the groups were combined for analysis. When breaking down physical activity into **low-**intensity and **moderate-to-vigorous** intensity LTPA, it seemed obvious that most of the benefit

comes from moderate-to-vigorous intensity LTPA. Increased moderate-to-vigorous intensity exercise increased the likelihood for MetS to resolve, and decreased the likelihood for MetS to develop, independent of changes in dietary intakes and BMI. Moreover, increased moderate-to-vigorous intensity LTPA decreased the prevalence of elevated fasting plasma glucose. Improvements in fasting plasma glucose, serum triglycerides, and HDL-cholesterol components of MetS associated with participation in structured resistance training, independent of changes in diet and other types of LTPA.

The dose-response association of moderate-to-vigorous intensity LTPA change with MetS status change was not as straightforward as it was for total LTPA. It may partly be related to the difficulty of precise assessment of LTPA frequency and intensity by recalling 12-month exercise habits. To reduce measurement variability and better reflect the actual levels of LTPA throughout the study, the questionnaires were administered yearly and the average of LTPA levels during follow-up was used.

The results of the favorable effects of moderate-to-vigorous intensity LTPA on resolution and development of MetS are consistent with the results of the uncontrolled Heritage Family Study (Boule et al. 2005). In addition, prospective cohort studies show that increased moderate-to-vigorous intensity LTPA is associated with a lower incidence of MetS during follow-up (Laaksonen et al. 2002b; Ekelund et al. 2005; Lakka and Laaksonen 2007). While most studies have focused on the incidence of MetS, Hassinen et al. (2010) also studied the resolution of MetS in a population-based cohort of elderly men and women. They found that higher cardiorespiratory fitness at baseline, measured by maximum VO_2 uptake, protected against MetS and was associated with higher resolution rate.

In the DPS cohort, increased moderate-to-vigorous intensity LTPA seemed to protect against development of MetS in both men and women. Higher cardio-respiratory fitness, which partly reflects higher levels of moderate-to-vigorous intensity LTPA, has been shown to predict a lower prevalence of MetS independent of major confounding factors in the Aerobics Center Longitudinal Study (LaMonte et al. 2005) and in the Dose-Response to Exercise Training Study (Hassinen et al. 2008). Of the components of MetS, increased moderate-to-vigorous intensity LTPA had the greatest effect on elevated fasting glucose in DPS, whereas the benefits regarding abdominal obesity, low HDL-cholesterol, and elevated blood pressure were not so clear and statistically insignificant.

Changes in low intensity LTPA did not associate with changes in MetS status. This finding is consistent with the results of the KIHD study, in which moderate-to-vigorous intensity, but not low-intensity LTPA was associated with the development of MetS (Laaksonen et al. 2002b). Changes in low-intensity LTPA in DPS had beneficial effects on elevated triglycerides, and changes in total LTPA improved elevated fasting glucose and dyslipidemia.

Increased LTPA, especially with moderate-to-vigorous intensity, and walking for exercise has been shown to decrease the risk of type 2 diabetes through a mechanism beyond weight loss alone (Laaksonen et al. 2005). In that detailed analysis, men and women whose average levels of moderate-to-vigorous intensity LTPA adhered to the current LTPA recommendations ($\geq$ 2.5 h/week) were 44% less likely to develop type 2 diabetes than those remaining less active (< 1 h/week) (Laaksonen et al. 2005). However, although low-intensity LTPA has not improved metabolic outcomes as consistently as more intense LTPA (Laaksonen 2007), the association of low intensity LTPA with lower risk of type 2 diabetes in DPS has been reported (Laaksonen et al., 2005). This suggests that total energy expenditure during LTPA may be more important than the intensity. The findings from the RISC study point in the same direction, showing that the accumulated daily physical activity, as measured objectively with an accelometer, was a major determinant of insulin sensitivity, whereas the time spent on moderate-to-vigorous physical activity did not affect insulin sensitivity independently of total activity (Balkau et al. 2008).

Differences in the study populations, in the methods for the assessment of physical activity, and in the measured metabolic outcomes may partly explain the differences between the various studies.

Regular participation in resistance training predicted favorable changes in MetS components by the end of the study. In shorter trials, resistance training has variably increased muscle mass, decreased fat mass and abdominal obesity, and improved insulin sensitivity (Miller et al. 1994; Cuff et al. 2003; Lakka and Laaksonen 2007; Sigal et al. 2007). Improvements in insulin sensitivity and metabolic risk factors may be mediated in part by changes in body composition, as well as steps in insulin signaling and glucose transport (Holten et al. 2004).

Only a few trials with long-term follow-up exist. The short-term, one-year results and long-term results with a mean of 4-year follow-up time in present study showed the

benefits of both overall moderate-to-vigorous intensity LTPA and resistance training in the prevention and treatment of MetS.

Physical activity behavior has changed over the past 30 years in Finland. The proportion of individuals who exercise during leisure time has increased, whereas physical activity at work or during commuting has decreased (Barengo et al. 2002; Helakorpi et al. 2008). Currently, about 30% of adult Finns report that their leisure time requires only little physical effort. On the other hand, in 2010 53% of men and 55% of women reported engaging in a minimum of 30 minutes of leisure-time physical activities at least three times a week (Helakorpi et al. 2011).

While most previous studies have investigated the effects of more strenuous exercise aimed primarily at improving physical fitness, more research is needed to study the effects of lighter daily physical activities and the avoidance of sedentary lifestyles on various health outcomes. The results of the present study support the efforts to increase or at least maintain LTPA, especially moderate-to-vigorous intensity LTPA, in the prevention and treatment of MetS.

6.7 Lifestyle intervention and prevention of type 2 diabetes in long-term

Controlled lifestyle intervention trials have shown the benefit of healthy lifestyle on delaying the deterioration of glucose tolerance to manifest type 2 diabetes (Tuomilehto et al. 2001; Knowler et al. 2002; Kosaka et al. 2005; Ramachandran et al. 2006). The follow-up of the DPS participants up to a median of 7 years showed that a marked difference in the cumulative incidence of type 2 diabetes could be sustained after the discontinuation of active counseling. The relative risk reduction of 43% was, however, less than the 58% seen during the intervention phase (Tuomilehto et al. 2001), but the cumulative incidence of type 2 diabetes was 23% in the intervention group and 38% in the control group within six years. The multivariate analyses of achieved intervention goals suggest that the effect of dietary composition and physical activity on type 2 diabetes risk is in large part, although not entirely, mediated through weight reduction achieved with lifestyle changes.

The Diabetes Prevention Program Outcomes study showed similar results with the present study; after 10 years of overall follow-up, the diabetes incidence was reduced

by 34% in the lifestyle treatment group compared with the control group (The Diabetes Prevention Program Research Group 2009). Furthermore, the relative risk reduction achieved in the present study was about the same as that reported by Pan et al. (1997) from the Da Qing IGT and Diabetes Study with 6 years of active intervention. Li et al. (2008) showed in the follow-up study that group-based lifestyle intervention used in the Da Qing study could prevent or delay type 2 diabetes up to 14 years after the active intervention. The long-term follow-up of drug trials shows the contrary. The lowering effect on diabetes incidence disappears after the discontinuation of medication. Furthermore, drugs may have unpleasant side-effects that, together with expenses, diminish the interest to use them for preventive purposes.

The participants of the Da Qing Diabetes Prevention study were leaner with a mean BMI of about 26 kg/m^2, and the changes in bodyweight during the active intervention and the follow-up period did not differ significantly by group. This suggests that other issues than weight alone are important, and weight change may work as a summary indicator of several dietary and activity factors (Tuomilehto et al. 2011).

An important question is how to motivate and empower people with MetS to adhere to long-term lifestyle changes and weight control. The GOAL Lifestyle Implementation Trial was designed to replicate the results from type 2 prevention trials in a more "real world" setting and with a more modest program delivered by existing health care personnel (Absetz et al. 2007). Absetz et al. (2007) reported that the participants of the GOAL study were as likely as the DPS participants to adopt a number of lifestyle changes. Group-based lifestyle counseling was a feasible method for prevention of type 2 diabetes in real life settings. Furthermore, in a follow-up they showed a maintenance of risk reduction for three years (Absetz et al. 2009). The FIN-D2D was a program for the implementation of the prevention of type 2 diabetes in a primary health care setting nationwide. FIN-D2D recruited high-risk subjects based on diabetes risk score (Lindström and Tuomilehto 2003). Moderate weight loss was effective in reducing diabetes risk (Saaristo et al. 2011). Surprisingly, a facilitated theory-based behavioral intervention was no more effective than an advice leaflet for promotion of physical activity in 365 subjects at high risk of type 2 diabetes during 1 year follow-up in a study by Kinmonth et al. (2008). These results point to the importance of individually-tailored and patient-centered solutions in exercise and lifestyle counseling.

From a public health perspective, the results of the present study have an important message: intensive lifestyle counseling that lasts for a limited time can yield long-term

benefits with a rather small maintenance effort. Furthermore, the analysis of the success score showed that most individuals who maintained the lifestyle goals for three years remained free of diabetes during the follow-up. This finding indicates that the true effects of healthy lifestyles result in a substantially better outcomes than those seen by intention-to-treat analysis. The results also highlight the benefit to offer obese, high risk individuals a comprehensive lifestyle counseling program with long-term re-enforcement and follow-up.

6.8 Limitations of the studies

6.8.1 Participants and generalization of the results

The FINRISK participants examined in study 1 represented ~60% of the original population-based study cohort. The prevalence of obesity, hypertension, and dyslipidemia were similar among men who did and did not attend the study, which strengthens reliability of the results. On the other hand, all the components of MetS were more prevalent in the female non-attendees of the glucose tolerance study, which could have caused underestimation of the prevalence of MetS in women.

The DPS participants were volunteers and willing to take part in a long-lasting trial that demanded individual activity from them. They were thus probably more health-conscious than the general population. A low number of withdrawals was a marker of high commitment. There were also no differences between the groups in number of withdrawals, which benefits the analyses.

All the DPS participants had IGT by the WHO 1985 criteria. In fact, 93 participants had fasting plasma glucose in the diabetes range by the WHO 1998 criteria. Over 70% had MetS at baseline. The DPS participants were thus at very high risk for diabetes and did not represent an average overweight individual. However, there is no reason to assume that same kind of intervention would not be efficient in subjects with a lower risk.

6.8.2 Dietary analyses

The nutrition intakes were estimated by collecting 3-day food records annually, which is a validated method in analyzing dietary intakes of groups. The average intake during the intervention period was used to reduce intra-individual variability. The energy intake calculated from the food records revealed some under-reporting. Nonetheless, the bias is small while the energy proportions of nutrients and not-absolute amounts were calculated, and the results were adjusted for the baseline intakes.

6.8.3 Physical activity assessment

The frequency, duration and intensity of LTPA during the preceding 12 months were estimated before each annual visit with questionnaires. The intensity was based on self-assessment and the recall of activities may have been incomplete. However, that should not influence the differences between the groups because the same assessment was used for all participants.

6.8.4 Study design

The analyses related to CVD risk factors other than elevated plasma glucose were secondary outcomes in the original DPS protocol. However, the prevention or treatment of MetS (Study 2 and 3) and the post-intervention follow-up (Study 4) were not foreseen when calculating the original sample size, and post hoc analyses have to be interpreted with caution.

All of the analyses were carried out by the intention-to-treat principle. The drop-out rates were low in both groups, but the number of those who developed diabetes differed significantly between the groups, and more participants stayed in the intervention group. We used the last observation carried forward as the end value for those who developed diabetes and for dropouts.

7. SUMMARY AND CONCLUSIONS

Former studies have shown that individuals with MetS have an approximately fivefold risk of developing type 2 diabetes and a twofold risk of CVD. Aside from coronary heart disease, cerebrovascular disease, and peripheral vascular disease, elevated blood glucose and blood pressure predispose to microvascular complications such as renal or retinal disease. MetS has also been associated with non-alcoholic fatty liver disease and obstructive sleep apnea. Discussions about the clinical significance of MetS compared to other tools to identify individuals at elevated risk of type 2 diabetes and CVD have emerged. However, MetS offers a simple public health concept and an easily identifiable starting point for clinical interventions. Recent interest has focused on the relationship between insulin resistance, low-grade inflammation and hormonal dysfunction of the adipose tissue.

Study 1

Obesity and MetS were already common in 1992 in middle-aged subjects in Finland, especially in men. The prevalence of MetS increased with age and worsening glucose metabolism. About every fourth man and woman had a BMI over 30 kg/m^2 and nearly 80% of the men had abdominal obesity. Around 30% of the individuals aged 45 to 64 years and ~75% of those with IGT had MetS in the population-based FINRISK 1992 cohort.

Study 2

Among all the DPS participants, the intensive and individual lifestyle counseling reduced the occurrence of overall MetS, abdominal obesity and elevated fasting glucose after the first year of intervention. Abdominal obesity and the prevalence of MetS were also reduced in the long term in the intervention group compared to the control group, with a median follow-up of 4 years.

Among the DPS participants with MetS at baseline, the intervention resulted in significant improvement in all MetS components at the first annual visit. By the end of

the study, even though glucose values tended to increase, the insulin resistance markers, i.e., fasting and 2-hour insulin concentrations, HOMA-IR index, and HDL-cholesterol were significantly improved in the intervention group compared to the control group. The participants in the intervention group showed a resolution of MetS over two times more often.

Nearly 50% of the individuals with MetS in the intervention group succeeded to lose ≥ 5% of their weight by the first annual follow-up visit. The long-term results were encouraging – over 30% still had a weight loss ≥ 5% at the end of the study. Weight loss was the most powerful predictor of MetS resolution, as was weight gain for MetS development. Long-term weight loss was associated with a decrease in all of the CVD risk factors measured.

These results suggest that, aside from type 2 diabetes prevention, lifestyle interventions with a comprehensive approach to correct several risk factors may also reduce the risk of CVDs in a long run.

Study 3

Increased participation in moderate-to-vigorous intensity LTPA and regular long-term participation in resistance training improved MetS status, i.e., increased the likelihood of MetS resolution and decreased the likelihood of MetS development in DPS participants. Physical activity, and especially resistance training, had benefits with respect to elevated plasma glucose and dyslipidemia, but improvements in abdominal obesity and blood pressure were not clearly seen. Prevention and resolution of MetS and related features might contribute to the protective effect of physical activity with regard to CVD risk factors.

Study 4

The participants in the DPS intervention group achieved more of the predefined intervention goals than those in the control group. Mean weight, total fat intake, and saturated fat intake were lower, while intake of carbohydrates, dietary fiber and physical activity was higher in the intervention group compared to the control group. A large part of the effects of lifestyle changes on type 2 diabetes risk was mediated through weight reduction. After the active intervention, the DPS participants were followed up to three years without specific intervention. The median intervention and follow-up time together was 7 years and total diabetes incidence rate was reduced by

43% in the intervention group compared to control group. The effect of lifestyle intervention on type 2 diabetes risk did not disappear after ending the active lifestyle counseling.

Future directions

Trends in population-based studies in Finland and the U.S. show some positive signs that the constant increase in obesity rate is slowing down. However, the increase in the number of people with MetS and type 2 diabetes will progress while urbanization continues with more sedentary lifestyles, "obesogenic" environments, and the constant availability of energy-rich foods. People also live longer and the number of senior citizens is set to increase, while childhood mortality declines at the same time. More community-based preventive actions are clearly needed.

The most significant modifiable risk factors for MetS and type 2 diabetes are overweight, abdominal obesity, physical inactivity, and dietary factors. Lifestyle changes are the first choice of therapy both in primary and secondary prevention of MetS. The potential to prevent type 2 diabetes in high-risk individuals, like those having MetS, through lifestyle intervention has been established in several clinical trials, and the long-term follow-up in present study shows that the effect is maintained up to three years after discontinuation of active intervention.

In addition to high-risk approaches, population-based strategies and community awareness are needed. Programs approaching families and children are important. Everyday living environments that have low barriers for commuting and leisure time physical activities are of benefit. While socioeconomic differences show associations with chronic diseases and the use of healthcare services, more information about optimal and attainable implementation programs is needed.

ACKNOWLEDGEMENTS

This series of studies was based on the data collected during years 1993−2004 in the Diabetes Prevention Study and its post-intervention follow-up conducted at the National Institute for Health and Welfare (THL; former National Public Health Institute) in Helsinki.

I express my deepest gratitude to my principal supervisor, Professor Johan Eriksson from University of Helsinki, for his guidance and encouragement. He was the one who asked me to join the DPS research team at the very beginning and start to run the DPS center in Tampere.

I am grateful to my other supervisor, Docent Jorma Lahtela from Tampere University Hospital, for his guidance and help during these years.

I owe my sincere thanks to the DPS principal investigators, Professor Matti Uusitupa from University of Eastern Finland and Professor Jaakko Tuomilehto from University of Helsinki, for their trust and constructive criticism during my writing process. Without their vision and enthusiasm DPS would not have come true.

I greatly thank Jaana Lindström, PhD and Markku Peltonen, PhD from the National Institute for Health and Welfare and David Laaksonen, MD, PhD, MPH, from University of Eastern Finland for their close collaboration and considerable help in carrying out the studies, analyzing the data, and preparing the manuscripts. They all guided me with kind advice and instructive cooperation.

I appreciate the work of the official reviewers of this thesis, Docent Liisa Hiltunen from University of Oulu and Docent Hannu Järveläinen from University of Turku, for their constructive criticism and suggestions, which helped me to improve this work.

I thank Professor Jukka Mustonen from the School of Medicine of the University of Tampere and Docent Heikki Oksa from Tampere University Hospital for being in my monitoring team and providing this opportunity to me.

I express my warmest thanks to the whole DPS research team and my other co-authors Sirkka Aunola, Helena Hämäläinen, Sirkka Keinänen-Kiukaanniemi, Anne Antikainen, Katri Hemiö, Pirjo Härkönen, Mauri Laakso, Timo Lakka, Marjo Mannelin, Merja Paturi, Jouko Sundvall, and Timo Valle for their contribution to the execution of the studies and revising the manuscripts.

Cordial thanks to the Tampere DPS team, Arja Putila, Hilkka Kaisto, Virpi Salminen, Marjukka Lauhkonen, and Pirjo Lehto. I owe my special thanks to Arja, who, with her kind personality, nursing, and organizing skills, has been of most importance. It has been a pleasure to work with you.

I am indebted to the whole personnel of the other DPS study centers in Helsinki, Kuopio, Oulu, and Turku. Without your enthusiastic work and counseling skills our intervention and the

results of the DPS study would not have been possible. Warm thanks are addressed to all of you.

I owe my sincere thanks to the all individuals who participated in the DPS study and took part year after year in the clinical visits and carefully fulfilled enormous amounts of questionnaires. I have learned a lot from you, too.

I am grateful to Sanna Parikka and Tommy Griscom for the careful revision of the language of this thesis. Thank you to Terttu Puskala from the THL library for helping me find the literature.

I thank my former boss Seppo A. Salo and my current boss Jorma Huttunen from the Finnish Diabetes Association for their support and my colleague Vuokko Kallioniemi, who trustingly replaced me during my research vacations. All my coworkers at the Diabetes Center should be recognized for their enthusiastic and innovative work with people with diabetes. Marja Puomio, Maija Ojala, Kati Hannukainen, and Outi Himanen have been my closest workmates during these years and taken on a great portion of the responsibilities within the work community. Thanks to Tarja Sampo for helping me with numerous written works.

Special thanks to Tero Kangas, Paula Kemppainen, Tapani Rönnemaa, Timo Sane and Sirkku Tulokas who have been my mentors in diabetology. Thank you to Kirsi Haikarainen from Duodecim, who has been my co-editor in the Diabetes book and from whom I have learned a number of things about writing.

I am deeply thankful to my husband Arto Parikka for his support and patience and to my children Sanna, Valtteri and Petteri Parikka, who have grown up to fine young persons during these years.

I owe my thanks to all my friends, who, despite my delving into research work and writing, have been there for me. My dearest friend Heljä has been of great support and a patient listener. The siblings of my husband and their lovely families, especially Miko and Mesi as well as Pinja, Petra and Katri have given me great times. Anita, Eija, Habiba, Katja and Leena, together with my coach Jarmo, have been taking care of my physical fitness and given me good competition at the tennis court.

The DPS study was supported by the Academy of Finland, the Juho Vainio Foundation, the Ministry of Education, the Novo Nordisk Foundation, the Yrjö Jahnsson Foundation, the Finnish Diabetes Research Foundation, the Finnish Foundation for Cardiovascular Research, and EVO funds from Tampere, Kuopio and Oulu University Hospitals.

Tampere, November 2011

Pirjo Ilanne-Parikka

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ORIGINAL COMMUNICATIONS

Prevalence of the Metabolic Syndrome and Its Components

Findings from a Finnish general population sample and the Diabetes Prevention Study cohort

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OBJECTIVE — To assess the prevalence of the metabolic syndrome (MetS) in two independent Finnish study cohorts.

RESEARCH DESIGN AND METHODS — The prevalence of the MetS by modified World Health Organization criteria was analyzed in different categories of glucose tolerance in a cross-sectional, population-based sample of 2,049 individuals (FINRISK) aged 45–64 years and in 522 participants of the Finnish Diabetes Prevention Study (DPS) with impaired glucose tolerance (IGT).

RESULTS — In the FINRISK cohort, the MetS was present in 38.8% of the men and 22.2% of the women. The prevalence was 14.4 and 10.1% in subjects with normal glucose tolerance, 74.0 and 52.2% in subjects with impaired fasting glucose, 84.8 and 65.4% in subjects with IGT, and 91.5 and 82.7% in subjects with type 2 diabetes in men and women, respectively. Among women, the prevalence of the MetS increased with increasing age. In the DPS cohort, the MetS was present in 78.4% of the men and 72.2% of the women with IGT.

CONCLUSIONS — The MetS was extremely common in middle-aged subjects The high prevalence in men was mostly due to their high waist-to-hip ratio. The prevalence of the MetS increased in both sexes with deterioration in glucose regulation. Approximately 75% of the subjects with IGT had the MetS. Because the syndrome includes the major risk factors for atherosclerotic vascular diseases and is the major antecedent for type 2 diabetes, concerted preventive action should be targeted to control all the features of the MetS.

Diabetes Care 27:2135–2140, 2004

The prevalence of type 2 diabetes is rapidly increasing worldwide (1,2), primarily due to the global increase in obesity and sedentary lifestyles (3). Subjects with impaired glucose tolerance (IGT) are at increased risk of developing type 2 diabetes and form an important high-risk group for actions aimed at preventing the disease (4–7).

Subjects with abnormal glucose metabolism are at increased risk for cardiovascular disorders and often exhibit various cardiovascular risk factors (8). The clustering of cardiovascular risk factors has been called the metabolic syndrome (MetS). Currently there are four definitions: the criteria of the World Health Organization (WHO) consultation group (9), the criteria of the European Group for the Study of Insulin Resistance (EGIR) (10), the criteria of the National Cholesterol Education Program (NCEP) Expert Panel (11), and the criteria of the American Association of Clinical Endocrinologists (12).

Type 2 diabetes and IGT are closely associated with the MetS (13). Clustering of the risk factors associated with this syndrome predicts the development of manifest diabetes and cardiovascular disease (14–20) Prevention of type 2 diabetes should therefore aim to prevent and treat several components of the MetS simultaneously.

The aim of this study was to assess the prevalence and clustering of components of the MetS using the WHO criteria in two independent middle-aged Finnish study cohorts: the population-based FINRISK study cohort and the participants of the Finnish Diabetes Prevention Study (DPS).

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Received for publication 20 November 2003 and accepted in revised form 16 June 2004.

Abbreviations: DPS, Diabetes Prevention Study; EGIR, European Group for the Study of Insulin Resistance; FPG, fasting plasma glucose concentration; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MetS, metabolic syndrome; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization; WHR, waist-to-hip-ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— The FINRISK survey took place in spring 1992 as part of the FINMONICA cardiovascular risk factor survey. The survey methods followed the WHO MONICA protocol (21) and are detailed elsewhere (22,23). In brief, a cross-sectional stratified random sample of 8,000 subjects aged 25–64 years from four regions of Finland was drawn from the national population register. A subsample of 3,300 individuals aged 45–64 years was formed to assess glucose metabolism; 3,201 of these subjects completed a postal questionnaire on medical history and made their first study visit. Clinical and metabolic characteristics related to blood pressure and dyslipidemia were analyzed in the present study. A total of 2,087 attended a second visit for a standard 75-g oral glucose tolerance test (OGTT) (24). Glucose status could be classified in 2,061 subjects, based on current use of diabetes medication ($n = 71$), fasting plasma glucose (FPG) value ($n = 88$), or OGTT value ($n = 1902$). After excluding type 1 diabetic patients ($n = 12$) from the assessment, 2,049 subjects were included in the further analysis of glucose tolerance and components of the MetS, representing 62% of the original 3,300 subjects.

The DPS was a randomized prospective controlled trial to assess the possibility of preventing type 2 diabetes by lifestyle intervention (25,26). The design of the DPS is described in detail elsewhere (27). Briefly, 522 overweight subjects (BMI ≥25 kg/m^2) aged 40–65 years and with IGT participated. The definition of IGT was based on the mean of two consecutive 2-h glucose values in OGTT (24). The Ethics Committee of Finland's National Public Health Institute approved the study protocol. All subjects gave written informed consent.

Both studies involved similar investigations, including a self-administered questionnaire, medical history, physical examination, and laboratory examinations. Those taking medication during the past week were recorded as being on medication. Blood pressure was measured from the right arm of the subject seated for 5 min before measurement. Systolic and diastolic blood pressure values were recorded as the mean of two measurements.

In FINNRISK, fasting and 2-h blood samples for plasma glucose were measured at the local laboratory by a hexokinase method. In the DPS, the plasma glucose concentrations during the OGTT were determined locally and confirmed at a central laboratory in Helsinki. All other blood samples in both studies were analyzed in the same central laboratory (National Public Health Institute, Helsinki). Cholesterol and triglyceride levels were determined by enzymatic assays (Boehringer Mannheim, Mannheim, Germany). HDL cholesterol was measured after dextran sulfate magnesium chloride precipitation of apo B–containing lipoproteins. Serum insulin was measured by a radioimmunoassay method (Pharmacia, Uppsala, Sweden). The intra-assay coefficient of variation (CV) for serum insulin was 5.3%, and the interassay CV was 7.6%.

Definitions of the MetS and its components

For the definition of the MetS, we used the WHO criteria (9) modified as follows: insulin resistance was defined by the top quartile distribution of fasting insulin among subjects without diabetes (10). Top quartile cutoff points were 9.42 and 9.80 mU/l for men and 8.20 and 9.75 mU/l for women in age-groups of 45–54 and 55–64 years, respectively. Different categories of glucose tolerance were calculated applying the WHO 1999 criteria (9) in venous plasma samples as follows: normal glucose tolerance (NGT): FPG <6.1 mmol/l and 2-h plasma glucose <7.8 mmol/l; impaired fasting glycemia (IFG): FPG 6.1–6.9 mmol/l and 2-h plasma glucose <7.8 mmol/l; impaired glucose tolerance (IGT): FPG <7.0 mmol/l and 2-h plasma glucose 7.8–11.0 mmol/l; diabetes: FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l, or current use of diabetes medication. Subjects were considered to have obesity if waist-to-hip-ratio (WHR) was >0.90 in men and >0.85 in women and/or BMI was >30 kg/m^2. Subjects were considered to have hypertension if blood pressure was ≥140/90 mmHg or if they were taking antihypertensive medication. Subjects were considered to have dyslipidemia if plasma triglyceride was ≥1.7 mmol/l and/or HDL cholesterol was <0.9 mmol/l for men and <1.0 mmol/l for women, or if they were using lipid-lowering medication.

A subject was considered to have the MetS if they had either NGT with insulin resistance, IFG, IGT, or diabetes and two or more of the following features: obesity, hypertension, or dyslipidemia.

Statistical analysis

The data were analyzed using statistical software (SPSS version 11.5; SPSS, Chicago, IL). Continuous numerical variables are presented as means ± SD unless otherwise indicated. The analysis included independent samples two-tailed *t* test for equality of means between sexes for variables distributed normally. Fasting serum insulin, 2-h serum insulin, and triglycerides were skewed, and the Mann-Whitney *U* test was used for them. The χ^2 test was used to analyze the dependency of categorical variables.

RESULTS

— The clinical and metabolic characteristics of the 3,201 subjects are presented in Table 1. The men had higher waist circumference, WHR, diastolic blood pressure, LDL cholesterol, and triglycerides but lower HDL cholesterol than the women. There was no marked sex difference in the proportion of those having BMI >30 kg/m^2. However, in terms of abdominal obesity, 78.1% of the men had WHR >0.9, whereas only 23.6% of the women had WHR >0.85. The prevalences of hypertension and dyslipidemia were significantly higher in men.

Drop outs

The men who failed to attend ($n = 602$, 39.1%) the second visit for the glucose tolerance assessment were slightly younger (53.5 vs. 54.7 years) and slimmer. Nevertheless, the prevalences of obesity (77.5 vs. 80.0%; $P = 0.252$), hypertension (65.1 vs. 66.6%; $P = 0.560$), and dyslipidemia (50.2 vs. 48.0%; $P = 0.40$) were similar in nonattenders and attenders. In contrast, the female nonattenders ($n = 550$, 33.1%) had significantly higher systolic blood pressure (145.8 vs. 140.7 mmHg; $P < 0.001$), higher prevalences of obesity (39.0 vs. 33.4%; $P = 0.026$), hypertension (63.8 vs. 55.2%; $P = 0.001$), and dyslipidemia (30.9 vs. 25.1%; $P = 0.013$).

Prevalence of insulin resistance and disturbances in glucose metabolism

Insulin resistance in subjects with NGT was present in 10.8% of the men and 15.1% of the woman. The prevalence of disturbances in glucose metabolism by sex and age-group is presented in Table 2.

Table 1—*Clinical and metabolic characteristics of the FINRISK cohort (n = 3,201) by sex*

	Men	Women	*P*
n	1,538	1,663	—
Age (years)	54.2 ± 5.9	54.5 ± 6.1	0.257
BMI (kg/m^2)	27.6 ± 3.8	27.4 ± 4.9	0.123
Waist circumference (cm)	97.8 ± 10.8	84.2 ± 11.9	<0.001
WHR	0.95 ± 0.07	0.81 ± 0.07	<0.001
Systolic blood pressure (mmHg)	144 ± 19	142 ± 21	0.098
Diastolic blood pressure (mmHg)	88 ± 11	84 ± 11	<0.001
Total cholesterol (mmol/l)	6.02 ± 1.04	5.98 ± 1.10	0.251
HDL cholesterol (mmol/l)	1.25 ± 0.33	1.51 ± 0.35	<0.001
LDL cholesterol (mmol/l)	3.94 ± 0.93	3.82 ± 0.98	0.001
Triclycerides (mmol/l)	1.96 ± 1.30	1.45 ± 0.92	<0.001
BMI (kg/m^2)			
<25.0	25.2	35.4	<0.001
25.0–29.9	49.8	38.3	<0.001
≥30	25.0	26.3	0.445
WHR >0.9 in men and >0.85 in women	78.1	23.6	<0.001
Hypertension	66.0	58.1	<0.001
Dyslipidemia	48.8	27.0	<0.001

Data are means ± SD or percent. Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of oral antihypertensive medication. Dyslipidemia: triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 in men or <1.0 mmol/l in women or use of lipid-lowering medication.

Abnormal glucose metabolism was found in 34.9% of the men and 21.3% of the women. The men had significantly higher prevalences of IFG and diabetes than the women. Diabetes was found in 10.1 and 6.8% of the men and women, respectively, whereas according to the questionnaires only 37.2% of the subjects with diabetic blood glucose values were aware of the condition.

Prevalence of the MetS and its features

In the FINRISK glucose tolerance study cohort, the overall prevalence of the MetS was significantly higher among men: 38.8% of the men and 22.2% of the women fulfilled the modified WHO criteria for the MetS. The prevalence of the various components was also significantly higher in men: obesity was observed in 79.8 and 33.2%, hypertension in 66.1 and 54.9%, and dyslipidemia in 52.4 and 29.0% of the men and women, respectively. The higher prevalence of obesity among men was due to abdominal obesity: 79.1 vs. 21.8% ($P < 0.001$) of the men and women had high WHR, while 26.5 vs. 24.5% ($P = 0.355$) had BMI >30 kg/m^2. If obesity had been defined only by BMI >30 kg/m^2, the prevalence of the MetS would have been 28.9% in men and 20.6% in women ($P < 0.001$).

The prevalence of the MetS and its components was separately assessed in the 45- to 54-year and 55- to 64-year age-groups, and the results are presented in Table 2. Age had no significant effect on the already high prevalence of the MetS and obesity among men, unlike among women. Elevated systolic blood pressure in both sexes, lower HDL cholesterol in

Table 2—*Prevalence (%) of MetS and its components in the glucose tolerance study subgroup (n = 2,049) of the FINRISK cohort by sex and age-group*

	Men			Women			
	45–54 years	55–64 years	*P*	45–54 years	55–64 years	*P*	*P* between sexes
n	427	509	—	535	578	—	—
MetS	36.2	41.4	0.116	16.5	27.9	<0.001	<0.001
NGT with insulin resistance	12.2	9.5	0.194	15.1	15.0	0.977	<0.004
IFG	14.5	12.4	0.337	5.8	3.6	0.089	<0.001
IGT	8.9	13.8	0.021	6.9	12.6	0.001	0.226
Diabetes	7.5	12.6	0.104	5.2	8.3	0.042	0.005
Obesity	77.6	81.9	0.104	26.9	39.4	<0.001	<0.001
BMI >30 kg/m^2	26.5	26.5	0.984	19.6	29.4	<0.001	0.355
Abdominal obesity	76.9	80.9	0.134	18.3	25.1	0.006	<0.001
Hypertension	60.7	71.5	<0.001	43.2	66.5	<0.001	<0.001
Systolic blood pressure ≥140 mmHg	46.6	62.3	<0.001	34.0	59.5	<0.001	<0.001
Diastolic blood pressure ≥90 mmHg	44.3	42.1	0.459	24.9	26.5	0.539	<0.001
Use of antihypertensive medication	15.0	20.6	0.010	11.0	21.1	<0.001	0.225
Dyslipidemia	51.7	53.0	0.712	21.1	36.8	<0.001	<0.001
Low HDL cholesterol (men <0.9 women <1.0 mmol/l)	9.4	14.0	0.029	4.7	6.4	0.229	<0.001
Triglycerides ≥1.7 (mmol/l)	44.7	45.6	0.799	15.7	29.6	<0.001	<0.001
Use of lipid-lowering medication	3.5	5.0	0.285	0.9	4.0	0.004	0.046

Obesity: BMI >30 kg/m^2 or WHR >0.9 in men and >0.85 in women. Abdominal obesity: WHR >0.9 in men and >0.85 in women. Hypertension: systolic ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. Dyslipidemia: triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 in men and <1.0 mmol/l in women or use of lipid-lowering medication.

Table 3—*Prevalence (%) of MetS and its components by WHO criteria in men and women in the FINRISK subgroup (n = 2,049) by glucose tolerance status*

	NGT (n = 1,482)			IFG (n = 177)			IGT (n = 218)			Diabetes (n = 172)		
	Men	Women	*P*	Men	Women	*P*	Men	Women	*P*	Men	Women	*P*
n	607	875	—	125	52	—	108	110	—	96	76	—
MetS	14.4	10.1	0.019	74.0	52.2	0.007	84.8	65.4	<0.001	91.5	82.7	0.084
Obesity	75.4	25.5	<0.001	80.8	46.2	<0.001	92.6	57.3	<0.001	93.1	81.6	0.013
Hypertension	61.9	49.9	<0.001	72.0	69.2	0.711	75.9	76.4	0.940	78.1	76.4	0.778
Dyslipidemia	44.7	22.0	<0.001	55.3	39.0	0.074	69.0	52.6	0.018	76.9	69.4	0.282

Obesity: BMI >30 kg/m^2 or WHR >0.9 in men and >0.85 in women. Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of oral antihypertensive medication. Dyslipidemia: triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 in men and <1.0 mmol/l in women or use of lipid-lowering medication.

men, and higher triglycerides in women were significantly more common in the 55- to 64-year age-group.

Prevalence of MetS in different categories of glucose tolerance

The MetS was observed in 12.3% of the subjects with NGT, in 63.1% with IFG, in 75.1% with IGT, and in 87.1% with diabetes. The prevalence of the MetS and its components in different categories of glucose metabolism is presented in Table 3. In all categories men had a higher prevalence of obesity and dyslipidemia than women. The MetS clustered most often together with obesity in all categories of glucose tolerance in men. In women it clustered most often with hypertension in NGT, IFG, and IGT categories but with obesity in those with diabetes.

The DPS cohort

The clinical and metabolic characteristics of the 522 DPS subjects with IGT and overweight are presented in Table 4. Mean BMI was significantly higher in women than men, but WHR was significantly higher in men. Men had slightly higher diastolic blood pressure and FPG, but lower HDL cholesterol. Altogether, 78.4% of the men and 72.2% of the women fulfilled the criteria for MetS. Obesity was seen in 96.5 and 66.3%, hypertension in 62.9 and 60.9%, and dyslipidemia in 51.2 and 48.6% of men and women, respectively.

CONCLUSIONS — In the FINRISK cohort of people aged 45–64 years, ~40% of the men and ~20% of women fulfilled the modified WHO criteria for the MetS. Among women the prevalence of the MetS increased with increasing age. The high prevalence among men was closely associated with abdominal obesity. If we had used only BMI >30 kg/m^2 for the criteria of obesity instead of high WHR or high BMI, the prevalence of the MetS would have been lower (~30%) in men but would have stayed in the same range in women. Our study conforms with the range found in other studies on Caucasian people. In general the MetS is observed in 15–30% of middle-aged people in industrialized western countries (8,28–31).

Our FINRISK cohort represented 62% of the original randomized, age- and sex-stratified, population-based FINRISK study cohort. The prevalences of obesity,

Table 4—*Clinical and metabolic characteristics of the DPS subjects by sex*

	Men	Women	*P*
n	172	350	—
Age (years)	55.9 ± 7.1	54.8 ± 7.1	0.124
BMI (kg/m^2)	29.9 ± 3.6	31.9 ± 4.8	<0.001
WHR	0.99 ± 0.05	0.89 ± 0.06	<0.001
Systolic blood pressure (mmHg)	137 ± 17	138 ± 18	0.412
Diastolic blood pressure (mmHg)	87 ± 9	85 ± 10	0.045
FPG (mmol/l)	6.3 ± 0.8	6.1 ± 0.7	0.010
2-h plasma glucose (mmol/l)	8.8 ± 1.6	9.0 ± 1.4	0.146
Fasting serum insulin (mU/l)	15.6 ± 8.5	14.4 ± 7.0	0.315
2-h serum insulin (mU/l)	93.1 ± 60.9	96.3 ± 66.6	0.454
Total cholesterol (mmol/l)	5.5 ± 0.9	5.7 ± 0.9	0.027
LDL cholesterol (mmol/l)	3.6 ± 0,8	3.6 ± 0,8	0.464
HDL cholesterol (mmol/l)	1.10 ± 0.28	1.26 ± 0.28	<0.001
Triclycerides (mmol/l)	1.8 ± 0.9	1.7 ± 0.7	0.419
MetS	78.4	72.2	0.082
Obesity	96.5	86.3	<0.001
BMI >30 kg/m^2	45.3	59.1	0.004
WHR >0.9 in men and >0.85 in women	96.5	75.3	<0.001
Hypertension	62.9	60.9	0.647
Systolic blood pressure ≥140 mmHg	38.2	44.0	0.181
Diastolic blood pressure ≥90 mmHg	39.4	33.1	0.161
Use of antihypertensive medication	29.1	29.2	0.745
Dyslipidemia	51.2	48.6	0.599
HDL cholesterol: <0.9 in men and <1.0 mmol/l in women	22.7	17.8	0.183
Triglycerides ≥1.7 mmol/l	44.8	39.0	0.205
Use of lipid-lowering medication	5.8	5.4	0.857

Obesity: BMI >30 kg/m^2 or WHR >0.9 in men and >0.85 in women. Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of oral antihypertensive medication. Dyslipidemia: triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 in men and <1.0 mmol/l in women or use of lipid-lowering medication.

hypertension, and dyslipidemia were similar in the men who did or did not attend the glucose tolerance study, which strengthens reliability of the results. In contrast, all the components were more prevalent in the female nonattenders of the glucose tolerance study, which could have caused underestimation of the prevalence of the MetS in women.

Impaired glucose regulation was closely associated with the syndrome. The prevalence of the MetS increased with established abnormalities in glucose metabolism from 12% in the subjects with NGT to 87% in those with manifest diabetes. The prevalence of the MetS was high and fairly similar in both study cohorts among those with IGT: 75% in the FINRISK and 73% in the DPS. The prevalence was higher among men in all categories of glucose tolerance and also increased with age, which is in accordance with previous studies. In the Finnish Botnia study, the MetS applying the WHO definition, was diagnosed in 10 and 15% of subjects with NGT, 42 and 64% of those with IFG or IGT, and 78 and 84% of those with type 2 diabetes in women and men, respectively (13). EGIR also found that the frequency of MetS by both WHO and EGIR definitions increased with age and was almost always higher in men than in women at a given age (31). In the Bruneck Study, the prevalence of insulin resistance syndrome in subjects aged 40–79 years was 66% in subjects with IGT and 84% among those with type 2 diabetes (32).

Different features of the MetS were surprisingly common in middle-aged individuals in the general population, especially in men. Obesity, hypertension, and dyslipidemia were all significantly more common among men. The high prevalence of obesity in men seemed to be due to their high WHR. Obesity, defined as high WHR (~78%), was clearly more common than obesity defined as BMI >30 kg/m^2 (~25%) in men, while both prevalences were quite similar in women (~25%). Over half of the men and women had hypertension, which is in accordance with the European cohorts published by EGIR (31). There were differences in the clustering of the components according to glucose status in men and women: whereas obesity was significantly more common among men than among women in all categories of glucose tolerance, the difference in the prevalence of hypertension and dyslipidemia between sexes declined with deteriorating glucose metabolism. The prevalence of dyslipidemia was more dependent on the presence of elevated triglycerides than of low HDL cholesterol.

In the FINRISK study, milder disturbances in glucose metabolism were quite common, especially in men: IFG or IGT was present in ~25% of the men and ~15% of the women. Around 10% had diabetes, but it was undiagnosed in over half of the cases.

Type 2 diabetes is preceded by a long period of milder disturbances in glucose metabolism (3). The Finnish DPS (26) and the Diabetes Prevention Program (33) in the U.S. have shown that the incidence of diabetes can be reduced by 58% with lifestyle changes in subjects with IGT. While the clustering of risk factors related to insulin resistance is an important predictor of the development of manifest diabetes, early ascertainment of the MetS in normal clinical consultation would prove useful for identifying those at risk.

In conclusion, the prevalence of the MetS in this Finnish setting was common in middle-aged subjects, especially men, and increased with age and worsening glucose metabolism. Our results support previous findings: the overall prevalence of MetS was ~30% in the population-based cohort and ~75% in subjects with IGT. The DPS study cohort, although comprised of volunteers for an intervention study, was quite similar to the IGT subjects in the Finnish general population. While prevention of type 2 diabetes also aims to minimize the associated vascular complications, preventive actions should focus on not only improving glucose tolerance but also on preventing and treating all components of the MetS.

Acknowledgments— This study was supported by grants from the Finnish Academy (grants 8473/2298, 40758/5767, 38387/54175, and 46558), the Ministry of Education, the Novo Nordisk Foundation, the Yrjö Jahnsson Foundation, the Juho Vainio Foundation, the Finnish Diabetes Research Foundation, and EVO funds from Pirkanmaa Hospital District and Kuopio University Hospital.

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Effect of Lifestyle Intervention on the Occurrence of Metabolic Syndrome and its Components in the Finnish Diabetes Prevention Study

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OBJECTIVE — The aim of this secondary analysis of the Finnish Diabetes Prevention Study was to assess the effects of lifestyle intervention on metabolic syndrome and its components.

RESEARCH DESIGN AND METHODS — A total of 522 middle-aged overweight men and women with impaired glucose tolerance were randomized into an individualized lifestyle intervention group or a standard care control group. National Cholesterol Education Program criteria were used for the definition of metabolic syndrome.

RESULTS — At the end of the study, with a mean follow-up of 3.9 years, we found a significant reduction in the prevalence of metabolic syndrome in the intervention group compared with the control group (odds ratio [OR] 0.62 [95% CI 0.40–0.95]) and in the prevalence of abdominal obesity (0.48 [0.28–0.81]).

CONCLUSIONS — The results suggest that lifestyle intervention may also reduce risk of cardiovascular disease in the long run.

Diabetes Care 31:805–807, 2008

Recent studies (1–4) have shown that lifestyle intervention reduces the risk of progression from impaired glucose tolerance (IGT) to manifest type 2 diabetes. The aim of this secondary analysis of the Finnish Diabetes Prevention Study (DPS) was to assess the effects of lifestyle intervention on metabolic syndrome and its components.

RESEARCH DESIGN AND METHODS

— The DPS design, subjects, and methods applied have previously been described (2,5,6). Altogether, 522 middle-aged (mean age 55 ± 7 years) and overweight (mean BMI 31.2 ± 4.6 kg/m^2) men (n = 172) and women (n = 350) with IGT were randomized into either an intensive lifestyle intervention group or a standard care control group. Blood samples were collected and an oral glucose tolerance test was performed at baseline and at each annual visit. Updated National Cholesterol Education Program 2005 criteria (7) were used for the definition of metabolic syndrome. Data were analyzed using SPSS (version 11.5; SPSS, Chicago, IL). For those participants who developed diabetes according to the World Health Organization guidelines of 1985 (8) or who dropped out during the study, the measurements from the last observation were used as the final end value. Wilcoxon's nonparametric test was used to compare the prevalence of metabolic syndrome and its components within the groups. Regression analyses adjusted for sex, age, blood pressure and cholesterol medications, and baseline status were applied to compare the prevalence of metabolic syndrome and its components between the groups.

RESULTS

— The prevalence of metabolic syndrome decreased during the first year from 74.0 to 58.0% vs. from 74.0 to 67.7% (P = 0.018 for the change between the groups) in the intervention and control groups, respectively. At the end of the study, 62.6% of subjects in the intervention group and 71.2% of subjects in the control group (P = 0.025 for the change between the groups) had metabolic syndrome, which corresponds to an age- and sex-adjusted odds ratio (OR) of 0.62 (95% CI 0.40–0.95) in the intervention group compared with the control group.

The prevalence of different components of metabolic syndrome at year 1 and at the end of the study are shown in Table 1. During the first year, there was a significant decrease in all components except elevated triglycerides in the intervention group, while the control group showed a significant decrease only in the prevalence of elevated blood pressure. From baseline to the end of the study, a significant decrease in the prevalence of abdominal obesity, elevated blood pressure, low HDL cholesterol, and elevated triglycerides was observed in the intervention

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Received for publication 15 August 2007 and accepted in revised form 24 December 2007.

Published ahead of print at http://care.diabetesjournals.org on 9 January 2008. DOI: 10.2337/dc07-1117. Clinical trial reg. no. NCT00518167, clinicaltrials.gov.

Abbreviations: DPS, Finnish Diabetes Prevention Study; IGT, impaired glucose tolerance.

Table 1—*Prevalence of metabolic syndrome and its components in the intervention group (IG) and in the control group (CG) at baseline, at year 1, and at the end of the DPS*

	Baseline			Year 1				End			
	IG	CG	*P* between groups*	IG	CG	*P* in IG from baseline to year 1	*P* in CG from baseline to year 1	*P* between groups†	IG	CG	*P* in IG from baseline to end	*P* in CG from baseline to end	*P* between groups†
n	265	257	—	256	250	—	—	—	265	257	—	—	—
Metabolic syndrome	74.0	73.9	0.913	58.0	67.6	<0.001	0.008	0.018	62.6	71.2	<0.001	0.297	0.025
Abdominal obesity	80.0	72.4	0.013	64.5	70.0	<0.001	0.209	0.002	67.9	72.4	<0.001	1.000	0.006
Elevated fasting glucose	74.7	77.4	0.411	64.8	74.8	0.001	0.336	0.023	78.8	80.9	0.174	0.225	0.744
Elevated blood pressure	80.0	80.1	0.937‡	69.5	70.8	<0.001	<0.001	0.770‡	73.2	75.8	0.004	0.096	0.470‡
Low HDL cholesterol	54.5	51.4	0.286§	48.6	52.4	0.036	0.662	0.111§	43.2	45.5	<0.001	0.047	0.277§
Elevated triglycerides	38.3	44.7	0.121§	34.8	44.4	0.241	0.705	0.156§	31.8	40.2	0.018	0.166	0.103§

Data are percent. Abdominal obesity: waist circumference ≥102 cm in men and ≥88 cm in women. Elevated fasting glucose: fasting plasma glucose ≥5.6 mmol/l. Elevated blood pressure: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, and/or use of antihypertensive medication. Low HDL cholesterol: HDL cholesterol <40 mg/dl (<1.03 mmol/l) in men and <50 mg/dl (<1.3 mmol/l) in women. Elevated triglycerides: serum fasting triglycerides ≥150 mg/dl (≥1.7 mmol/l). *Adjusted for age and sex. †Adjusted for age, sex, and baseline value. ‡Adjusted for blood pressure medications. §Adjusted for lipid medications.

group, but only low HDL cholesterol was observed in the control group. At the end of the study, between-group comparisons showed that lifestyle intervention reduced abdominal obesity (OR 0.48 [95% CI 0.28–0.81], adjusted for age, sex, and baseline value).

CONCLUSIONS — In this secondary analysis of DPS data, we found that after a mean follow-up of 3.9 years, a significant reduction in the prevalence of metabolic syndrome and abdominal obesity were observed in the intervention group compared with that in the control group. These data provide evidence of benefits associated with lifestyle intervention beyond the prevention of diabetes.

The prevalence of metabolic syndrome, abdominal obesity, and elevated blood glucose decreased significantly in the intervention group compared with the control group during the first year, when the intervention was at its most intense. During the subsequent years, there were some relapses, as expected. Nevertheless, by the end of the study, the proportion of subjects with metabolic syndrome and abdominal obesity was still significantly lower in the intervention group. Abdominal obesity and insulin resistance are the main elements of metabolic syndrome (10–12). Uusitupa et al. (13) have shown earlier in a subgroup of DPS participants that a change in body weight strongly correlated with a change in insulin sensitivity. No increase in abdominal obesity was observed in the control group, indicating that the limited advice given to individuals in the control group was probably helpful in stopping progression of obesity. Our results were comparable with those of the U.S. Diabetes Prevention Program (DPP) study (9). In the DPP study, a significant increase in metabolic syndrome was observed in the control group; in our study, the prevalence of metabolic syndrome tended to be lower in the control group, indicating that the "mini-intervention" among control group participants had at least some effect on the occurrence of metabolic syndrome.

The significant decrease in elevated fasting glucose concentration observed after the first year deteriorated during the subsequent years. This is not surprising because all individuals had IGT at baseline. Furthermore, the recently updated cutoff point for elevated fasting plasma glucose criteria in metabolic syndrome is 5.6 mmol/l, while the mean fasting glu-

cose at baseline among DPS participants was 6.1 mmol/l. It would apparently be important to find and treat individuals with metabolic syndrome earlier, before IGT has developed.

In summary, compared with the standard care offered to the control group, the intensive and individualized lifestyle intervention in the DPS reduced the occurrence of abdominal obesity and the overall prevalence of metabolic syndrome in the long term. The occurrence of elevated fasting glucose, elevated blood pressure, low HDL cholesterol, and elevated triglycerides did not significantly differ between groups. Since metabolic syndrome is a major risk factor for type 2 diabetes and cardiovascular disease, these results suggest that lifestyle intervention may also reduce the risk of cardiovascular disease in the long run, but a longer follow-up is needed for confirmation.

Acknowledgments— This study was supported by grants from the Finnish Academy (grants 8473/2,298, 40758/5767, 38387/54175, and 46558), the Ministry of Education, the Novo Nordisk Foundation, the Yrjö Jahnsson Foundation, the Juho Vainio Foundation, the Finnish Diabetes Research Foundation, and the competitive research funding of the Pirkanmaa Hospital District and Kuopio University Hospital.

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Leisure-Time Physical Activity and the Metabolic Syndrome in the Finnish Diabetes Prevention Study

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OBJECTIVE — To assess the effects of leisure-time physical activity (LTPA) and resistance training on metabolic syndrome (MetS) and its components in a post hoc analysis of the Finnish Diabetes Prevention Study, a randomized controlled lifestyle counseling trial.

RESEARCH DESIGN AND METHODS — A cohort of 486 middle-aged overweight men and women with impaired glucose tolerance were followed for an average of 4.1 years. The intervention and control groups were combined in the analyses. LTPA was assessed by questionnaires, dietary intake by food records, and features of the MetS by anthropometric and biochemical measures annually. Resistance training sessions were documented for 137 participants.

RESULTS — Increased moderate-to-vigorous LTPA, even after adjustments for changes in dietary intakes of total and saturated fat, fiber, and energy, and change in BMI was associated with a greater likelihood for resolution (29.7 vs. 19.1%; $P = 0.004$ in the upper versus lower third of change) and a lesser likelihood for development (23.5 vs. 44.7%; $P = 0.041$) of the MetS. Of the components of the MetS, the increase in moderate-to-vigorous LTPA was associated most strongly with improvement of glycemia. Among the 137 participants who participated in resistance training, MetS components were favorable in individuals who were in the upper third of participation rate (median 51 times/year) compared with individuals in the lowest third (median 8.5 times/year).

CONCLUSIONS — Increased moderate-to-vigorous LTPA was associated with a decreased likelihood of developing the MetS and an increased likelihood of its resolution in individuals at high risk for type 2 diabetes.

Diabetes Care 33:1610–1617, 2010

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Received 21 November 2009 and accepted 16 April 2010. Published ahead of print at http://care.diabetesjournals.org on 22 April 2010. DOI: 10.2337/dc09-2155. Clinical Trial Registry No.: NCT00518167; http://www.clinicalstrials.gov.

The metabolic syndrome (MetS) is a constellation of interrelated metabolic risk factors, including abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia, and elevated blood pressure, often accompanied by a prothrombotic and proinflammatory state (1,2). The underlying pathophysiology of the MetS is unclear, but both insulin resistance and abdominal obesity are considered main components (1,2). The MetS increases the risk of both type 2 diabetes (3) and cardiovascular disease (4,5).

Recent recommendations for the prevention and treatment of the MetS and its components promote increased physical activity (including aerobic and resistance exercise), a healthy diet, and weight loss (2,6–8). In lifestyle interventions trials, the incidence of type 2 diabetes has been reduced by more than half in individuals with impaired glucose tolerance, and the prevalence of the MetS has also been decreased (9,10). In the Finnish Diabetes Prevention Study (DPS), increased moderate-to-vigorous leisure-time physical activity (LTPA) was strongly associated with a lower risk of type 2 diabetes, independently of dietary changes and weight loss (11).

Some prospective epidemiological studies and uncontrolled trials have suggested that increased moderate-to-vigorous exercise decreases the incidence or prevalence of the MetS (8,12,13). However, data on the role of changes in LTPA in the prevention and treatment of the MetS in long-term studies are limited. Therefore, we conducted a post hoc analysis of the Finnish DPS. Our hypothesis was that the change in LTPA and participation in resistance training would be associated with the change in the MetS and its components.

RESEARCH DESIGN AND METHODS

— A detailed description of the design, subjects, and methods applied in the DPS has been reported previously (14). In brief, the DPS was a randomized lifestyle intervention study in 522 middle-aged overweight participants with impaired glucose tolerance, aimed at

the prevention of type 2 diabetes. In the present study, we included those 486 participants (249 in the intervention and 237 in the control group) who had completed a questionnaire quantifying LTPA at baseline and during yearly follow-up visits (11). A subgroup of 137 participants was taking part in supervised resistance training sessions. The study protocol was approved by the ethics committee of the National Public Health Institute in Helsinki, and all subjects gave written informed consent.

Intervention

The aim of the intervention was to encourage people to make healthy lifestyle choices. The participants in the intervention group were given detailed and individualized dietary and exercise counseling as described elsewhere (15). Endurance exercise was recommended to increase aerobic capacity and cardiorespiratory fitness. Session for supervised and individually tailored progressive circuit-type resistance training with moderate intensity were recommended twice a week and offered free of charge in three of the five study centers.

The participants in the control group were given general information about healthy food choices, physical activity, and weight loss at baseline, but no individualized counseling was offered.

Assessment of physical activity

The validated Kuopio Ischemic Heart Disease risk factor study questionnaire (11,12) was used for the assessment of physical activity. The participants estimated the frequency, average duration, and intensity of different forms of exercise for individual months during the past 12 months. Based on the reported intensity of different activities and their corresponding metabolic equivalent (MET) values, the total LTPA was divided to low-intensity and to moderate-to-vigorous intensity LTPA (13). Low-intensity LTPA (<3.5 METs) included activities such as gardening, picking berries, casual walking, and bicycling at recreational intensity. Moderate-to-vigorous LTPA (≥3.5 METs) included activities such as brisk walking, jogging, skiing, swimming, rowing, forest work, gymnastics, resistance training, ball games, snow shoveling, and heavy housework.

The duration of total LTPA and its components were calculated as hours/week from the baseline to the end of the follow-up. The changes were calculated by subtracting averaged follow-up value from the corresponding baseline value (11). The participation in resistance training was recorded electronically when the participants visited the resistance training facilities and was analyzed as sessions/year.

Other measurements

Medical history and 3-day food records were collected at baseline and at each annual visit. Average intakes of energy (kcal/day), carbohydrates (E%), total fat (E%), saturated fat (E%), and dietary fiber (g/1,000 kcal) were calculated. The average values from years 1–3 were used to measure dietary intakes during follow-up (11).

Anthropometry and blood pressure were assessed as described previously. Plasma glucose was determined locally according to standard guidelines. Serum total and HDL cholesterol and triglyceride levels were determined by enzymatic methods (Boehringer Mannheim, Germany).

For the definition of the MetS, we used the National Cholesterol Education Program 2005 criteria (6).

Statistical analysis

The data were analyzed using SPSS statistical software (version 11.5; SPSS, Chicago, IL). The baseline values are given as mean ± SD, as median with 0.25–0.75 interquartile range, or as percentages. The Student two-tailed *t* test, Mann-Whitney *U* test (fasting and 2-h serum insulin, triglycerides, and LTPA), and χ^2 test were applied to compare the differences at baseline and during the follow-up. For participants who dropped out or developed diabetes during the study, the measurements at the last observation year was used as the end value.

The primary outcome measure was the change in the MetS status in the combined intervention and control group from baseline to the end, i.e., resolution of the MetS from baseline, development of MetS, or no change with LTPA changes as explanatory variables. Secondary outcome measures were the changes of the MetS components. The change of different LTPA was categorized into thirds. The association with the change in MetS status and its components was analyzed with multinominal regression. The models were adjusted for age, sex, intervention group, and DPS study years (model 1) with further adjustments for changes in diet (intake of total fat, saturated fat, fiber, and energy) (model 2) and BMI (model 3). The change in low-intensity LTPA was also adjusted for the change in moderate-to-vigorous LTPA and vice versa. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline clinical and metabolic characteristics

In the combined study cohort, 74.3% had the MetS at baseline. The participants with the MetS at baseline had significantly higher BMI, waist circumference, blood pressure, fasting and 2-h glucose, fasting and 2-h insulin, and serum triglyceride levels and lower serum HDL cholesterol levels (Table 1).

In general, men exercised more than women. Women without the MetS reported significantly more hours per week spent on total and low-intensity LTPA during the previous 12 months than women with the MetS.

Changes in LTPA during the follow-up

The median for total LTPA increased from 7.2 (3.6–10.8) at baseline to an average of 7.7 (4.8–11.7) hours per week ($P = 0.061$) in men and from 5.3 (2.8–8.6) to 5.8 (3.2–9.0) hours per week ($P = 0.016$) in women during the follow-up. The median for moderate to vigorous LTPA increased from 2.3 (0.9–4.8) to 3.1 (1.8–4.9) ($P \leq 0.001$) hours per week in men and from 1.4 (0.3–3.5) to 2.5 (1.1–4.1) ($P \leq 0.001$) hours per week in women. There was no significant change in low-intensity LTPA.

LTPA changes and the incidence for resolution and development of the MetS

Of the 361 participants meeting the MetS criteria at baseline, 20.8% ($n = 75$; 26.6% in the intervention and 14.7% in the control group; $P = 0.005$) showed resolution during the follow-up. Of the 126 participants not meeting the MetS criteria at baseline, 31.2% ($n = 39$; 30.8% in the intervention and 31.7% in the control group; $P = 0.95$) developed MetS during the follow-up. The development of the MetS was associated with weight gain and less LTPA in both groups.

The change in total LTPA was associated with the change in MetS status (resolution, no change, development) after adjustment for age, sex, intervention

Table 1—*Baseline characteristics of the participants according the absence (MetS$^-$) or presence (MetS$^+$) of the MetS*

	All	MetS$^-$	MetS$^+$	*P*
n	486	125	361	—
Group allocation				0.843
Intervention	249	65	184	
Control	237	60	177	
Sex				0.003
Male [*n* (%)]	162 (33.3)	55 (34.0)	107 (66.0)	
Female [*n* (%)]	324 (66.7)	70 (21.6)	254 (78.4)	
Age (years)	55.4 ± 7.0	55.8 ± 7.1	55.3 ± 7.0	0.476
40–49 (%)	27.0	27.2	26.9	
50–59 (%)	33.1	28.8	34.6	
≥60 (%)	39.9	44.0	38.0	
Weight (kg)	86.3 ± 14.3	80.3 ± 10.0	88.4 ± 14.9	<0.001
BMI (kg/m^2)	31.2 ± 4.5	28.8 ± 3.4	32.1 ± 4.6	<0.001
Waist (cm) (all)	101.2 ± 11.0	94.7 ± 8.1	103.5 ± 11.0	<0.001
Men	104.2 ± 9.7	97.3 ± 6.0	107.7 ± 9.4	
Women	99.8 ± 11.4	92.7 ± 9.0	101.7 ± 11.2	
Fasting glucose (mmol/l)	6.1 ± 0.7	5.8 ± 0.7	6.3 ± 0.7	<0.001
2-h glucose (mmol/l)	8.9 ± 1.5	8.6 ± 1.4	9.0 ± 1.5	0.014
Fasting insulin (mU/l)	13 (10–18)	10 (8–13)	14 (11–19)	<0.001
2-h insulin (mU/l)	79 (54–120)	60 (38–77)	89 (63–134)	<0.001
Serum total cholesterol (mmol/l)	5.6 ± 0.9	5.7 ± 0.8	5.6 ± 0.9	0.064
Serum HDL cholesterol (mmol/l)	1.21 ± 0.29	1.39 ± 0.24	1.15 ± 0.28	<0.001
Serum triglycerides (mmol/l)	1.56 (1.18–2.09)	1.20 (0.96–1.43)	1.72 (1.34–2.29)	<0.001
Lipid-lowering medication (%)	5.4	3.2	6.2	0.576
Systolic blood pressure (mmHg)	138 ± 18	133 ± 20	140 ± 16	<0.001
Diastolic blood pressure (mmHg)	86 ± 10	82 ± 11	87 ± 9	<0.001
Antihypertensive medication (%)	35.3	16.8	41.7	<0.001
Total LTPA (all) (h/week)	5.7 (3.1–9.3)	6.9 (4.3–10.1)	5.1 (2.8–9.1)	0.001
Men	7.2 (3.6–10.8)	7.5 (3.8–10.4)	6.9 (3.4–10.9)	0.503
Women	5.3 (2.8–8.6)	6.7 (4.3–9.8)	4.9 (2.6–8.2)	0.002
Moderate-to-vigorous LTPA (all)	1.7 (0.5–4.0)	1.9 (0.6–4.4)	1.6 (0.4–3.8)	0.165
Men	2.3 (0.9–4.8)	2.1 (1.1–4.7)	2.4 (0.7–4.9)	0.725
Women	1.4 (0.3–3.5)	1.7 (0.4–4.2)	1.3 (0.3–3.5)	0.481
Low-intensity LTPA	3.0 (1.2–5.9)	4.1 (1.9–7.2)	2.9 (1.1–5.3)	0.004
Men	3.2 (1.4–6.9)	3.7 (1.9–7.2)	3.0 (1.2–6.9)	0.268
Women	2.9 (1.2–5.6)	4.4 (1.5–7.2)	2.8 (1.1–4.6)	0.011

Data are means ± SD for normally distributed or medians (interquartile ranges) for skewed parameters or percentages.

group, and DPS study years (model 1, Fig. 1*A*) and dietary intakes (model 2, Fig. 1*A*). The change in moderate-to-vigorous LTPA was even more strongly associated with the change in MetS status in analyses adjusting for the variables in model 1 and changes in low-intensity LTPA. The resolution of the MetS was seen in 29.7 versus 19.1% ($P = 0.004$), and the development of MetS was seen in 23.5 versus 44.7% ($P = 0.041$) in the upper versus lower third of change in moderate-to-vigorous LTPA. The associations remained significant after further adjustments for changes in diet (model 2) and BMI (model 3) (Fig. 1*B*). Changes in low-intensity LTPA were not associated with the change in MetS status (Fig. 1*C*).

LTPA changes and the components of the MetS

The increase in total LTPA was associated with a decrease in the prevalence of hyperglycemia ($P = 0.020–0.053$), low HDL cholesterol ($P = 0.018–0.057$), and hypertriglyceridemia ($P = 0.002–0.003$) (Table 2). Increased moderate-to-vigorous LTPA decreased the prevalence of elevated fasting glucose ($P = 0.003–0.018$), but no association with abdominal obesity ($P = 0.065–0.181$), low HDL cholesterol ($P = 0.098–0.232$), and high blood pressure ($P = 0.068–0.151$) was found. In contrast, an increase in low-intensity LTPA was associated with an improvement in hypertriglyceridemia ($P = 0.006–0.004$), but not any of the other components of the MetS.

Resistance training and the components of the MetS

In the subgroup of 137 individuals taking part in supervised resistance training, the median attendance rate was 27.0 (13.4–42.9) sessions/year during the entire study. Of the MetS status components, the resistance training attendance rate was associated, even after adjustment for dietary and BMI changes, with improvements in hyperglycemia ($P = 0.127–0.029$), hypertriglyceridemia ($P = 0.046–0.081$), and low HDL cholesterol ($P < 0.001–0.002$), but not with elevated blood pressure or abdominal obesity (Table 3).

CONCLUSIONS — Increased moderate-to-vigorous LTPA during the 4.1-

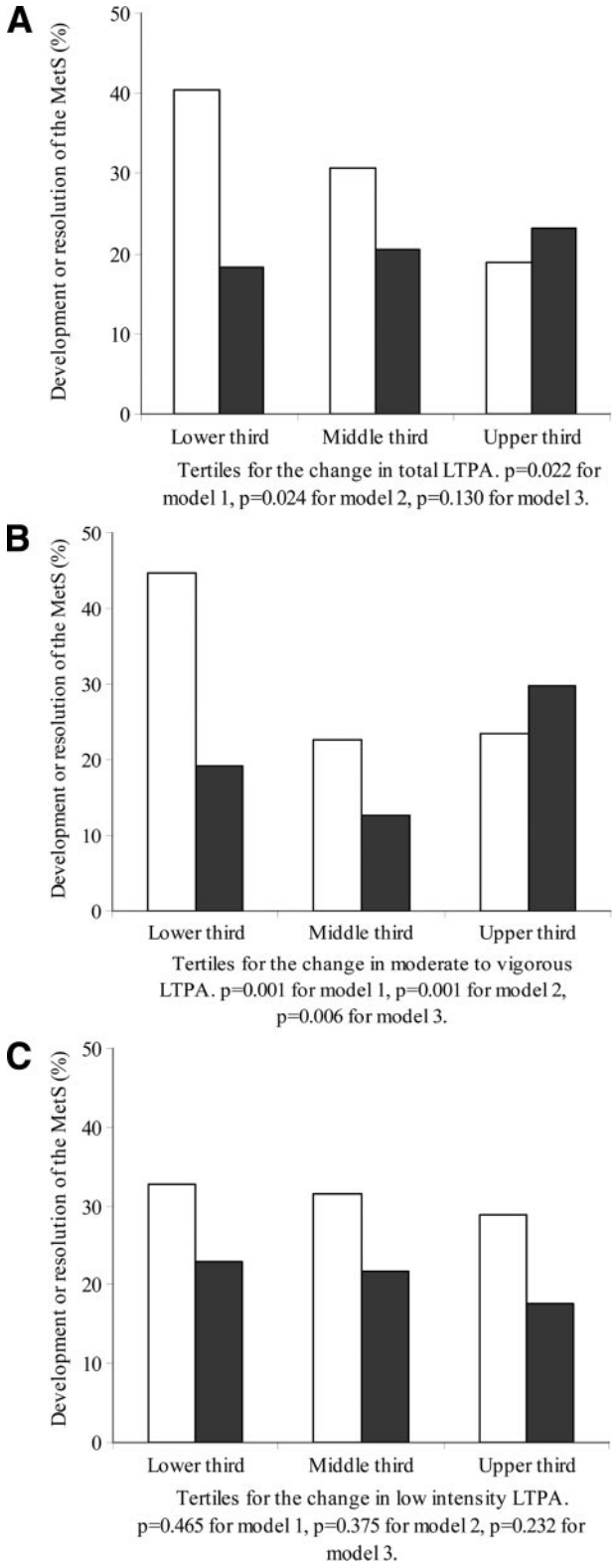

Figure 1—*Incidences (%) for the development (for individuals without MetS at baseline,* n = *125) (□) and the resolution (for individuals with MetS at baseline,* n = *361) (■) of the MetS according to LTPA change tertiles for total LTPA* (A)*, moderate-to-vigorous LTPA* (B)*, and low-intensity LTPA* (C)*. Model 1: adjustments for age, sex, intervention group, and DPS study years. The change in low-intensity LTPA was also adjusted for change in moderate-to-vigorous LTPA and vice versa. Model 2: model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber, and energy. Model 3: model 2 and change in BMI.*

year follow-up increased the likelihood for the MetS to resolve and decreased the likelihood for the MetS to develop, independently of changes in diet and body weight. Moreover, increased moderate-to-vigorous LTPA decreased the prevalence of hyperglycemia. Improvements in fasting plasma glucose, serum triglycerides, and HDL cholesterol, independently of changes in diet, lifestyle LTPA, and other types of LTPA, were associated with participation in resistance training.

Overall, strong and mostly linear dose-response associations of the change in total LTPA with the development and resolution of the MetS were seen. When breaking down physical activity into moderate-to-vigorous LTPA and low-intensity LTPA, it seems evident that most of the benefit was from moderate- to vigorous-intensity LTPA. Changes in moderate-to-vigorous LTPA were associated with the change in metabolic status, even independently of the changes in BMI, but the association was not linear across categories. Changes in low-intensity LTPA were not associated with the development or resolution of the MetS. Why the dose-response association was not apparent for moderate-to-vigorous LTPA is unclear, but it may be related to the difficulty in the precise assessment of LTPA. Overall, however, our findings support efforts to increase or at least maintain LTPA, especially moderate-to-vigorous LTPA, in the prevention and treatment of the MetS.

In this analysis of the DPS, the intervention and control groups were combined. In separate analysis, there was a significant difference between the groups in the resolution of the MetS. However, there was no difference in the development of MetS between groups; ~30% of those without MetS at baseline developed MetS in both groups during the follow-up. This may be due the selection of the participants. They were individuals at high risk for type 2 diabetes and for the MetS. During the follow-up, 22% developed type 2 diabetes (11). While the development of MetS was associated with weight gain and less LTPA, those subjects who developed the MetS appeared to not adhere with our intervention. The apparent favorable effects of moderate-to-vigorous LTPA on resolution and development of the MetS are consistent with the results of the uncontrolled Heritage Family Study (16) and some prospective cohort studies showing that increased moder-

Table 2—*Incidences (%) for development and resolution of the MetS components according to LTPA change tertiles for total, low-intensity, and moderate-to-vigorous LTPA during the follow-up*

		Tertiles for total LTPA change median (0.25–0.75 interquartile range) (h/week)			
	Incidence (%)	Lower −3.2 (−5.5 to −1.6)	Middle 0.6 (0.1 to 1.2)	Upper 3.8 (2.4 to 5.8)	*P* for trend
Abdominal obesity					0.119*
Development	4.3%	7.4	2.5	3.1	0.184†
Resolution	11.1%	8.6	12.3	12.3	0.408‡
Elevated fasting glucose					0.020*
Development	12.4%	17.4	13.0	6.8	0.033†
Resolution	8.9%	8.1	10.5	8.0	0.053‡
Elevated triglycerides					0.002*
Development	9.3%	11.1	6.8	9.9	0.002†
Resolution	14.4%	6.2	20.4	16.7	0.003‡
Low HDL cholesterol					0.018*
Development	7.8%	12.3	6.8	4.3	0.013†
Resolution	16.5%	13.6	13.6	22.6	0.057‡
Elevated blood pressure					0.661*
Development	4.7%	5.6	5.6	3.1	0.643†
Resolution	9.7%	8.0	9.3	11.8	0.800‡

*Model 1: adjustments for age, sex, intervention group, and DPS study years. The change in low-intensity LTPA was also adjusted for change in moderate-to-vigorous LTPA and vice versa. †Model 2: model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber, and energy. ‡Model 3: model 2 and change in BMI.

ate-to-vigorous LTPA was associated with a lower incidence of the MetS during follow-up (8,12,17). In the DPS cohort, increased moderate-to-vigorous LTPA seemed to protect against developing the MetS in both men and women. Higher cardiorespiratory fitness, which partly reflects higher levels of moderate-to-vigorous LTPA, has predicted a lower prevalence of the MetS independently of major confounding variables also in women in the Aerobics Center Longitudinal Study (18) and in the Dose-Responses to Exercise Training Study (19). Changes in low-intensity LTPA were not associated with changes in the MetS status. These findings are consistent with the results of the Kuopio Ischemic Heart Disease study, in which moderate-to-vigorous, but not low-intensity, LTPA was associated with development of the MetS (12). When examining specific components of the MetS, increased moderate-to-vigorous LTPA had the greatest effect on impaired fasting glucose, whereas the benefit on abdominal obesity, low HDL cholesterol, and high blood pressure was not significant. In contrast, changes in low-intensity LTPA had benefits on hypertriglyceridemia, but not on the other components of the MetS, and changes in total LTPA improved impaired fasting glucose and dyslipidemia.

In intervention trials, low-intensity LTPA has less consistently improved metabolic outcomes than more intense LTPA (8). However, we have previously reported that increased low-intensity and moderate-to-vigorous LTPA were similarly associated with a lower risk of type 2 diabetes in the Finnish DPS, suggesting that total energy expenditure on LTPA was more important than intensity (11). In line with that finding, the accumulated daily physical activity as measured with an accelerometer was a major determinant of insulin sensitivity, and time spent on moderate-to-vigorous physical activity did not affect insulin sensitivity independently of total activity in the European Relationship between Insulin Sensitivity and Cardiovascular Risk Study (20). The differences may be explained by differences in study populations and specific metabolic outcomes. More information on the long-term metabolic benefits of low-intensity LTPA in different age-groups and risk groups is nonetheless needed.

Regular participation in resistance training predicted favorable changes in MetS components. We found that a higher participation rate in resistance training was associated with benefits on impaired fasting glucose, hypertriglyceridemia, and low HDL cholesterol, but not abdominal obesity or blood pressure. In 3- to 6-month trials, resistance training has variably increased muscle mass, decreased fat mass and abdominal obesity, and improved insulin sensitivity in obese adults, hypertensive patients, older men, and older type 2 diabetic patients (8,21,22). In individuals with type 2 diabetes, resistance training resulted in similar improvements of glycemic control as aerobic exercise (23), although the effect on glucose tolerance in impaired glucose tolerance has been less clear (8). Improvements in insulin sensitivity and metabolic risk factors may be mediated in part by changes in body composition, but strength training may also independently affect steps in insulin signaling and glucose transport (24). Based on meta-analyses of trials, resistance training may decrease blood pressure (25), but effects on dyslipidemia have been variable (8).

Our findings suggest that there is a graded benefit in the frequency of resistance training in the prevention or treatment of the MetS components, with rather substantial benefits for individuals engaging in resistance training on median once a week compared with individuals engaging in resistance training on median less than once a month. In the abovementioned studies showing an improvement in insulin sensitivity in individuals

Table 2—*Continued*

Tertiles for low LTPA change median (0.25–0.75 interquartile range) (h/week)				Tertiles for moderate-to-vigorous LTPA change median (0.25–0.75 interquartile range) (h/week)			
Lower −3.2 (−5.6 to −1.7)	Middle 0.1 (−0.4 to 0.5)	Upper 3.1 (1.8 to 5.1)	*P* for trend	Lower −1.5 (−3.1 to −0.5)	Middle 0.5 (0.2 to 0.8)	Upper 2.6 (1.8 to 3.8)	*P* for trend
			0.718*				0.065*
4.9	4.9	3.0.1	0.753†	6.2	2.5	4.3	0.083†
12.3	10.5	10.5	0.725‡	9.3	6.8	4.3	0.181‡
			0.941*				0.003*
11.8	12.3	13.0	0.928†	19.1	11.7	6.2	0.011†
7.5	9.3	9.9	0.984‡	8.6	8.0	9.9	0.018‡
			0.006*				0.491*
9.9	6.2	11.7	0.005†	12.3	8.0	7.4	0.526†
8.0	19.3	16.0	0.004‡	14.9	12.4	16.0	0.672‡
			0.762*				0.098*
7.4	9.3	6.8	0.668†	11.7	6.2	5.6	0.086†
16.7	14.2	18.5	0.807‡	14.8	13.6	21.3	0.232‡
			0.921*				0.068*
4.9	4.3	5.0	0.883†	7.4	4.3	2.5	0.066†
9.9	11.1	8.1	0.824‡	6.8	8.0	14.3	0.151‡

at risk for type 2 diabetes and in glycemic control in patients with type 2 diabetes, training frequency was generally two to three times per week. The metabolic benefits of resistance training at a lower frequency may become apparent only after much longer periods of training than in previously published trials, which have usually lasted 3–6 months. However, longer-term trials are needed to test this hypothesis.

Strengths of the DPS include its repeated assessments of LTPA and dietary intake. However, the present analyses are post hoc. Furthermore, the intervention had several components. Detailed assessment of the individual lifestyle components allows statistical disentanglement of their individual effects, but residual confounding is possible. Moreover, we did not objectively measure physical activity. Decreases in LTPA may have been related to factors that themselves may be related to the development of the MetS. Adherence to resistance training was on average poor. When this study was conducted in the early 1990s, it was uncommon for middle-aged and overweight individuals to attend resistance training facilities, where most of the clientele were young and fit. Some also encountered difficulties with transportation and time schedules.

In conclusion, increased participa-

Table 3—*The average resistance training attendance rate per year and the change (development and resolution) in the MetS components among a subgroup of 137 participants*

		Tertiles for average yearly attendance rate for resistance training median (0.25–0.75 interquartile range)			
	Incidence (%) (n = 137)	Lower 8.5 (5.5–13.4)	Middle 27.0 (21.9–32.7)	Upper 50.7 (42.3–67.2)	*P*
Abdominal obesity					0.438*
Development	0.0	0.0	0.0	0.0	0.537†
Resolution	10.2	4.4	13.0	13.0	0.549‡
Elevated fasting glucose					0.127*
Development	16.8	13.3	26.1	10.9	0.157†
Resolution	5.1	6.7	2.2	6.5	0.029‡
Elevated triglycerides					0.046*
Development	10.2	11.1	17.4	2.2	0.067†
Resolution	20.4	11.1	21.7	28.3	0.081‡
Low HDL cholesterol					0.000*
Development	10.9	15.6	17.4	2.2	0.001†
Resolution	18.2	6.7	26.1	21.7	0.002‡
Elevated blood pressure					0.982*
Development	3.6	4.4	2.2	4.3	0.967†
Resolution	10.2	8.9	10.9	10.9	0.957‡

*Model 1: adjustments for age, sex, group, DPS study years, averaged low-intensity LTPA, and LTPA other than gymnastics and calisthenics. †Model 2: model 1 and adjustments for change in dietary intakes of total fat, saturated fat, fiber, and energy. ‡Model 3: adjustment for model 2 and change in BMI.

tion in moderate-to-vigorous physical activity and regular long-term participation in resistance training improved the MetS status among men and women with impaired glucose tolerance in the Finnish DPS. Physical activity and resistance training also more specifically had benefits with respect to hyperglycemia and dyslipidemia, but improvements in abdominal obesity were not clearly seen. Resolution or prevention of the MetS and related features might contribute to the protective effect of physical activity on type 2 diabetes.

Acknowledgments— This study was supported by grants from the Finnish Academy (grants 8473/2298, 40758/5767, 38387/54175, 46558), the Ministry of Education, the Novo Nordisk Foundation, the Yrjö Jahnsson Foundation, the Juho Vainio Foundation, the Finnish Diabetes Research Foundation, and the Finnish Foundation for Cardiovascular Research and Competitive Research Funding of the Pirkanmaa Hospital District, Tampere, and of Kuopio University Hospital, Kuopio.

No potential conflicts of interest relevant to this article were reported.

P.I-P. designed the study, researched the data, and wrote the manuscript. D.E.L. designed the study, researched the data, and contributed to writing the manuscript. J.G.E. and T.A.L. contributed to study design and edited the manuscript. J.L., M.P., S.A., and S.K.-K. contributed to data collection and coordination and reviewed the manuscript. M.U. and J.T. are the principal investigators of the DPS study and participated in reviewing/editing the manuscript.

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Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study

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Lancet 2006; 368: 1673–79

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Summary

Background **Lifestyle interventions can prevent the deterioration of impaired glucose tolerance to manifest type 2 diabetes, at least as long as the intervention continues. In the extended follow-up of the Finnish Diabetes Prevention Study, we assessed the extent to which the originally-achieved lifestyle changes and risk reduction remain after discontinuation of active counselling.**

Methods **Overweight, middle-aged men (n=172) and women (n=350) with impaired glucose tolerance were randomly assigned to intensive lifestyle intervention or control group. After a median of 4 years of active intervention period, participants who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. Diabetes incidence, bodyweight, physical activity, and dietary intakes of fat, saturated fat, and fibre were measured.**

Findings **During the total follow-up, the incidence of type 2 diabetes was 4·3 and 7·4 per 100 person-years in the intervention and control group, respectively (log-rank test p=0·0001), indicating 43% reduction in relative risk. The risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat and increased intake of dietary fibre, and increased physical activity. Beneficial lifestyle changes achieved by participants in the intervention group were maintained after the discontinuation of the intervention, and the corresponding incidence rates during the post-intervention follow-up were 4·6 and 7·2 (p=0·0401), indicating 36% reduction in relative risk.**

Interpretation **Lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counselling was stopped.**

Introduction

The pandemic of type 2 diabetes is an enormous public health problem.[1,2] Studies using lifestyle intervention in people with impaired glucose tolerance have shown that the progress to manifest type 2 diabetes can be prevented or postponed.[3–8] Lifestyle intervention in these studies lasting for 3–6 years emphasised bodyweight control, physical activity, and dietary modification. Reduction in relative risk achieved in the intervention group compared with the control group ranged from 30% to 67%, as shown in a recent meta-analysis.[9] The Finnish Diabetes Prevention Study[5] and the US Diabetes Prevention Program[6] both revealed a 58% relative risk reduction in the progression from impaired glucose tolerance to type 2 diabetes, during a mean intervention period of about 3 years.

However, whether the risk reduction achieved during active counselling for lifestyle changes will last after discontinuation of the intervention is not known. The extended follow-up of the Diabetes Prevention Study was designed to assess the long-term results of the lifestyle intervention originally aimed at reducing the risk for developing type 2 diabetes in high-risk individuals.

Methods

The Diabetes Prevention Study was a randomised controlled trial aimed at prevention of type 2 diabetes by lifestyle intervention. The study design has been described in detail previously.[10] The study protocol was approved by the ethics committee of the National Public Health Institute in Helsinki, Finland, and all study participants gave written informed consent. Randomisation started in 1993 and was completed in 1998 (figure 1). The first interim analysis was done in March, 2000.[5] According to the recommendation of the endpoint committee, the intervention period was discontinued at each participant's next yearly clinic visit, after a median follow-up of 4 years. Subsequently, we decided to continue to monitor the participants who had remained free of diabetes. This report consists of the data obtained until Dec 31, 2004, ie, post-intervention follow-up for a median of 3 years, with median total follow-up of 7 years.

Participants

Originally, 522 men and women in five study centres were randomised at the baseline visit to one of the two treatment modalities, the intervention group with intensive diet-exercise counselling (n=265, the proportion

of women 66%) or the control group (n=257, the proportion of women 69%). Overweight (mean body-mass index 31·1 kg/m^2), middle-aged (mean age 55 years) participants with impaired glucose tolerance based on two 75 g oral glucose tolerance tests by the WHO 1985 criteria[11] were eligible for the study. Mean fasting plasma glucose at baseline was 6·1 (SD 0·8) mmol/L and mean plasma glucose value 2 h after the 75 g oral glucose load was 8·9 (1·5) mmol/L without significant differences between the two groups. The overall proportion of participants who were lost to follow-up was 10% in the intervention group and 8% in the control group (p=0·3619 Fisher's exact test; figure 1).

Intervention

The main goals of the intervention were: weight reduction of 5% or more; less than 30% of the daily energy intake from fat; less than 10% of the daily energy intake from saturated fat; fibre intake 15 g per 1000 kcal or more; and moderately intense physical activity 30 min per day or more. The duration of intervention ranged from less than 1 year (indicating withdrawal before the first yearly visit) up to 6 years, with median length of 4 years. The implementation of the intervention programme has been previously reported.[12] Briefly, the participants in the intervention group were given detailed and individualised counselling to achieve the lifestyle goals. They had seven personal counselling sessions with the study nutritionist during the first year and every 3 months thereafter. The median number of dietary counselling sessions per participant was 20 thus indicating excellent compliance with the study protocol. The participants were also advised to increase their level of physical activity, and were offered free of charge, supervised, 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.

The participants in the control group were given general verbal and written health behaviour information at baseline without specific individualised advice. At the last intervention period visit all the participants were given a summary of their laboratory test results during the intervention period, including the glucose values, and they were also told about the findings of the randomised trial.

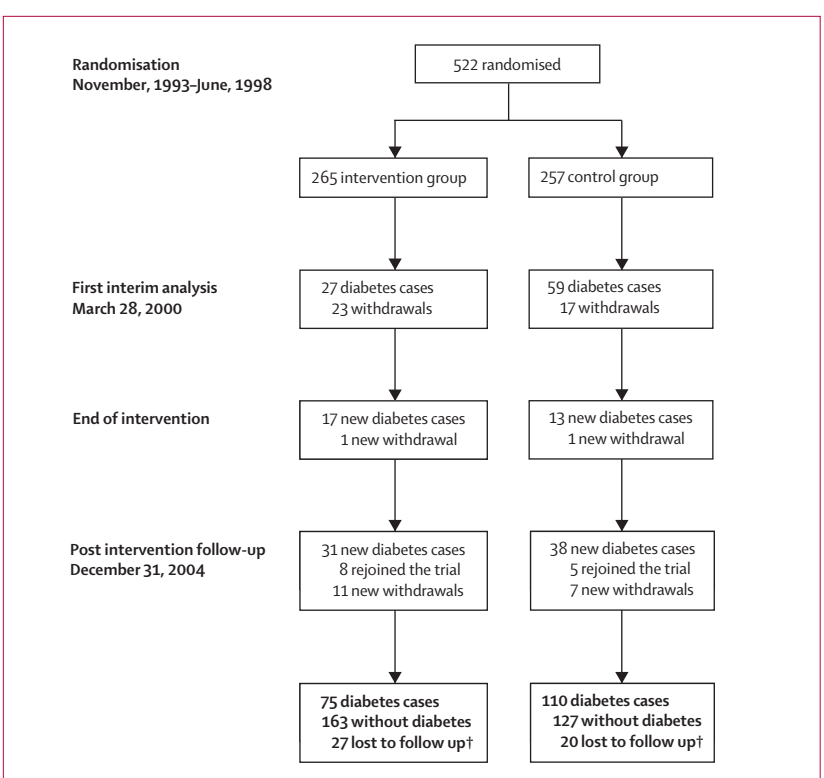

Figure 1: **Trial profile**
*After the decision to end the intervention period, the intervention was continued until each participant's next scheduled yearly clinic visit. End date thus varied from March, 2000, to Dec, 2001. †Participants who were lost to follow-up were treated as censored observations in the analyses.

Post-intervention follow-up

All individuals who participated in the Diabetes Prevention Study were invited to take part in the post-intervention follow-up. During this follow-up, all study participants had a yearly visit with the study nurse. The visits included the same procedures as during the intervention period, and were similar for all participants irrespective of their former randomisation group. No specific diet or exercise counselling was provided.

Procedures and measurements

The parameters measured every year included fasting and post load (75 g oral glucose tolerance test) plasma glucose after a 12-h fast. During the intervention, plasma glucose was measured locally according to standard guidelines. During the post-intervention follow-up, centralised glucose assays were established enzymatically with the hexokinase method (Thermo Electron Oy, Vantaa, Finland).

A clinical examination was done and questionnaires including questions about physical activity were obtained at baseline and at every yearly visit. Individuals who reported that they "mostly read, watch TV, and spend time in other ways that are not physically demanding" during their spare time were categorised as physically inactive, and those who reported "walking, bicycling, or other exercise for at least 4 hours per week" were categorised as achieving the physical activity goal. All study participants completed a 3-day food record with a picture booklet of portion sizes of typical foods.[13] The average intakes of total fat (proportion of the total daily energy intake), saturated fat (proportion of the total daily energy intake), and dietary fibre (g per 1000 kcal) from the baseline and 1-year, 2-year, and 3-year visits of the intervention period were calculated using a dietary analysis programme and the Finnish Food Composition

Database (Fineli) developed at the National Public Health Institute, Helsinki, Finland.[14] The dietary analyses were repeated at the first post-intervention follow-up visit to clarify the maintenance of the dietary changes after the intervention had been discontinued.

The study participants were categorised according to their success in achieving the five predefined lifestyle goals (0=not achieved, 1=achieved) by the 3-year visit, with mean physical activity and nutrient intakes during the years 1, 2, and 3. For those who either dropped out or were diagnosed with diabetes before the 3-year visit, the last observation for bodyweight was used for calculating weight reduction. A success score from 0 to 5 was calculated as the sum of the achieved goals. The analysis was repeated at the first post-intervention follow-up-visit.

The development of type 2 diabetes was the primary endpoint. Since the study was started before the current criteria for diabetes were introduced,[15] diabetes was defined according to WHO 1985 criteria,[11] ie, either fasting plasma glucose of 7·8 mmol/L or more, or 2-hour post-challenge plasma glucose of 11·1 mmol/L or more. The diagnosis of diabetes was confirmed by a second oral glucose tolerance test.

Statistical analysis

Kaplan-Meier survival curves were calculated to estimate the probability of remaining free of diabetes in the two groups. Participants who were lost during 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. The proportionality assumption of the model was assessed with graphical methods (ie, the log-log plot). All comparisons of the endpoints were based on the intention-to-treat principle.

Mean levels of bodyweight, nutrient intakes, and physical activity during the study were compared between the groups with analysis of covariance, adjusting for the level of respective variable at baseline. Further, analysis of covariance was used to examine changes in these variables from the last intervention period visit until the first post-intervention examination. In this analysis, adjustment was made for the level of respective variable at the last visit during intervention. In further analyses, the Cox model was used to analyse the relation between the success score and the incidence of diabetes. First, the success score variable was included in the model as categorical variable, with those who did not achieve any of the lifestyle goals as reference category. Additionally, test of linear trend was done including the success score as continuous variable in the model. In these analyses the groups were pooled. The analyses were adjusted for treatment group, study centre, sex, age, and the baseline 2-h post-challenge plasma glucose concentration. Analyses were done with the statistics package Stata version 8.0.

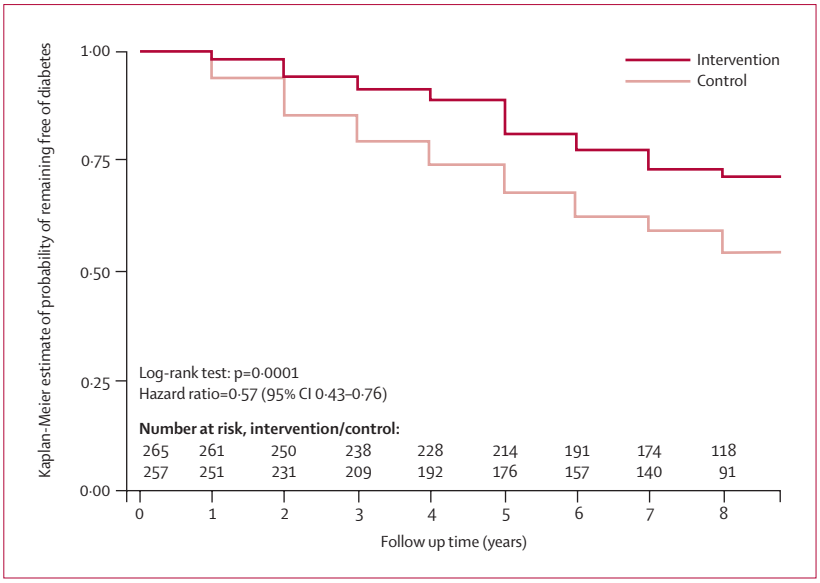

Figure 2: **Diabetes by treatment group**
Follow-up time is truncated at 8 years, since number of participants at risk beyond this point was low, but they are included in the calculation of hazard ratios.

Role of the funding source

The sponsors of the study had no role in study design, the collection, analysis, or interpretation of the data, or in the writing of the report. The corresponding author had full access to all data in the study and had the final responsibility to submit for publication.

Results

The total number of cases of diabetes diagnosed during the overall follow-up of 7 years was 75 in the intervention group and 110 in the control group (figure 1). The incidence rates were 4·3 (95% CI 3·4–5·4) and 7·4 (6·1–8·9) per 100 person-years in the intervention and control group, respectively (p=0·0001 log-rank test). The corresponding hazard ratio was 0·57 (0·43–0·76; figure 2). The cumulative incidence of diabetes at year 6 was 23% in the intervention group and 38% in the control group, with an absolute risk reduction of 15% (7·2–23·2). The number of people needed to be treated to prevent one case of type 2 diabetes by lifestyle intervention was 22 for 1 year. The mean bodyweight and the intake of total and saturated fat were lower in the intervention group compared with that in the control group during the intervention (table 1). Further, intake of dietary fibre and physical activity were higher in the intervention group.

In the intervention and the control group, respectively, 10% and 27% of the participants did not achieve any of the predefined goals by the 3-year examination, whereas 14% and 6% achieved four or five goals (p<0·0001 for Fisher's exact test). There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow-up. Incidence rate per

100 person-years ranged from 8·4 (95% CI 6·2–11·3) in the participants who did not achieve any of the goals at the 3-year visit, to 2·0 (1·0–4·3) in those who achieved four or five of the goals. The hazard ratios were 1·00, 0·85 (0·57–1·28), 0.66 (0·40–1·09), 0·69 (0·38–1·26), and 0·23 (0·10–0·52) for success score from 0, 1, 2, 3, to 4–5, respectively (test for trend p=0·0004).

To assess the independent effects of achieving the success score components at the 3-year examination on diabetes incidence during the total follow-up, all five variables for lifestyle goal were first individually included in a Cox model. Univariate hazard ratios (95% CI) were 0·45 (0·31–0·64) for weight reduction from baseline, 0·65 (0·45–0·95) for intake of fat, 0·59 (0·31–1·13) for intake of saturated fat, 0·69 (0·49–0·96) for intake of fibre, and 0·62 (0·46–0·84) for physical activity, comparing those who did or did not achieve the respective goal. When all five success score components were simultaneously included in the Cox model, the multivariate-adjusted hazard ratios for diabetes (95% CI) were 0·43 (0·30–0·61) for weight reduction, 0·80 (0·48–1·34) for intake of fat, 0·55 (0·26–1·16) for intake of saturated fat, 0·97 (0·63–1·51) for intake of fibre, and 0·80 (0·57–1·12) for physical activity. Furthermore, weight change from baseline was significantly associated with the achievement of each of the other four lifestyle goals, and consequently, success score was strongly and inversely correlated with weight reduction. The 3-year weight reduction was 0·5%, 2·1%, 4·3%, 4·7%, and 8·7% for success score from 0, 1, 2, 3, to 4–5, respectively (test for trend p<0·0001). Additionally, all the dietary goals (total fat, saturated fat, and fibre) were significantly associated with each other (p for all <0·0001). Achievement of the fat intake goal or the fibre intake goal was associated also with the physical activity goal (p=0·0019 and p<0·0001, respectively).

To explore whether the reduced long-term risk of type 2 diabetes in the intervention group could be attributed solely to a reduced risk during the actual intervention of the study, we excluded all participants who were diagnosed with diabetes during the intervention (n=116) and calculated the incidence rates exclusively for the post-intervention follow-up. The median post-intervention follow-up time was 3 years, and the number of incident new cases of type 2 diabetes was 31 in the intervention group of 221 people at risk, and 38 in the control group of 185 people at risk. The corresponding incidence rates were 4·6 and 7·2 per 100 person-years, respectively (log-rank test p=0·0401), ie, 36% relative risk reduction (figure 3).

Bodyweight, physical activity, and nutrient intakes in those without diabetes at the end of the intervention are shown in table 2. The differences in these variables between the groups remained favourable for the intervention group during the post-intervention follow-up. The proportion of physically active individuals decreased in the control group. Conversely, 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 of saturated fats than the intervention group.

	Intervention		Control		p*
	n	Mean	n	Mean	
Bodyweight (kg)					
Baseline	265	86·7	257	85·5	0·3267
Year 1	256	82·2	250	84·8	<0·0001
Year 3†	256	83·4	251	85·2	<0·0001
Last intervention period visit†	257	84·3	251	85·6	<0·0001
Proportion of physically active (%)‡					
Baseline	261	64	257	67	0·5192
Year 1	252	86	245	69	<0·0001
Year 3†	256	82	251	71	0·0003
Last intervention period visit†	256	81	251	71	0·0013
Energy proportion of fat (%)					
Baseline	264	36	255	37	0·0670
Year 1	254	33	245	35	0·0001
Year 3†	254	32	246	34	<0·0001
Energy proportion of saturated fat (%)					
Baseline	264	16	255	17	0·0188
Year 1	254	14	245	16	<0·0001
Year 3†	254	13	246	15	<0·0001
Dietary fibre (g per 1000 kcal)					
Baseline	264	11·7	255	11·7	0·9431
Year 1	254	14·2	245	12·5	<0·0001
Year 3†	254	14·1	246	12·7	<0·0001

*p for test of equality between groups, adjusting for baseline level. †Last observation brought forward for individuals who dropped out or became diabetic during the study. ‡Individuals who reported walking, cycling, or other moderate intensity activity for at least 4 h per week categorised as physically active.

Table 1: **Bodyweight, physical activity, and dietary intake during the intervention period of the study**

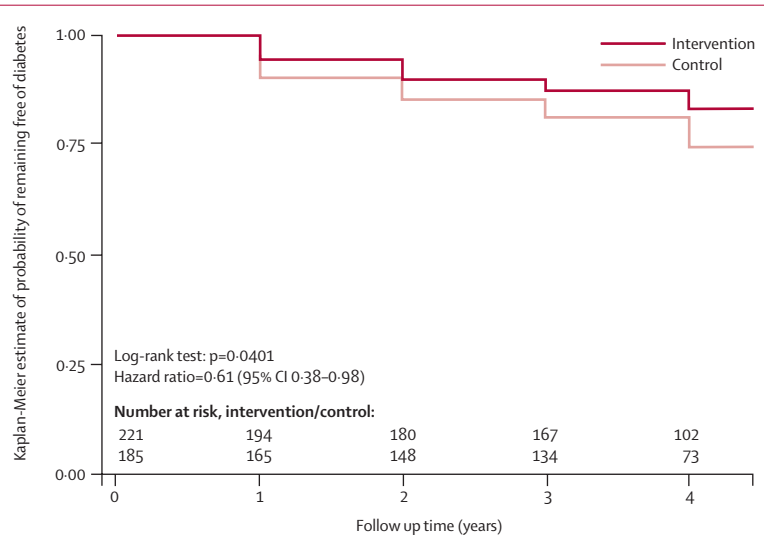

Figure 3: **Diabetes by treatment group during the post-intervention follow-up period**
Follow-up time is truncated at 4 years, since number of participants at risk beyond this point was low, but they are included in calculation of hazard ratios.

The success score analysis was repeated to analyse the effect of maintained lifestyle changes on the diabetes incidence during the post-intervention follow-up. In the intervention and control groups, respectively, 7% and 14% of the participants did not achieve any of the lifestyle goals at the first follow-up visit, 32% and 40% achieved one, while 18% and 7% achieved at least four out of the five goals (p=0·0042 for Fisher's exact test). The incidence rate of diabetes per 100 person-years was 8·0 (95% CI 4·2–15·4) in the group that did not achieve any of the goals, compared with 3·8 (1·7–8·5) in the group with 4 or 5 goals achieved. The hazard ratios were 1·00, 0·96 (0·45–2·04), 0·37 (0·15–0·93), 0·78 (0·32–1·91) and 0·54 (0·20–1·49) for the success score from 0, 1, 2, 3, to 4 or 5, respectively (p=0·1089).

Univariate hazard ratios (95% CI) for diabetes incidence during the post-intervention follow-up were 0·55 (0·30–1·02) for achieving the weight reduction goal, 0·74 (0·44–1·27) for achieving the fat intake goal, 1·01 (0·54–1·89) for achieving the saturated fat intake goal, 0·72 (0·40–1·30) for achieving the fibre intake goal, and 0·62 (0·36–1·06) for achieving the physical activity goal, compared with those who did not achieve the respective goal at the first post-intervention follow-up examination. When all five variables for lifestyle goals were simultaneously analysed, the adjusted hazard ratios were 0·52 (0·28–0·96) for weight reduction from baseline, 0·67 (0·35–1·31) for the intake of fat, 1·62 (0·68–3·85) for the intake of saturated fat, 0·77 (0·38–1·57) for the intake of fibre, and 0·82 (0·46–1·48) for physical activity.

	Intervention		Control		p*	p†
	n	Mean	n	Mean		
Bodyweight (kg)						
Baseline	190	84·9	165	84·0	0·5174	
Last intervention visit	190	81·8	165	83·3	<0·0001	
First post-intervention follow-up visit	190	83·1	165	84·0	0·0032	0·1482
Proportion of physically active (%)‡						
Baseline	184	70	164	70	0·9102	
Last intervention visit	187	88	164	76	0·0035	
First post-intervention follow-up visit	187	86	164	71	0·0005	0·0273
Energy proportion of fat (%)						
Baseline	187	36	159	37	0·1879	
Year 3‡	187	31	159	34	0·0002	
First post-intervention follow-up visit	187	31	159	33	0·0174	0·1189
Energy proportion of saturated fat (%)						
Baseline	187	16	159	17	0·0676	
Year 3‡	187	13	159	15	<0·0001	
First post-intervention follow-up visit	187	12	159	14	0·0001	0·0128
Dietary fibre (g per 1000 kcal)						
Baseline	187	11·9	159	11·9	0·9750	
Year 3‡	187	14·5	159	12·9	0·0003	
First post-intervention follow-up visit	187	13·6	159	12·6	0·0071	0·4577

*p for test of equality between the groups, adjusting for the baseline level. †p for test of equal change between the groups from the last intervention period visit to the first post-intervention follow-up visit, adjusting for the level at the last intervention visit. ‡Individuals who reported walking, cycling, or other moderate intensity activity for at least 4 h a week were categorised as physically active.

Table 2: **Bodyweight, physical activity, and dietary intakes of participants of the post-intervention follow-up period who were without diabetes at the end of the intervention**

Discussion

Individually randomised controlled lifestyle intervention studies have shown the benefit of healthy lifestyle on delaying the deterioration of glucose tolerance to manifest type 2 diabetes, at least as long as the intervention continues.[5–8] Our study with a median of 7 years total follow-up shows that a marked difference in the cumulative incidence of diabetes can be sustained after the discontinuation of active counselling. The absolute difference in diabetes risk between the intervention and control groups was about 15% during the initial trial period and also remained the same during the post-intervention follow-up. The relative risk reduction of 43% was, however, less than the 58% seen during the original study,[5] as expected from the increasing cumulative diabetes incidence in both groups.

The earlier Da Qing IGT and Diabetes Study[4] with clinics randomly assigned either to diet, exercise, or diet plus exercise intervention showed a 31%, 46%, and 42% risk reduction, respectively, after a 6-year intervention. The relative risk reduction achieved in our study was about the same after a similar period even though the duration of active intervention was shorter. Thus, from a public health point of view there is an important message: an intensive lifestyle intervention lasting for a limited time can yield long-term benefits in reducing the risk of type 2 diabetes in high-risk individuals.

The achieved changes in physical activity and dietary habits seemed to be maintained at least 1 year after the discontinuation of the intervention. The differences between the groups persisted despite a possible dilution effect, since the control group participants can be considered to have received a reinforced mini-intervention when they were provided with their own glucose results and told about the main findings of the Diabetes Prevention Study at the end of the intervention period. Still, a modest difference in bodyweight change from baseline between the intervention and control groups was preserved. Our results confirm the findings from earlier studies showing that interventions can have long-term effect on lifestyle,[16,17] and offer encouraging evidence for the efficacy of comprehensive lifestyle intervention even without large reduction in weight.

Analysis of the success score showed that most people who maintained the lifestyle goals at 3-year visit remained free of diabetes during the extended follow-up. This finding indicates that the true effect of healthy lifestyle results in a dramatically better outcome than that seen by the intention-to-treat analysis of the treatment effect. Each of the success score components at the 3-year visit

(except that for saturated fat intake) was significantly associated with the reduction in diabetes risk in univariate analyses, but when all the components were included into the model simultaneously, only the effect of weight reduction remained significant. Analyses from the first post-intervention follow-up visit revealed similar tendency; however, the only significant association was between weight reduction and diabetes risk in the multivariate model. The findings suggest that dietary composition and physical activity are important in diabetes prevention but their effect on diabetes risk is in large part, although not entirely, mediated through resulting weight reduction. Nevertheless, because of the multicollinearity shown by the fact that weight change correlated with all the other intervention goals, the interpretation of the results should be made cautiously.

Our findings do not allow us to distinguish between the carry-over effect from the intervention, and the ongoing effect of lifestyle during the post-intervention follow-up, on diabetes incidence. In a subgroup analysis of the Diabetes Prevention Study population, we showed a marked improvement in insulin sensitivity concomitantly with weight loss, whereas insulin secretion did not change significantly.[18] This finding suggests that the prolonged benefit of the lifestyle intervention on the diabetes risk could partly be attributed to a correction of insulin resistance, which, on the other hand, might result in a preservation of the beta cell function. Even so, we cannot rule out the effect of maintaining lifestyle changes after the original intervention period. The question concerning the risk reduction in those in whom the success score or its components changed during the post-intervention follow-up period would be of interest, but unfortunately at the present our data have restricted statistical power for this kind of subgroup analyses.

About a third of participants in the intervention group met none or only one of the predefined goals 1 year after the intervention. Adherence to the intervention is a specific challenge for future diabetes prevention programmes. Oral antidiabetic medications have been shown to prevent diabetes, and could be an option for those who have not responded satisfactorily to lifestyle intervention. However, medications seem to lower blood glucose as long as they are taken, but much of their effect dissipates as soon as the drug is discontinued.[6,19–21] Unfortunately, there has thus far been no pharmacological trial specifically targeted to people at high risk of diabetes and who were unable to change their lifestyle.

Some limitations of the present study have to be addressed. The analyses related to the post-intervention follow-up period of the Diabetes Prevention Study were not planned in the original study protocol, and post hoc analyses have to be interpreted with caution. The post-intervention follow-up was not foreseen while calculating the original sample size,[10] and because of low numbers of people at risk and cases of diabetes the statistical power remains restricted. Furthermore, the study participants were volunteers and willing to take part in a long-lasting trial and thus were probably more health-conscious than the general population. A low number of withdrawals is a marker of high commitment, but since there was no difference between the groups it is also an advantage in the analyses. Future studies will reveal if the results from this clinical trial can be transposed into usual health-care settings. Also the generalisability of our findings in other populations must be studied.

Based on the Kaplan-Meier analysis, around 50% of people with impaired glucose tolerance will develop diabetes during 10 years when no active intervention is applied. Although a lifestyle intervention alone, even if successful, does not necessarily prevent type 2 diabetes in all individuals, it will still postpone the onset of the disease. Even delaying the onset of diabetes can have a substantial effect on subsequent morbidity, and therefore on the cost-effectiveness of diabetes prevention.[22] Whether the lifestyle intervention used in the Diabetes Prevention Study reduces diabetes-related microvascular and macrovascular complications in the long run is still to be proven, and such an assessment is planned in the future after an adequate number of cases and person-years have been accumulated.

The high diabetes incidence even in the intervention group of our study suggests that preventive actions should probably be targeted to all high-risk individuals, even before impaired glucose tolerance is present. The lifestyle intervention used in the Diabetes Prevention Study has formed the basis for the implementation programme for the prevention of type 2 diabetes in Finland.[23] This programme identifies high risk individuals with a simple, validated risk score questionnaire[24,25] and thus is likely to reach people at an earlier stage in the process leading to diabetes. Although a population-based strategy to fight the pandemic of type 2 diabetes is urgently needed, an individualised approach to guide people at high risk is also warranted. A simple lifestyle intervention seems to work well. However, further research is needed to reveal the optimum and most cost-efficient strategy, intensity, and duration of such an intervention. The results from the extended follow-up of the Finnish Diabetes Prevention Study nevertheless show that the effect of lifestyle intervention on diabetes risk does not disappear after active lifestyle counselling is stopped.

Contributors

J Lindström and P Ilanne-Parikka had joint responsibility for writing this manuscript and share the primary authorship of this paper. M Peltonen did the statistical analyses and participated in writing the manuscript. S Aunola, J G Eriksson, K Hemiö, H Hämäläinen, P Härkönen, S Keinänen-Kiukaanniemi, M Laakso, A Louheranta, M Paturi, J Sundvall, and T T Valle contributed to data extraction and revised the manuscript. J Tuomilehto and M Uusitupa are the principal investigators of the study and participated in writing the manuscript.

Acknowledgments

We thank Zygimantas Cepaitis, Martti Hakumäki, Anja Ilmanen, Hilkka Kaisto, Kaija Kettunen, Hannele Kivelä, Arja Kylliäinen, Ritva Läärä, Paula Nyholm, and Arja Putila for their skillful assistance in the study; and Marja-Riitta Taskinen and Antti Aro for their participation in the endpoint committee. This study was supported by the Academy of Finland (grants 8473/2298, 40758/5767, 38387/54175, 46558), Juho Vainio Foundation, Ministry of Education, Novo Nordisk Foundation, Yrjö Jahnsson Foundation and Finnish Diabetes Research Foundation, and EVO funds from Tampere, Kuopio, and Oulu University Hospitals.

Conflict of interest statement

We declare that we have no conflict of interest.

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