DIAVIP

Diabetes Prevention in Primary Care
- Implications for Physical Activity

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Skaraborgsstudien
DIAVIP

Walking is man´s best medicine
Hippocrates 460-479 B.C.

To Eric
Johan and Stefan

DIAVIP - Diabetes Prevention in Primary Care

Implications for Physical Activity

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ABSTRACT

Aim: The overall aim was to study the effect of physical activity in individual with impaired glucose tolerance (IGT) and insulin resistance. We set out to: 1. Evaluate different screening instruments to identify individuals with IGT; 2. Study feasibility and metabolic effects of an intervention focusing on physical activity in individuals with IGT; 3. Study the association between self-reported physical activity and circulating concentrations of the inflammatory marker CRP in IGT-subjects; 4. Study the predictive value of insulin resistance on cardiovascular disease (CVD) in individuals without diabetes considering the modifying effect of physical activity.

Methods: Paper I, II and III: The FINDRISC questionnaire was delivered by mail to people in the Skaraborg County. Individuals with a risk-score ≥15 underwent testing of their fasting blood glucose and an oral glucose tolerance test (OGTT, 75 g). In addition, opportunistic screening by asking three short questions was used to identify individuals with impaired glucose metabolism in primary care. Fifty-two individuals with IGT participated in an explorative randomized controlled trial comparing two different interventions, focusing on increased physical activity, with usual care. The participants were metabolically phenotyped at baseline and after one year. Paper IV and V: A population-based survey was performed 2002 – 2005 in the Skaraborg County. A total of 2816 individuals, 35-75 years old, participated and they were characterized with anthropometry blood sampling for estimation of HOMA, random blood glucose and an OGTT. Validated

questionnaires on lifestyle were completed. The participants were restudied after 8 years and information on hosipital care for CVD diagnoses and mortality was collected.

Results: The FINDRISC questionnaire was sent out to 9734 individuals and was found to have a positive predictive value (PPV) for impaired glucose metabolism of 55% but was less efficient to identify IGT-subjects (PPV=16%). The short questionnaire might be used as an additive tool for screening at the Health Care Unit or in an advertisement. Our method to implement physical activity in individuals with IGT showed tendencies to decrease body weight, waist circumference and sagittal diameter, in the intensive care group compared with the basic care and the control groups. Vigorous self-reported physical activity eliminated the difference observed in circulating CRP concentrations in male IGT-subjects compared with men showing normal glucose tolerance. Finally, data from the same Skaraborg cohort showed that self-reporting a high level of leisure time physical activity, such as jogging or swimming ≥ 2 hrs/week eliminated the apparent increased risk of insulin-resistant male individuals to develop CVD.

Conclusions: FINDRISC is an efficient screening tool for detection of undiagnosed individuals with impaired glucose metabolism while the opportunistic screening method was less efficient but may be used as an additive tool in primary care. Our intervention method aiming at an increased physical activity also induced less calorie intake in IGT-subjects. However, the collective lifestyle changes observed with intensive care decreased waist-circumference and sagittal diameter compared with individuals with IGT given usual care. Finally, more vigorous physical activity than generally recommended may be required to limit subclinical inflammation in male IGT-subjects and to protect male insulin-resistant individuals from developing cardiovascular disease.

Keywords: impaired glucose tolerance, prevention, primary care, insulin resistance, physical activity, cardiovascular disease, screening, inflammation

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Typ 2 diabetes (vuxendiabetes) föregås ofta av ett stadie med antingen förhöjt fastesocker värde (IFG = lätt förhöjt blodsocker i fasta) eller så kallad nedsatt glukostolerans, IGT (IGT= socker koncentrationen i blodet stiger för högt efter att man druckit koncentrerad sockerlösning, dvs man är intolerant mot socker). Både individer med IFG och IGT har en starkt ökad risk att utveckla diabetes. Dock vet man sedan mer än 10 år tillbaka att utvecklingen av typ 2 diabetes kan förhindras eller uppskjutas om individer med IGT ändrar livsstil genom att gå ner i vikt och börja motionera. Detta är klart visat i tre stora studier där deltagarna fick mycket hjälp med att förändra sin livsstil. Alla tidigare studier är baserade på individer med IGT eftersom personer med IFG inte verkar ha samma goda effekt av kost och motion som individer med IGT. Både individer med IGT och de med IFG har ett visst mått av nedsatt insulinkänslighet (oförmåga att tillgodogöra sig insulinets effekt) men de med IGT har främst en nedsatt känslighet i muskler medan med IFG främst har en nedsatt insulinkänslighet i levern. För att hitta personer med IGT måste man idag göra en så kallad glukosbelastning, dvs personen får, efter en natts fasta, dricka koncentrerad sockerlösning och sedan vänta i två timmar varefter blodsocker tas. Eftersom det är en tidskrävande undersökning görs mycket få glukosbelastningar i Sverige idag. Däremot behöver man bara ta ett fastande blodprov för att hitta individer med IFG.

Det är idag känt att individer med förstadier till typ 2 diabetes har en ökad risk för hjärtkärlsjuklighet, men det är oklart exakt vad det är som påverkar risken och inte heller om graden av fysisk aktivitet kan förändra risken. Vidare är det tydligt visat att fysisk aktivitet generellt är viktigt samt att det spelar stor roll för vår hälsa men om ökad motion i sig minskar risken för utveckling av typ 2 diabetes och dess följdsjukdomar är mindre väl beskrivet.

Syfte

Syftet med den här avhandlingen var främst att se om det var möjligt att omsätta erfarenheterna från de stora internationella studierna i diabetesprevention till vanlig klinisk praxis. För att göra det behövde vi också undersöka befintliga metoder och eventuellt

utveckla nya bättre metoder att hitta individer med IGT. Ytterligare ett syfte var att undersöka om nedsatt insulinkänslighet på för övrigt friska individer hade någon betydelse för utvecklingen av hjärtkärlsjukdom. Slutligen studerades också sambandet mellan nedsatt insulinkänslighet, inflammation, fysisk aktivitet och hjärtkärlsjukdom.

Metod

För att hitta individer med IGT som skulle kunna delta i en studie med fokus på fysisk aktivitet skickades frågeformuläret FINDRISC (0−26 poäng) ut till 9734 individer, 35−75 år gamla. Deltagare med riskpoäng ≥15 inbjöds att komma för ett fasteblodsocker och om det var normalt, genomgick de en glukosbelastning. Efter glukosbelastningen tillfrågades de med IGT om att delta i en studie. De 52 personer som deltog lottades till att vara med i en intensivgrupp, en basgrupp eller till en kontrollgrupp.

För att undersöka effekten av fysisk aktivitet beträffande inflammation samt risken för hjärtkärlsjukdom hos individer med nedsatt insulinkänslighet användes data insamlade i Skaraborgsprojektet 2002-2005. Då genomgick 2816 individer från Vara och Skövde en glukosbelastning och en omfattande hälsoundersökning. Efter åtta år har även data på dödlighet och sjuklighet tagits fram från det nationella slutenvårdsregistret och dödsorsaksregistret. En återundersökning av dessa deltagare pågår också och deltagarna från Skövde är idag färdigundersökta. I denna grupp samt i screening på två vårdcentraler och i en annons i lokaltidningen testade vi även tre enkla frågor samt ett slumpmässigt taget blodsocker för att hitta individer med IGT och jämförde med utfallet från FINDRISC.

Resultat

I första artikeln redovisar vi resultatet från deltagare i FINDRISC med poäng ≥15. Bland de som genomgick glukosbelastning hade 11% typ 2 diabetes, 16% IGT och 29% IFG. Under första året i studien slutade 7 deltagare varav 3 fick typ 2 diabetes och inte ville vara med längre, 3 ville avsluta sitt deltagande av andra skäl och en deltagare dog av skäl som inte kunde kopplas till studien. Denna studie fann att de som hade en risk poäng ≥15 var äldre (medelålder 65 år) och att många hade flera andra sjukdomar. Trots detta hade de som var med i intensivgruppen större viktnedgång samt större

minskning av midjemått och bukhöjd än övriga grupper. Det visade sig dock vara svårt att isolera en livsstilsförändring med fysisk aktivitet från kostförändringar eftersom de flesta i intensivgruppen även hade ändrat sin kost.

När inflammation studerades, med hjälp av markören högkänsligt CRP (hs-CRP), visade sig män med IGT ha hade högre hs-CRP än de med normala blodsocker. Däremot de som tränade minst två timmar per vecka hade helt normalt hs-CRP trots att de hade IGT.

Män med nedsatt insulinkänslighet visade sig också ha klart ökad risk för framtida hjärtkärlsjukdom. Detta kunde dock inte ses hos kvinnor och inte heller hos män som tränade minst två timmar veckan

De tre enkla frågor som utvecklades i projektet för att hitta individer med IGT, föll väl ut i annonsen och vid screeningen på vårdcentral.

Slutsatser

FINDRISC var en bra enkät för att hitta individer med störningar i glukosomsättningen, men inte så bra när det gällde att hitta individer med just IGT. Istället skulle man kunna använda sig av tre enkla frågor annonserade i lokaltidningen eller på vårdcentralen i framtiden. En intensiv insats i primärvården med fokus på fysisk aktivitet var dock väl genomförbar och resultaten i intensivgruppen var positiva. Man bör dock vara medveten om att en satsning på ökad fysisk aktivitet många gånger medför en kostförändring. En nedsatt insulinkänslighet kan förebåda hjärtkärlsjukdom hos män men risken kan modifieras av en hög grad av fysisk aktivitet. Hög grad av fysisk aktivitet verkar också ha god effekt på låggradig inflammation hos män med IGT.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Margareta I Hellgren, Max Petzold, Cecilia Björkelund, Hans Wedel, Per-Anders Jansson, Ulf Lindblad. Feasibility of the FINDRISC questionnaire to identify individuals with impaired glucose tolerance in Swedish primary care. A cross-sectional population-based study. Diabet Med. 2012. Dec; 29(12): 1501-5.

II. Margareta I Hellgren, Bledar Daka, Per-Anders Jansson, Ulf Lindblad. Screening in primary care for individuals with impaired glucose tolerance (Submitted).

III. Margareta I Hellgren, Max Petzold, Héléne Berteus-Forslund, Hans Wedel, Per-Anders Jansson, Ulf Lindblad. Feasibility of a randomized controlled intervention with physical activity in participants with impaired glucose tolerance recruited by FINDRISC - a pilot study. (Accepted for publication in Scandinavian Journal of Public Health).

IV. Margareta I Hellgren, Bledar Daka, Max Petzold, Charlotte A Larsson, Per-Anders Jansson, Ulf Lindblad. C-reactive protein concentrations differ by sex, physical activity and glucose tolerance: A cross-sectional population-based study in Sweden. (Submitted).

V. Margareta I Hellgren, Bledar Daka, Per-Anders Jansson, Ulf Lindblad, Charlotte A Larsson. Insulin resistance predicts cardiovascular morbidity in men without diabetes mellitus and this effect is modified by level of physical activity. (Submitted).

CONTENT

ABBREVIATIONS

CI	Confidence Interval
CVD	Cardio Vascular Disease
DPP	Diabetes Prevention Project
DPS	Diabetes Prevention Study
DIAVIP	DIAbetes preVention In Primary care
FFA	Free Fatty Acids
f-Insulin	Fasting plasma insulin concentration
fP-glucose	Fasting plasma glucose concentration
HOMAir	Homeostasis Model Assessment of insulin resistance
HsCRP	High sensitive C-reactive protein
IFG	Impaired fasting glucose
IGM	Impaired glucose metabolism
IGT	Impaired glucose tolerance
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
OR	Odds Ratio
SD	Standard Deviation
VSC	Vara – Skövde cohorten 2002−2005
VSC-10	The follow-up of the VSC-cohort 2011-2014
WHO	World health organization

1 INTRODUCTION

1.1 The prevalence and epidemiology of type 2 diabetes

Type 2 diabetes is one of the most common chronic diseases in the world today and is considered to be one of the most serious threats against health by WHO [1]. The prevalence worldwide has increased from about 347 million cases in 1980 to approximately 541 million cases in 2008 and is projected to reach 552 million people in 2030 [2]. Today, diabetes contributes to a vast extent to the burden of diseases in large countries such as India and China [3] [4] mainly due to a westernized lifestyle characterized by overweight and physical inactivity [5]. In contrast to the increase of type 2 diabetes worldwide the incidence in Sweden has been quite stable over the past 10 years with an overall prevalence of 3-4% [6-9]. Nevertheless, diabetes remains a major health problem with considerable costs for society and suffering for the individual. The purpose of this thesis was to explore possible mechanisms and actions to prevent development of type 2 diabetes in a primary care setting.

1.2 Glucose metabolism

In clinical practice there are three main methods to evaluate glucose metabolism. In ordinary clinical practice a fasting plasma glucose is frequently used, but glucose metabolism can also be measured by an oral glucose tolerance test (OGTT) [10]. The OGTT is performed after an overnight fast and is a measurement of fasting plasma glucose followed by a plasma glucose two hours after an oral ingestion of 75 g glucose. Another way to measure glucose metabolism is by testing HbA1c, a measurement of glycosylated hemoglobin reflecting the average glucose level over the past 2−3 months [11].

Glucose is an essential nutrient for the human metabolism and while most of the cells in the body can make use of other nutrients, such as fat and protein, the brain is totally dependent on a continuous supply of glucose. To satisfy this need glucose is stored in the liver as glycogen and released under fasting conditions [12]. The uptake of glucose in skeletal muscle, liver and adipose tissue as well as the release from glycogen to glucose is regulated by insulin [13]. While type 1 diabetes is due to a failure of insulin production in the

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beta-cells, type 2 diabetes is mainly due to a loss of sensitivity to insulin in the target cell [14].

Type 2 diabetes is usually initiated by an increase in weight combined with physical inactivity that promote signalling in inflammatory pathways which in turn results in insulin resistance in individuals prone to develop diabetes [13]. Beta-cell failure is also present in individuals with type 2 diabetes and over the time there is a continuous destruction of the beta-cells with a progressive decrease in insulin secretion.

1.2.1 Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

Type 2 diabetes is preceded by a "prediabetic" stage with either increased fasting glucose (IFG) or impaired glucose tolerance (IGT) or sometimes both. Individuals with IFG have a slightly increased concentration of fasting plasma glucose, while IGT is characterized by an increased 2-hour glucose concentration (Table 1). The mechanisms behind IFG and IGT is different in several ways, which can be demonstrated by glucose and insulin concentrations during an OGTT [15]. IFG is defined by slightly increased blood glucose concentrations at baseline reflecting increased hepatic glucose production (Table 1) [15]. When individuals with IFG undergo an OGTT, glucose increases rapidly over the first 30-60 minutes, reaches a peak after 60 min and declines to normal values after 120 minutes. Serum insulin may be increased already in the fasting state as a consequence of a hepatic resistance. If the insulin concentrations present a near normal curve during an OGTT this suggests a normal insulin sensitivity in skeletal muscles because a majority of glucose uptake takes place in muscle cells. In individuals with isolated IGT, the fasting blood glucose is normal and likewise the initial response to a glucose load is similar compared with normal glucose tolerant individuals but the increased concentrations remain after 2 hours, indicating insulin resistance primarily in skeletal muscle. The gold standard for measurement of insulin sensitivity is by the euglycemic hyperinsulinemic clamp procedure [16], but for practical reasons in epidemiological contexts insulin resistance is usually calculated by the Homeostasis Model Assessment of insulin resistance (HOMAir), an algorithm based on fasting insulin and fP-glucose concentrations (fS-Insulin x fP-Glucose/22.5) [17].

Apart from skeletal muscle and liver, insulin resistance is also manifested in adipose tissue [18]. Insulin is a potent inhibitor of lipolysis, however, individuals with IGT and individuals show increased fasting free fatty acid (FFA) concentrations indicating a resistance towards the antilipolytic action

of insulin. Unsuppressed FFA aggravate insulin resistance in the periphery and keep a vicious cycle going [18]. From this follows that hyperinsulinemia indicates resistance towards the anti-lipolytic effect of insulin in IGT subjects. Taken together, all individuals diagnosed with IFG and IGT to some extent display beta-cell dysfunction as well as insulin resistance in the liver, skeletal muscle and adipose tissue [14].

1.3 Diagnoses of type 2 diabetes, IFG and IGT

1.3.1 Type 2 diabetes

The definition of type 2 diabetes is based on recommendations from the WHO from 1998 [10] and includes a fasting plasma glucose of ≥7.0mmol/L or a 2-hour venous glucose of ≥7.8mmol/L alternatively a random venous plasma glucose of ≥ 11.1mmol/L with symptoms indicating hyperglycaemia. Two consecutive tests are required for diagnosis except when symptoms are present. From January 2014 an HbA1c ≥48mmol/L will be added to the diagnostic criteria in Sweden. All measurements have to be repeated twice or exist together with one of the other diagnostic criteria (Table 1).

Table 1. Values for diagnoses of type 2 diabetes and other categories of hyperglycemia

	Glucose concentration, mmol l^{-1} (mg dl^{-1})		
	Whole blood Venous	Whole blood Capillary	Plasma* Venous
Diabetes Mellitus:			
Fasting	≥6.1 (≥110)	≥6.1 (≥110)	≥7.0 (≥126)
or			
2-h post glucose-load	≥10.0 (≥180)	≥11.1 (≥200)	≥11.1 (≥200)
or both			
Impaired Glucose Tolerance (IGT):			
Fasting (if measured)	<6.1 (<110)	<6.1 (<110)	<7.0 (<126)
and			
2-h post-glucose load	≥6.7 (≥120) and <10.0 (<180)	≥7.8 (≥140) and <11.1 (<200)	>=7.8 (≥140) and <11.1 (<200)
Impaired Fasting Glucose (IFG):			
Fasting	≥5.6 (≥100) and <6.1 (<110)	≥5.6 (≥100) and <6.1 (<110)	≥6.1 ≥110) and <7.0 (<126)
and (if measured)			
2-h post-glucose load	<6.7 (<120)	<7.8 (<140)	<7.8 (<140)

*Corresponding values for capillary plasma are: for Type 2 Diabetes, fasting ≥7.0 (>=126), 2-h ≥12.2 (≥220); for Impaired Glucose Tolerance, fasting <7.0 (<126) and 2-h ≥8.9 ≥160) and <12.2 (<220); and for Impaired Fasting Glycaemia ≥6.1 (≥110) and <7.0 (<126) and if measured, 2-h <8.9 (<160).

1.3.2 IFG and IGT

According to WHO, IFG is defined as a fasting plasma glucose of 6.1−7.0 mmol/L [10]. Today, this definition is under debate and the American diabetes association (ADA) has decided on a lower value for IFG, i.e. ≥5.6 mmol/L since 2003 [19]. A discussion about another threshold in Europe is ongoing. IGT is defined as fP-glucose of <7.0mmol/L combined with a 2-hour plasma glucose of ≥7.8 mmol/L and <11.1mmol/L (Table 1).

1.4 Complications of abnormal glucose tolerance

A well-established fact is that type 2 diabetes is associated with both micro- and macrovascular complications. Microvascular complications cause mainly nephropathy, neuropathy and retinopathy [20] while macrovascular complications present themselves as an increased risk to develop cardiovascular diseases such as angina and myocardial infarction as well as stroke and peripheral artery disease [21].

Less known is that pre-diabetes per se already causes complications, and several studies have shown that individuals with IGT and IFG have about fifty per cent increased risk to develop cardiovascular disease [22-25], even if IGT seems to be more deleterious than IFG [26]. The extent to which these complications are due to the abnormally increased fasting plasma glucose, the fasting insulin, the decreased insulin sensitivity or some other factor in the pre-diabetic state is under debate. Nephropathy, neuropathy and retinopathy are directly related to increased fasting plasma glucose as well as to an increased 2-hour post-load glucose [27]. Moreover, studies aimed at decreasing glucose concentrations, have shown disappointing results concerning macrovascular complications [28-30].

1.5 Development of type 2 diabetes

Transition from normal glucose tolerance to IFG and IGT, respectively, is to some extent due to different factors thus having implications for prevention strategies. IFG is predicted by smoking and family history, while 2-hour glucose concentrations are more associated with obesity and level of physical activity [31]. Both individuals with IGT and IFG are at increased risk to develop type 2 diabetes. Persons with normal glucose tolerance have an annual conversion rate to diabetes of 0.5% while individuals with isolated IFG and IGT have an annual conversion rate of 4-6%. A combination of IFG and IGT is even more predictive with about 10% annual conversion rate [32]. Major risk factors for development of type 2 diabetes are a family history of diabetes, obesity, physical inactivity, stress and sleep disturbances.

1.5.1 Family history of diabetes

It is a well-known fact that one cannot choose one's parents, even if it would be desirable from a diabetic point of view [33]. Individuals with both maternal and paternal diabetes have an increased risk for offspring type 2 diabetes or abnormal glucose tolerance corresponding to an odds ratio (OR) 6.1 (95% CI) and 5.2 (95% CI) respectively, relative to individuals with no

parental type 2 diabetes [34]. For individuals with maternal diabetes the odds ratios for diabetes or abnormal glucose tolerance are 3.4 (95% CI, 2.3−4.9) and 2.7 (95% CI, 2.0−3.7), respectively. Among individuals with paternal type 2 diabetes the risk increase is about the same, 3.5 (95% CI, 2.3−5.2) and 1.7 (95% CI, 1.2−2.4) respectively. The risk of developing diabetes thus seems similar for maternal and paternal diabetes in a simple additive model, but those with maternal diabetes seems to have a greater risk for other disturbances in glucose metabolism, i.e. OR of 1.6 (95% CI, 1.1−2.4) [34].

1.5.2   Over weight and obesity

If inheritance is something that is totally beyond control of the individual, obesity is not. Only a small percentage of obesity is due to genetic factors and the main reason for obesity is an excess of food intake and a decreased amount of physical activity. Overweight is defined as a BMI (estimated by the formula body weight in kg/height^2 in m) $\geq$ to 25 kg/m^{-2} and obesity as a BMI $\geq$ to 30 kg/m^{-2}. According to the WHO database the prevalence of overweight in Sweden 2009 was around 30% and of obesity 11% [35]. Today, actually more people die from overweight than from underweight [35].

The definition of obesity is based on measurements of body weight and height and is independent of the distribution of the weight. As skeletal muscle weighs more than fat a body builder would have a high BMI without the particular risks connected to obesity. In contrast to BMI waist circumference predicts per cent body fat robustly [36] and is well correlated with metabolic disturbances as well as to cardiovascular disease [37]. In addition to BMI and waist circumference another way to evaluate the negative effect of overweight is to measure sagittal diameter (the distance between the back and the highest point of the abdomen measured in a supine position), which is considered by some to be the best way to predict cardiovascular disease [38].

Mechanism of obesity

Excess of energy is stored as triglycerides predominantly in the subcutaneous abdominal adipose tissue but also in the visceral fat depot in the presence of a hypertrophy but also fat cell hyperplasia, or both. Obesity is correlated with an increased concentration of free fatty acids in circulation [39]. Free fatty acids, in turn, increases insulin resistance in skeletal muscle and increases lipolysis [39]. Excess amount of adipose tissue also induces chronic low-grade inflammation indicated by an increase of inflammatory markers such as TNF-alfa, IL-6 and C-reactive protein (CRP) [40]. Chronic inflammation is a

critical factor underlying insulin resistance and metabolic disturbances [41]. However, the exact mechanism by which abdominal and visceral obesity affects metabolism is not completely understood but associations with metabolic disturbances and insulin resistance, VLDL, HDL and inflammatory markers pave the way for cardiovascular disease.

1.5.3 Physical activity

Regular physical activity is one of the most important lifestyle factors for longevity [42]. There are even indications that the more the better, at least to a certain degree [43]. Even if the salutogenic effect of physical activity is still waiting to be completely explained there are indications of an anti-inflammatory effect as well as beneficial metabolic and psychological effects have been indicated [44].

Measuring physical activity

It is a challenge to measure physical activity and fitness and validated measurements are needed. It is also of value to differentiate between physical activity and fitness. While measuring physical activity is a measurement of movement in space, not considering heart rate, fitness is a measurement of movement in relation to energy expenditure. Measuring physical activity can thus be done by self-rated scales, by step-counters or equivalent measurements whereas a registration of heart rate is required to evaluate fitness. Fitness and physical activity are both related to cardiovascular health even if measuring fitness is usually more objective and reliable [45].

1. Self rated physical activity. Many different questionnaires have been developed to measure physical activity. A review from 2008 that evaluated 23 different questionnaires found that only two of these assessed most types of physical activity over one year and had acceptable criterion validity [46]. Apart from reporting error, the main reasons for inaccurate validity were that the questionnaire did not reflect all activity energy expenditure in daily living or that the time period was not defined [47]. At a group level neither over- nor underreporting was more prevalent [46]. Simple questionnaires seem to be valid when using four categories of physical activity. The advantage of questionnaires is that they are both easy to administer and inexpensive.
2. Bicycle tests. The most validated and frequently used bicycle test is the Åstrand bicycle test developed in the 1950s. This bicycle test is a test of aerobic capacity (physical fitness) with continuous measurements of blood pressure and heart rate during a sub-maximal test. This test is

only validated for young, physically fit men and not always applicable for a general population [48].

3. Accelerometers. Accelerometers are mechanic and computerized devices to be worn at the wrist or around the waist, usually for 7−10 days continuously measuring all movements and in some cases also heart rate (for example Acti-Heart) [49]. The gold standard for measuring fitness is the use of doubled labelled water (DLW), which is both expensive and complicated. In a study from 2013 in adolescents, DLW was used to validate an accelerometer and a questionnaire. Both the accelerometer and the questionnaire were positively correlated with total energy expenditure but the questionnaire was not correlated with physical activity total expenditure [50].

4. Walking tests. A 6-minute walking test is recommended for individuals with impairments such as heart and pulmonary diseases and is easy to perform with small physical requirements for the participants [51].

Effects of physical activity

From a public health perspective, few, if any, of the pharmaceutical substances we use to treat patients in primary care are as effective as a lifestyle intervention with physical activity. Higher levels of physical activity seem to be salutogenic and associated with fewer cardiovascular events in repeated population-based studies [52-55]. The mechanism behind this positive effect is not quite clear but likely to be mediated by lowering several different risk factors [56]. The effect on insulin sensitivity is well documented both in individuals with impaired glucose tolerance [57] and in individuals with type 2 diabetes [28]. In addition physical activity decreases blood pressure [58] and cholesterol [59].

Inflammation is known to be one of the most important predictors of cardiovascular disease [60, 61] and several studies have indicated that physical activity has an anti-inflammatory effect demonstrating a decrease in CRP [62, 63] and other inflammatory markers [56]. The amount of physical activity that is needed to achieve this positive effect is unclear and it is likely that more physical activity is needed for individuals with other risk factors, such as abnormal glucose tolerance [64]. The anti-inflammatory effect of physical activity is shown in population-based cross-sectional studies [62, 65] and confirmed in prospective studies engaging both men [66] and women [67]. It is known that subclinical inflammation increases with age [68] but possible differences between genders are not established. Some studies find basically the same levels of subclinical inflammatory status measured by hs-CRP [68] while others show generally higher concentrations in women [69].

1.5.4 Stress and sleep disturbances

Work overload and traumatizing or frustrating life events increases concentrations of circulating catecholamine and cortisol. Cortisol is a main product of the hypothalamic-pituary-adrenocortical axis and a marker of stress reactivity [70]. Cortisol also increases insulin resistance, and association have been found between stress, sleep disturbances, overweight and diabetes [71-73]. Physical activity is also known to have a positive effect on stress and depression [74].

1.6 Screening methods for abnormal glucose tolerance

The method, most frequently used, to detect individuals with previously unknown diabetes is opportunistic screening with a fasting plasma glucose, and that instrument is also recommended by the American Diabetes Association every third year after the age of 40 years. However, fasting plasma glucose is not an efficient way to detect individuals with IGT. This was clearly shown by Vaccaro in a study from 2005 as half of the individuals with IGT were not detected in a test with fasting blood glucose in spite of using the ADA-criteria for IFG [75].

Several screening instruments have been developed to identify new cases of impaired glucose metabolism, most of them based on known risk factors. Most screening instruments have focused on detection of impaired glucose metabolism (diabetes and/or IGT and/or IFG) and not on individuals primarily susceptible to lifestyle changes.

1.6.1 The FINDRISC questionnaire

When a search was conducted for screening instruments for use in primary care 8 different screening instruments for abnormal glucose tolerance were readily found, whereof FINDRISC [76] seemed to be the most frequently used screening method in Europe. FINDRISC is based on eight well known risk factors and was developed in Finland as a practical tool to estimate type 2 diabetes risk (score 0−26). Data from the evaluation of FINDRISC shows that it is an efficient tool for detection of impaired glucose metabolism with a PPV of 74.2% for men and 57.3% for women and a negative predictive value of 52.8% and 57.3% for men and women respectively, using a cut-off level of 15. The articles from Finland are focused on diabetes and glucose metabolism and the applicability for IGT cannot be evaluated [76] (Table 2).

In Italy a research group has been using a modification of the FINDRISC

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score (score 0−20), selecting individuals with one or more of the following risk factors: family history of premature cardiovascular events, hypertension, dyslipidemia, left ventricular hypertrophy, smoking and/or presence of the metabolic syndrome [77]. In this IGLOO – study, the screening questionnaire was evaluated both as an instrument to detect type 2 diabetes and to detect IGT. When testing all those with a cut-off level of 9 with a fasting blood glucose and defining IFG according to the American diabetes association criteria (5.6-6.9 mmol/l), 83% of all with unknown type 2 diabetes were identified and 57% of cases with IGT. This strategy would require the measurement of fasting plasma glucose (FPG) in 64% of the patients and an OGTT in 38%. A two-stage procedure with a fasting plasma glucose initially and an OGTT on those with fasting plasma glucose ≥5.6mmol/l would detect 78% of all with IGT, but as many as 56% had a fasting plasma glucose ≥5.6 mmol/L and would have to be further examined with an OGTT [77].

1.6.2 Other questionnaires

In Denmark another instrument, based on almost the same risk factors, was developed from the population in the Inter99 study and the ADDITION pilot study. With a cut-off of 31 the sensitivity for IGT was 46.5% [78]. The German Diabetes Risk Score (score 118−983), based on three different cohort studies in Europe focused more on dietary matters such as whole-grain bread, alcohol and smoking. The probability of developing type 2 diabetes within 5 years was 0.3% in the group with a score of 300 and increased to 23.2% in the group with a score of 750 points. Data for IGT were not evaluated [79].

Griffin et al. developed the Cambridge risk score, based primarily on self-reported data. The area under the receiver-operating characteristic (ROC) curve was 80% for type 2 diabetes. If a high cut-off was used, 30.3% would have IGT compared with using a low cut-off, whereby 16.4% would have IGT. Sensitivity and specificity for IGT were not calculated [80].

1.6.3 Questionnaires and examinations

At the University of Rotterdam another risk score was developed whereby data from a simple examination were added to a self-reported questionnaire. The examination did not add anything significant to the specificity or sensitivity of the risk score. Specificity and sensitivity for IGT was not calculated but 15% who scored positive in the first phase had IGT [81] .

In AUDRISC, developed in Australia, ethnicity was taken into account. Data for IGT were not reported [82] (Table 2).

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Another way to detect diabetes and IGT is to concentrate on a particular risk factor such as overweight, waist-hip ratio or waist circumference. Balkau et al used the top third of each for screening for abnormal glucose tolerance and found no significant differences between these variables and a high sensitivity and specificity for all three measurements. Data for IGT were not calculated [83].

Another simple method to detect individuals with IGT, using a random plasma glucose, was proposed by Ziemer et al. However, IFG was better identified and had an area under the ROC curve of 0.75 compared to 0.67 for IGT. Also, the presence of risk factors was associated with a higher positive predictive value for type 2 diabetes and for pre-diabetes [84].

Sommanavar examined random plasma glucose values for detection of type 2 diabetes and IGT and found that the optimal cut point was 6.6 mmol/L for IGT with a sensitivity of 64.7% and a specificity of 65.5%. The positive predictive value was 27.2% and the area under the curve was 71.5% [85].

The different screening methods are presented in Table 2.

Concluding this chapter there are well-validated questionnaires for abnormal glucose tolerance but no efficient methods for the detection of individuals with IGT except an oral glucose tolerance test, which is both time-consuming and expensive. Questionnaires have primarily focused on the detection of type 2 diabetes, and several efficient questionnaires have been developed for this purpose. Screening for impaired glucose metabolism in general also differs from screening for individuals with IGT, susceptible to lifestyle changes, in another aspect. Screening instruments for impaired glucose metabolism are more sensitive and specific the higher the blood glucose is and the more disease-loaded the individual is. Spijkerman et al showed that false positive individuals detected by the Cambridge risk score had significantly higher mortality risk than true negative individuals [86]. Accordingly, we will find that many individuals with impaired glucose metabolism detected by screening will be generally unhealthier and needing medical care, and that other methods, alternatively lower cut-off levels will be needed to find individuals appropriate for primary prevention with lifestyle interventions.

The FINDRISC questionnaire does not assess IGT, but as shown by the Italian study, even when selecting individuals at risk from the outset and testing everyone with a fasting blood glucose, we would still have to perform an OGTT on 56% of the population to find 78% of all those with IGT [77]. Sommanavar found that when using a random blood glucose test and a cut-point of 6.6 mmol/L, the sensitivity and specificity was about 60% without

prior selection. From this perspective, one may expect that a combination of a questionnaire and a random blood glucose test should provide a simple and efficient way to detect individuals who need further testing with OGTT.

A two-stage selection method, combining a pre-screening instrument such as the Italian modified FINDRISC questionnaire, the Danish risk score or the Cambridge risk score, with a random blood glucose cut-off of 6.6 mmol/L as proposed by Sommanavar, remains to be evaluated.

Table 2. Screening methods for impaired glucose metabolism

Screening	Number of participation	Age	Screening tool / Inclusion criteria	Sensitivity (%)	Specificity (%)	PPV	NPV	AUC	LR
FINDRISC Finland [103]	2966	45−74	Questionnaire Random	SDM Score				SDM	
				>11 Male 66.1		21.7	94.0	Male 0.72	
				Female 70.0		11.4	96.0	Female 0.73	
				>15 Male 29.8		29.6	90.8		
				Female 37.7		94.6	94.6		
				AGT				AGT	
				>11 Male 45.6		65.9	57.7	Male 0.65	
				Female 53.4		45.2	72.4	Female 0.66	
				>15 Male 16.9		74.2	52.8		
				Female 26.7		57.3	69.7		
			IGT	Not evaluated					
FINDRISC IGLOO [104]	1377	55−75	Questionnaire + One or more of the risk factors: family history of premature CV-events, hypertension, dyslipidemia, left ventricular hypertrophy, or smoking. Individuals with prior CV-events were excluded.	SDM					
				Score >9 86	41	23	93		
				+FBG >6.1 79	78	43	95		
				+FBG >5.6 83	30	30	94		
				SDM or IGT					
				Score >9 77	45	48	76		
				+FBG >6.1 55	84	69	74		
				+FBG >5.6 69	65	56	76		
				Score >9 45	77	48	76		
				+FBG >5.5 86	44	50	83		
			IGT or diabetes	+FBG >6.0 68	75	64	78		

Study	N	Age	Test	Sens	Spec			AUC	OR
DESIR France [110]	3576	40−64	The upper 30% obese of the population						
			Male:						
			BMI >27	77	69			0.75	2.5
			Waist >96	74	71			0.72	2.5
			WHR >0.96	66	70			0.76	2.2
			Female						
			BMI >26	77	71			0.66	2.6
			Waist >88	82	69			0.74	2.6
			WHR >0.86	77	70			0.77	2.5
			IGT	Not evaluated					
The Rotterdam Study + The Hoorn study [81]	Rotterdam 1016	Rotterdam 55−75	The Rotterdam study + The Hoorn study Baan	78	55	8	98		
	Hoorn 2364	Hoorn 50−74		72	55	7.2	7.2		
Herman et al [87]	Newly diagnosed diabetes 164 + 3220 without diabetes	US-population	Questionnaire Random	79	65	10			
			IGT	Not evaluated					
AUSDRISK Australien Lei Chen [82]	6060 2757 Men 3303 Women	>25	Questionnaire Random	Score >12 74	67.7	12.7			
			IGT	Not evaluated					
Diabetes	1077	40−64	Questionnaire	77	72	80			2.76

Risk Score. Griffin [80]			Random				
			IGT. The prevalence of IGT differed from 16.4% to 30.0 in the high score cohort.				
Ziemer et al [84]	990 individuals voluntary recruited	18−65	Not diabetic, not pregnant, have been working for the last 2 weeks, not taking steroids				
				40	93		80
			Diabetes IGT				67
Sommanavar [85]	1333 randomly selected individuals	45.5	A random population, non-diabetic				
			Diabetes , cut-point random blood glucose 7.7 mmol/L	86.5	80.7	42.0	90
			IGT, cut-point for random blood glucose 6.6 mmol/L	64.7	65.5	27.2	71

1.7 Prevention of type 2 diabetes

As IFG is predominantly related to family history, smoking and male sex, whereas IGT is to a large extent due to overweight and unhealthy diet, strategies for prevention have to be individualized [88]. As individuals with IGT are highly susceptible for lifestyle interventions concerning diet and physical activity most studies have concentrated on this particular pre-diabetic condition. Three high quality studies currently exist that have targeted individuals with IGT; the Chinese Da Qing study [89], the Finnish DPS study (Diabetes Prevention Study 2001) [90] and the American DPP study (Diabetes Prevention Project) [91].

1.7.1   The Chinese Da Qing study

This Chinese study was the first more extensive study concentrating on lifestyle interventions to prevent type 2 diabetes in individuals with IGT. A total of 577 individuals with IGT were randomized to either a control group, an intervention with diet, an intervention with physical activity or an intervention with both diet and physical activity [89]. An interesting observation was that almost half of the participants were lean (BMI<25). In the diet group, participants with a BMI ≥25 were recommended to lose 0.5 −1.0 kg per month until reaching the goal of a BMI ≤23. Information and support were provided on an individualized basis, and in addition group sessions were held, weekly during the first month, monthly during the next three months, and afterwards every third month. For those in the exercise group the goal was increased mild physical activity for 30 minutes a day, and for those younger than 50 years the goal was one hour of mild exercise a day. Recommendations were individualized and support was provided as in the group allocated to a dietary intervention. Participants in the group with both diet and exercise received a combination of the treatment in the separate groups. At follow-up after 6 years the interventions with diet, exercise and diet-exercise were associated with a reduction in risk of developing diabetes with 31%, 46% and 42% respectively. The cohort was followed up for the next 20 years and compared to participants in the control group. The participants in the combined diet-exercise group had a reduced diabetes incidence of 43% but no difference was found between the groups in the rates of the first CVD events, CVD mortality or all-cause mortality [92].

1.7.2   The DPS-study

In this Finnish study 522 individuals (mean age 54 years) were enrolled in a trial that focused on diet and physical activity, with diabetes conversion as primary end-point. The participants were carefully informed of the goals in

the study, i.e. weight reduction of at least 5%, a total intake of fat less than 30% of energy consumed, saturated fat less than 10% of energy consumed, an increase in fibre of at least 15 g per 1000 kcal and physical activity at least 30 minutes daily. In addition, the participants were recommended ingestion of whole-grain products, vegetables, fruits, low-fat milk and meat products, soft margarines, and vegetable oils rich in monounsaturated fatty acids. The dietary advices were individually tailored to each participant in the intervention group and based on food records completed four times a year. All participants also had 7 sessions with a nutritionist during the first year and one session every third month during the next 2 years. Participants in the intensive care group were also given individualized advice about physical activity [90]. Mean time of enrolment was 3.2 years. The overall incidence of conversion to type 2 diabetes in the intervention group was reduced by 58%. Success rate correlated with the amount of goals achieved, whereof three goals were concerning diet and one concerning physical activity [90]. Interestingly however, just as in the Da Qing study, at the ten year follow-up no significant decrease in cardiovascular disease was found in participants in the intensive care group, despite maintaining good results concerning glucose metabolism [93].

1.7.3 The DPP-study

This study from 2002 was performed in the US and enrolled 3234 persons with elevated fasting plasma glucose (5.4 mmol/L–6.9 mmol/L) and impaired glucose tolerance. In addition, participants were overweight, i.e. a BMI of at least 25 kgm^{-2} and for Asians 22 kgm^{-2}. Mean age was 51 years and mean BMI 34.0 kgm^{-2}. Participants were randomized to one of three groups 1) metformin (850 mg twice a day) 2) a lifestyle modification program with goals of at least 150 minutes of physical activity per week and a 7% weight loss or 3) placebo treatment [91]. End-point was conversion to type 2 diabetes. The lifestyle intervention group was offered a specially designed 16-lesson curriculum covering diet, exercise and behaviour modification. Participants were supported on a one-to-one basis over the first 24 weeks and thereafter with individual sessions as well as group sessions. Also in this study the results showed decreased conversion rate to type 2 diabetes of 58% with lifestyle interventions. The results for the participants randomized to metformin treatment were not quite as good as for lifestyle changes and showed a decreased conversion rate of 31%. Mean follow-up time was 2.8 years. After a follow-up time of ten years the results concerning cardiovascular disease were just as disappointing as in the Finnish diabetes prevention study with no significant differences between the groups [94].

1.7.4 Diabetes prevention studies in Sweden

An early prevention study was carried out by Eriksson et al 1975−1979 in 48 year old men (n=288) with IGT, and was followed up on several occasions until 12 years later. The outcomes were cardiovascular morbidity and mortality. This study is actually the only diabetes prevention study showing positive results on mortality rates with a 6.5 versus 14.0 events per 1000 person years (p=0.009) [95]. Another study with diet and physical activity, which focused on diabetes prevention, was carried out in northern Sweden 1995−2000 and showing good results concerning cardiovascular risk factors but the results only persisted as long as the intervention was on-going. In a study from 2005 Brekke et al. could show that positive changes in lifestyle, blood lipids and fasting insulin could be achieved and maintained for 2 years in a non-diabetic population at risk of type 2 diabetes [96]. Increased physical activity seemed to be the easiest lifestyle intervention to be preserved [97]. However, to our knowledge no studies including individuals with IGT with focus on isolated physical activity have been published thus far.

1.7.5 Diabetes prevention in clinical practice

With the aim of translating the results of the diabetes prevention studies to a public health context, the Finnish research group launched the European DE-plan (Diabetes in Europe − Prevention using Lifestyle, Physical Activity and Nutritional intervention) [98]. The DE-plan was not structured as a study. The aim was to test how to implement current research into clinical settings within existing health care systems. To our knowledge only four studies have presented results from the implementation of the DE-plan. In a preventive study in Greece Makriladis et al. recruited participants to the study using the FINDRISC questionnaire with a cut-off of ≥15 and implemented the programme launched in the DE-plan. The inclusion criterion in this study was the metabolic syndrome. Although the study lacked a control group the participants in the study improved on many measures included in the metabolic syndrome during the year of the study [99]. Interventions were implemented in Pakistan [100] and Spain [101] with a follow-up time from 8 months and 4 years respectively. Participants in the Spanish study were recruited with FINDRISC, and a program with diet and physical activity was carried out with a significant reduction in the progression to type 2 diabetes, i.e. 36.5% [101]. The study from Pakistan showed a decrease in cardiovascular risk markers after 8 months [100].

Sweden has not taken part in the DE-plan but has still been very active in lifestyle interventions in primary care. The first large-scale program for cardiovascular prevention started in 1985 in Norsjö, Västernorrland County Council area [102]. The same year another preventive programme especially

addressing women was launched in Strömstad, a small town in southern Sweden [103]. Physical activity on prescription in primary care has been validated with positive results [104] as has the effect of simple recommendations concerning physical activity and diet [105]. A large-scale multistage population-based strategy for type 2 diabetes prevention was planned in Stockholm from 1996. The intervention addressed community development, policy advocacy, education, lifestyle changes and supportive environments and focused on behavioral risk factors known to cause type 2 diabetes such as physical inactivity, obesity, tobacco use and a high fat/low fibre diet [106]. The results concerning type 2 diabetes conversion are not published yet.

1.8 Gender differences

That men and women are different in many aspects is obvious and gender differences are apparent with regard to the frequency and severity of risk factors for diabetes and cardiovascular disease but also with regard to how disease is perceived. A common perception, also in research, is that type 2 diabetes is more common in men, but according to the most recent Diabetes Atlas (2011) type 2 diabetes is as prevalent in women as in men [107]. In premenopausal women free from type 2 diabetes, sex hormones seem to protect quite effectively against cardiovascular disease, and women develop their first cardiovascular event about 10 years later than men [108]. On the other hand, the risk of cardiovascular disease increases four-fold in women with type 2 diabetes as compared to two-fold in men [109] and catches up with the risk in men [110]. The reason for these results are multiple and explained differently by different researchers. In a meta-analyses from 2002 Kanaya et al. explain the gender difference as mainly due to differences between men and women concerning cardiovascular risk factors, such as age, cholesterol, hypertension and smoking [111]. The risk factor profile differs in several ways: 1) risk factors seem to be more deleterious in women than in men 2) women with type 2 diabetes often have more than one risk factor, and 3) risk factors seem to be treated less aggressively in women than in men [111]. In contrast, Huxley et al found a significant difference (1.46, CI: 1.14−1.88) in coronary heart disease due to type 2 diabetes between men and women independent of other risk factors [109]. This study also acknowledged a greater difference between women with and without type 2 diabetes as compared to men with and without type 2 diabetes [109]. Still, it is important to remember that even if the relative risk for cardiovascular disease is higher in women with type 2 diabetes than in men with type 2 diabetes, the absolute risk of cardiovascular disease is still higher in men, both with and without type 2 diabetes [111].

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As previously mentioned, non-diabetic individuals with measures of impaired glucose metabolism seem to have an increased risk of cardiovascular disease. These findings, however, are very divergent. While some researchers find fasting plasma glucose to be predictive of CVD, and particularly in women [112], others do not find any such relationship, in men or in women [113, 114]. With regard to insulin resistance, measured by HOMA index, the results differ even more. While some researchers find a strong predictive value of insulin resistance in both men and women [115], others find no association at all in women [116], and some find an association only in women [117]. The actual mechanism, the predictive value of different measurements of glucose metabolism and possible gender differences are still unclear. Most likely the diverging results are due to differences between cohorts regarding the ages of the participants, exclusion criteria and other methodological aspects.

2 AIM

2.1 General aim

The aim of this thesis was to study the feasibility of a screening process for impaired glucose metabolism in clinical practice, followed by an intervention with focus on physical activity to prevent progression to type 2 diabetes in individuals with IGT. A further aim was to study the interaction between physical activity, inflammation and insulin resistance.

2.2 Specific aims

- To explore the efficiency of the FINDRISC questionnaire to detect individuals with IGT in a Swedish population.

- To evaluate opportunistic screening using a three question tool for the detection of individuals with IGT and compare the method with the FINDRISC questionnaire.

- To explore the feasibility and efficiency of an intervention focusing on physical activity to prevent diabetes and control metabolic risk factors in individuals with IGT.

- To investigate the association between inflammation and IGT and to consider the modifiable effect of self-reported physical activity.

- To explore insulin resistance as a risk factor for cardiovascular disease in individuals free from diabetes, and exam the modifying effect of physical activity.

3 METHODS

3.1 DIAVIP

PAPERS I AND III

The FINDRISC questionnaire and a BMI table were sent to the total population of 9734 individuals, aged 35−75 years, in a defined geographical area of Skövde, a middle-sized town in the Västra Götaland Region of Sweden. The population of 13 939 inhabitants, was socio-economically heterogeneous with few of foreign descent. Individuals with previously diagnosed were identified when this diagnosis was found in their medical record at the health care unit, and excluded from the mailing list. All recipients were encouraged to fill out the questionnaire and, regardless of risk-score obtained, return it to the health care centre. All in all, 5452 (58%) individuals returned the questionnaire. Responders scoring ≥15 were informed that they were at increased risk of developing type 2 diabetes and were advised to visit the health care centre for a fasting plasma glucose examination. All of those with a risk score ≥15 who did not respond to the invitation by mail, were contacted by telephone to make sure they had understood the invitation and the included information correctly. For further information on glucose examination see flow-chart (Figure 1). The OGTT was performed after an overnight fast and capillary plasma glucose was measured in the fasting state and at 30 and 120 min after the glucose load. Glucose was measured with the plasma-calibrated HemoCue Glucose 201 system (HemoCue AB, Ängelholm, Sweden). Impaired fasting glucose (IFG), IGT and type 2 diabetes was defined according to WHO 1998. See (Table 1).

Because we needed to find more individuals with IGT and because they were also generally exposed to a heavy burden of comorbidities (heart disease, arthralgia, kidney diseases, see results) we decreased the cut-off to ≥11 for the last 3295 individuals.
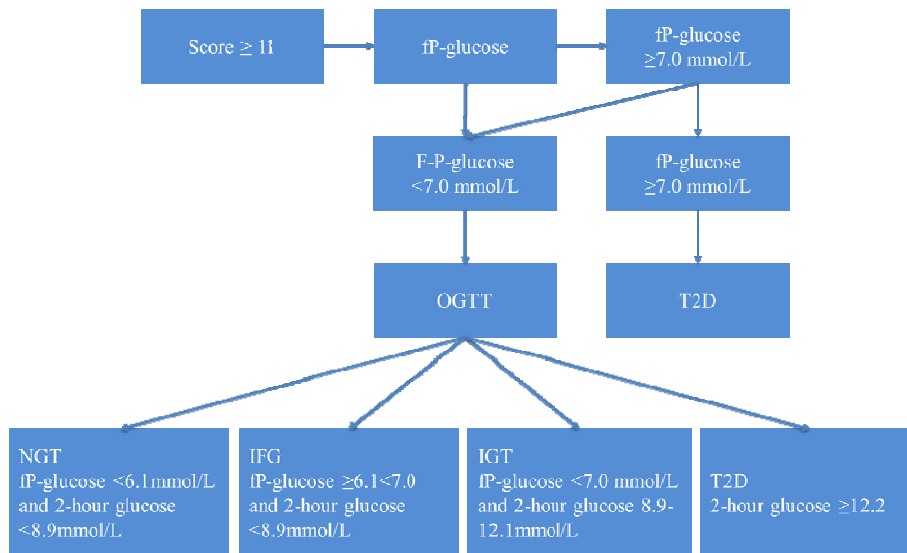
22

Figure 1. Flow-chart of the diagnostic procedure. T2D: type 2 diabetes.

Examination

All participants were examined by a specially trained nurse.

Examinations included:

1) Blood pressure, measured twice after a five minutes rest in a standardized sitting position with the arm supported at the heart level. The mean value of two measurements was registered [118].
2) Anthropometric measures: physical examinations including waist circumference (WC) measured to the nearest cm at the widest part between the lower chest and spina iliaca anterior superior, body weight measured to the nearest 0.1 kg on a calibrated scale, body height measured to the nearest cm (light indoor cloth and no shoes) [119] and sagittal diameter measured in a supine position as the distance between the back and the highest point of the abdomen [120].
3) Questionnaires for medical history i.e. diabetes, cardiovascular disease, asthma etc, socio-economic and lifestyle factors such as smoking and alcohol habits as well as leisure time physical activity [119]. Questionnaires about diet were also completed [121]. The dietary questionnaire was developed within the

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Swedish Obese Study (SOS) and has been repeatedly validated and used in many high ranked publications and we have previous experience of that questionnaire. The nurse helped to collect the questionnaires and to complete missing data. Participants also received help to complete a family history for cardiovascular disease, hypertension and diabetes in first-degree relatives. Information on medications taken was also collected.

4) Non-invasive physiologic measures – electrocardiography (ECG) and a standardized exercise test (bicycle) for VO2max [48].

5) Blood samples were drawn for analyses of serum insulin, glycosylated haemoglobin (HbA1c) serum cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and hs-CRP.

The intervention

All participants were randomly allocated to one of three arms in a specially developed computer programme:

1. Control group (n=15). Received information verbally and in writing and treatment as usual at the health care centre.

2. Basic intervention group (n=18): Received information as the control group, a card giving them the possibility to examine their blood glucose without cost whenever it suited them, a personal nurse to contact when needed, a prescription for physical activity and, if attending the information session, they were given a step counter.

3. Intensive intervention group (n=19): Similar as to the basic intervention and the IGT participants were also invited to participate in group sessions focusing on physical activity using motivational consultation (eight sessions whereof six planned during the first six months and two the last six months). A lifestyle coach (nurse), a nutritionist and a physiotherapist mutually chaired these sessions.

Follow-up

After one year, all participants repeated the phenotyping performed at baseline. A telephone interview concerning changes in physical activity and diet during the past year was also conducted. The interviewer was not informed of the participants' group allocation.

3.2 The Skaraborg Project

PAPERS II, IV, V

The Skaraborg Hypertension Project was launched in 1977 with the intention to improve blood pressure control among residents in the county of Skaraborg. The project presented guidelines for the detection, treatment and follow-up of men and women with hypertension [122]. The project was evaluated including an extended follow-up of the prognosis of hypertension [123]. Next, population-based studies on high blood pressure and type 2 diabetes were undertaken in the municipality of Skara, which participated in the initial project. A cohort of patients with hypertension and/or type 2 diabetes seen in primary care was identified using a contemporary random population sample as reference 1992−1994 [124, 125]

Between 2002 and 2005, a randomly chosen sample of the population in Vara and Skövde, two small municipalities in the South West of Sweden, i.e. the Vara-Skövde Cohort (VSC), were invited to participate in a survey within the Skaraborg Project [119]. The municipality of Vara was representative of an agricultural population while the population and infrastructure of Skövde was more diverse. The protocol was designed with an intentional three-fold oversampling of individuals younger than 50 years (2/3). Participation rates were high, i.e. 81% and 70% in Vara and Skövde, respectively, comprising 2816 individuals, 30−75 years old, who completed the study. A follow-up on fatal and all non-fatal cardiovascular events has just recently been obtained (spring 2013), and a complete 10-year follow-up basically repeating the baseline protocol is ongoing (VSC-10). At the follow-up, however, the FINDRISC questionnaire and a random plasma glucose test were included.

Examination

Participants were invited by mail for blood tests followed by a physical examination. An OGTT was performed after an overnight fast (12 hours) and blood samples collected. During the 2-hours waiting period, questionnaires about lifestyle, physical activity and diet were administered and completed. The blood tests were followed up by a careful examination about one week later. Two specially trained nurses performed the examination and informed the participants about their cholesterol, plasma glucose and the results from the OGTT.

Assessment of physical activity

Assessment of leisure time physical activity (LTPA) was based on four answer alternatives to the question "How much physical effort do you put

yourself through in your leisure time per week" 1) *Inactive or mostly inactive*, e.g. reading or watching television; 2) *Slightly active*, explained as at least 4 hours (= 240 minutes) activity e.g. leisure time walking, cycling, gardening and walking or cycling to or from work; 3) *Moderate, less strenuous LTPA,* e.g. exercise such as jogging, swimming and tennis at least 2 hours a week; 4) *Strenuous physical activity* e.g. jogging, swimming and tennis several times a week. Participants who reported moderate or strenuous physical activity (level 3−4) were aggregated and categorized as moderate/high LTPA while those who reported inactive or slightly active (level 1−2) were categorized as sedentary/low LTPA.

Blood tests

Measurements of plasma glucose and diagnosis of type 2 diabetes conformed to international guidelines [1]. The analyses of fasting plasma glucose were performed using the modified glucose dehydrogenas method from Hemocue (Hemocue AB, Ängelholm). Plasma total cholesterol and HbA1c were analysed using standard methods at the local hospital. All other samples were frozen at -82^0 C and analysed later on demand. Low density lioproteins (LDL), high density lipoproteins (HDL) and triglycerids were analysed at the Departement of Clinical Chemistry, Skåne University Hospital, Lund. Hs-CRP concentration was analysed with an enzyme immunoassay using an accredited method at the Department of Clinical Chemistry, Skåne University Hospital Fasting plasma insulin was analysed by enzyme immunoassay in the same department [126].

Physical examination

All participants were examined and interviewed by the two specially trained study nurses using structured questionnaires regarding demographic background and lifestyle. A standard physical examination was performed with waist circumference measured to the nearest cm at the widest part between the lowest rib and spina iliaca anterior superior, body weight measured to the nearest 0.1 kg on a calibrated scale and height measured to the nearest cm (light indoor clothing and no shoes) [119]. Blood pressure was measured in a supine position after five minutes rest. The pressure was measured twice and the mean was used for analyses according to international guidelines [127].

3.2.1 Screening for IGT

Our aim in the second paper was to explore the efficiency of a tool using three short questions (The Skövde Form) to detect individuals with IGT. The

questions were the following, "Do you have hypertension? Do any of your first-degree relatives have diabetes? Are you overweight (BMI $\geq$25 kg m^{-2})?" A BMI table was added to the questionnaire. If the answer was yes in response of two of the questions or to one question combined with a random plasma glucose of $\geq$7.2 mmol/L they were invited for an OGTT. The Skövde form was used in the opportunistic screening at two health care units, one in the city of Gothenburg (population 500.000), and one in the middle-sized town Skövde, in Sweden (population 50.000). The form was also advertised in the local newspaper. In the advertisement people were informed of the opportunity to participate in a study aimed at a lifestyle intervention. The advertisement was published in the local newspaper on one weekday day and on one Saturday.

For comparison the predictive value of the FINDRISC questionnaire with a cut-off $\geq$15 and cut-off $\geq$12 was tested in the Skövde cohort (VSC-10).

4 STUDY POPULATIONS

4.1 PAPER I

This study is based on the DIAVIP population (Figure 2). Data for all participants with a risk score ≥15 who returned the FINDRISC questionnaire (n=525) are presented in this paper, including differences between those who accepted the invitation for an OGTT (n=302) and those who did not (n=223). Under *Results* we also present the results for the total population with a risk score ≥11 who participated in an OGTT (not published).

4.2 PAPER II

This paper is based on the follow-up of the Skövde sub-cohort of VSC-10 and aimed to test the performance of the Skövde form for detection of individuals with IGT. From the Skövde sub-cohort we included all with full data on the required variables: BMI, family history of diabetes, data on prevalent hypertension, a complete FINDRISC questionnaire, a random plasma glucose test and results from the OGTT (n= 538). Individuals who participated in the opportunistic screening in the two Health Care units were included (n=52) as were all individuals who responded to the advertisement in the local newspaper (n=54).

4.3 PAPER III

This paper reports a randomized clinical trial, DIAVIP, addressing individuals with IGT. Participants were recruited from those accepting the invitation to show up for an OGTT with a risk score ≥11, and free from diabetes. From those (n=302) with a FINDRISC score ≥15 we found 48 individuals (16%) with IGT and among those with a score 11−14 (n=90), another 15 individuals (16%) with IGT were detected. Since 11 participants declined from further participation, the final population was 52 individuals with IGT..

Inclusion- and exclusion criteria in DIAVIP were:
- age 35−75 years old
- IGT confirmed by an OGTT
- no history of diabetes (self-reported)
- no somatic or psychiatric disorder that would limit the ability to comply with the study protocol (self-reported)
- signed informed consent

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Follow-up

At follow-up one participant had died from causes not related to the study. Six of the participants were lost to follow-up and excluded. Of those, three participants developed type 2 diabetes and did not want to come for another examination, one person moved to another city and one person considered herself generally too ill to continue in the study and another person without reason just reported that she did not want to participate further. After one year the remaining participants (n=45) underwent the same examination as at baseline including blood tests, ECG and bicycle test.
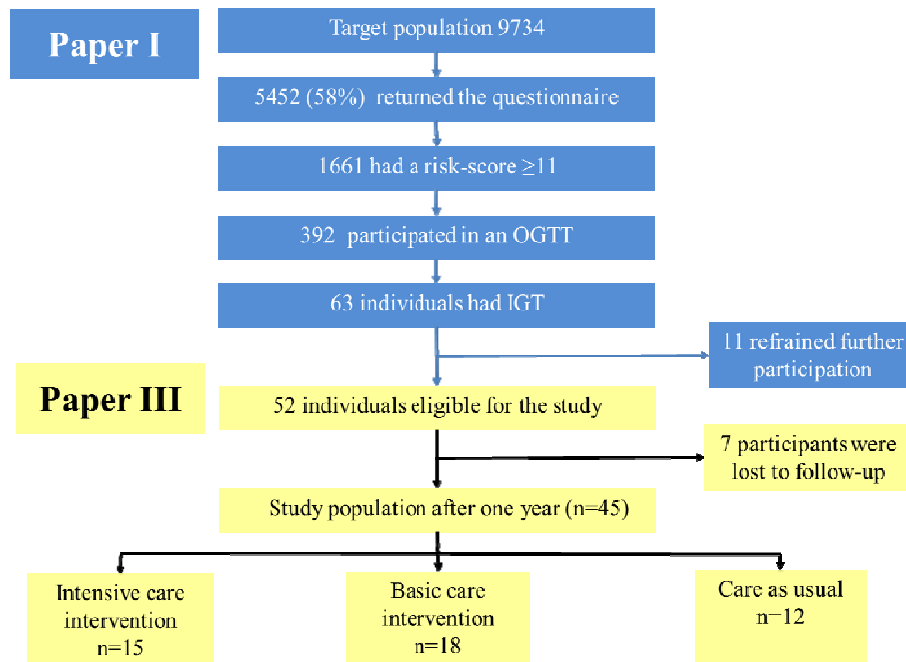

Figure 2. Flow-chart of paper I and III.

4.4   PAPER IV

Paper IV is based on the Vara-Skövde Cohort (VSC) within the Skaraborg Project and focused on CRP in individuals with IGT and the extent to which low grade inflammation is modified by level of physical activity. Results for CRP were reported for 2813 participants. In agreement with other studies [64] those with CRP >10 mg/L (n=91) were excluded to eliminate individuals with an inflammatory diseases. We also excluded those with IFG (n=129), those with manifest diabetes (n=158), individuals with inconclusive OGTT

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(n=2) and all with lacking information on physical activity, BMI and smoking (n=85). Thus, the study population was reduced to 2367 participants.

4.5 PAPER V

This paper is a prospective longitudinal study with a mean follow-up time of eight years based on the VSC from the Skaraborg Project. The aim was to evaluate insulin resistance at baseline as a risk factor for cardiovascular disease during follow-up. From the original 2816 individuals we excluded all with diabetes (n=158), either self-reported or any on anti-diabetic medication. We also excluded all with known cardiovascular disease (CVD) with or without diabetes (n=80) and pregnant women (n=9). In addition data concerning previous CVD or diabetes were missing in six individuals who were also excluded, leaving 2563 participants remaining for the study. Over a mean follow-up of eight years data for incident CVD were tracked through record linkage with the National Swedish Hospital Discharge Register and Mortality registers.

5 STATISTICAL METHODS

5.1 PAPER I-V

All data were analysed in SPSS base system for Macintosh 18.0 and standard methods were used for descriptive statistics. Differences in means between groups were analysed with general linear models. All statistical tests were two-sided and significance was considered at $p<0.05$.

5.2 PAPER I

Associations between categorical variables were tested with Chi-square tests, and statistical significance was assumed when $p<0.05$. Positive predictive values associated with having a FINDRISC risk-score ≥15 were calculated for IGT, IFG, type 2 diabetes and impaired glucose metabolism.

5.3 PAPER II

Positive predictive values were estimated for detection of IGT and IGM with FINDRISC and with the Skövde form. Sensitivity and specificity were calculated in the follow-up of the Skaraborg project (VSC-10). Sensitivity and specificity for the Skövde form used in opportunistic screening and in advertising could not be calculated.

5.4 PAPER III

Intra-individual changes in risk factor levels between baseline and one year follow-up were calculated with paired samples t-test. Differences in baseline variables between the three groups were analysed with ANOVA and Chi-square tests. Differences between changes in groups were analysed with linear regression models where difference was modelled as an interaction term. All analyses were adjusted for differences in age and gender and 2-sided 95% CI were presented.

5.5 PAPER IV

Group differences in continuous variables were analysed using general linear models with 95% CI. Associations between variables were estimated by Pearson's correlation coefficients. Variables with a skewed distribution (HOMAir and CRP) were analysed after log-conversion. Two-way

interaction terms were used to explore the interaction between sex and IGT and between IGT and sedentary/low LTPA, respectively, in the association with CRP in men and women separately.

5.6 PAPER V

In this study SPSS for Macintosh 20 was used for statistical analyses. The risk of CVD associated with concentrations of fasting plasma insulin, fasting plasma glucose and HOMAir was evaluated by Cox regression analyses with 95% CI. All data were adjusted for age, BMI, hypertension, ApoB/ApoA1, smoking, alcohol consumption, physical activity, and educational level. Analyses on the total sample (men and women combined) were also adjusted for sex. Potential effect measure modification from physical activity on the risk of CVD in association with HOMAir, was explored by stratification and by interaction terms, i.e. two-way interaction between HOMAir and sex, and three-way interaction between HOMAir, sex and physical activity. Both components in the algorithm were also tested separately. As the distributions of f-insulin and HOMAir were skewed, they were analysed after log-conversion with 2 as base. For comparative purposes, insulin, HOMAir, and glucose were standardized using one standard deviation as unit. For comparison of mean values these data were anti-logged.

6 RESULTS

6.1 PAPER I

Feasibility of the FINDRISC questionnaire to identify individuals with impaired glucose tolerance in Swedish primary care. A cross-sectional population-based study.

6.1.1 Results

The response rate was 58% and of those 5452 individuals, 525 had a risk score ≥15. All were invited for an OGTT and 302 (58%) responded to the invitation. The analyses showed no significant differences between responders and non-responders except for a higher consumption of fruit in responders. For this paper only data for individuals with a score ≥15 were reported. We found a PPV for type 2 diabetes of 11%, for IGT of 16% and for IFG 29%.

Among the last 3295 questionnaires, 325 individuals had a risk score 11-14 and 90 of those came for an OGTT (30%). Among those, we found 24 with IFG (27%), 15 with IGT (17%) and seven with type 2 diabetes (8%). Altogether 213 individuals (3.9% of the responders) had impaired glucose metabolism (IFG, IGT or type 2 diabetes). Data on the total population, characterized by a risk score of <11, 11−14 and ≥15 are shown in Table 3.

Table 3. Risk factors for impaired glucose metabolism in different score-groups

Variables in FINDRISC	Score <11 n=3735 (68.5%)	Score 11-14 n=1136 (20.8%)	Score ≥15 n=525 (9.7%)	P-value for trend
Mean age (SD)	54 (12)	61 (11)	64 (9)	<0.001
BMI <25 (%)	53.9	19.4	8.9	
25−<30 (%)	42.2	57.9	48.0	
≥30 (%)	3.8	22.6	43.2	<0.001
Waist circumference <94 men; <80 women (%)	47.8	6.4	1.3	
94−102 men; 80−88 women (%)	36.2	43.4	23.1	
>102 men; >88 women (%)	16.0	50.1	75.6	<0.001
Physical activity at least 30 min/day (% yes)	70.5	54.0	41.6	<0.001
Daily intake of fruit and vegetables (% yes)	82.9	79.1	73.3	<0.001
Ongoing medication for hypertension (% yes)	10.1	28.7	56.4	<0.001
Former history of high plasma glucose (% yes)	1.6	8.6	41.4	<0.001
Family history of diabetes − no relatives	73.7	33.1	14.5	
second-degree relatives	16.1	22.5	22.6	
first-degree relatives	10.0	44.0	62.9	<0.001
Number of participants undergoing an OGTT n (%)	0	90 (28)	302 (58)	
NGT (%)[1]		44 (49)	135 (45)	
IFG (%)[1]		24 (26.7)	86 (28.5)	
IGT (%)[1]		15 (16.7)	48 (15.9)	
Type 2 Diabetes (%)[1]		7 (7.8)	33 (10.9)	

[1] Percentage of those who were examined with an OGTT.

6.1.2 Discussion

This study indicates that FINDRISC is an efficient tool for the detection of individuals with impaired glucose metabolism, but less efficient for the detection of individuals with IGT. By use of FINDRISC the detection rate of individuals with impaired glucose metabolism increased 1.5- to 3-fold as compared to that expected in a population survey [32]. However, IGT is more frequent than IFG in most unselected population [128] and this was also

found in the Skaraborg Project where 7.7% had IGT and 6.5% IFG (Paper II). That the FINDRISC questionnaire detects primarily individuals with IFG is supported by a Bulgarian study where individuals with at least one risk factor for type 2 diabetes more often displayed IFG or type 2 diabetes than IGT [129]. In our population with a risk score ≥15 the proportion of IGT subjects was similar to that in the Bulgarian study, but IFG was by far the most common component of impaired glucose metabolism in our cohort. These data indicate that many individuals with IGT will remain undetected by FINDRISC.

The high detection rate for IFG is of particular interest as those individuals are fairly resistant against lifestyle interventions, contrary to individuals with IGT. Remarkably, the detection rate for IGT was as high in individuals with a risk score ≥11 as in those with a risk score ≥15.

The percentage of individuals with impaired glucose metabolism was lower in our population than in the Finnish population, 55% as compared with 66% [76]. Most likely, this is due to the screening procedure with postal questionnaires, causing a selection bias and recruiting individuals more health conscious than non-responders. The risk score is based on known risk factors for type 2 diabetes development and consequently the burden of risk factors increased in parallel with an increased score. The FINDRISC questionnaire is a better instrument for the detection of individuals with IFG than those with IGT. A possible reason for the better detection of IFG is the weighting of risk factors whereby family history and former high blood glucose are highly weighted and stronger predictors of IFG than of IGT [31].

In conclusion, FINDRISC is a valuable tool for screening of impaired glucose metabolism but the efficiency to detect individuals with IGT is limited. The present data thus indicate that additional methods to FINDRISC are needed to identify IGT individuals for implementation of lifestyle changes.

6.2 PAPER II

Screening in primary care for individuals with impaired glucose tolerance

6.2.1 Results

All in all, complete data were available for 538 individuals from the VSC-10. Among them 6.5% had IFG (n=38), 7.7% had IGT (n=45) and 3.1% had screen detected type 2 diabetes (n=18). Using the Skövde form, an affirmative answer to two of the three questions or one positive answer and a

random blood glucose ≥7.2 mmol/L, identified 32.4% (n=190) of the VCS-10 population. The FINDRISC questionnaire with a cut-off ≥15 identified 11.3% (n=66) of the VCS-10 population and with a cut-off of ≥12, 27% (n= 158) of the VCS-10 population was identified. When the Skövde form was used 9 OGTTs had to be performed to find one individual with IGT while only six OGTTs had to be performed in the group identified with the FINDRISC questionnaire using a cut-of ≥15. Corresponding number of individuals needed to examine with an OGTT using a risk-score ≥11 was nine (Table 4).

In the opportunistic screening at the Health Care Unit using the Skövde Form, the detection rate for IGM was 40.4% (n=21) and 17% (n=9) for both IGT and type 2 diabetes. The corresponding detection rate for the screening instrument used in an advertisement was 35 % (n=19) for IGM, 17 % (n=9) for IGT and 7% (n=4) for type 2 diabetes. Consequently, six OGTTs were needed to detect one individual with IGT in both the opportunistic screening and when advertising was used (Table 4).

Table 4. Performance of different screening tools for impaired glucose metabolism (IGM), IGT and type 2 diabetes.

	FINDRISC in a random population cut-off ≥15 n=66			FINDRISC in a random population cut-off ≥12 n=158			The Skövde form in a random population n=190			The Skövde form Advertisement n=54			The Skövde form opportunistic screening at Health Care Unit n= 52		
	IGM n=28	IGT n=12	T2D n=8	IGM n=45	IGT n=17	T2D n=13	IGM n=58	IGT n=21	T2D n=17	IGM n=19	IGT n=9	T2D n=4	IGM n=21	IGT n=9	T2D n=9
% of total study population	4.8	2.1	1.4	7.8	2.9	2.2	10.0	3.6	3.0						
PPV	42.4	18.2	12.1	28.5	10.7	8.2	30.5	11.1	8.9	35.2	16.6	7.4	40.4	17.3	17.3
NPV	85.9	93.7	98.0	86.8	93.5	98.8	89.1	94.2	99.7						
Sensitivity	28.0	27.3	44.4	81.8	45.0	72.2	57.4	87.5	94.4						
Specificity	92.0	89.8	89.6	76.3	73.5	74.0	72.8	68.7	69.5						

6.2.2 Discussion

The main finding in this study was that the Skövde form could be used as an additive tool to detect individuals with IGT. The three questions could be used either as opportunistic screening at the Health Care Unit or advertised in the local newspaper. Nevertheless, it would take too many OGTTs, i.e. n=9, to detect one person with IGT when used to identify a high-risk population.

On the other hand, the most frequently used questionnaire, i.e. FINDRISC, is a very good screening instrument for IGM in a random population, whereas the detection rate for IGT is only about 16% (Paper I). Another problem when it comes to general screening is that not all individuals are interested in joining a clinical study whereas advertising had the advantage to attracts individuals more motivated for participation in a lifestyle intervention.

Collectively, for recruitment of individuals with IGT, opportunistic screening or an advertisement with three short questions may advantageously be used, but in a public health perspective FINDRISC with a risk-score ≥15 seems to be the most efficient tool.

6.3 PAPER III

Feasibility of a randomized controlled intervention with physical activity in participants with impaired glucose tolerance recruited by FINDRISC

6.3.1 Results

In this study population the mean FINDRISC score at was 16.4, and the mean age was 64 years. Men and women (20 men and 25 women) were equally distributed between the intervention groups. Half of the participants with IGT had combined IGT and IFG (43%) and were equally distributed between the groups. Men showed a trend to be more afflicted by ischemic heart disease than women, 30% and 8%, respectively, (p=0.064). Medical history for obstructive sleep apnoea in men and women was similar, 15% and 4%, respectively (p=0.317). Risk factor levels for ischemic heart disease and stroke were high in the study population. In particular, a systolic blood pressure with a mean value of 148 mmHg (SD 19), a mean BMI of 30 kg/m^2 and a mean hs-CRP concentration of 4.3 mg/L (SD 3.9). The comorbidity in the population was also considerable. Apart from a high prevalence of hypertension (29%, n=15) and hyperlipidemia (56%, n=29), 19% (n=10) were on medication with analgesics and 10% (n=5) were on treatment for depression. In addition 16% (n=9) were afflicted by ischemic heart disease and 3 participants had been treated for stroke (6%).

Only 33 (75%) of the study participants could complete the bicycle test and few could be evaluated by VO_2 max. In the interview, 69% of the participants in the intensive care group reported a considerable increase in their physical activity (5 or 6 on a 6 graded scale), while 17% in the basic group and 44% in the control group reported an equal increase. Mean increase of scale points in the different groups was 3.0, 2.8 and 3.8, in the control group, the basic care group and in the intensive care group, respectively, with no statistically significant difference between them (p=0.137). Most participants reported an increase in walking or biking. Interestingly, 60% of the participants reported some changes in diet.

Risk factors for ischemic heart disease, i.e. systolic and diastolic blood pressure (12 mmHg, CI 5.0–19.3, p=0.003; 7 mmHg, CI 2.4–11.0, p=0.005), body weight (3 kg, CI 0.6–5.5, p=0.017), BMI (1 kg/m^2, CI 0.3–5.5, p=0.013), waist circumference (3 cm, CI 0.4–5.6, p=0.026) and sagittal diameter (1,2 cm, CI 0.1–2.3, p=0.028) decreased significantly within individuals in the intensive care group, and systolic blood pressure (8 mmHg, CI 1.4–18.4, p=0.025) decreased in the basic intervention group. No other differences were significant in the three groups (data not shown).

Waist circumference was significantly more reduced in the intensive care group compared with the care as usual group, and wsagittal diameter and triglycerids (p=0.012) were significantly more reduced compared with the basic care group, when adjusted for differences in age and sex. However, the differences were no longer observed, when adjusted for differences in energy intake (Table 5).

Table 5. Differences between groups at one-year follow-up. Positive differences represent a decrease from the first year to follow-up.

	Intensive care – Care as usual			Basic care - Care as usual			Intensive - Basic care		
	Mean difference	P	95% CI	Mean difference	P	95% CI	Mean difference	P	95% CI
Adjusted for age and gender									
Body weight (Kg)	2.5	0.082	-0.1;1.8	0.05	0.974	-1.0;1.0	2.5	0.063	-0.0;1.8
Waist (cm)	3.9	0.027	0.5;7.3	1.1	0.490	-2.2;4.4	2.7	0.088	-0.4;7.3
Sagittal[a] Diameter (cm)[b]	1.2	0.062	-0.1;2.5	0.04	0.621	-1.2;1.3	1.2	0.040	0.1;2.5
HOMAir	0.07	0.890	-0.9;1.1	0.56	0.259	-0.4;1.6	-0.49	0.281	-1.4;0.4
Adjusted for age, gender and differences in energy intake[c]									
Body weight (Kg)	1.88	0.253	-1.4;5.2	0.02	0.989	-3.1;3.1	1.86	0.216	-1.1;4.9
Waist (cm)	3.2	0.089	-0.5;6.9	0.5	0.793	-3.0;3.9	3.2	0.089	-0.7;6.2
Sagittal Diameter (cm)	0.88	0.224	-0.6;2.3	- 0.21	0.757	-1.6;1.2	1.1	0.091	-0.2;2.3
HOMAir	0.18	0.721	-0.8;1.2	0.54	0.259	-0.4;1.5	-0.37	0.424	-1.3;0.6

Data based on differences between baseline values and values at one year follow-up and differences are compared between the groups. All data are analysed with general linear models and adjusted for age and gender.

[a]Missing data for one person in the intensive care group. [b]Missing data for one person in the control group concerning sagittal diameter, [c]Missing data about energy intake for one participant in the intensive care group and one in the basic care group. BP= Blood pressure, BMI= Body mass index, LDL=low density lipoprotein, HDL= high density lipoprotein

6.3.2 Discussion

The main findings in this explorative randomized controlled study were firstly that individuals with IGT, recruited by FINDRISC exhibit high co-morbidity and, secondly, that an intervention with physical activity also leads to changes in diet. We also found that it takes more than just an examination, a prescription of physical activity and a step counter to increase physical activity over time (one year), and indeed that the group sessions seem to be essential. In spite of this an intervention was applicable and efficient concerning several severe risk factors for CVD.

FINDRISC is frequently used in Europe for lifestyle interventions but the high co-morbidity rate has not been reported elsewhere. As a confirmation of the burden of chronic diseases the mean value of CRP was 4.3 mg/L (SD 3.9) while normal CRP concentrations rarely exceed 1.0 mg/L. One reason for the under-reporting of co-morbidity in previous studies may be that most other studies using FINDRISC have included all individuals at increased risk and not only those with IGT. Of notice is that the participants in the major diabetes prevention studies (the DPP and the DPS study) were not recruited by questionnaires primarily, but recruited from previous studies [90, 91].

The efficiency of lifestyle interventions was convincingly shown in both the DPP and the DPS study but required close surveillance and an implementation would need considerable additional resources, usually not at hand in clinical practice. Our study was feasible in clinical practice and the protocol for the intervention was applicable. However, for future studies the strategy for the protocol should be one intensive intervention with assessment, prescription of physical activity, a step counter and group sessions and the inclusion of one control group. Other ways of recruitment should also be considered as well as other methods to estimate fitness. In this study we used the standardised Åstrand submaximal test, and several participants could not do it at all while another 75% of the participants could only be evaluated with the Borg scale. The time of the group sessions should also be flexible to make the sessions available also to individuals working during the daytime. In this study the group sessions were held during the daytime and thereby caused a problem for working participants.

An intervention with physical activity is feasible in ordinary primary care but for studies exploring the isolated effect of physical activity we need other strategies.

6.4 PAPER IV

C-reactive protein concentrations differ by sex, physical activity and glucose tolerance: A cross-sectional population-based study in Sweden.

6.4.1 Results

In this study of 2367 individuals, 92% (n=2177) showed normal glucose tolerance and 8% (n=190) had IGT. The mean age was 47 (SD 11.0) years and mean BMI was 26.4 (SD 4.2) kg m^{-2}. Most cardiovascular disease risk factors were more prevalent in individuals with IGT compared to those with normal glucose metabolism (Table 6). CRP was significantly higher in individuals of both sexes with IGT compared to those with normal glucose metabolism (p<0.001). However, when adjusted for age, BMI and smoking, the significant difference between those with IGT and those with normal glucose tolerance was no longer present in women (p=0.795) (Table 6). Moreover, CRP was significantly higher in women than in men when adjusted for age, BMI and smoking (p=0.004).

The difference between CRP in men with IGT, as compared to men with NGT, was completely absent in physically active men (activity level 3−4). The association with self-reported physical activity was also verified by a significant interaction between LTPA (low 1−2 vs. high 3−4) and IGT (yes/no) in men in for the association with the circulating CRP concentration (p = 0.029) (Table 7).

Table 6. Cardiovascular risk factors among male and female participants with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), in the Vara-Skövde Cohort 2002−2005.

	Men			Women		
	NGT (*n*=1072)	IGT (*n*=78)	*P*-value	NGT (*n*=1105)	IGT (*n*=112)	*P*-value
CRP (mg/L)	1.7 (1.6)	2.8 (2.3)	<0.001	1.9 (2.0)	2.8 (2.3)	0.795
Waist circumference (cm)	93[a] (9)	100[a] (11)	<0.001[a]	83[a] (12)	91[a] (14)	<0.001[a]
BMI (kg/m^2)	26.5[a] (3.3)	28.5[a] (4.1)	<0.001[a]	25.9[a] (4.6)	29.4[a] (6.3)	<0.001[a]
LDL (mmol/L)	3.4 (0.9)	3.3 (0.9)	0.081	3.1 (0.9)	3.4 (0.8)	0.795
HDL (mmol/L)	1.2 (0.3)	1.2 (0.3)	0.300	1.4 (0.3)	1.3 (0.4)	0.001
TG (mmol/L)	1.4 (0.8)	2.0 (1.6)	<0.001	1.1 (0.5)	1.5 (0.7)	<0.001
Blood pressure						
Systolic (mmHg)	122 (14)	132 (19)	0.012	116 (16)	131 (22)	<0.001
Diastolic (mmHg)	71 (10)	76 (12)	0.275	68 (10)	73 (11)	0.003
Heart rate (beats/min)	62 (8)	66 (9)	0.002	64 (8)	66 (9)	0.060
HOMA-IR	1.4 (0.9)	2.4 (1.5)	<0.001	1.2 (0.8)	2.2 (1.6)	<0.001

Data are mean ± SD; NGT, Normal Glucose Tolerance; IGT, Impaired Glucose Tolerance; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; HOMA-IR, ApoA, Apolipoprotein A; ApoB, Apolipoprotein B;
[a] *D*ifferences between means for participants with normal glucose tolerance and IGT, respectively, were estimated using general linear models adjusting for differences in age BMI, and smoking.

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Table 7. Distribution of circulating CRP concentrations in male and female participants with NGT and IGT according to the level of self-reported leisure time physical activity.

Level of physical activity		CRP mg/L NGT-group Mean (SD)	CRP mg/L IGT-group Mean (SD)	CRP mg/L Net difference	Confidence interval (95%)	P-value
Men	1	2.06 (1.88) *n*=81	4.30 (1.95) *n*=10	2.24	0.933; 3.548	0.024
	2	1.78 (1.58) *n*=539	2.38 (1.63) *n*=50	0.60	0.121; 1.072	0.004
	3+4	1.52 (1.45) *n*=452	1.62 (1.48) *n*=18	0.10	-0.794; 0.610	0.796
P for trend		0.003	0.001			
Women	1	2.89 (2.33) *n*=66	3.27 (2.42) *n*=9	0.38	-1.344; 2.113	0.636
	2	2.05 (1.68) *n*=693	2.06 (1.73) *n*=87	0.01	-0.401; 0.373	0.969
	3+4	1.68 (1.54) *n*=346	1.76 (1.60) *n*=16	0.08	-0.883; 0.724	0.969
P for trend		<0.001	0.054			

Mean value of CRP and confidence interval are analysed with a general linear model. The net difference and P-value correspond to differences in CRP concentrations between the NGT- and IGT-groups. Activity level 1 and 2 correspond to sedentary and low LTPA, respectively, and levels 3 and 4 correspond to moderate/high LTPA. CRP, C-reactive protein; NGT, normal glucose tolerance; IGT, impaired glucose tolerance. All data are adjusted for age, BMI, and smoking

6.4.2 Discussion

The main finding of this study was that concentrations of CRP were higher in men with IGT as compared with men showing normal glucose tolerance, but the difference was no longer present in men performing moderate to vigorous physical activity. Thus, sedentary men with IGT may to be more vulnerable to inflammation. Of interest is that more physical activity than generally recommended may be required to limit inflammation.

The high level of physical activity needed to limit inflammation in individuals with IGT is in accordance with a prior study from the population in the Finnish Diabetes Prevention Study (DPS) where intense physical activity was needed to observe lower CRP concentrations [64]. Also, in support of our results no association between exercise and CRP was observed in the American Diabetes Prevention Project (DPP) [130] where only 30 minutes daily of less than moderate physical activity was recommended. This level is by far too little as compared to the level of physical activity that was needed to limit inflammation in this present study. Subclinical chronic

inflammation, measured with a hs-CRP method is an established predictor of cardiovascular disease [61], while on the other hand, many studies have shown the positive effect of physical activity on cardiovascular outcomes [52, 55, 131-133]. If and how physical activity can limit inflammation is still unclear but has been indicated in several studies [66, 134], even if results are divergent [135]. Both the American, the Finnish and the Chinese Da Quing study could show significant and convincing results of a lifestyle intervention with circa 60% reduction of type 2 diabetes development over a time period of about three years [89-91]. In spite of this, no long-term preventive effect on CVD could be observed at follow-up ten years later or even after 20 years in the Chinese study [92, 93]. As a slight increase in LTPA decreased conversion to type 2 diabetes, but did not normalize inflammation, it is tempting to speculate that more vigorous activity is required for individuals with IGT to reduce inflammation than to prevent or delay conversion to overt type 2 diabetes [130].

In this study we found a significant difference in CRP concentrations between men and women, contrary to the big NHANES study where no such differences could be found [136]. The gender difference found here may be due to our relatively young population because young women have known higher circulating CRP levels than elderly women [137].

In summary, self-reported exercise was inversely associated with circulating CRP concentrations in the total study population. Moreover, men with IGT, reporting sedentary/low levels of LTPA, were especially vulnerable to inflammation. However, a moderate to vigorous level of physical activity seems to be needed to control subclinical inflammation in male IGT-subjects.

6.5 PAPER V

Insulin resistance predicts cardiovascular morbidity in men without diabetes mellitus and this effect is modified by level of physical activity.
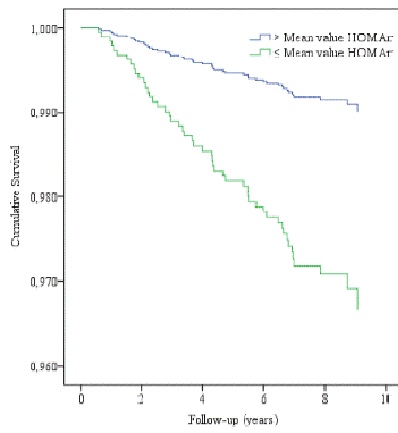
6.5.1 Results

Risk factors at baseline show considerable differences between men and women whereby men had higher levels of systolic and diastolic blood pressure (Δ = 4.8 mmHg, 95% CI 5.0−19.3, Δ 3.7−5.9) ApoB/ApoA1 (Δ =0.09, 95% CI 0.1−0.1), triglycerides (Δ =0.3 mg/dL, 95% CI 0.3−0.4), HOMAir (Δ =0.16, 95% CI 0.1−0.3), fasting insulin (Δ =0.44 mIU/L, 95% CI 0.1−0.8), and fasting glucose levels (Δ =0.2mmol/L, 95% CI 0.2−0.2). Women on the other hand had significantly higher heart rate (Δ =2 heart beats/min, 95% CI 1.4−2.7). Differences between gender were also observed
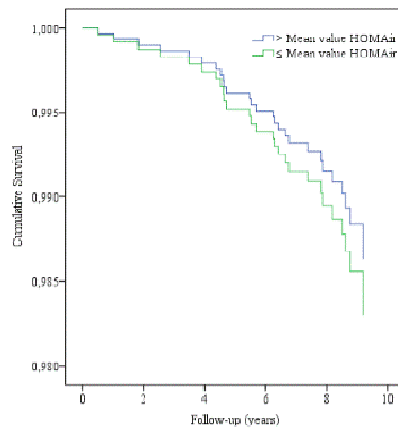
concerning exercise habits where 50% of highly educated men performed vigorous exercise as compared with 30% of women in the same education category (p<0.001). When stratifying the data also for level of physical activity (level 1−2 vs 3−4), all risk factors apart from blood pressure showed significantly more beneficial levels in both men and women reporting high levels of physical activity compared with those reporting lower levels.

In the total study population, 76 incident events of CVD were found, whereof 26 in women and 50 in men. The mean follow-up time was 8.0 (SD 1.3) years. Insulin resistance measured by HOMAir was significantly predictive of CVD (HR 1.8, 95% CI 1.3−2.4) in the total study sample. However, when the data were stratified by sex (Table 8), the association was present solely in men (HR 1.8 95% CI 1.3−2.4). This association remained when adjusting for BMI, ApoB/ApoA1-ratio, hypertension, alcohol consumption, education and smoking, both in separate and in multivariate analyses (Table 8). However, when the data were stratified by physical activity level, the significant predictive value of HOMAir was no longer present among men performing a high level of physical activity HR 1.0 (95% CI 0.6−1.6). This pattern could not be confirmed in women. In men reporting physical activity level 1−2 (sedentary or slightly active 240 min/week), the age-adjusted HR for CVD prediction was 2.3 (95% CI 1.5−3.4) for HOMAir and 2.7 (95% CI 1.7−4.4) for fasting insulin (Figure 3). No association was seen between CVD and fasting glucose in either men or women.
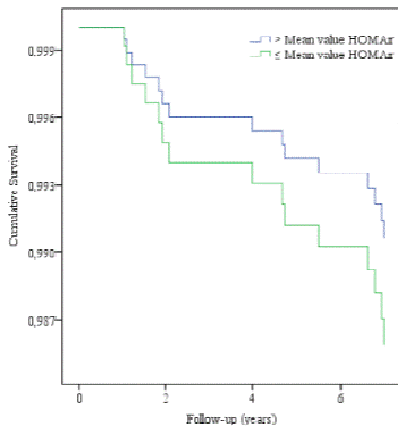
A sex-stratified two-way interaction analysis between physical activity and HOMAir with regard to CVD morbidity confirmed the interaction in men (p age-adjusted = 0.009). In spite of limited power in women due to few CVD-events, sex differences were also confirmed in the total sample by a two-way interaction analysis between sex and HOMAir (p age-adjusted = 0.021), and by a three-way interaction analysis between sex, HOMAir, and physical activity, (p age-adjusted = 0.002). All interaction terms remained statistically significant after additional adjustments for BMI, ApoB/ApoA1, hypertension, smoking, alcohol intake, smoking, and educational level (data not shown).
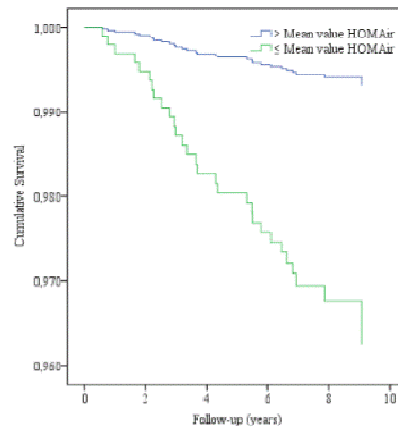
A. Time to cardiovascular event in men according to a mean split of HOMA-values. Mean calculated from logarithmic HOMA values in men only.

B. Time to cardiovascular event in women according to a mean split of HOMA-values. Mean calculated from logarithmic HOMA-values in women only.

C. Time to cardiovascular event in men performing physical activity at level 1–2 (sedentary or slightly active) according to a mean split of HOMA-values. Mean calculated from logarithmic HOMA-values in men only.

D. Time to cardiovascular event in men performing physical activity at level 3–4 (moderately to very active) according to a mean split of HOMA-values. Mean calculated from logarithmic HOMA-values in men only.

Figure 3. Survival to first cardiovascular event in men and women exposed to insulin resistance according to a mean split of HOMAir values.

Table 8. The risk of cardiovascular disease associated with HOMAir, fasting plasma glucose and fasting plasma insulin in men, women and total sample. Vara/Skövde cohort 2002−2005, Sweden.

	Men n=1303			Women n=1260			Total n=2563		
Number of events	27			50			77		
	HR	CI	P-value	HR	CI	P-value	HR	CI	P-value
Adjusted for age									
HOMAir	1.8	1.3−2.4	<0.001	1.1	0.8-1.5	0.673	1.3	1.1−1.6	0.004
fP-insulin	1.8	1.3−2.4	<0.001	1.1	0.8-1.5	0.612	1.3	1.1−1.6	0.003
fP-glucose	1.2	1.0−1.6	0.120	1.0	0.7-1.3	0.946	1.1	0.9−1.3	0.420
Adjusted for age, bmi, ApoA/ApoB and hypertension									
HOMAir	1.8	1.2−2.5	0.001	1.0	0.7-1.5	0.967	1.3	1.1−1.7	0.018
fP-insulin	1.7	1.2−2.5	0.001	1.0	0.7-1.5	0.932	1.3	1.0−1.7	0.014
fP-glucose	1.2	0.9−1.5	0.271	0.9	0.7-1.3	0.558	1.0	0.8−1.3	0.828
Adjusted for age, smoking, physical activity and education									
HOMAir	1.6	1.2−2.2	0.003	1.0	0.7-1.5	0.945	1.3	1.0−1.6	0.034
fP-insulin	1.6	1.2−2.2	0.003	1.0	0.7-1.5	0.911	1.3	1.1−1.7	0.016
fP-glucose	1.2	0.9−1.5	0.299	1.0	0.7-1.3	0.808	1.1	0.9−1.3	0.581

HOMAir was entered into the Cox regression after log-conversion with 2 as base. F-insulin, HOMAir, and f-glucose were standardized using one standard deviation as unit. Thus, HR for CVD represents the risk increase per 1 standard deviation of the different risk factors and they were evaluated by Cox regression analyses with 95% CI.

6.5.2 Discussion

In the present study, insulin sensitivity was predictive of cardiovascular disease in men but not in women. However, the predictive value was completely absent in men performing moderate to vigorous physical activity. It is interesting to note that a higher level of physical activity than generally recommended seemed necessary. General recommendations include physical activity 30 minutes daily but in this study four hours of slight physical activity per week did not seem to be enough to modify the association between insulin sensitivity and cardiovascular disease. These findings were confirmed by statistically significant interaction terms between sex, insulin resistance and physical activity.

The positive predictive value of fasting insulin and insulin resistance on CVD morbidity has been demonstrated in previous studies [115] even if the mechanism is not clearly understood. Most likely, several factors contribute, including the negative effect of insulin resistance on the endothelium [138, 139]. Abdominal obesity, high concentrations of LDL, low concentrations of HDL, high blood pressure and physical inactivity are all related to insulin resistance in a complex fashion [138, 140]. Abdominal adiposity contributes to increased free fatty acid levels as well as to subclinical inflammation [141]. Inflammation in itself decreases insulin sensitivity, and taken together causes endothelial damage with an increased production of pro-coagulant factors such as fibrinogen associated with a prothrombotic risk [142].

Fasting glucose was not predictive of CVD whereas both HOMAir and fasting insulin was significantly predictive of CVD in men. This is in accordance with the results from the large diabetes prevention studies with excellent results on diabetes prevention, but after a follow-up time of 10−20 years still no significant effect concerning cardiovascular prevention [92, 93]. Just recently the large LOOK AHEAD study on individuals with type 2 diabetes was stopped because lack of results concerning CVD morbidity albeit significant decreases were observed in HbA1c and other metabolic risk factors [28]. Actually, no glucose regulating studies have shown convincing results concerning CVD outcomes [29, 30]. Insulin resistance reflects a more complex patophysiology and our own results suggest that it is the insulin component of the HOMA index that relates to CVD morbidity. This finding is supported by previous studies by Hanley et al [143] and Jeppesen et al [144]. The results of this study are thus in accordance with that the predictive ability of HOMAir with regard to CVD may be an effect of the underlying insulin resistance mirrored by plasma insulin and not the glucose concentration.

The predictive value of insulin resistance could only be found in men in this study. Previous reports have confirmed a sex difference but the nature of this observation is under debate. While a review by Gast et al. found a significant association between insulin resistance and CVD morbidity in both men and women [115], Folsom et al. only found an association in women [117] whereas Ferrara did not find any relationship between insulin resistance, gender and CVD risk in individuals without diabetes [116]. Most likely this is an effect of different inclusion and exclusion criteria. In the study by Ferrera a high percentage of participants were black with a high event rate for CVD [116] while the Folsom study was based on an elderly population [117]. Still, a part of the non-significant results in this present study may be due to a type 2 error based on the limited number of cardiovascular events among women. Another possible interpretation might be that other salutogenic mechanisms protect women from CVD and suppress the deleterious effect of an increased insulin resistance in this relatively young cohort. It is well known that premenopausal women without type 2 diabetes have a generally lower risk of developing CVD as compared to men [145], although in subjects with diabetes the CVD risk in women actually becomes similar to the known risk in men [110, 111]. Thus, whatever the underlying mechanisms are for this increase, the current results may indicate that the protective effect of being a woman is still intact in insulin resistant subjects without type 2 diabetes. However, this needs to be confirmed in future studies with extended follow-ups and also including other populations.

Interestingly the predictive effect of a decreased insulin resistance could not be seen in men performing moderate to vigorous physical activity, notably more physical activity than generally recommended. The salutogenic effect of physical activity is well documented but what happens on the cellular level is not known in detail. Most likely a complex interaction exists between several risk factors such as insulin resistance [140, 146, 147], blood pressure [56], HDL cholesterol [148], inflammation [64, 134, 149] and endothelial function [138], converging to an improved metabolic profile. In summary, insulin resistance predicted CVD morbidity in men, but not in women and a higher level of physical activity in men modified the association.

7 GENERAL DISCUSSION

The focus of this thesis has been on: a) screening for impaired glucose metabolism, b) prevention of type 2 diabetes in primary care, and c) prediction of the potentially modifying effect of self-reported physical activity on insulin resistance, inflammation and cardiovascular disease (CVD).

Screening

Screening for impaired glucose metabolism has been an issue for the last 60 years [150], and several screening methods have been developed for impaired glucose metabolism but few, if any, for impaired glucose tolerance [151]. The aim in paper III was to explore the feasibility and effect of a randomized intervention with physical activity in individuals with IGT. For recruitment of participants to the study, some type of screening instrument was required. Based on international experiences, the FINDRISC questionnaire was chosen. As the detection rate for impaired glucose metabolism in the Finnish cross-sectional study was high, i.e. 74% for men and 57% for women [76], we expected to find a high percentage of individuals with IGT with use of this questionnaire. However, we made several important observations during this recruitment process, and the detection rate for IGT of 16%, using a FINDRISC score ≥15 (internationally recommended), was not nearly as high as expected (paper I). In contrast, we detected a surprisingly high percentage of individuals with IFG, i.e. 28% (paper I). For comparison, the prevalence of IGT in the VSC-10 cohort was 7.7% while the prevalence of IFG was only 6.5% (paper II). Also, other studies have confirmed that FINDRISC mainly detects individuals with IFG [129]. Most likely, this is due to the high weighting of a family history of diabetes and the fact that previous measurements of increased plasma glucose are more predictive of IFG than of IGT. In consequence, individuals with IGT remain undetected to a large extent when using questionnaires such as FINDRISC (paper I, II and III). Furthermore, we also found that detected IGT-patients were older and demonstrated high co-morbidity (paper I and III).

Due to these problems encountered when seeking to identify individuals with IGT, a questionnaire with three short questions was developed within the project (paper II). One may speculate about whether it is important to develop methods for detection of individuals with IGT. Nevertheless, contrary to IFG, individuals with IGT are difficult to detect in the general population. In fact, even individuals with a normal fasting plasma glucose and HbA1c <42 mmol/L may have IGT.

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If screening is to be used for a condition, where cost-effectiveness is also a priority, a way to clarify the efficiency of a screening procedure is to present the numbers needed to screen (NNTS). Originally, NNTS was the number of people needed to screen to eliminate one event, such as CVD death or morbidity [152]. The current case concerns the number of persons needed to screen in order to find one person with the expected condition, i.e. type 2 diabetes and IGT. In primary care screening for type 2 diabetes is usually done with a fasting or a random plasma glucose, which is both convenient and inexpensive. With regard to IGT, the procedure of performing an OGTT is time-consuming and thus, more expensive. Based on a prevalence rate of 7.7 % in VSC -10 (paper II), the NNTS would be 14, which is not very cost-effective. In paper I and II we found FINDRISC with a risk score ≥15 to be efficient when screening for impaired glucose metabolism where NNTS was only 2.3, while NNTS for IGT was 5.5. The NNTS found for the Skövde form in the VCS-10 population was 9, and used in an advertisement or in opportunistic screening at the Health Care Unit 6 and 5.8 respectively. However, the advantage with the advertisement was that individuals interested in lifestyle changes were found.

Interventions

Whereas the large diabetes prevention studies have shown a remarkable effect on diabetes prevention in individuals with IGT [89-91] they have required considerable extra resources [153]. It is therefore not realistic to expect an implementation of this intensive intervention in primary care. Thus, the feasibility of two interventions, designed to be applicable in ordinary care was explored in paper III. The basic care intervention was very easy to implement and could be adopted without any changes in the primary care infrastructures, whereas the intensive intervention required group sessions (paper III), available at some health care units. The intensive intervention was successful with positive results concerning some metabolic variables, but the basic care intervention was no better than usual care (paper III). That the effect of a few informative sessions early during the course of a one-year intervention was not enough to create persistent changes has been shown before [154]. In spite of this, we expected that this particular group, i.e. persons with IGT, would be extra motivated. However, group sessions conducted continuously over the year still seemed to be necessary also in this particular group. In spite of an isolated focus on physical activity, the intervention led to changes in diet (paper III). This fact can be of use for upcoming lifestyle interventions in primary care, as changes in level of physical activity are easier to implement than diet changes aiming at weight loss and have shown better results by far with regard to cardiovascular prevention. However, the number of participants in the study was limited, so

the concept needs to be explored in a larger population.

In fact, bearing in mind the good results shown in the landmark diabetes prevention studies [90, 91], there are few previous reports from implementations in ordinary care. The large scale European project, the DE-plan, was announced in 2008 as a way to implement the results of the studies in ordinary care [98]. Unfortunately, very few results from this project have been reported. This is presumably due to difficulties with regard to the recruitment of individuals with IGT (paper I), as fasting glucose, or possibly HbA1c, is the most frequent method to evaluate glucose metabolism in primary care. Further, as in most previous studies, participants were carefully observed and supported by frequent individual meetings, which is not applicable in a clinical setting. Our study identified the problems and can be used as a guide for future recruitment and implementations (paper I and III).

Inflammation

Different aspects of inflammation are critical factors in the development of cardiovascular disorders [60, 61, 155] and several circulating biomarkers, such as CRP, PAI-I and IL-6 [149, 156], may assess degree of systemic inflammation. Subclinical inflammation is associated with several chronic diseases, adiposity, cardiovascular disease and type 2 diabetes [136], and individuals who already have IGT also display increased circulating CRP concentrations [157]. In paper IV we analysed inflammation with hs-CRP, as it is well validated and even proposed as a general marker for CVD [61]. However, it should be noted that CRP is likely to be solely a marker and not the cause of inflammation. CRP concentrations also increase with age, and most studies report women to have higher concentrations than men; however this effect seems to be present only in pre-menopausal women [69, 136]. In accordance with former studies, higher concentrations of CRP were found in men with IGT than in men with normal glucose tolerance (paper IV), but this difference could not be found in women. On the other hand, women, when all ages were combined, had higher concentrations of CRP than men in this relatively young cohort (paper IV). Most interestingly, however, was that the difference in CRP concentration between men with IGT and those with normal glucose tolerance was completely lost in men performing moderate to vigorous physical activity. It is noteworthy that this inhibiting effect on CRP was not seen in the group reporting slight physical activity (e.g. walking and cycling for at least 4 hours per week), which is within the generally recommended levels (30 minutes of light physical activity daily) [158]. The effect of physical activity on inflammatory markers is supported in some previous studies [66, 159], and in correspondence with the results of paper IV, the Finnish DPS study reported that a high level of physical activity was

indeed needed to limit inflammation in individuals with IGT [64]. Thus, according to our results, men with IGT reporting sedentary/low levels of LTPA are at risk to develop subclinical inflammation, and more than 240 minutes of mild physical activity per week actually seem to be required to control this subclinical inflammation (paper IV).

Prediction of CVD and the effect modification by physical activity

The predictive value of different measurements of glucose metabolism in individuals free from diabetes, has been explored in previous studies, indicating that individuals who already have IFG and IGT, particularly IGT, are at increased risk of micro- and macrovascular complications [32, 160]. In paper V we explored the risk of CVD associated with insulin resistance and found it to be high in men. We also studied the different components of the algorithm for HOMAir separately and could conclude that the predictive effect of CVD relates to fasting insulin concentration. These results are supported by previous studies where the predictive value of fasting glucose completely disappeared when adjusted for other risk factors [113], whereas insulin, HOMAir and C-peptide all have been proven to independently predict CVD [115, 161]. In contrast, we found no significant risk at all of either insulin resistance or fasting insulin in women (paper V). Considering the limited number of events in the present study the absence of significant results might be due to a type 2 error. Still, no association between insulin resistance and CVD was found in non-diabetic women. Thus, one may conclude that insulin resistance that develops prior to the development of type 2 diabetes does not eliminate the protective effect of being a woman. As results from previous studies concerning the predictive value of insulin resistance in women are also divergent [115-117], the explanation for this gender difference remains unclear.

General recommendations for prevention of CVD include physical activity; however, such recommendations are based on results from individuals with normal glucose tolerance [54]. In paper IV we stratified for level of physical activity (low vs. high) and found that men performing moderate to vigorous physical activity seemed to be protected from the risk of CVD conferred by insulin resistance. Thus, one may speculate that more physical activity is required for CVD protection in individuals with impaired glucose metabolism as compared to those with normal glucose tolerance.

The observation that a higher level of physical activity than generally recommended eliminated the predictive value of HOMAir on CVD completely supports the results from paper IV, where only moderate to

vigorous physical activity was associated with normal concentrations of CRP. The salutogenic effect of physical activity on CVD is well documented [56, 133, 162], however the exact mechanism behind this is unclear and is likely to involve multiple factors. An indication of the importance of a high level of physical activity is the negative long-term results from the large diabetes prevention studies. In spite of the positive effect on type 2 diabetes progression (58% reduction), no significant difference in CVD incidence was shown after 10 years [93, 163]. In both these studies the focus was on diet and body weight, and only 30 min/day of slight physical activity was recommended, which is less than level 3-4 in paper IV and V. Again, in the large LOOK-AHEAD study, addressing individuals with type 2 diabetes, a lifestyle intervention with diet and physical activity (175 minutes of moderate-intensity physical activity per week) was stopped due to lack of positive results concerning cardiovascular outcomes even after 10 years [28]. Also in this study the focus was on weight reduction, and as the mean BMI at baseline was 36 kg/m^2 one may assume that the level of physical activity was limited. It would be of great interest to determine whether individuals performing more physical activity than routinely recommended may have better outcomes.

Methodological considerations

The decision to use the FINDRISC questionnaire to recruit individuals with IGT was based on the cross-sectional study by Saaristo [76], where 74% of men and 57% of women had impaired glucose metabolism when scoring ≥15 in the questionnaire. In our study only participants with a risk-score ≥11 were examined with an OGTT, and thus we could not comment on sensitivity and specificity. The main purpose of using the FINDRISC questionnaire was to recruit individuals with IGT for the intervention in paper III. As the detection rate of IGT in the relatively young population of the Skaraborg Project was 8% (paper IV), we expected it to be at least 20% in this high-risk cohort selected by the FINDRISC questionnaire with a risk score ≥15 (paper I). After finding the detection rate to be only 16% and that IGT-patients detected also had high co-morbidity, we lowered the cut-off to ≥ 11 for the last 3295 questionnaires. Still, the number of participants with IGT was only 52, which is a limitation in paper III. Another important limitation was the problem associated with the evaluation of fitness. The Åstrand submaximal test, used in several previous studies and well validated [48], proved to be inapplicable for most of the participants in this study. Not all study participants managed to perform a bicycle test at all, and further, in those who did, the value of VO$_2$max was considered unreliable, and we had to rely on the Borg scale. We also used the questionnaire from the Skaraborg Project, but since the

participants generally had a very low level of physical activity, this four-graded scale was not sufficiently refined to enable the detection of slight changes in exercise level.

One of the experiences from the recruitment process was the limited usefulness of FINDRISC with regard to the detection of individuals with IGT. Thus, we developed the Skövde Form to be used in opportunistic screening and in the local newspaper (paper II). The main problem with the opportunistic screening at the Health care unit was to engage the staff to distribute the questionnaire, and consequently the number of OGTTs performed was limited. Also, the calculation of BMI was not considered easy to perform by all individuals answering the questionnaire. Thus, one might consider whether waist circumference should be substituted for BMI, as it is easier to measure and is an equally good predictor of impaired glucose metabolism.

A limitation in both paper IV and paper V was the low number of individuals performing a high level of physical activity. In paper IV we focused on individuals with IGT, and only 16 women had both IGT and reported a high level of physical activity. Based on these data, it is difficult to rule out a type 2 error. Furthermore, in paper V where we stratified for physical activity and explored the predictive value of insulin resistance on CVD, few women were affected by cardiovascular events. Although this could be expected in such a relatively young cohort, CVD events were particularly few among women performing moderate to vigorous physical activity, where there were actually only 5 events. Thus, the results need to be interpreted with caution, and further studies are required. Another limitation in paper IV and V was that all data concerning physical activity were self-reported.

The gold standard for assessment of insulin sensitivity is the glucose clamp technique, but this procedure is not applicable in epidemiological contexts. As a substitute we used the HOMA index in paper V. The validity of the HOMAir algorithm is well documented, both for individuals with normal glucose tolerance, and in those with IGT and the algorithm has been frequently used in previous studies [17].

Future implications for primary health care

The cornerstone of this thesis has been prevention. Prevention can be launched either with a high-risk strategy or a population strategy [164]. In paper I, II and III we detected pre-diabetic high-risk individuals with the

FINDRISC questionnaire and the Skövde form. One problem with a high-risk intervention is the cost for screening. In paper I we screened all inhabitants, 35-75years old, in a certain area in Skövde by sending the FINDRISC questionnaire by mail. This turned out to be little value for money. From 9734 mail-delivered questionnaires we detected 64 individuals with IGT and 33 individuals with type 2 diabetes. For the future, questionnaires available in pharmacies, libraries, and dentist practices with an invitation to contact the Health Care Unit if scoring 15 points or more may be recommended. On the other hand, one advantage with this high-risk strategy was that we found individuals motivated to participate in an intervention.

Our experience from paper III, clearly demonstrates that eight group sessions during one year combined with individual assessment and advice, prescription of physical activity and a step counter, induced lifestyle-changes and may be used in clinical practice in the future. Even if the intervention with physical activity also unintentionally led to dietary changes our recommendation for group strategies in clinical practice would be to include one or two sessions about diet. Still, we find no reason to focus on body weight as physical activity is by far better documented concerning the preventive effect on CVD [55, 131]. Furthermore, time of the day, for the sessions should be flexible and take participants needs into account.

One of the conclusions of this thesis was that it is likely that different levels of physical activity is needed to promote health for individuals free of metabolic abnormalities and for those with insulin resistance. It is likely that more vigorous physical activity is required for CVD protection in individuals with IGT and type 2 diabetes than for prevention of type 2 diabetes in individuals with IGT. A challenge in clinical practice is the fact that IGT-subjects are usually overweight and unaccustomed to physical activity, underlining the importance of mutual communication for the introduction of physical activity. Still the goal has to be more physical activity than generally recommended.

From a public health perspective there may be other disadvantages with a high-risk strategy, besides the costs, which need to be considered. Firstly, there is a risk that the intervention fails when support is withdrawn. However, the large type 2 diabetes prevention studies showed a better metabolic profile also after ten years in the intervention group than in the control group [92, 93, 163]. Still, the intervention probably has to persist for more than one year as several previous studies have shown negative results from short time interventions [165].

Secondly, maybe the most important disadvantage with a high-risk strategy is that even if individuals detected with a screening instrument have a higher risk to develop type 2 diabetes, most new cases will remain undetected [164].

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Thus, population based strategies are needed to control the determinants of incidence. In consequence, the Swedish National Institute of Public Health has published recommendations and guidelines for lifestyle interventions [166]. Further strategies are also needed for infrastructural changes to increase possibilities to bike, to walk and to jog. Fortunately there is nothing contradictory in a high-risk and a population based strategy and at best a combination of these two strategies with easily available questionnaires (such as the FINDRISC or the Skövde form), assessment at the Health Care Unit, group sessions, and population-based strategies may limit new cases of type 2 diabetes in Sweden.

Future studies

Hitherto major lifestyle intervention studies focused on type 2 diabetes prevention have been based on individuals with IGT. However, detection of individuals with IGT requires an OGTT, which is seldom conducted in primary care, and to this day no optimal screening instruments exist to identify individuals with IGT. Thus, screening instruments need to be developed and assessed. However, even if individuals with IGT have more to gain through lifestyle interventions than persons with IFG, those with IFG are also at high risk of developing type 2 diabetes. Moreover, IFG is easier to detect and common in primary care (paper I). Thus, the characteristics and risks of IFG patients should be further explored. Preventive actions should also be explored and developed for this condition. HbA1c is a new diagnostic tool, and the experiences and associations with IGT and IFG are unclear. Thus, studies concerning a possible cut-off level for HbA1c that may indicate a need for interventions with lifestyle or medication should be performed. Similarly, a potential cut-off level for HbA1c that would motivate an OGTT should also be further explored.

Despite that the intervention performed in the DIAVIP study focused solely isolated physical activity, it nevertheless also induced changes in diet (paper III). Therefore, other strategies are needed to explore the effect and mechanisms of isolated physical activity. For future studies in this field, group sessions are essential but such studies would probably require strict regulations concerning amount and type of physical activity. In addition, dietary changes during the study period should be discouraged. Most importantly however, the assessment of physical activity and fitness needs to be objective, and different methods of measurements have to be tested and adapted to the ability of the participants.

The level of physical activity needed to prevent CVD in individuals with impaired glucose metabolism, either with IGT, IFG or type 2 diabetes,

remains to be elucidated. Our studies (paper II and IV) indicate that more physical activity than generally recommended is needed to affect CRP in individuals with IGT, and to affect the increased risk of CVD from insulin resistance in non-diabetic men. However, this observation needs to be confirmed in future studies more specifically aimed at looking thoroughly into the exact levels of physical activity needed for cardiovascular prevention.

The interaction between gender, insulin resistance and physical activity is not completely understood and needs to be further explored, preferably in other longitudinal studies. For example, more studies are needed with regard to the somewhat contradictory association between CRP and CVD. I.e., high concentrations of CRP are considered predictive for CVD [60, 61], yet premenopausal women had an increased CRP as compared to men in our study (paper II), and in some other studies [69], but were still protected against CVD. Also, differences in attitudes between men and women influence compliance and tailored intervention strategies thus need to be investigated.

8   CONCLUSIONS – GENERAL AND SPECIFIC

8.1   General conclusion

A screening process for impaired glucose metabolism in primary care, followed by an intervention with physical activity is feasible, but new screening methods for IGT needs to be developed. Self-reported physical activity was shown associate with limited subclinical inflammation in individuals with IGT and was also related to the predictive value of insulin resistance with regard to development of CVD.

8.2   Specific conclusions

1)   FINDRISC, with a risk score ≥15, had a high positive predictive value for impaired glucose metabolism (55%) but was less efficient for the detection of individuals with IGT (16%).

2)   For recruiting individuals with IGT an advertisement with three basic questions may advantageously be used, but in a public health perspective FINDRISC with a risk score ≥15 may be the most efficient tool.

3)   An intervention with physical activity in individuals recruited by FINDRISC, was feasible and had an effect on several risk factors, in spite of a high co-morbidity in the study population. We also recognized that an intervention with focus on physical activity induced changes in diet.

4)   The inflammatory marker CRP was increased in individuals with IGT compared with individuals with normal glucose tolerance, but for men with IGT self-reporting more vigorous physical activity, this difference was not seen.

5)   Insulin resistance measured with HOMAir predicted cardiovascular disease in men without type 2 diabetes, but not in corresponding men self-reporting more vigorous physical activity.

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