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BODY SIZE, BODY COMPOSITION AND GLUCOSE TOLERANCE

With Special Reference to Adult Height, Body Surface Area, Fat and Lean Body Mass

Simo Rehunen

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To my family

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SIMO REHUNEN: Body Size, Body Composition and Glucose Tolerance with Special Reference to Adult Height, Body Surface Area, Fat and Lean Body Mass
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ABSTRACT

Body size and body composition have long interested mankind and their assessments are considered key factors for the evaluation of overall health status. Although the role of obesity – mostly applying body mass index (BMI) as a marker of obesity – in insulin resistance and type 2 diabetes (T2D) is well established, it is not fully understood how body size and body composition, i.e lean and fat mass, are associated with glucose tolerance/metabolism and development of T2D.

This study aimed to investigate the association of the combined effect of adult height and BMI, and body surface area (BSA) on glucose tolerance among middle-aged individuals at increased cardiovascular risk (n = 2659) from the Harjavalta Risk Monitoring for Cardiovascular Disease Project, and the association of the combined effect of lean and fat mass on glucose regulation and subsequent development of T2D among persons without diabetes at baseline (n = 1617 and n = 704, respectively) from the Helsinki Birth Cohort Study (HBCS).

Anthropometric measures and oral glucose tolerance test (OGTT) were performed in all individuals, and body composition was assessed in HBCS.

Taller people had lower 2-hour plasma glucose (2hPG) than shorter people, up to a BMI of 35 kg/m^2. The smaller the adjusted BSA of the person, the higher the proportion of newly diagnosed T2D based on 2hPG. High lean mass index (lean mass/height^2) accompanied with high fat mass index (fat mass/height^2) was associated with insulin resistance in men, whereas in women lean mass had little influence on glucose tolerance. Higher adiposity increased 2hPG values. The combination of high fat mass index and high lean mass index was associated with an elevated risk of developing T2D during a 15-year follow-up.

There is a possibility that the diagnosis of T2D made by an OGTT is a false positive result in a relatively smaller person, and a false negative result in a relatively larger person. Hence, it is questionable whether OGTT has a major clinical importance. Contrary to a general belief muscle mass – the predominant part of lean mass – is not protective against T2D. High muscle mass accompanied with fatness seems to be detrimental for glucose homeostasis and predict development of T2D. Fatness is the major determinant of glucose intolerance.

KEYWORDS: body size, body composition, oral glucose tolerance test, insulin resistance, type 2 diabetes

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Yleislääketiede
SIMO REHUNEN: Kehon koon ja koostumuksen vaikutus glukoosinsietoon – mielenkiinnon kohteina aikuispituus, kehon pinta-ala sekä kehon rasvaton ja rasvamassa
Väitöskirja, 136 s.
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Syyskuu 2021

TIIVISTELMÄ

Kehon koko ja koostumus ovat kiehtoneet ihmisiä kautta aikojen, ja niillä on keskeinen asema terveyttä tutkittaessa. Vaikka lihavuuden merkitys insuliiniresistenssiin ja tyypin 2 diabetekseen on hyvin tunnettu, ei tiedetä täysin, miten kehon koko ja koostumus eli rasvamassa ja rasvaton massa vaikuttavat glukoosinsietoon ja diabeteksen kehittymiseen.

Tämän tutkimuksen tavoitteena oli selvittää aikuispituuden ja lihavuuden yhteisvaikutus sekä kehon pinta-alan yhteys glukoosinsietoon keski-ikäisillä sydän- ja verisuonitautiriskihenkilöillä (n = 2659) Harjavallan valtimotautien ehkäisyprojektista. Lisäksi selvitettiin rasvattoman ja rasvamassan yhteisvaikutus glukoosinsäätelyyn ja diabeteksen kehittymiseen ei-diabeetikoilla (n = 1617 and n = 704, vastaavasti) Helsingin syntymäkohorttitutkimuksesta (HBCS).

Antropometriset mittaukset ja glukoosirasituskoe tehtiin kaikille tutkituille ja kehon koostumuksen mittaus HBCS:n osallistujille.

Kahden tunnin glukoosiarvo oli matalampi pitkillä kuin lyhyillä henkilöillä aina painoindeksiin 35 kg/m^2 asti. Mitä pienempi kehon pinta-ala, sitä suurempi todennäköisyys on saada diabetesdiagnoosi kahden tunnin glukoosiarvon perusteella. Suuri rasvaton massa -indeksi (rasvaton massa/pituus^2) yhdistyneenä suureen rasvamassaindeksiin (rasvamassa/pituus^2) oli yhteydessä insuliiniresistenssiin miehillä, kun taas naisilla rasvaton massa -indeksi ei vaikuttanut glukoosinsietoon. Kahden tunnin glukoosiarvot nousivat rasvakudoksen lisääntyessä. Suuri rasvaton massa -indeksi suuren rasvamassaindeksin kanssa oli yhteydessä diabeteksen kehittymiseen 15 vuoden seurannan aikana.

On mahdollista, että pienikokoisilla henkilöillä glukoosirasituskokeen perusteella tehty diabetesdiagnoosi on väärä positiivinen, kun taas kookkailla väärä negatiivinen. On siis kyseenalaista, onko glukoosirasituskokeella enää kliinistä merkitystä. Vastoin yleistä uskomusta lihasmassa, joka muodostaa suurimman osan rasvattomasta massasta, ei suojaa diabetekselta. Sen sijaan lihavilla suuri lihasmassa vaikuttaa olevan haitallista glukoosiaineenvaihdunnalle ja altistaa diabeteksen kehittymiselle. Rasva on glukoosi-intoleranssin tärkein tekijä.

AVAINSANAT: kehon koko, kehon koostumus, glukoosirasituskoe, insuliiniresistenssi, tyypin 2 diabetes

Table of Contents

Abbreviations

AHA	American Heart Association
ANOVA	Analysis of variance
ASM	Appendicular skeletal muscle
AUDIT	Alcohol Use Disorders Identification Test
BCAA	Branched-chain amino acid
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CHD	Coronary heart disease
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DXA	Dual energy X-ray absorptiometry
FPG	Fasting plasma glucose
FFA	Free fatty acid
FFM	Fat-free mass
FM	Fat mass
FMI	Fat mass index
HARMONICA	Harjavalta Risk Monitoring for Cardiovascular Disease
HbA_{1C}	Hemoglobin A_{1c}
HBCS	Helsinki Birth Cohort Study
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
HOMA-β	homeostatic model assessment of β-cell function
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IGF	Insulin-like growth factor
LDL	Low-density lipoprotein
LM	Lean mass
LMI	Lean mass index
LTPA	Leisure-time physical activity

MET	A metabolic equivalent of task
MMI	Muscle mass index
OGTT	Oral glucose tolerance test
OR	Odds ratio
RR	Risk ratio
rRR	Ratio of relative risks
SD	Standard deviation
T2D	Type 2 diabetes mellitus
TG	Triglycerides
TWA-MET	A time-weighted average intensity of a metabolic equivalent of task
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
2hPG	2-hour plasma glucose

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Rehunen S. K. J., Kautiainen H., Eriksson J. G. & Korhonen P. E. Adult height and glucose tolerance – a re-appraisal of the importance of body mass index. *Diabetic Medicine* 2017, 34(8), 1129–1135. https://doi.org/10.1111/dme.13382

II Palmu S., Rehunen S. K. J., Kautiainen H., Eriksson J. G. & Korhonen P. E. Body surface area and glucose tolerance – The smaller the person, the greater the 2-hour plasma glucose. *Diabetes Research and Clinical Practice* 2019, 107, 107877. https://doi.org/10.1016/j.diabres.2019.107877

III Rehunen S. K. J., Kautiainen H., Korhonen P. E. & Eriksson J. G. Lean body mass is not beneficial, but may be detrimental for glucose tolerance – Splitting body mass index according to body composition. *Primary Care Diabetes* 2020, 14(6), 747–752. https://doi.org/10.1016/j.pcd.2020.05.003

IV Rehunen S. K. J., Kautiainen H., Korhonen P. E. & Eriksson J. G. A high lean body mass is not protecting from type 2 diabetes in the presence of a high body fat mass. *Diabetes & Metabolism* 2021, 47(6), 101219. https://doi.org/10.1016/j. diabet.2020.101219

In addition, some previously unpublished data are presented.

1 Introduction

The global epidemics of obesity and type 2 diabetes (T2D) in combination with an aging population represent a serious challenge to healthcare and global economy. A concomitant increase in T2D parallels the increased incidence of obesity. Nearly one third of the world´s adult population is overweight or obese (World Health Organization, 2020), and 1 in 11 adults has T2D (International Diabetes Federation, 2019). The highest prevalence of T2D is among the older adults (Harris et al., 1998; Menke et al., 2015). Up to 1 of every 4 health care euros is spent on diabetes-related health care (American Diabetes Association, 2018).

One of the diagnostic criteria for T2D is based on elevated 2-hour plasma glucose (2hPG) after a standard oral glucose tolerance test (OGTT) (World Health Organization, 2006; American Diabetes Association, 2020). Increased 2hPG is known to be an independent risk factor for all-cause and cardiovascular disease (CVD) mortality (Barrett-Connor & Ferrara, 1998; Shaw et al., 1999; DECODE Study Group, 2001, Huang et al., 2016). However, since in the previous studies adjustments were not made for either body size (i.e. body height or body surface area (BSA)) or body composition, it is questionable whether the results are fully reliable.

Moreover, short adult stature is a well documented risk factor for all-cause mortality and cardiovascular morbidity (Stefan et al., 2016). Height is also inversely associated with a higher incidence of T2D (Shrestra et al., 2019).

In 1969, the American Diabetes Association proposed an estimation of BSA in order to define the appropriate glucose load to be used during OGTT (Klimt et al., 1969). This statement has been since forgotten, as in 1980 the World Health Organization (WHO) presented the still valid global guideline of the standardization of OGTT with a uniform glucose load of 75 g (Keen et al., 1979; World Health Organization, 1980).

Although the relationship of excess adiposity to insulin resistance and T2D is a long-recognized phenomenon (Hanson et al., 1995; Kopelman, 2000; Kahn et al., 2006), it is obscure whether body composition, i.e. lean mass and fat mass, relate to the development of T2D. In clinical practice obesity is typically estimated by body mass index (BMI). A downside of BMI is that it does not account for body

composition and it is less applicable to older adults (Winter et al., 2014). Instead, measurement of body composition and splitting BMI into lean mass index (LMI) and fat mass index (FMI), defined as lean/fat mass divided by the square of height analogously to BMI, may be a more suitable approach.

The present thesis was undertaken to investigate the association of body size and body composition to glucose regulation: specifically, the aim was to explore the association of the combined effect of adult height and BMI and BSA to glucose tolerance among individuals at CVD risk in a primary care setting; and to examine the combined effect of LMI and FMI on glucose tolerance and subsequent development of T2D among a representative sample of 60 years old people.

2 Review of the Literature

2.1 Impaired glucose tolerance

2.1.1 Definition and prevalence

Diabetes is a chronic state of hyperglycemia (i.e. elevated blood glucose concentrations), resulting from impairments in insulin secretion, insulin action or both (World Health Organization 2006, American Diabetes Association, 2020). As opposed to type 1 diabetes, where insulin deficiency is absolute, in type 2 diabetes (T2D), the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (American Diabetes Association, 2013).

Globally, the World Health Organization (WHO) published the first diagnostic criteria for diabetes in 1979 (National Diabetes Data Group, 1979). One year later, standardization of 2-hour oral glucose tolerance test (OGTT) with a uniform glucose load of 75 g was proposed by WHO (Keen et al., 1979; World Health Organization, 1980). These criteria have later been endorsed and redefined several times. There have been other definitions of T2D put forward by different organizations including the American Diabetes Association (ADA) and the International Diabetes Federation. Today, T2D and other hyperglycemic states are diagnosed according to elevated fasting glucose (FPG) concentrations, elevated glucose concentrations after a standard OGTT, elevated hemoglobin A_{1c} (HbA_{1C}), or by a random plasma glucose concentration ≥ 11.1 mmol/l with diabetes specific symptoms (World Health Organization, 2006; World Health Organization, 2011; American Diabetes Association, 2020). Table 1 shows the diagnostic criteria for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and T2D according to the WHO and the ADA criteria (World Health Organization, 2006; World Health Organization, 2011; American Diabetes Association, 2020). Presence of IFG and/or IGT and/or HbA_{1C} 5.7–6.4% (39–47 mmol/mol) is defined as prediabetes (American Diabetes Association, 2020.

In Finland, the diagnosis of hyperglycemic states is based upon the WHO criteria (Type 2 Diabetes: Current Care Guideline, 2020). Hyperglycemia increases the risk of future development of micro- and macrovascular complications – including diabetic retinopathy (Fong et al., 2003), diabetic nephropathy (Molitich

et al., 2003), diabetic neuropathy (Hicks & Selvin, 2019), peripheral arterial disease (Selvin & Erlinger, 2004), cardiovascular disease (CVD) (Emerging Risk Factors Collaboration, 2010), heart failure and atrial fibrillation (Rørth et al., 2018) - is elevated.

Table 1. Classification of impaired glucose regulation (World Health Organization, 2006; World Health Organization, 2011; American Diabetes Association, 2020).

	NORMAL	IFG	IGT	DIABETES
Fasting plasma glucose (mmol/l)	≤ 6.0 (WHO) ≤ 5.5 (ADA)	6.1-6.9 (WHO) 5.6-6.9 (ADA)		≥ 7.0
2-hour plasma glucose* (mmol/l)	< 7.8		7.8-11.0	≥ 11.1
Random glucose (symptomatic patient) (mmol/l)				≥ 11.1
Hemoglobin A1C				≥ 6.5% (48 mmol/mol)

* Venous plasma glucose 2 hours after ingestion of a 75 gram oral glucose load
IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ADA, American Diabetes Association; WHO, World Healt Organization

In a meta-analysis with 97 prospective studies, T2D was associated with all-cause mortality (hazard ratio (HR) 1.80; 95% CI 1.71–1.90), cancer death (HR 1.25; 95% CI 1.19–1.31), and vascular death (HR 2.32; 95% CI 2.11–2.56) (Rao Kondapally Seshasai, 2011). In the recent meta-analysis consisting of 35 prospective studies the pooled HRs for all-cause mortality in persons with T2D was 2.33 (95% CI: 2.02–2.69) in women and 1.91 (95% CI: 1.72–2.12) in men, and for vascular death 3.79 (95% CI: 3.01–4.78) in women and 2.13 (95% CI: 1.86–2.44) in men compared with their healthy counterparts (Xu et al., 2019). In a meta-analysis perfomed by Huang et al. IFG according to IFG-ADA or IFG-WHO criteria and IGT were associated with an increased risk of composite CVD (relative risk (RR) 1.13, 1.26, and 1.30 for IFG-ADA, IFG-WHO, and IGT, respectively), coronary heart disease (CHD) (1.10, 1.18, and 1.20, respectively), stroke (1.06, 1.17, and 1.20, respectively), and all-cause mortality (1.13, 1.13 and 1.32, respectively) (Huang et al., 2016). However, in eleven studies included in this meta-analysis focusing upon individuals with IGT and all-cause mortality, body size (i.e body height or body surface area) or body composition were not adjusted for. Additionally, in a previous meta-analysis, 7 out of 8 studies included failed to show significant associations between IGT and CVD (Ford et al., 2010). Nevertheless, the fixed-effects summary estimate of RR for CVD 1.20 (95% CI: 1.07 to 1.34)

was presented because of the results of men in the DECODE study (DECODE Study Group, 2001) was weighted 40.3%.

Diabetes is a global public health burden. Since 1980, the number of adults with diabetes worldwide has quadrupled from 108 million to 422 million in 2014 (NCD Risk Factor Collaboration, 2016b). Nowadays, nearly one in eleven adults has T2D (International Diabetes Federation, 2019). The prevalence of T2D increases with increasing age (Harris et al., 1998; Menke et al., 2015). Furthermore, almost one out of two individulas aged 65 years or more is in a prediabetic state in the United States (Menke et al., 2015).

In Finland, approximately 400,000 individuals have T2D (Koski, 2019). According to a Finnish population based study performed in almost 3000 adults aged 45–74 years the prevalence of T2D was 16% in men and 11 % in women, while the prevalence of IFG was 9% and 5% and IGT 15% and 16%, respectively (Peltonen et al., 2006). Overall, abnormal glucose regulation was present in 42% of the men and in 33% of the women (Peltonen et al., 2006). Further, it has been estimated that the absolute annual incidence of T2D in individuals with IFG or IGT varies from 5 to 10% (Gerstein et al., 2007).

2.1.2 Risk factors

Hyperglycemia and glucose metabolism are greatly affected by several modifiable (environmental) and unmodifiable (largely genetic) demographic, behavioral and clinical risk factors (Alberti et al., 2007). Modifiable and non-modifiable risk factors as well as diseases associated with T2D are presented in Table 2.

The most important modifiable risk factors are overweight, obesity, unhealthy diet and physical inactivity. The relationship of excess adiposity to T2D is a long-recognized phenomenon (Hanson et al., 1995; Kopelman, 2000; Kahn et al., 2006). Degree and duration of overweight or obesity positively influence risk of T2D (Field et al., 2001; Schienkiewitz et al., 2006;) For example, during 10 years of follow-up among men with BMI $\geq$ 35 kg/m^2 the incidence of T2D was 40-fold compared to men with BMI 18.5–21.9 kg/m^2 (Field et al., 2001). In women the corresponding incidence of T2D was 30-fold (Field et al., 2001). Moreover, weight reduction makes a major contribution to reducing the risk of T2D (Hamman et al., 2006) as well as to remission of established T2D (Lean et al., 2018).

Overweight, obesity and T2D are mainly driven by the disproportionate caloric consumption and quality of diet (Hu, 2011). Quality of fats and carbohydrates are important predictors of T2D, independent of BMI and other risk factors (Hu et al. 2001). While glycemic load, trans fat and processed and red meat are strongly associated with increased T2D risk (Hu, 2011; Barnard et al., 2014), higher

consumption of high-fibre diet including fruits and vegetables is associated with decreased risk of T2D (de Munter et al., 2007).

The risk of T2D is lower among physically active individuals compared to inactive ones (Helmrich et al., 1991; Lynch et al., 1997), even if they have IGT (Pan et al., 1996; Tuomilehto et al., 2001; Kowler et al., 2002). In addition, exercise habits play a key role in weight management (Tuomilehto et al., 2001, Lakka & Bouchard, 2005) and in glucose regulation through decreased insulin resistance (Goodpaster & Wolf 2004). Moreover, large Finnish and US studies have shown that lifestyle changes including both exercise and diet intervention can reduce the risk of developing T2D in individuals with IGT by almost 60% (Tuomilehto et al., 2001; Kowler et al., 2002).

The relationship between sleep and T2D has been identified as a multifaceted phenomenon (Cappuccio et al., 2010; Li et al., 2016). The quality and quantity of sleep affect both body weight regulation and glucose metabolism (Spiegel et al., 2009). On the other hand, obesity affects sleep, e.g. obesity is one of the primary causes of obstructive sleep apnea, which itself is a risk factor for further obesity and sleep deprivation (Romero-Corral et al., 2010; Kahal et al., 2018).

Notably, multiple highly correlated modifiable risk factors such as obesity, physical inactivity, poor diet and poor sleep are often present simultaneously (Tuomilehto et al., 2001; Lakka & Bouchard, 2005; Hu et al., 2007; Cappuccio et al., 2010; Li et al., 2016).

Table 2. The risk factors and associated diseases of type 2 diabetes (Alberti et al., 2007).

MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS	ASSOCIATED DISEASES
Overweight, obesity	Aging	Cardiovascular disease
Unhealthy diet	Birth size	Dyslipidemia
Physical inactivity	Family history	Hypertension
Sleep duration	Male gender	Metabolic syndrome
Smoking	Genetic factors	Sleep apnea
Cardiometabolic fitness	Gestational diabetes	Depression
Statin therapy	Race or ethnicity	Polycystic ovary syndrome
		Periodontal disease

The unmodifiable factors contributing to the development of hyperglycemia include e.g. age, male gender, family history of diabetes, genetic factors and body size at birth (Forsén et al., 2000; Fletcher et al., 2002).

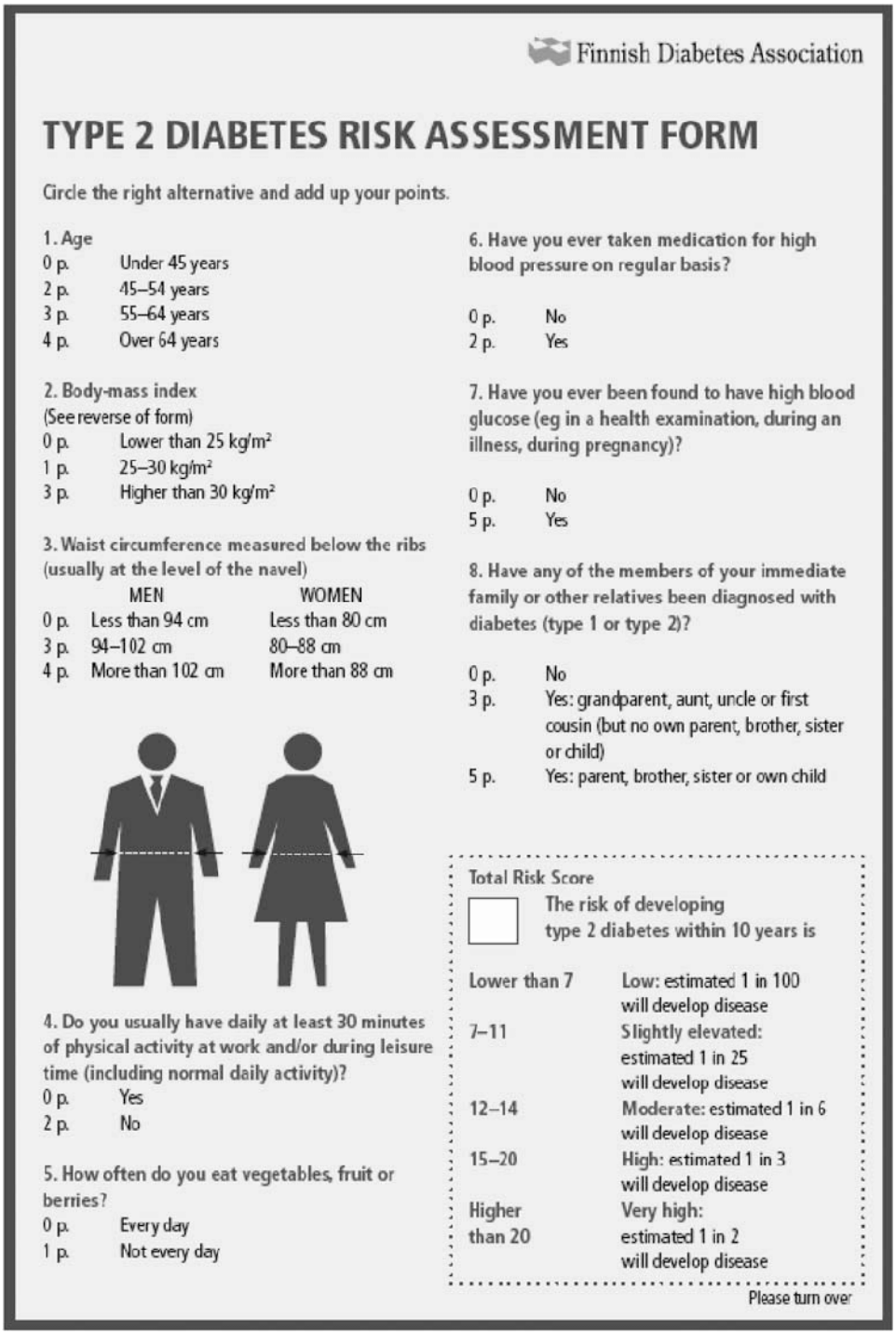
There is compelling evidence that individual risk of T2D is strongly influenced by genetic factors (Willemsen et al., 2015). Over the past decade, successive waves

of T2D genome wide association studies have delivered more than 80 robust genetic variants (McCarthy, 2010; Voight et al., 2010; Choet al., 2011; Kooner et al., 2011, Morris et al., 2012, DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, 2014, Steinthorsdottir et al., 2014). Most genes are associated with pancreatic β-cell function, while some are associated with insulin resistance (McCarthy, 2010). However, with limited exceptions (Huyghe et al., 2013; Steinthorsdottir et al., 2014), the variants driving known association signals are also common with individually modest impacts on T2D risk. Variation at known loci explains only a minority of observed T2D heritability (Morris et al., 2012, DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, 2014).

Also environmental chemicals, systemic inflammation, increased caloric intake, nutritient composition, smoking, statin use and in-utero environmental factors are risk factors for T2D (DeFronzo, 2009; Eriksson, 2011; Kahn, 2014; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014; Crandall et al., 2017).

Several noninvasive tools have been developed to estimate and screen the accumulation of diabetes risk factors. Of those the Finnish Diabetes Risk Score (FINDRISC) or its variants have been the most widely adopted (Schwarz et al., 2009; Brown et al., 2012). FINDRISC is a globally used composite T2D risk score questionnaire (Lindström & Tuomilehto, 2003) (Figure 1).

FINDRISC and its construct, as well as sensitivity and specificity have been extensively studied and validated (Lindström & Tuomilehto, 2003; Lindström et al., 2008; Schwarz et al., 2009; Cos et al., 2015, Zhang et al., 2015). Even if the FINDRISC was originally developed to determine the future T2D risk, subsequent studies have presented that it can also be used to detect individuals with impaired glucose metabolism (Saaristo et al., 2005; Zhang et al., 2014) and predict other adverse health events, such as CHD, stroke and overall mortality (Silventoinen et al., 2005; Heidemann et al., 2009).



Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

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

2. Body-mass index
(See reverse of form)
0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

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

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

4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?
0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?
0 p. Every day
1 p. Not every day

6. Have you ever taken medication for high blood pressure on regular basis?
0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?
0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?
0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score
The risk of developing type 2 diabetes within 10 years is

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

Please turn over

Figure 1. Finnish Diabetes Risk Score (FINDRISC). Reprinted with permission from the Finnish Diabetes Association (Lindström & Tuomilehto, 2003).

2.2 Insulin resistance

2.2.1 Definition and measuments

Insulin resistance is a fundamental concept associated with the etiology of T2D (Reaven 1988; Goldstein 2002; Kahn et al., 2014). As early as the 1930s, Sir Harold Percival Himsworth and collegues described the existence of a type of diabetes caused not by a lack of insulin but rather by insensitivity to insulin. By performing two OGTTs in the same individual, one with, and one without a concomitant injection of insulin, Himsworth observed that subjects with insulin insensitivity were unable to lower their glucose levels after insulin injection compared to insulin-sensitive subjects. He noted that this type of diabetes was more common, but not confined to elderly and may be preceded by obesity (Himsworth, 1936). Himsworth also found that weight loss not only removed the symptons of diabetes but also restored the glucose tolerance to almost normal (Himsworth, 1949). The condition Himsworth described is now known as insulin resistance, commonly defined as the resistance to insulin-stimulated glucose uptake (Reaven, 1988), or the inability of target tissues to respond to normal circulating concentrations of insulin (Goldstein, 2002).

There are some conditions, such as pregnancy and puberty, where insulin resistance can be regarded physiological (Wallace & Matthews, 2002). However, in most cases insulin resistance is a pathologic condition with numerous harmful effects in the body (Reaven, 1988; Kahn et al., 2014). Insulin resistance and hyperinsulinemia typically precede the onset of T2D by years or even decades (Reaven, 1988; Goldstein, 2002; Kahn et al., 2014). In other words, the development and progression of T2D and its preceding stages can be viewed as a continuum of increasing insulin resistance, increasing blood glucose concentrations, and first increasing and eventually declining secretion of insulin from pancreatic β-cells (Figure 2).

Although FPG and even OGTT levels may be normal, hyperinsulinemia and insulin resistance *per se* have been shown to associate with cardiovascular (CV) risk factors, such as hypertension, hypertriglyceridemia and low HDL cholesterol levels. In the 1940s, Jean Vague was the first to propose that an upper body, or masculine fat distribution was a significant predictor of the adverse health consequences of obesity and, in particular, its metabolic and cardiovascular abnormalities (Vague, 1996). A combination of the aforementioned risk factors was named “Syndrome X” (Reaven, 1988), and has later been renamed as the “insulin resistance syndrome” (Reaven 2004) or metabolic syndrome (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). In addition to these risk factors, insulin resistance increases the likelihood of

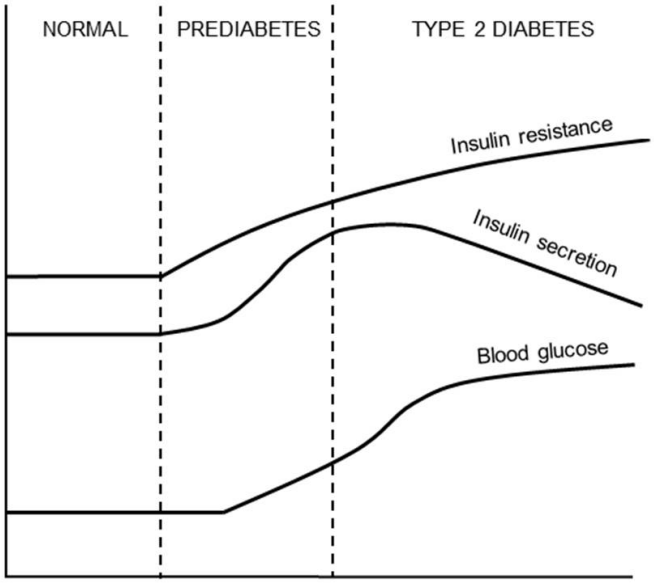


Figure 2. Continuum of type 2 diabetes. Modified from Type 2 Diabetes BASICS (International Diabetes Center, 2000).

many different abnormalities, such as endothelial dysfunction, procoagulant factors, hemodynamic changes, increased inflammatory markers, and abnormal uric acid metabolism, thereby associating with not only T2D and CVD, but also hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, sleep apnea and certain forms of cancer (Reaven 2004).

Pathogenesis of insulin resistance and further T2D originates from fatness and dysfunction of adipocytes (Kahn & Flier, 2000). Subcutaneous adipose tissue accounts for about 85% of all body fat (Thomas et al., 1998), independently correlates with metabolic complications of obesity (Smith et al., 2001) and acts as a physiological "sink" for excess lipid storage during times of limited energy expenditure (Freedland, 2004). When this storage capacity is exceeded, fat begins to accumulate ectopically, especially viscerally. Visceral adipose tissue is highly metabolically active and is associated with hyperinsulinemia, systemic inflammation, development of T2D and CVD, as well as mortality (Björntorp, 1990; Hunter et al., 2010; Chait & den Hartigh, 2020). Interestingly, subcutaneus adipose tissue blood flow (ATBF) is tightly linked to its metabolic function and is downregulated in obesity (Frayn & Karpe, 2014). ATBF has been been found to associate inversely with BMI (Frayn & Humphreys, 2012), and the ATBF response to OGTT has been shown to be reduced in obese people (Jansson et al., 1998).

Collectively, adipocytes, muscle, liver (which is mainly responsible for the glucose production into the circulation in the fasting state) (DeFronzo et al., 1989),

and pancreatic β-cells comprise the harmonious quartet, or perhaps more appropriately, the dysharmonious quartet, since together they sing a very bad tune for the (pre)diabetic individual (DeFronzo, 2009) (Figure 3). Considerable evidence implicates deranged adipocyte metabolism and altered fat topography in the pathogenesis of insulin resistance/glucose intolerance (Reaven, 1988; Groop et al., 1989; Kashyap et al., 2003; Bays et al., 2004; DeFronzo, 2004; Bays et al., 2008). Enlarged fat cells are resistant to antilipolytic effect of insulin, leading to day-long elevation in the plasma free fatty acid (FFA) concentration (Groop et al., 1989; Groop et al., 1991; Bays et al., 2004; DeFronzo, 2004; Bays et al., 2008). Chronically increased plasma FFA levels stimulate gluconeogenesis (Williamson et al., 1966; Ferrannini et al., 1983; Bevilacqua et al., 1987), induce muscle and hepatic insulin resistance (Golay et al., 1988; Roden et al., 1996), and impair insulin secretion (Carpentier et al., 2000; Kashyap et al., 2003). These FFA-induced disturbances are referred to as lipotoxicity. Dysfunctional fat cells produce excessive amounts of insulin resistance–inducing, inflammatory, and atherosclerotic-provoking adipocytokines, such as leptin (La Cava, 2017) and fail to secrete normal amounts of insulin-sensitizing adipocytokines such as adiponectin (Bays et al., 2004; Bays et al., 2008).

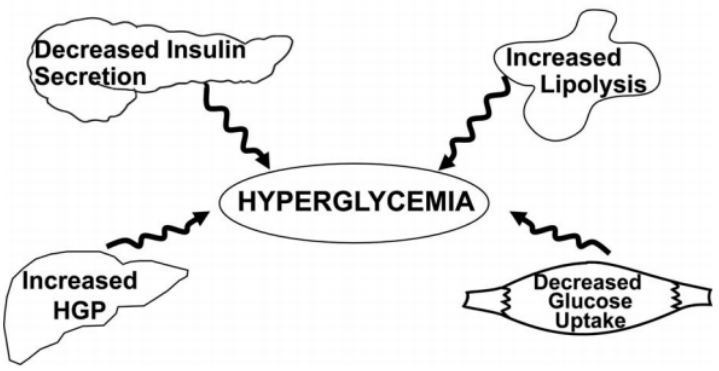


Figure 3. The disharmonious quartet. Reprinted from DeFronzo (2009), American Diabetes Association, From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus, 2009. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. HGP, hepatic glucose production.

Enlarged fat cells are insulin resistant and have diminished capacity to store fat (Salans et al., 1974; Bray et al., 1977). When adipocyte storage capacity is exceeded, lipid "overflows" into muscle, liver and pancreatic β-cells, causing muscle and hepatic insulin resistance and impaired insulin secretion (Bays et al., 2004; Bays et al., 2008). Insulin resistance is manifested in muscle by impaired

glucose uptake following ingestion of a meal and results in postprandial hyperglycemia (Abdul-Ghani & DeFronzo, 2010). In liver, insulin resistance leads to an overproduction of glucose during the basal state despite the presence of fasting hyperinsulinemia (DeFronzo et al., 1989) and an impaired suppression of hepatic glucose production in response to insulin (Groop et al., 1989).

The different methods to assess insulin resistance have been reviewed by Wallace & Matthews (Wallace & Matthews, 2002) and, more recently, by Cersosimo et al. (Cersosimo et al., 2014). The golden standard for measuring insulin resistance is the hyperinsulinemic-euglycemic clamp technique (DeFronzo et al., 1979). Developed by DeFronzo et al. in 1979, this procedure presumes that at high doses of insulin infusion, the hyperinsulinemic state is sufficient to entirely suppress glucose production from liver and that there is no alteration in blood glucose concentrations under steady-state conditions. Under such conditions, the rate of glucose infused equals to the rate of whole-body glucose disposal or metabolizable glucose and corresponds the amount of exogenous glucose necessary to completely compensate for the hyperinsulinemia.The smaller the amount of glucose needed to maintain the predetermined blood glucose concentration is, the greater is the degree of insulin resistance (DeFronzo et al., 1979). However, this method is very rarely used in the clinical setting or in large studies, due to its timeconsuming and fairly invasive nature.

Instead, in addition to OGTT, more simple methods such as the homeostatic model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985), have been developed to evaluate insulin resistance based on venous blood sampling. The other methods used to measure insulin resistance (the intravenous glucose tolerance test with minimal model, the insulin sensitivity test, the short insulin sensitivity test, the Matsuda Index, and the Quantitative Insulin Sensitivity Check Index (QUICKI)) are beyond the scope of this review.

In contrast to the euglycemic clamp method which measures stimulated insulin sensitivity, the HOMA-IR method estimates basal insulin resistance from fasting plasma insulin and glucose concentrations. This method compares favorably with other models and has the advantage of requiring only a single plasma sample assayed for insulin and glucose (Wallace et al., 2004). HOMA-IR has been shown to correlate well with the hyperinsulinemic-euglycemic clamp ($R=0.88$, $p < 0.0001$) (Matthews et al., 1985; Bonora et al., 2000). HOMA-IR can be counted simply by the equation (fasting plasma glucose × fasting plasma insulin)/22.5 (Matthews et al., 1985).

To date, there is no defined cut-off value for defining insulin resistance according to HOMA-IR that would apply to different populations. HOMA-IR varies according to age, sex, and ethnicity, and it is probable that different cut-off values will be needed for different populations. WHO encourages the cut-off being

set at the 75th percentile of a non-diabetic population (Alberti & Zimmet, 1998). According to this recommendation, the cut-off for HOMA-IR has varied from 2.0 in a Swedish population (Hedblad et al., 2000) to 3.8 in a French population (Marques-Vidal et al., 2002).

The HOMA model can also be used for the estimation of pancreatic β-cell function (the homeostatic model assessment of β-cell function, HOMA-β) (Matthews et al., 1985). The equation of HOMA-β is (20 × fasting plasma insulin)/(fasting plasma glucose − 3.5) (Matthews et al., 1985). HOMA-β is recommended to be reported together with HOMA-IR (Wallace et al., 2004). Namely, if HOMA-β is reported in isolation, one might conclude erroneously that the subject has failing β-cells, as opposed to appropriately low secretion, when the sensitivity of the body is high.

The ratio of adipocytokines leptin and adiponectin has also been proposed as an efficacious parameter of insulin resistance (Inoue et al., 2006; Finucane et al., 2009; Bravo et al., 2017). Excess adiposity is associated with lower production of anti-inflammatory adiponectin and higher secretion of proinflammatory leptin (Yadav et al., 2013). As a result, the higher leptin/adiponectin ratio, the higher insulin resistance (Inoue et al., 2006; Finucane et al., 2009; Bravo et al., 2017).

2.3 Body size

2.3.1 Adult height

2.3.1.1 Overview

Height is a feature that has fascinated researchers for centuries. Height is the most recognizable parameter in human anthropometrics, and is widely used as diagnostic and therapeutic tool. In utero, length measures provide an estimate of fetal development, and in early childhood and puberty, it is widely used to evaluate hormonal and nutritional status. Height is used in calculations of BMI and BSA during adolescence and adulthood, enabling assessment of risk of metabolic diseases and appropriate drug dosing. In elderly people monitoring height allows estimation of bone loss and incidence of frailty (Finigan, 2008).

An estimated 80% of variability in attained height is genetically determined, but environmental factors such as nutrition, childhood disease burden, socioeconomic conditions and geographical location, among others, may also affect individuals' height (Silventoinen et al., 2003; Silventoinen, 2003; Visscher, 2006).

Height matters for health; it is inversely associated with risk of CVD but positively associated with risk of cancer. In the largest study on this topic, including data from 121 prospective studies with more than 1 million people, a 6.5 cm increase in height was associated with reduced all-cause mortality (RR 0.97) and with reduced mortality from all vascular causes (RR 0.94). By contrast, tall stature was associated with increased total cancer mortality (Emerging Risk Factors Collaboration, 2012). Possible mechanisms underlying the divergent associations of height with cardiometabolic disease and cancer might include environmental factors, such as increased energy intake during pregnancy, early childhood, and puberty. These might due to fact that taller people present increased insulin-like growth factor 1 (IGF1) and IGF2 concentrations and bioavailability and increased insulin and branched-chain aminoacid (BCAA) concentrations. Increased IGF1, IGF2, insulin and BCAA signalling might induce cell proliferation, resulting in skeletal and organ growth and reduce insulin resistance, while promoting cancer growth (Stefan et al., 2016). On the other hand, CVD and cancer are competing causes of death, so a higher observed risk of cancer for taller people might be the effect of lower CV mortality. Thus, health-care providers should bear in mind that tall people might clinically have fewer CVDs, which might cause underestimation of their increased cancer risk (Stefan et al., 2016).

2.3.1.2 Adult height and type 2 diabetes

Although height is generally non-modifiable, short stature has emerged as a potential risk factor for T2D. Thus, increasing knowlegde of its potential effects may contribute to the development of more accurate risk prediction models and may allow individuals to change their other behaviours to help reduce the risk of T2D (Shrestha et al., 2019).

In a recent meta-analysis consisting of 16 studies (9 cross-sectional studies and 7 cohort studies) with 261,496 individuals adult height was inversely associated with T2D (effect estimate=0.88, 95% CI 0.81 to 0.95) (Shrestha et al., 2019). The finding was similar to a previous meta-analysis conducted in 2012, in which the summary RR was 0.85 (95% CI 0.76 to 0.96) (Janghorbani et al., 2012). The latter meta-analysis took into account examination of sex differences and found no gender-related associations between adult height and T2D (Shrestha et al., 2019).

Height and BMI are correlated, and given the strong positive relationship between BMI and T2D (Colditz et al., 1990), BMI may be a potential confounder of the association of height and T2D. Among 16 studies included in a recent meta-analysis, five studies adjusted for BMI (Njølstad et al. 1998; Kumari et al., 2004; Conway et al., 2012; Hoque et al., 2014; Furer et al., 2015;) and two studies (Bozorgmanesh et al., 2011; Smits et al., 2012) adjusted for factors alike to BMI,

such as weight or waist circumference. In general, these studies showed inverse associations between height and risk of T2D after adjustment for BMI. However, there was insufficient information available for conducting subgroup analyses based on adjustments for BMI. In the EPIC-Potsdam study the association of height with T2D risk appeared to be stronger among normal-weight (BMI < 25 kg/m^2) individuals (HR per 10 cm, 0.14 among men, 0.33 among women) compared with overweight/obese individuals (HR 0.64 and 0.70, respectively) (Wittenbecher et al., 2019). Similarly, in the Shanghai Women's Health Study and the Shanghai Men's Health Study, in which a larger/taller leg length was inversely related to risk of T2D, this association completely diminished when adjusted for BMI (Conway et al., 2012). This may indicate that a higher T2D risk with higher BMI counteracts beneficial effects related to height. Given the negative correlation between height and body fat percentage (Asao et al., 2012, Wittenbecher et al., 2015), adjusting for BMI may at least in part inappropriately account for beneficial effects of a higher proportion of lean body mass with higher stature.

Although height is seemingly associated with T2D, it is likely an indicator of risks that reflect both biological and environmental factors (Furer et al., 2015). Biological links, although plausible, remain speculative. A potential biological pathway linking height and T2D could be fetal programming of metabolism (Barker et al., 1993; Luo & Karlberg, 2000), as high IGF1, a major determinant of fetal and childhood growth, also predicts reduced risk of adult T2D (Sandhu et al., 2002).

Leg length, an indicator of long bone growth in childhood, appears to be more important than trunk length in the associations with T2D (Lawlor et al., 2002; Wittenbecher et al., 2019). Wittenbecher el al. demonstrated that sitting height adjusted for total height was related to increased T2D risk in men, while among women both higher leg length and sitting height contributed to lower T2D risk (Wittenbecher et al., 2019). They suggested that, among boys, growth before puberty, which relates more strongly to leg length, has a more favourable impact on later diabetes risk than growth during puberty (assuming that truncal bones are last to stop growing (Tortora & Grabowski, 2003)), while for girls both growth periods seem to be important.

Tall people tend to be more insulin sensitive compared with shorter people (Lawlor, 2002; Asao, 2006; Stefan et al., 2016; Vangipurapu et al., 2017). Rapid height growth during puberty and taller adult height have also been associated with increased concentrations of IGF1 (Ben-Shlomo et al., 2003), which contribute to insulin sensitivity and increased lipid oxidation (LeRoith & Yakar, 2007). On the other hand, data from the Finnish Metabolic Syndrome in Men (METSIM) cohort suggest that height is also positively associated with pancreatic β-cell function (Vangipurapu et al., 2017). Interestingly, in this study greater height was related to

improvements in both insulin sensitivity and pancreatic β-cell function over time, independent of the baseline status of these two variables, age, waist circumference (WC), physical activity and smoking. However, whether the use of indices of insulin sensitivity and pancreatic β-cell function derived from OGTT in these studies is meaningful in the context of evaluation of height is questionable given that response to a fixed glucose load depends on the total amount of tissue for uptake and metabolism of glucose (Sicree et al., 2008; Faerch et al., 2013). In fact, considering the inverse association between height and glucose regulation Sicree et al. (Sicree et al., 2008) presumed that this association is due to fact that taller persons have more lean mass (LM) (Hansen et al., 1999). A close correlation of LM with height was presented already in 1960s (Hume, 1966).

A substantial proportion of the inverse association between height and T2D is attributable to lower liver fat content (Stefan et al., 2008; Wittenbecher et al., 2019). Wittenbecher et al. presented that adjustment for the fatty liver index (surrogate for liver fat) substantially weakened the associations between height and T2D risk specifically in women (Wittenbecher et al., 2019). In a study of Stefan et. al. adult height correlated negatively with liver fat content and positively with insulin sensitivity (Stefan et al., 2008). No correlation between adult height and total or visceral fat was found. These findings suggest that mechanisms underlying the relation between greater height and lower T2D risk might include reduced ectopic lipid storage, a characteristic that strongly affects the extent of insulin sensitivity (Shulman 2014; Stefan et al., 2008; Stefan & Häring 2013), in addition to measures of overall or visceral adiposity.

Both height (Silventoinen, 2003) and T2D (Chen et al., 2012) are influenced by genetic factors, and these could also be potential confounders of their association. However, investigation of genetically determined height has only suggested a trend for decreased risk of T2D so far (Nelson et al., 2015). Recent studies linking genetically determined height to CVD support that height is associated with CV risk and this risk might at least in part be mediated by cardiometabolic risk factors relevant for T2D, namely blood pressure (BP), blood lipids and inflammation (Nelson et al., 2015; Nüesch et al., 2016).

Child and adult socio-economic status are positively associated with height (Silventoinen, 2003; Jousilahti et al., 2000; Batty & Leon, 2002) and negatively associated with T2D (Agardh et al., 2011). Components of sosio-economic status were adjusted for in eight studies focusing on association between height and glucose regulation (Han et al., 1998; Lawlor et al., 2002; Kumari et al., 2004; Schulze et al., 2006; Conway et al., 2012; Hoque et al., 2014; Furer et al., 2015; Vangipurapu et al., 2017). Only in one study, the association between adult height and T2D remained statistically significant (Furer et al., 2015).

Height can be used in T2D risk prediction models, besides other risk factors. For example, in the German Diabetes Risk Score, points assigned per 1 cm of waist circumference or 1 year of age correspond to about 3 cm and 2 cm of height, respectively (Mühlenbruch et al., 2014). Thus, clinicians should be encouraged to consider height for risk assessment. On the other hand, attained height might represent an estimate of early childhood factors and their effects on later cardiometabolic and cancer risk (Stefan et al., 2016; Wittenbecher et al., 2019). In terms of prevention of height-related T2D risk, interventions likely need to focus on determinants of growth during pregnancy, early childhood, puberty and early adulthood.

2.3.2 Body surface area

2.3.2.1 Overview

In the nineteenth century, Herman von Helmholz (1821-1894) and simultaneously Robert Mayer (1814-1878) went to develop the laws of conservation of mass and energy (Helmholtz, 1847; Mayer, 1862). This work ultimately formed the basis for the law of body surface area (BSA), which was formulated by German Max Rubner (1854-1932) (Rubner, 1902). He observed a consistent linear relationship between metabolic rate and BSA among mammals regardless of species and sizes (Rubner, 1883). As a result it became commonplace to index physiological variables to BSA, which is the area of the external surface of the body, expressed in square meters (m^2). BSA is usually calculated according to the Mosteller formula (Mosteller, 1989): $(\text{weight} \times \text{height} / 3600)^{½}$.

BSA is used for determining metabolic, electrolyte and nutritional requirements, and drug dosage. As examples, renal function is measured by the glomerular filtration rate (GFR) which is calculated in regard to BSA (Geddes et al., 2008). The cardiac index is a measure of cardiac output divided by BSA, giving a better approximation of the required cardiac output (Reynolds & Hochman, 2008). Chemotherapy and pharmacotherapies are often dosed according to the patient's BSA. In adults, the rule of nines is used to determine the total percentage of BSA burned for each major section of the body. If the burns do not fully cover such a section, burns are measured by using the patient's palm including fingers as a reference point for 1% of BSA (Wallace, 1951).

2.3.2.2 Body surface area and type 2 diabetes

In 1969, the Committee of the Statistics of the American Diabetes Association proposed an estimation of BSA in order to define the appropriate glucose load to be

used during OGTT (Klimt et al., 1969). In 1970s, the larger glucose load per square meter of BSA was shown to result in significantly greater blood glucose responses (Chandalia H. B., Boshell, 1970; Peterson & Reaven, 1971). Additionally, the increase in the plasma insulin response was much greater than the increase in plasma glucose response indicating that glucose load is an important determinant of plasma insulin response (Peterson & Reaven, 1971).

In 1980, WHO recommended the global standardization of OGTT with a uniform glucose load of 75 g (Keen et al., 1979; World Health Organization, 1980). This recommendation is still valid (American Diabetes Association, 2020). Hence, it is not surprising that studies concerning BSA and glucose tolerance are sparse. In a study of Ting et al. smaller surface area of head, both arms and both legs, obtained by 3D body surface scanning was associated with increased risk of developing T2D among Taiwanese people (Ting et al., 2018). There was no association between trunk surface area and incidence of T2D.

In the assessment of insulin sensitivity by the hyperinsulinemic-euglycemic clamp, glucose disposal rate is expressed as a function of metabolic body size, such as BSA (Lillioja & Bogardus, 1988). However, this technique is impossible to use in primary care setting.

2.3.3 Body mass index

2.3.3.1 Overview

Obesity is among the leading causes of death and disability globally. Obesity is associated with both increased fat cell size and number within adipose tissue (Hirsch & Batchelor. 1976; Hausman et al., 2001). Even though the gold-standard definition of obesity by the WHO is an excess in body fatness (> 25% in men and > 35% in women) (World Health Organization, 1995), BMI is the most common measure used/applied in the classification of adiposity among adults in both clinical practice and epidemiological studies because of its affordability and universal availability (Table 3) (World Health Organization, 2000).

Overweight and obesity are major risk factors for CVD (Piepoli et al., 2016), including CHD, stroke (Klein et al., 2004; Poirier et al., 2006), atrial fibrillation (Tedrow et al., 2010), and venous thromboembolism (Wattanakit et al., 2012).

In a meta-analysis of 10.6 million adults in Asia, Australia, New Zealand, Europe, and North America from 239 prospective studies all-cause mortality was lowest at BMI levels of 20.0 to 24.9 kg/m^2 during a median 13.7 years follow-up period (Global BMI Mortality Collaboration, 2016). For BMI over 25.0 kg/m^2, mortality increased approximately log-linearly with BMI; the HR per 5 kg/m^2 units

higher BMI was 1.39 (1.34–1.43) in Europe and 1.29 (1.26–1.32) in North America (Global BMI Mortality Collaboration, 2016).

The worldwide prevalence of overweight and obesity is high and is increasing (Ng et al., 2014; NCD Risk Factor Collaboration, 2016b). WHO estimates that more than 1.9 billion adults are overweight, of these over 650 million are obese. As a result, nearly a third of the world´s adult population is overweight or obese (World Health Organization, 2020). In Finland, according to the FinHealth 2017 Study more than half of the citizens (2.5 million) aged 30 years or older are overweight, of these 1 million are obese. The mean BMI was 27.5 kg/m² among Finnish women and 27.7 kg/m² among men (Koponen et al., 2018).

Table 3. World Health Organization criteria for the classification of body mass index (World Health Organization, 2000).

CLASSIFICATION	BMI (KG/M^2)
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	≥ 25.00
Pre-obese	25.00–29.99
Obese	≥ 30.00
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

The causes of obesity are multifactorial: environmental, behavioral, and genetic factors can all contribute to its development. It is commonly agreed that the environment, rather than biology, is driving the obesity epidemic through discouraging expenditure of energy, leading to an imbalance between energy intake and energy consumption (Hill et al., 2003). The obesity problem seems to originate from childhood, according to a meta-analysis of 15 prospective studies, 55% of obese children will be obese in adolescence, and 80% of obese adolescents will be obese in adulthood (Simmonds et al., 2016). Overweight and obesity are influenced by genetics with heritability estimates ranging from 40% to 75% (Wardle et al., 2008).

2.3.3.2 Body mass index and type 2 diabetes

Obesity is the major risk factor for T2D development. A meta-analysis combining 18 prospective cohort studies including 590,251 people reported that the RR of T2D for obese persons compared with those with normal weight was 7.19 (95% CI

5.74 to 9.00) and compared with overweight individuals 2.99 (95% CI 2.42 to 3.72) (Abdullah et al., 2010).

Hartemink et al. conducted a meta-analysis that detected a dose–response relationship between BMI and T2D. It was shown that per one kg/m^2 increase in BMI, the risk of T2D increased by 18% (95% CI 1.16% to 1.20%) (Hartemink et al., 2006). Meta-analysis data from Japan, Australia and New Zealand demonstrated a stronger association between BMI and the risk of T2D in subjects younger than 60 years of age compared with people older than 70 years (Asia Pacific Cohort Studies Collaboration, 2006). Similar findings have been extended to adults younger than 40 years of age in a Chinese cohort study, in which BMI had a greater risk on incident T2D in earlier adulthood than in later adulthood (Chen et al., 2018).

Young-onset obesity has been reported to have more genetic predisposition to metabolic disorders, and resulted in chronically increased levels of proinflammatory circulating FFAs and cytokines and decreased levels of protective factors (e.g., adiponectin), which reduce insulin sensitivity and impair insulin secretion (Lumeng & Saltiel, 2011; Reinehr et al., 2016). Individuals with young-onset obesity tend to have an inactive lifestyle, which might also contribute to the development of adiposity, insulin resistance, hyperglycemia and other CV risk factors (Gustat et al., 2002; Dollman et al., 2005). Therefore, obese youth lose the protective effects of a young age with regard to T2D risk. Moreover, aging is often accompanied by an increase in fat mass and progressive loss of muscle mass, which is a dominant part of LM, even in the absence of changes in body weight and BMI (Kyle et al., 2001; Newman et al., 2005). An additional process associated with ageing is fat redistribution. Subcutaneous fat is redistributed to visceral fat that pose higher metabolic risk (Hunter et al., 2010). However, these age-related changes in BMI should theoretically increase the diabetes risk associated with BMI, rather weaken the association between BMI and T2D. Accordingly, it remains uncertain whether BMI is an appropriate measure of obesity in older individuals.

2.3.4 Waist circumference, waist-to-hip ratio, waist-to-height ratio

2.3.4.1 Overview

If BMI is widely used as an index of general adiposity, WC, waist-to-hip ratio (WHR) and waist-to-height-ratio (WHtR) are used as surrogate anthropometric measures of abdominal obesity (Ashwell et al., 1996; Alberti & Zimnet, 1998; Alberti et al., 2003; Parikh et al., 2009). Currently, the most often used definitions

for central obesity among Caucasians are WC of 102 cm and 88 cm (Lean et al., 1995), or of 94 cm and 80 cm (International Diabetes Federation, 2006)), or WHR of 0.95 and 0.80 (Lean et al., 1995) in men and in women, respectively. For WHtR, a cutoff value of 0.5 for both men and women and individuals of Caucasian, Asian, and Central American origin can be used for the prediction of cardiometabolic risk. This value was the mean value of the suggested boundary values regarding several CVD risk factors (Browning et al., 2011). This cutoff has been used to support the simple public health message "keep your waist circumference to less than half your height" (Browning et al., 2011).

Many studies have shown that a larger WC is associated with increased all-cause mortality even after adjusting for BMI (Bigaard et al., 2003; Janssen et al., 2005; Koster et al., 2008; Pischon et al., 2008; Zhang et al., 2008). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, reporting on nearly 15,000 deaths out of more than 350,000 subjects in nine countries, 5 cm increase of WC was associated with 17% increase of mortality risk in men and 13% increase of mortality risk in women (Pischon et al., 2008). In a meta-analysis including 58,609 subjects from 23 studies, higher WC was also associated with higher mortality in the elderly subjects with both normal and overweight BMI (de Hollander et al., 2012). Additionally, data from the Korean National Health Insurance Service health checkup consisting of 23 million adults presented a linear association between WC and all-cause mortality across all BMI categories even in the subjects with normal or overweight BMI (Kim et al., 2019).

In a meta-analysis of nine cohort studies of 82,864 British adults, a one SD higher in WC and WHR was related to a higher risk of CVD mortality (HR (95% CI)): 1.15 (1.04-1.27) and 1.15 (1.05-1.25), respectively. The risk of CVD also increased linearly across quintiles of both these markers with a 66% increased risk in the highest quintile of WHR (Czernichow et al., 2011). In addition, several studies have demonstrated that WHR has a linear positive association with all-cause mortality (Lahmann et al., 2002; Simpson et al., 2007; Welborn & Dhaliwal, 2007; Pischon et al., 2008; Zhang et al., 2008; Petursson et al., 2011).

Furthermore, WHtR has been shown to have a linear positive relationship with all-cause mortality (Welborn & Dhaliwal, 2007; Pischon et al., 2008; Taylor et al., 2010; Carmienke et al., 2013), whereas Petursson et al. found a linear positive relationship in Norwegian men in contrast to a J-shaped relation in women (Petursson et al., 2011).

Savva et al. compared in their meta-analysis the association of BMI and WHtR with cardiometabolic risk and found that WHtR was superior to BMI; pooled ratio of relative risks (rRR) for CVD mortality was 0.42 (95% CI: 0.35–0.50), and for all-cause mortality 0.49 (95% CI: 0.41–0.59). WHtR was also superior to BMI in detecting incident CVD in both Asians (rRR: 0.64, 95% CI: 0.57–0.72) and non-

Asians (rRR: 0.75, 95% CI: 0.64–0.87) (Savva et al., 2013). In addition, Aswell et al., presented that WHtR is more predictive of years of life lost than BMI (Ashwell et al., 2014).

In the EPIC study, RR of all-cause mortality in the highest as compared with the lowest quintile of the WHtR was 2.22 (95% CI, 1.94–2.55) among men and 2.03 (95% CI, 1.76–2.34) among women in the multivariable-adjusted model (including BMI), whereas for WC RR was 2.05 (95% CI, 1.80–2.33) for men and 1.78 (95% CI, 1.56–2.04) for women (Pischon et al., 2008).

A prospective (11 years) study of body size and risk for stroke among more than 45,000 women below age 60 showed that, in contrast to BMI, the measures of abdominal obesity (WHtR > WC > WHR) are strong predictors of stroke in women (Lu et al., 2006).

Gelber's analysis of data from more than 32,000 women with the follow-up of 5.5 years and more than 16,000 men with the 14 years of follow-up led the authors to conclude that "WHtR demonstrated statistically the best model fit and strongest associations with CVD" (Gelber et al., 2008).

2.3.4.2 Waist circumference, waist-to-hip ratio, waist-to-height ratio and type 2 diabetes

WC, WHR and WHtR predict strongly and independently risk of T2D (Carey et 1997 al.; Sargeant et al., 2002; Snijder et al., 2004; Wang et al., 2005; Chei et al., 2008; Xu et al., 2010; Jia et al., 2011; Zhao et al., 2012; Huerta et al., 2013).

Lee's meta-analysis in 2008 including 88,000 individuals found that the area under the curve values predicting risk of T2D were ranked in this order: WHtR (highest), WC = WHR and BMI (lowest) (Lee et al., 2008). In the meta-analysis of 15 papers, WHtR was shown to have a modestly but statistically greater importance than BMI and WHR in prediction of T2D (Kodama et al.; 2012). Ashwell´s meta-analysis involving more than 300,000 adults in several ethnic groups found that WHtR and WC were superior to BMI for identifying T2D in both sexes (Ashwell et al., 2012). WHtR was a better discriminator than WC for T2D among both sexes in Ashwell´s meta-analysis (Ashwell et al., 2012), whereas measuring height in addition to WC appeared to have no additional benefit in Kodama´s meta-analysis (Kodama et al.; 2012). Additionally, a systematic review in individuals aged 65 years or more demonstrated that WC, WHR and WHtR are better indicators in predicting risk for CVD, metabolic syndrome and T2D compared to BMI (Corrêa et al., 2016).

2.4 Body composition

2.4.1 Definition and measurements

Body composition has long interested mankind and its assessment is considered a key factor for the evaluation of general health status of humans. Conjecture on body composition can be traced back to antiquity. Circa 440BC, Hippocrates proposed the idea that as a whole organism the human body is composed of four "constituents", blood, phlegm, black bile, and yellow bile. Nowadays, technological advances have helped to expand knowledge of human body composition variability throughout the life-cycle in health and disease (Wang et al., 1999).

Body composition comprises fat mass (FM) and fat-free mass (FFM) (the 2-compartment model). In the so-called 3-compartment model, FFM includes bone mineral and LM, indicating soft tissues other than fat, i.e. mostly muscle. In the 4-compartment model, the FFM consists of water, protein and mineral. (Fuller et al., 1992, Khalil et al., 2014). The most frequently applied model to evaluate body composition in clinical practice and epidemiology splits the body mass into FM and FFM. FFM is often called lean body mass or LM. This text adopts the bicompartment model and the term lean mass.

Body composition is prone to constant changes in order to adapt to current requirements. These changes are regulated by multiple factors, including nutrition, physical activity, hormonal factors, immunity and inflammation (Veldhuis et al. 2005). Variations in FM among the reference population are due to several factors, but are believed to follow aging factors in addition to gradual changes in lifestyle (Kyle et al., 2001).

Considering the association of body composition and mortality, in the Health Professionals Follow-up Study including 38,006 men, predicted FM showed a strong positive monotonic association with mortality, whereas predicted LM showed a strong U-shaped association with mortality (Lee et al., 2018).

Anthropometric and skin fold thickness measurements are traditional, simple and inexpensive methods for body fat estimation to assess the size of specific subcutaneous fat depots (Roubenoff et al., 1995, Wells, J. C., & Fewtrell, 2006).

Bioimpedance analysis (BIA) is a widely used, non-invasive, low-cost method to evaluate body composition for both epidemiological and clinical purposes (Marra et al., 2019). The theory and fundamentals of BIA are revied comprehensively by Khalil et al. (Khalil et al., 2014).

Compared to BMI, anthropometric and skin fold methods, BIA has been shown to be more precise for determining FM or LM (Kyle et al., 2000), and offers

trustable results in the estimation of fatness across human tissues (Heitmann, 1994). BIA uses the electrical properties of the body to estimate the total body water and from that FM (Kyle et al., 2004; Preedy et al., 2012; Khalil et al., 2014). FM is considered as a non-conductor of electric charge and is equal to the difference between body weight and LM, whereas LM is considered as the conducting volume that helps the passing of electric current due to conductivity of electrolytes dissolved in body water. Total body water is the major compound of LM and is equal to 73% in normal hydration subjects (Gento et al., 2004; Khalil et al., 2014). Figure 4 presents measurement pathways of eight-polar BIA: two electrodes are in contact with the palm (E1, E3) and thumb (E2, E4) of each hand and two with the anterior (E5, E7) and posterior aspects (E6, E8) of the sole of each foot.

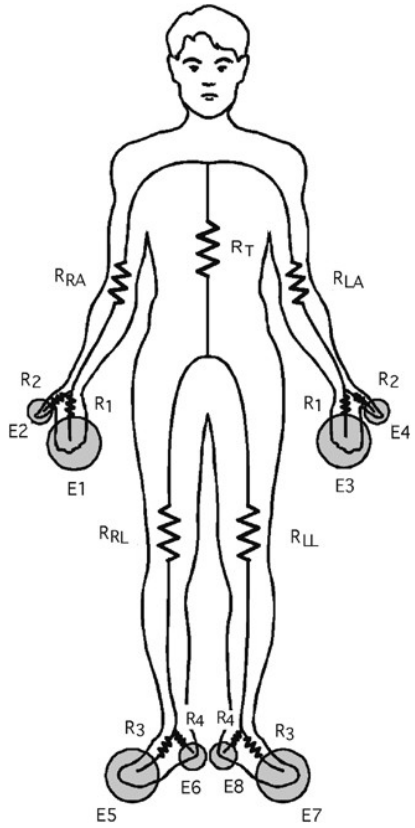


Figure 4. Measurement pathways of eight-polar BIA. The subject stands with her or his soles in contact with the foot electrodes and grabs the hand electrodes. Reprinted by permission from Springer Nature: European Journal of Clinical Nutrition, Accuracy of an eight-point tactile-electrode impedance method in the assessment of total body water, Bedogni et al., 2002. RRA, resistance of right arm; RT, resistance of trunk; RLA, resistance of left arm; RRL, resistance of right leg; RLL,resistance of left leg.

Potential error sources are variations in limb length (usually estimated from body height), recent physical activity, nutrition status, tissue temperature and hydration, blood chemistry, ovulation and electrode placement (Preedy et al., 2012). BIA requires different model parameters to be used depending on age, gender, level of physical activity, amount of body fat and ethnicity in order to be reliable (Dehghan & Merchant, 2008; Haroun et al., 2010). Dual energy X-ray absorptiometry (DXA) is the current reference method for the assessment of body composition, mainly because it provides accurate estimates of bone mineral, fat, and lean soft tissue (the 3-compartment model) (Mazess et al., 1990; Marra et al., 2019). BIA method has been validated against DXA and is acceptably reliable for body composition (Malavolti et al., 2003; Ling et al., 2011; Sillanpää et al., 2014).

The more accurate methods to measure FM and LM according to bicompartment model have been reviewed recently by Lemos & Gallagher and Borga et al. (Lemos & Callagher, 2017; Borga et al., 2018). These methods include hydrostatic weighing (densitometry), air displacement plethysmography, hydrometry (deuterium dilution), computed tomography, echo-MRI (magnetic resonance imaging), and total body potassium counting. However, these methods are characterized by complex measurement protocols and require specialized expertise and costly equipment, making their application in clinical settings very limited.

FM and LM are commonly expressed as absolut weight or percentages of body weight. However, there are potential confounders in these approaches. For example, tall patients with protein-energy malnutrition can exhibit values for FM and LM similar to those of shorter well-nourished individuals. Moreover, obese people with higher total LM have lower relative LM compared to normal-weight people, when LM is indexed to body weight, as increases in FM translate to reductions in the LM fraction of body weight. To obviate such difficulties, in 1990 VanItallie et al. introduced indices for FM and LM relative to body height similar to BMI (VanItallie et al., 1990). Fat mass index (FMI) and lean mass index (LMI) are calculated as FM or LM divided by height squared (kg/m^2).

2.4.2 Body composition and type 2 diabetes

Several cross-sectional studies have investigated body composition in persons with T2D compared with healthy controls. The results have not been entirely consistent. In a substudy of the Look AHEAD clinical trial, participants with T2D had more LM and more truncal fat mass, yet, less total FM, than healthy controls (Heshka et al., 2008). Maiolo et al. found non-significantly more LM and less FM in women with T2D compared to women with normal glucose tolerance (Maiolo et al., 2002).

In the Health ABC study, muscle and abdominal adipose tissue areas were larger in persons with T2D than in persons with normal glucose tolerance (Goodpaster et al., 2003). Svendsen & Hassager detected more total FM in premenopausal but not in postmenopausal women with T2D compared with healthy controls and found no difference for total LM in T2D and healthy women irrespective of age or menopausal status (Svendsen & Hassager, 1998). Additionally, Poynten et al. observed no difference in either LM or FM between weight and BMI-matched controls and persons with T2D (Poynten et al., 2003).

Both in the longitudinal Health ABC Study and in the Danish Diet, Cancer and Health cohort study, total LM was positively associated with a higher incidence of T2D (Larsen et al., 2016; Baker et al., 2019). This association appeared to be largely explained by the fact that those with more muscle mass also generally have more body fat because no association remained significant after adjusting for body size and body composition. Kalyani et al. observed in the Baltimore Longitudinal Study of Aging, that higher total LM was associated with a higher risk of T2D even after accounting for total FM (Kalyani et al., 2020). Hong et al. reported a positive relationship between body fat percentage and incident T2D in Korean men and women with a median age of 39 years (Hong et al., 2017). However, both in the study by Kalyani et al. and in the study by Hong et al., opposite findings were observed. In other words, relative LM, i.e. LM indexed to body weight, was inversely associated with the incidence of T2D in men in the study of Kalyani et al. and in both genders in the study of Hong et al. (Hong et al., 2017; Kalyani et al., 2020). Nevertheless, participants with low relative LM may have high relative FM, and the latter may be the cause of their higher incidence of T2D. Undoubtedly that might be the case in the Korean study in which body fat percentage was calculated (Hong et al., 2017).

Lee et al. reported that appendicular skeletal muscle (ASM, sum of muscle mass of arms and legs) and ASM/height^2 were positively correlated with insulin resistance in Korean men and women aged 70 years (Lee et al., 2015). However, based on their finding of an inverse association between ASM indexed to body weight and insulin resistance, they assumed that lower skeletal muscle mass is associated with glucose intolerance imitating surmises of similar studies dealing with the association between LM or muscle mass indexed to body weight and glucose tolerance (Srikanthan et al., 2010; Srikanthan & Karlamangla, 2011; Moon, 2014). Anyhow, this potential confounder is of concern when LM is indexed to body weight, as described previously.

Furthermore, in a Japanese study of Sakai et al. they postulated that reduced muscle mass is associated with decreased pancreatic β-cell function based on a positive association between ASM/height^2 and HOMA-β albeit they likewise found

a positive relationship between ASM/height^2 and HOMA-IR (Sakai et al., 2016). This one-dimensional approach is also of concern, because one might deduce mistakenly that the person had failing β-cells, as opposed to appropriately low secretion because of good insulin sensitivity (Wallace et al., 2004).

In a study including 99 postmenopausal women, after having found a positive correlation between muscle mass indexed to height and HOMA-IR even after adjusting for visceral fat mass, Lebon et al. dare to question “is a small muscle mass index really detrimental for insulin sensitivity” (Lebon et al., 2012).

3 Aims

This thesis aimed to investigate the relationship between body size and glucose tolerance among apparently healthy middle-aged persons at risk for cardiovascular disease and diabetes and to investigate the association of body composition with glucose regulation and development of T2D in a representative sample of 60 years old Finnish people without diabetes. The specific aims are the following:

1. To evaluate the association between adult height and glucose tolerance during an OGTT, and the combined effect of height and BMI on glucose concentrations (Study I).
2. To assess the association between BSA and glucose concentrations during an OGTT (Study II).
3. After splitting BMI into LMI and FMI to study the combined effect of LMI and FMI on glucose regulation based upon findings in the OGTT and homeostasis model assessment of insulin resistance (Study III).
4. To explore the combined effect of baseline LMI and FMI on subsequent development of T2D over a 15-year follow-up (Study IV).

4 Materials and Methods

4.1 Study population

Study I & II

Study data were obtained from a population-based survey, the HARMONICA (Harjavalta Risk Monitoring for Cardiovascular Disease) project, which was carried out in the rural towns of Harjavalta and Kokemäki in south-western Finland from August 2005 to September 2007. The formulation of the HARMONICA Project is illustrated in Figure 5.

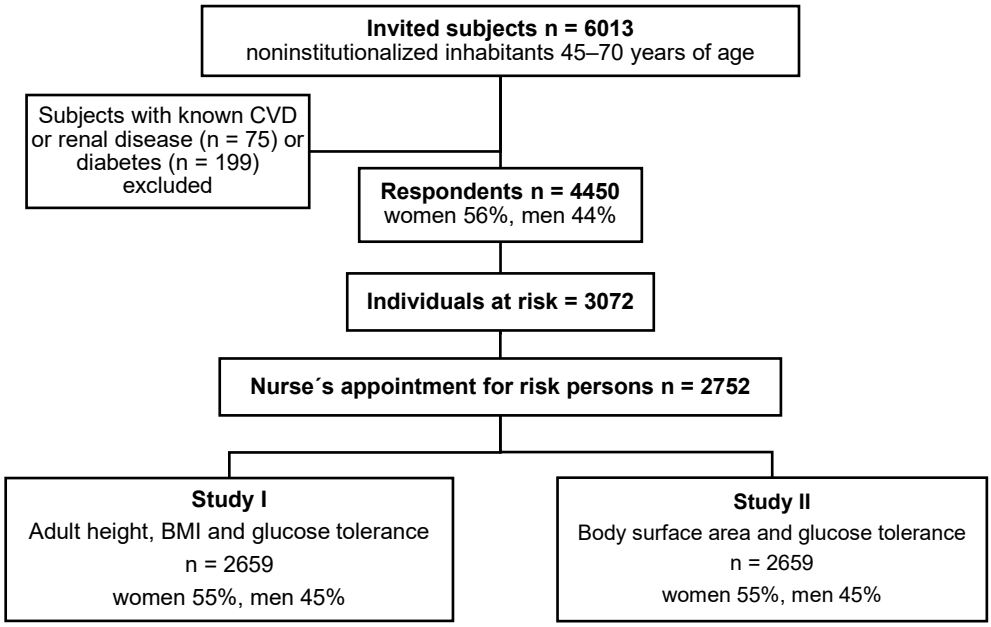


Figure 5. Formulation of the study population I & II.

The project used a two-stage screening method to identify individuals at risk of CVD or T2D from the communities. An invitation participate in to the project, a CVD risk factor survey, tape for the measurement of WC, and a T2D risk

assessment form (FINDRISC) (Lindström & Tuomilehto, 2003) were mailed to all home-dwelling members of the population aged 45–70 years (n = 6013). In the risk factor survey, the participants were asked to report their WC measured at the level of the umbilicus, latest measured BP, use of antihypertensive medication, history of gestational diabetes or hypertension, and family history (parents/sibling) of CHD, myocardial infarction or stroke. Considering WC and BP, WC ≥ 80 cm in women and ≥ 94 cm in men (in Harjavalta) and BP ≥ 140/90 mmHg were defined as being at increased CV risk. Participants were asked to return the risk factor survey back to the healthcare centre if they were willing to participate. The participation rate was 74% (4450/6013).

Participant who had at least one of the abovementioned risk factors or a FINDRISC score ≥12 in Harjavalta or, for logistic reasons ≥15 in Kokemäki (n = 3072) but did not have known CVD or renal disease (n = 75) or diabetes (n = 199) were invited to further examinations performed by a trained study nurse. Of those, 2752 were willing to participate. The number of study participants with sufficient data was 2659.

Study III & IV

Studies III-IV utilize data from the Helsinki Birth Cohort Study (HBCS). The original cohort includes 13,345 individuals born in Helsinki between 1934 and 1944 at one of the two public birth hospitals (Helsinki University Hospital and Midwives' Hospital), visited child welfare clinics in the city, and lived in Finland in 1971 when a unique personal identification number was assigned to all Finnish residents, which was used to link the individuals to register data.

Of the cohort members who were born at the Helsinki University Hospital (n=8760), in the year 2000 a random sample of 2691 were invited to take part in a clinical examination in order to reach for a target of 2000 participants. During 2001–2004, 2003 cohort members participated in clinical measurements and data were also gathered on lifestyle and social factors and diseases. From this clinical study cohort, 704 participants attended another clinical examination between 2017 and 2018, these are including in this thesis. Individuals who declined to participate the second examination did that mostly due to own or a family member's health conditions. Figure 6 shows the formulation of the samples for studies III-IV.

Participants with prevalent diabetes in the first clinical examination were excluded. Study III includes 1617 of the total 2003 participants with sufficient data who attended the first clinical examination between 2001 and 2004. Study IV includes 704 individuals who took part in the clinical examinations in 2001–2004 and 2017–2018.

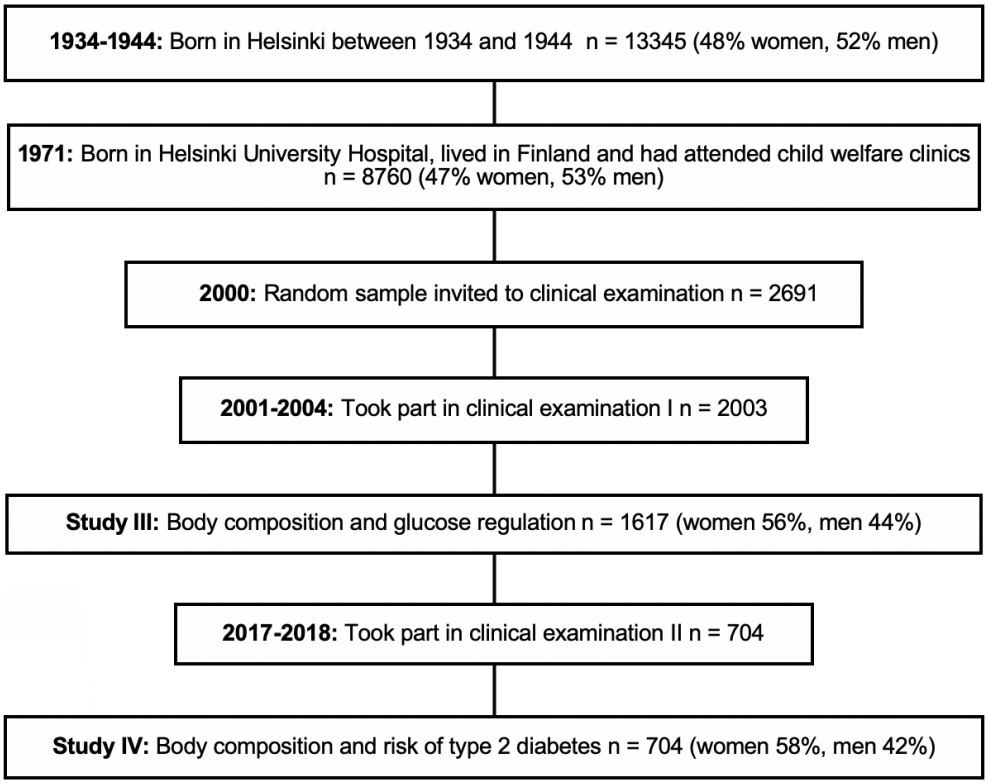


Figure 6. Formulation of the study population III & IV.

4.2 Methods

4.2.1 Questionnaires

Before the enrolment examination, the subjects completed self-administered questionnaires concerning their health and lifestyle habits, sociodemographic factors and medication.

4.2.1.1 Sociodemographic factors

The sociodemographic factors considered in this thesis were age, gender and education years. The study subjects were asked to report their years of education.

4.2.1.2 Lifestyle Associated Factors

Lifestyle associated factors considered were smoking, alcohol use and level of leisure-time physical activity (LTPA).

In the questionnaire of the HARMONICA Project, subjects were asked to provide information on smoking (never, ever and current smoking) and current frequency of LTPA for at least 30 minutes. Smoking status was dichotomized to current/not current smoking. Alcohol use was assessed by the Alcohol Use Disorders Identification Test, AUDIT (Babor et al., 1989).

In the HARMONICA Project, the level of LTPA was classified into three categories: high (LTPA for at least 30 min six or more times a week), moderate (LTPA for at least 30 min four to five times a week), and low (LTPA for at least 30 min at a time for a maximum of three times a week).

In HBCS, LTPA was assessed with the validated 12-month Kuopio Ischemic Heart Disease questionnaire (Lakka & Salonen, 1992). With the questionnaire information on type, mean duration/month and mean frequency/month of LTPA was collected. A specific metabolic equivalent of task (MET, 1 MET = 3.5 ml of $O_2/kg^{-1}/min^{-1}$ or 1 $kcal/kg^{-1}/h^{-1}$) was defined for each reported activity (n = 47) including both non-conditioning (e.g., housework) and conditioning (e.g., resistance training) physical activity to determine the absolute intensity of the activities. LTPA was reported in Study III as a time-weighted average intensity (TWA-MET) (Wasenius et al., 2012), and in Study IVas METhours per week.

4.2.1.3 Baseline Medication

Medications considered in Studies I and II were antihypertensive medication, and medication for lipid disorders and depression/anxiety. Information of medication was gathered from questionnoires and medical records.

4.2.2 Physical Examination

After completing the abovementioned questionnaires, participants attended an enrolment examination performed by a trained study nurse.

4.2.2.1 Anthropometrics

Weight and height were measured with subjects in a standing position without shoes and outer garments, WC was measured at the level midway between the lower rib margin and iliac crest, hip at the level of great trochanters with a soft tape. BMI was calculated as weight (kg) divided by the square of height (m^2). BSA was calculated according to the Mosteller formula [weight (kg) x height (cm)/3600]^{½} (Mosteller, 1989). WHtR was calculated as WC divided by height in cm while waist-to-hip ratio WHR was calculated as WC divided by hip circumference.

In Study I, height measurement were transformed to a gender-specific standardized score (z score) for the study population. Standardized values were divided into five height level categories using z values: I (<-1.5), II (-1.5 to < -0.319), III (-0.319 to < 0.319), IV (0.319 to < 1.15), and V (≥ 1.15) corresponding to height level categories containing 12.5, 25, 25, 25 and 12.5% of the total distribution. The participants were also divided into four BMI groups (< 25.0 kg/m^2; 25.0-29.9 kg/m^2; 30.0-34.9 kg/m^2; ≥ 35 kg/m^2).

In Study II, subjects were divided into five BSA levels: I <1.70 m^2, II 1.70–1.87 m^2, III 1.88–2.02 m^2, IV 2.03–2.22 m^2, V > 2.22 m^2, corresponding 12.5, 25, 25, 25, and 12.5% of the total distribution.

4.2.2.2 Blood pressure

BP was measured by the study nurse with a calibrated mercury sphygmomanometer (HBCS: Omron Matsutaka Europe, Hoofdorp, the Netherlands) with participants in a sitting posture, after resting at least five minutes (HARMONICA) and ten minutes (HBCS) with the cuff placed on the arm. The mean of two readings taken at intervals of at least two minutes was used determine BP level. In HBCS, participants who used medication for hypertension were requested not to take their medication on the morning of clinic attendance.

4.2.3 Laboratory measurements

Before the enrolment examination, laboratory tests were determined in blood samples obtained after at least 12 hours of fasting. OGTT was performed by measuring FPG and 2hPG after ingestion of a glucose load of 75 g of anhydrous glucose dissolved in water. In the HARMONICA Project, glucose values were measured from capillary whole blood with the HemoCue Glucose 201+ system (Ängelholm, Sweden). The analyzer converts the result from capillary whole blood to capillary plasma glucose values. In HBCS, plasma glucose concentrations were measured according to the hexokinase method. Glucose disorders were classified according to the WHO 1999 criteria in Studies I and II (World Health Organization, 1999). On the basis of 2-hour capillary plasma glucose alone, participants were classified into categories of newly diagnosed diabetes, IGT and normal glucose tolerance if their 2-hour glucose concentrations were ≥ 12.2, 8.9–12.1, and < 8.9 mmol/l, respectively. On the basis of fasting capillary plasma glucose alone, participants were classified into categories of newly diagnosed diabetes, IFG and normal fasting glucose, using cut-off levels of ≥ 7.0, 6.1–6.9 and ≤ 6.0 mmol/l, respectively. In Study II, IFG and IGT were combined into

intermediate hyperglycemia. In Study III, prediabetes was classified according to the ADA criteria: IFG 5.6–6.9 mmol/l or IGT 7.8–11 mmol/l (American Diabetes Association, 2015). In Study IV, participants were determined to have T2D if they reported to have T2D diagnosed by a physician based on a questionnaire, or if their FPG value was ≥ 7.0 mmol/l or HbA_{1C} value was ≥ 6.5% (48 mmol/mol) (American Diabetes Association, 2020). Composite incidence of T2D was calculated based on these criteria.

In HBCS, plasma insulin concentrations were determined by two-site immunometric assay. The HOMA-β and HOMA-IR for an index of the β-cell function and insulin resistance were calculated using the following formulas: HOMA-β (%) = (20 × FPI)/(FPG − 3.5) and HOMA-IR = FPG × FPI/22.5, respectively, where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mmol/l) (Matthews et al., 1985)

Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured enzymatically (Olympus AU604). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald's formula (Friedewald et al., 1972).

High-sensitivity C-reactive protein **(**hs-CRP**)** was measured with a fotometric immunochemical method. Fasting serum adiponectin and leptin concentrations were determined by Luminex technique.

4.2.4 Body Composition

In HBCS, body composition was assessed by BIA using the InBody 3.0 eight-polar tactile electrode system (Biospace Co, Ltd, Seoul, Korea) (Malavolti, 2003). The instrument estimates LM and FM by segmental multi-frequency (5, 50, 250, and 500 kHz) analysis. The measurements were made with the subject standing in light indoor clothing on the four foot electrodes on the platform of the analyzer and gripping the two palm and thumb electrodes. LM and FM indices were calculated as follows: LM index (LMI, kg/m^2) = $LM/height^2$ and FM index (FMI, kg/m^2) = $FM/height^2$.

In Studies III & IV, FMI and LMI were divided according to median values, separately for men and women, after which four body composition categories were created: (A) low FMI and low LMI (LFLL), (B) low FMI and high LMI (LFHL), (C) high FMI and low LMI (HFLL), (D) high FMI and high LMI (HFHL). In Study III, for the combined analysis of LMI, FMI and glucose tolerance participants were divided into tertiles of FMI and LMI. By dividing participants into these categories, the aim was to reduce confounding between fat and lean mass indices.

4.2.5 Statistical analyses

The data are presented as means with standard deviations (SD) or as proportions with percentages. In each statistical analysis $p < 0.05$ was considered as statistically significant, and the 95% CIs are shown.

The normality of variables was evaluated using the Shapiro–Wilk W test. A bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of a violation of the assumptions.

In Study I, statistical significance for the hypothesis of linearity was evaluated by using generalized linear models (analysis of variance and regression analysis). Multiple linear regression models were used to identify the appropriate risk factors of the PG indices using standardized regression coefficients β. The β value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. The β is measured in units of standard deviation. Cohen's standard for β values above 0.10, 0.30 and 0.50 represent small, moderate and large relationships, respectively.

In Study II, statistical significances for the unadjusted hypothesis of linearity across categories of BSA were evaluated by using the Cochran-Armitage test for trend, logistic models, and an analysis of variance with an appropriate contrast. The relationship between diabetes and BSA was modelled using restricted cubic splines (with 4 knots, placed according to Harrell's recommended percentiles) logistic regression model. Regression analyses were used to identify the relative effects of height and weight as predictors of FPG and 2hPG using standardized regression coefficients β. Correlation coefficients were calculated by the Pearson method.

In Study III, relationship between LMI and FMI modeled using linear regression analysis. Main effects of LMI and FMI and their interaction tested using analysis of variance (ANOVA) or logistic models. Box-Cox transformations were performed on hs-CRP, adiponectin, and leptin to normalize the distribution.

In Study IV, statistical comparisons between the four body composition categories were made by using chi-square test or generalised linear models (ANOVA, logit models) with appropriate distribution and link functions. Adjusted models included sex, LTPA, education years and BMI at baseline as covariates. Relationships between FMI and LMI index were derived from linear regression models. The significance for pairwise comparisons were correct for multiplicity using Hommel's multiple comparison procedure (at significance level 0.05).Stata 14.1, 15.1 or 16.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

4.2.6 Ethical issues

The ethics committee of the Satakunta Hospital District reviewed and approved the study protocol of the HARMONICA project, whereas HBCS was approved by the Ethics Committee for Epidemiology of Helsinki and Uusimaa Hospital District. Written informed consent was obtained from each participant before any procedures were carried out.

5 Results

5.1 Adult height, body mass index and glucose tolerance (I)

Study I included 2659 individuals (58 ± 7 years, 55% women) at increased risk for CVD. Table 4 shows the characteristics of the men and women according to the five height groups. In men, height was positively associated with years of education, WC and LDL, and inversely with age, systolic and diastolic BP and statin use.

In women, height was positively associated with years of education and current smoking status, and inversely with age, BMI, systolic BP, and use of statins and antihypertensive medication.

Age-adjusted associations between height and glucose concentrations during OGTT are shown in Figure 7. Among both men and women, height was inversely associated with 2hPG, but not with FPG. 2hPG concentrations did not differ between men and women (7.41±2.43 mmol/l vs. 7.41±2.12 mmol/l, p = 0.61). Men had slightly higher FPG values than women (5.77±1.25 mmol/l vs. 5.59±3.20 mmol/l, p = 0.072).

The participants were divided into four BMI groups (< 25.0 kg/m^2; 25–29.9 kg/m^2; 30-34.9 kg/m^2; ≥ 35 kg/m^2) for further age-adjusted analysis of the relationship between height and 2hPG (Figure 8). Height was inversely related with 2hPG in the three lowest BMI groups, but in the highest BMI group this association was not present. 2hPG concentrations increased with increasing BMI (p for linearity < 0.001) from 6.93±1.84 mmol/l in BMI group < 25 kg/m^2 to 8.47±2.90 mmol/l in BMI group ≥ 35 kg/m^2.

In multiple linear regression analysis, height showed a negative relationship with 2hPG in both genders independently of adiposity (BMI), age, and other possible confounding factors (Table 5).

Table 4. Participant characteristics according to height level.

	HEIGHT LEVEL CATEGORY					
Men	I N=128	II N=338	III N=293	IV N=259	V N=166	P for linearity
Height, cm	165 (3)	172 (2)	177 (1)	181 (2)	188 (3)	
Range	154.5-168.5	169.0-174.5	175.0-178.5	179.0-184.0	184.5-198.5	
Age, years	60 (6)	59 (7)	58 (7)	57 (7)	55 (6)	<0.001
Education years	9.2 (2.3)	9.9 (2.6)	9.9 (2.3)	10.5 (2.6)	10.7 (2.5)	<0.001
Body mass index, kg/m^2	29.3 (4.7)	28.8 (4.2)	28.7 (4.3)	28.4 (3.9)	28.5 (4.5)	0.074
Waist circumference, cm	100 (12)	100 (11)	101 (11)	102 (11)	105 (12)	<0.001
New glucose disorder, n (%)						
Diabetes	18 (14)	39 (12)	30 (10)	26 (10)	8 (5)	0.010
IGT	3 (2)	1 (0)	4 (1)	1 (0)	2 (1)	0.63
IFG	20 (16)	60 (18)	42 (14)	38 (15)	24 (14)	0.38
Total cholesterol, mmol/l	5.21 (1.02)	5.24 (0.98)	5.25 (0.98)	5.26 (0.98)	5.33 (1.04)	0.28
HDL cholesterol, mmol/l	1.42 (0.39)	1.41 (0.43)	1.38 (0.37)	1.41 (0.37)	1.36 (0.52)	0.29
LDL cholesterol, mmol/l	3.14 (0.85)	3.21 (0.86)	3.23 (0.87)	3.26 (0.93)	3.34 (0.98)	0.036
Triglycerides, mmol/l	1.47 (0.86)	1.43 (0.75)	1.50 (0.81)	1.43 (0.78)	1.54 (0.83)	0.49
Blood pressure, mmHg						
Systolic	143 (19)	143 (19)	144 (19)	141 (18)	138 (17)	0.004
Diastolic	85 (9)	86 (10)	88 (11)	87 (10)	86 (9)	0.040
Current smokers, n (%)	27 (21)	82 (24)	50 (17)	57 (22)	39 (24)	0.92
AUDIT score	7.5 (5.7)	6.8 (5.7)	7.2 (5.7)	6.7 (5.4)	6.4 (5.0)	0.095
LTPA						0.32
Low	34 (28)	67 (20)	61 (21)	63 (25)	34 (21)	
Moderate	54 (44)	175 (53)	136 (48)	127 (51)	74 (47)	
High	34 (28)	86 (26)	89 (31)	60 (24)	51 (32)	
Current medication, n (%)						
Statins	24 (19)	46 (14)	47 (16)	25 (10)	20 (12)	0.048
Antihypertensives	53 (41)	115 (34)	118 (40)	76 (29)	53 (32)	0.059
Antidepressants	4 (3)	10 (3)	5 (2)	6 (2)	5 (32)	0.77
Women	I N=167	II N=385	III N=393	IV N=350	V N=180	
Height, cm	153 (3)	158 (1)	163 (1)	167 (1)	173 (3)	
Range	144.5-155.5	156.0-160.5	161.0-164.5	165.0-169.5	170.0-182.5	
Age, years	61 (6)	59 (7)	59 (7)	57 (7)	55 (7)	<0.001
Education years	9.7 (2.8)	10.2 (2.5)	10.6 (2.8)	11.2 (3.0)	11.6 (2.8)	<0.001
Body mass index, kg/m^2	30.0 (6.0)	29.9 (5.9)	28.6 (5.4)	28.2 (5.2)	27.9 (5.6)	<0.001
Waist circumference, cm	90 (14)	92 (13)	92 (13)	92 (13)	93 (14)	0.13
New glucose disorder, n (%)	5.52 (0.96)	5.56 (1.03)	5.54 (0.90)	5.41 (0.91)	5.40 (0.94)	0.073
Diabetes						
IGT	19 (11)	27 (7)	30 (8)	17 (5)	10 (6)	0.34
IFG	3 (2)	4 (1)	4 (1)	3 (1)	0 (0)	0.12
Total cholesterol, mmol/l	19 (11)	36 (9)	47 (12)	48 (14)	21 (12)	0.25
HDL cholesterol, mmol/l	1.42 (0.39)	1.41 (0.43)	1.38 (0.37)	1.41 (0.37)	1.36 (0.52)	0.057
LDL cholesterol, mmol/l	3.14 (0.85)	3.21 (0.86)	3.23 (0.87)	3.26 (0.93)	3.34 (0.98)	0.37
Triglycerides, mmol/l	1.47 (0.86)	1.43 (0.75)	1.50 (0.81)	1.43 (0.78)	1.54 (0.83)	0.61
Blood pressure, mmHg						
Systolic	141 (17)	141 (18)	140 (19)	138 (19)	134 (16)	<0.001
Diastolic	82 (10)	83 (9)	83 (9)	82 (10)	83 (10)	0.81
Current smokers, n (%)	12 (7)	56 (15)	60 (15)	47 (14)	33 (19)	0.029
AUDIT score	2.6 (3.4)	2.8 (3.5)	2.8 (3.4)	2.9 (2.9)	3.0 (3.0)	0.21
LTPA						0.43
Low	26 (16)	61 (16)	53 (14)	45 (13)	24 (14)	
Moderate	75 (47)	181 (48)	204 (53)	166 (49)	102 (57)	
High	60 (37)	135 (36)	128 (33)	126 (37)	51 (29)	
Current medication, n (%)						
Statins	24 (14)	50 (13)	45 (11)	43 (12)	11 (6)	0.031
Antihypertensives	74 (44)	136 (35)	124 (32)	105 (30)	49 (27)	<0.001
Antidepressants	8 (5)	23 (6)	25 (6)	20 (6)	9 (5)	0.96

IGT, impaired glucose tolerance; IFG, impaired fasting glucose; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity

Data are mean (SD), except where indicated.

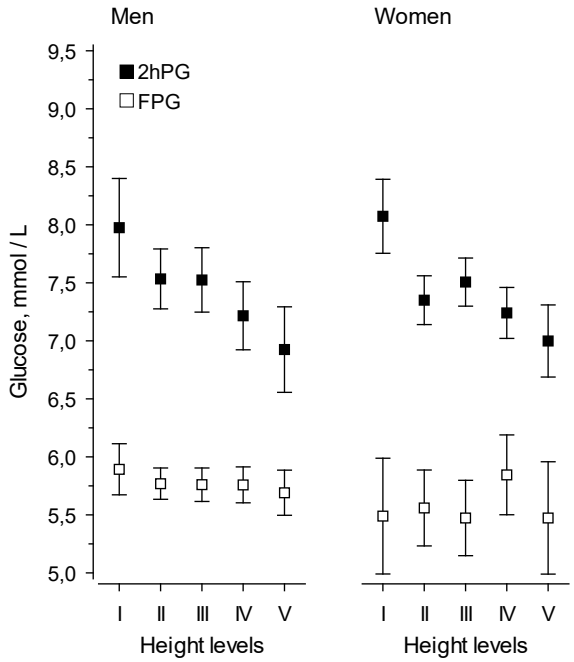


Figure 7. Age-adjusted mean fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) by height level and gender. Error bars are for 95% confidence intervals. Dashed lines indicate mean FPG and 2hPG values of men and women.

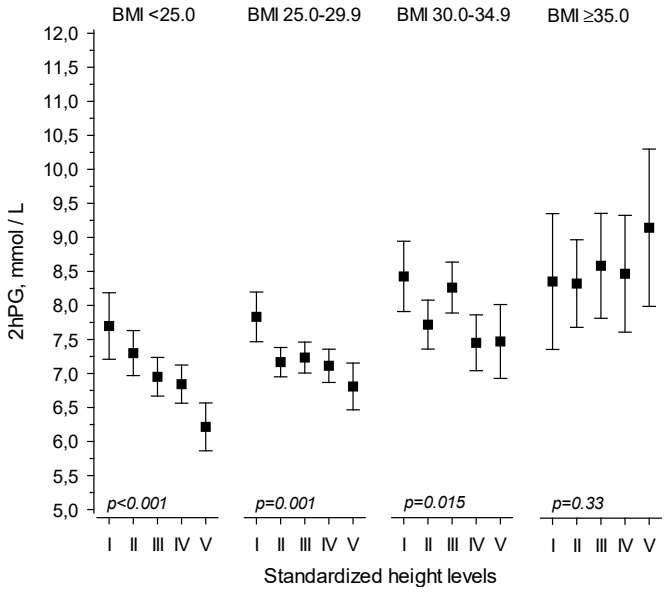


Figure 8. Age-adjusted mean 2-h plasma glucose (2hPG) by height level and BMI group. Error bars are for 95% confidence intervals. Dashed lines indicate mean 2hPG of BMI group. P values indicate the significance for linearity.

Table 5. Multiple linear regression models for the relationship between selected cardiovascular risk factors, fasting plasma glucose and 2-h plasma glucose concentration in men and women.

	MEN		**WOMEN**	
	β* (95% CI)	P-value	β* (95% CI)	P-value
Fasting plasma glucose				
Height	-0.01 (-0.07 to 0.05)	0.72	0.03 (-0.03 to 0.08)	0.36
Age	0.07 (0.00 to 0.13)	0.044	-0.02 (-0.08 to 0.04)	0.57
Education years	-0.03 (-0.09 to 0.04)	0.43	-0.03 (-0.09 to 0.03)	0.28
Body mass index	0.20 (0.15 to 0.26)	<0.001	0.13 (0.07 to 0.18)	<0.001
Total cholesterol	-0.05 (-0.11 to 0.00)	0.062	-0.04 (-0.09 to 0.01)	0.14
Current smoker	0.11 (0.05 to 0.16)	<0.001	0.01 (-0.04 to 0.06)	0.72
LTPA				
Low	Reference	0.55	Reference	0.79
Moderate	-0.02 (-0.10 to 0.05)		0.04 (-0.04 to 0.12)	
High	-0.02 (-0.10 to 0.05)		0.02 (-0.06 to 0.10)	
2-h plasma glucose				
Height	-0.10 (-0.15 to -0.04)	<0.001	-0.09 (-0.14 to -0.04)	<0.001
Age	0.22 (0.15 to 0.28)	<0.001	0.17 (0.11 to 0.22)	<0.001
Education years	-0.10 (-0.16 to -0.04)	0.002	-0.05 (-0.11 to 0.01)	0.078
Body mass index	0.19 (0.14 to 0.25)	<0.001	0.20 (0.14 to 0.25)	<0.001
Total cholesterol	-0.08 (-0.13 to -0.02)	0.006	-0.08 (-0.13 to -0.03)	0.001
Current smoker	0.01 (-0.05 to 0.06)	0.84	-0.04 (-0.09 to 0.01)	0.14
LTPA		0.079[2]		0.068**
Low	Reference		Reference	
Moderate	0.02 (-0.06 to 0.09)		-0.02 (-0.10 to 0.06)	
High	-0.06 (-0.13 to 0.01)		-0.06 (-0.14 to 0.01)	

* Standardized β-coefficient. ** P for linearity

5.2 Body surface area and glucose tolerance (II)

Figure 9 presents the interplay between height, BMI and BSA. The effect of height on BSA is more pronounced than that of BMI.

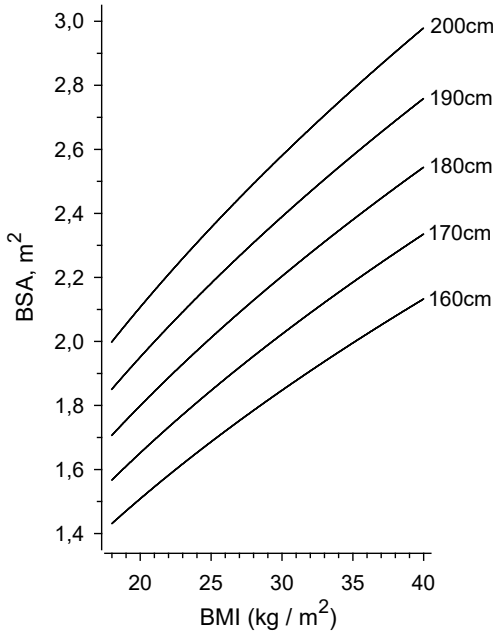


Figure 9. Relationship between height, body mass index (BMI) and body surface area (BSA).

Study II included 2659 individuals (58 ± 7 years, 55 % women) at increased risk for CVD. Table 6 shows the characteristics of the participants according to the five BSA level groups. The two lowest BSA categories were dominated by women, the two highest by men. Participants with higher BSA were younger, had higher systolic and diastolic BP, higher plasma glucose and triglyceride levels, and lower HDL cholesterol and total cholesterol levels. BSA was positively associated with other anthropometric measures, e.g. height, BMI and WC, AUDIT score, use of statins and antihypertensive medication, but inversely with LTPA.

Table 6. Participant characteristics according to body surface area level.

	BODY SURFACE AREA LEVEL CATEGORY					
	I	II	III	IV	V	P for
	N=332	N=674	N=668	N=662	N=323	linearity
BSA, m^2	1.63	1.79	1.95	2.11	2.35	..
Range	<1.70	1.70-1.87	1.88-2.02	2.03-2.22	>2.22	
Women, n (%)	318 (96)	571 (85)	339 (51)	172 (26)	75 (23)	<0.001
Age, years	59 (7)	59 (7)	58 (7)	58 (7)	57 (7)	<0.001
Education years	10.6 (2.8)	10.5 (2.7)	10.3 (2.7)	10.3 (2.7)	10.3 (2.6)	0.12
Height, cm	159 (5)	164 (6)	169 (7)	175 (8)	179 (9)	<0.001
Weight, kg	60 (5)	71 (4)	81 (4)	92 (6)	112 (12)	<0.001
BMI, kg/m^2	23.9 (2.6)	26.6 (2.8)	28.7 (3.7)	30.5 (4.2)	35.5 (5.9)	<0.001
WC, cm	79 (7)	88 (7)	96 (7)	103 (8)	116 (11)	<0.001
FPG, mmol/l	5.38 (1.26)	5.41 (0.77)	5.59 (1.04)	5.75 (1.14)	6.13 (1.68)	<0.001
2hPG, mmol/l	7.39 (2.19)	7.23 (1.88)	7.34 (2.17)	7.44 (2.45)	7.99 (2.81)	<0.001
TC, mmol/l	5.50 (0.96)	5.47 (0.97)	5·41 (0.95)	5.30 (0.98)	5.25 (1.03)	<0.001
HDL-C, mmol/l	1.82 (0.46)	1.71 (0.44)	1.53 (0.41)	1.41 (0.39)	1.27 (0.33)	<0.001
LDL-C, mmol/l	3.20 (0.83)	3.21 (0.89)	3.28 (0.87)	3.25 (0.90)	3.25 (0.94)	0.29
Triglycerides, mmol/l	1.13 (0.64)	1.25 (0.64)	1.36 (0.67)	1.52 (0.83)	1.76 (0.85)	<0.001
Blood Pressure, mmHg						
Systolic	139 (19)	139 (19)	140 (18)	142 (18)	144 (20)	<0.001
Diastolic	81 (10)	82 (9)	84 (10)	86 (10)	89 (11)	<0.001
Current smoker, n (%)	60 (18)	109 (16)	112 (17)	121 (18)	61 (19)	0.47
AUDIT score	3.1 (4.0)	3.6 (4.1)	4.7 (4.8)	5.7 (5.2)	6.2 (5·5)	<0.001
LTPA, n (%)						<0.001
Low	41 (13)	72 (11)	110 (17)	140 (22)	105 (34)	
Moderate	140 (43)	341 (52)	339 (52)	324 (51)	150 (48)	
High	144 (44)	243 (37)	199 (31)	177 (28)	57 (18)	
Current medication, n (%)						
Statins	31 (9)	65 (10)	84 (13)	109 (16)	46 (14)	<0.001
Antihypertensives	69 (21)	178 (26)	211 (32)	277 (42)	168 (52)	<0.001

BSA, body surface area; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; HDL, high-density lipoproteinl; LDL, low-density lipoprotein; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity. Data are mean (SD), except where indicated.

BSA was inversely associated with the 2hPG and 2hPG/FPG ratio in all categories of glucose tolerance after adjustment for age, gender, WC, alcohol intake, current smoking, and LTPA (p for linearity < 0.001) (Figure 10). There was an interaction between the BSA and 2hPG/FPG ratio (p < 0.001) but not between BSA and 2hPG (p = 0.70).

The adjusted proportion of new T2D diagnoses based on the OGTT is shown in Figure 11. BSA was inversely related with new T2D diagnoses (p for linearity < 0.001).

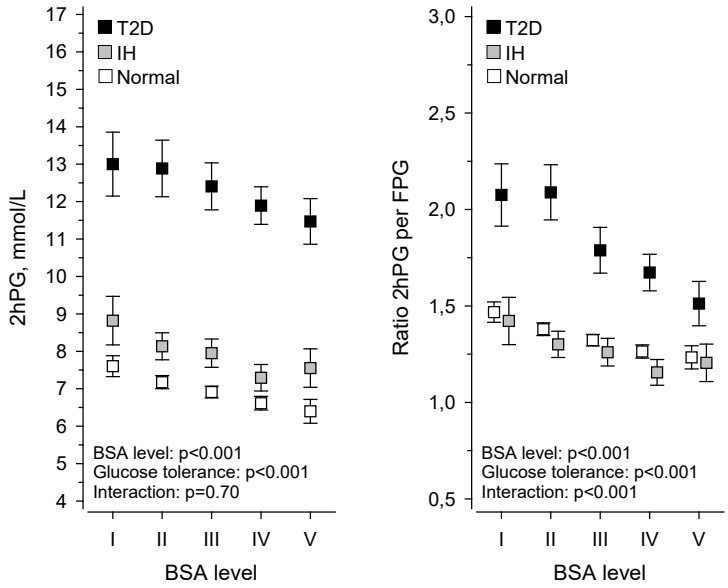


Figure 10. Mean 2-hour plasma glucose (2hPG) and 2hPG per fasting plasma glucose (FPG) ratio by body surface area and glucose tolerance category. Adjusted for age, smoking status, leisure time physical activity, alcohol intake, waist circumference and gender. Error bars are for 95% confidence intervals. The dashed line indicates the 2hPG diagnostic cut-off value for type 2 diabetes. IH, intermediate hyperglycemia.

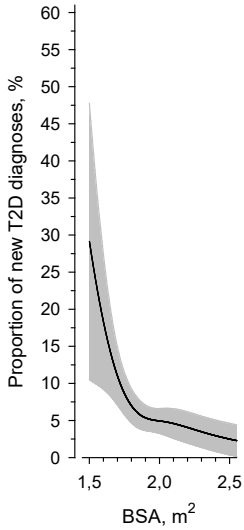


Figure 11. Proportion of newly diagnosed type 2 diabetes (T2D) based on 2hPG values according to body surface area (BSA). The curves were derived from a 4-knot restricted cubic splines logistic regression models. The models were adjusted for age, sex, smoking status, leisure time physical activity, alcohol intake, and waist circumference. The grey area represents a 95% confidence interval.

5.3 Body composition and glucose regulation (III)

The study included 1617 participants without diabetes (mean age 61 ± 3 years, 56% women). Figure 12 shows the relationship between FMI and LMI of the participants. The relation of FMI to LMI was linear in both genders, but the contribution of FMI was more pronounced in women [β-coefficient 0.68 (95% CI: 0.65 to 0.71)] than in men [β 0.54 (95% CI: 0.49 to 0.59)], $p < 0.001$.

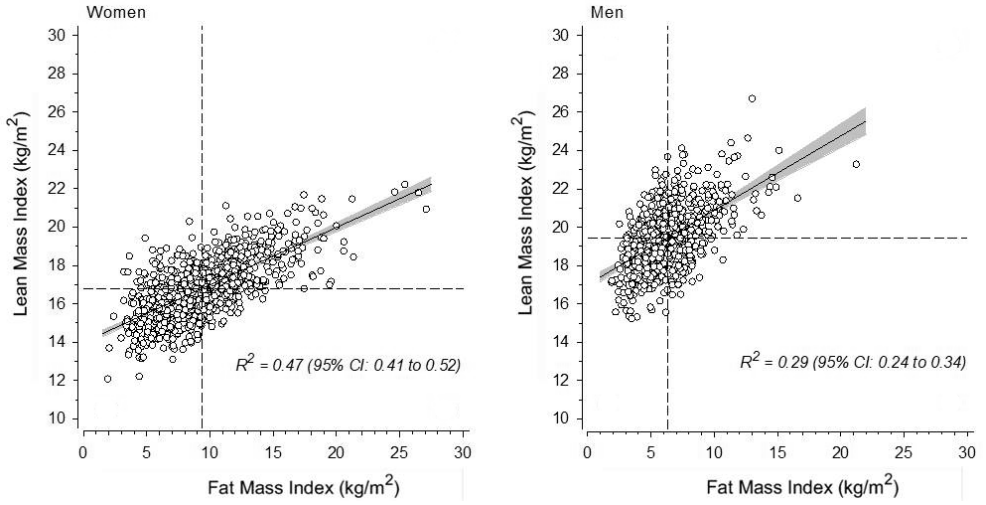


Figure 12. The relationship between between fat mass index (FMI) and lean mass index (LMI) in women and men. The line shows estimated linear regression with 95% confidence intervals. The dashed lines indicate medians of FMI and LMI.

The baseline characteristics of the men and women are presented in Table 7 based on gender-specific categorization as having low or high FMI or LMI (divided around the median). In both men and women, FMI and LMI showed a positive association with WC and BMI with a statistically significant interaction.

Both men and women with low FMI had lower systolic and diastolic BP, lower concentrations of plasma triglycerides, hs-CRP and leptin, and higher concentrations of HDL cholesterol and adiponectin than persons with high FMI. LMI had a weaker effect on diastolic BP in men, likewise on systolic BP in women. FMI had the main effect on the differences in hs-CRP in both genders, whereas LMI had the main effect on adiponectin levels in men.

LMI and FMI were positively related to leptin/adiponectin ratio, a proxy for insulin resistance.

Table 7. Participant characteristics according to categorization as having low or high fat mass index (FMI) or lean mass index (LMI).

	FMI LOW		FMI HIGH		P-VALUES		
	LMI low	LMI high	LMI low	LMI high	Main effects		Inter-action
Men					FMI	LMI	
Number (% of total)	255 (36)	145 (20)	104 (15)	206 (29)			
Lean mass, kg	57 (5)	65 (5)	56 (4)	66 (7)			
Fat mass, kg	14 (3)	16 (3)	23 (3)	27 (7)			
Fat %	19 (4)	19 (3)	28 (2)	28 (4)			
Age, years	61 (3)	60 (2)	62 (3)	61 (3)	<0.001	0.006	0.95
Education years	12.9 (4.0)	13.3 (3.8)	11.7 (3.6)	12.3 (3.6)	<0.001	0.10	0.84
Weigth, kg	74 (7)	85 (7)	82 (7)	97 (11)	<0.001	<0.001	0.005
Heigth, cm	177 (6)	179 (6)	174 (6)	177 (6)	<0.001	<0.001	0.299
Birth weigth, g	3405 (466)	3551 (453)	3459 (567)	3515 (504)	0.81	0.010	0.25
Waist, cm	91 (7)	97 (6)	101 (5)	110 (9)	<0.001	<0.001	0.009
BMI, kg/m^2	23.7 (1.7)	26.7 (1.3)	27.1 (1.2)	31.0 (2.9)	<0.001	<0.001	0.005
LTPA, TWA-MET	2062 (1365)	1703 (1311)	1971 (1356)	1813 (1283)	0.015	0.93	0.34
Current smoker, % (n)	28 (71)	29 (42)	25 (26)	27 (55)	0.31	0.70	0.98
Blood pressure, mmHg							
Systolic	141 (19)	144 (18)	147 (19)	149 (18)	<0.001	0.058	0.82
Diastolic	88 (11)	89 (9)	91 (10)	93 (10)	<0.001	0.011	0.46
Cholesterol, mmol/l							
Total	5.76 (0.99)	5.90 (1.02)	5.83 (1.25)	5.82 (1.08)	0.93	0.48	0.41
LDL	3.59 (0.80)	3.79 (0.86)	3.71 (1.01)	3.66 (0.89)	0.90	0.33	0.095
HDL	1.60 (0.43)	1.51 (0.36)	1.45 (0.37)	1.36 (0.30)	<0.001	0.002	0.96
Triglycerides, mmol/l	1.26 (0.60)	1.34 (0.60)	1.51 (0.74)	1.77 (0.94)	<0.001	0.003	0.11
hs-CRP,mmol/l	2.7 (5.7)	2.2 (3.7)	3.5 (4.1)	3.5 (4.5)	<0.001	0.37	0.68
Adiponectin, µg/ml*	5.4 (4.2)	4.6 (3.8)	5.0 (3.7)	4.0 (3.7)	0.12	<0.001	0.37
Leptin, ng/ml*	9.2(15.0)	9.3 (15.1)	16.9 (32.9)	17.5 (16.6)	<0.001	0.12	0.087
Leptin to adiponectin ratio*	3.05 (8.14)	3.49 (5.18)	4.97 (7.38)	7.24 (8.93)	<0.001	<0.001	0.049
Women							
Number (% of total)	370 (41)	134 (15)	102 (11)	301 (33)			
Lean mass, kg	42 (4)	48 (4)	42 (3)	48 (5)			
Fat mass, kg	18 (4)	20 (4)	28 (4)	34 (8)			
Fat %	29 (5)	28 (4)	38 (3)	40 (4)			
Age, years	61 (3)	61 (3)	61 (3)	61 (3)	0.19	0.95	0.43
Education years	12.5 (3.7)	12.7 (3.4)	12.1 (3.7)	11.5 (3.3)	0.004	0.55	0.12
Weigth, kg	63 (7)	72 (6)	73 (7)	86 (11)	<0.001	<0.001	<0.001
Heigth, cm	164 (6)	166 (5)	161 (5)	163 (6)	<0.001	<0.001	0.27
Birth weigth, g	3329 (453)	3422 (458)	3272 (458)	3398 (482)	0.25	0.002	0.64
Waist, cm	81 (7)	87 (7)	92 (6)	101 (10)	<0.001	<0.001	0.014
BMI, kg/m^2	23.4 (2.1)	26.0 (1.6)	27.9 (1.6)	32.4 (3.9)	<0.001	<0.001	<0.001
LTPA, TWA-MET	2165 (1452)	2164 (1522)	2086 (1750)	1923 (1346)	0.20	0.51	0.51
Current smoker, % (n)	19 (72)	25 (34)	20 (20)	21 (64)	0.40	0.26	0.48
Blood pressure, mmHg							
Systolic	138 (20)	142 (21)	145 (21)	148 (19)	<0.001	0.032	0.99
Diastolic	85 (10)	87 (9)	90 (11)	90 (10)	<0.001	0.092	0.30
Cholesterol, mmol/l							
Total	6.02 (0.95)	6.16 (1.04)	6.37 (1.09)	6.17 (1.01)	0.025	0.72	0.030
LDL	3.60 (0.83)	3.80 (0.90)	3.94 (0.97)	3.83 (0.87)	0.007	0.56	0.024
HDL	1.88 (0.43)	1.76 (0.43)	1.72 (0.42)	1.64 (0.39)	<0.001	0.003	0.57
Triglycerides, mmol/l	1.20 (0.62)	1.35 (0.72)	1.53 (0.65)	1.58 (0.76)	<0.001	0.059	0.38
hs-CRP,mmol/l*	2.8 (5.6)	2.3 (3.4)	4.7 (5.3)	4.2 (5.7)	<0.001	0.81	0.40
Adiponectin, µg/ml*	9.4(6.6)	8.9 (6.8)	8.0 (5.8)	6.8 (5.2)	<0.001	0.012	0.80
Leptin, ng/ml*	15.2 (12.0)	16.1(11.4)	29.8 (20.7)	34.9 (22.6)	<0.001	0.022	0.55
Leptin to adiponectin ratio*	2.61 (3.13)	5.05 (11.72)	6.51 (8.72)	8.20 (9.60)	<0.001	0.001	0.77

* Box-Cox transformation.

LTPA, leisure-time physical activity; TWA-MET, a time-weighted average intensity metabolic equivalent.

Data are mean (SD), except where indicated.

The participants were divided into tertiles of FMI and LMI for the combined analysis of LMI, FMI, and glucose concentrations during OGTT, adjusted for age, smoking status and LTPA (Figure 13). Among men in the middle and high FMI levels, LMI was positively related with FPG. The p-value for interaction between FMI and LMI was p = 0.065. In both men and women, FMI showed a positive association with FPG and 2hPG (p for linearity < 0.001 for FPG and 2hPG in both genders). LMI showed no association with 2hPG concentrations.

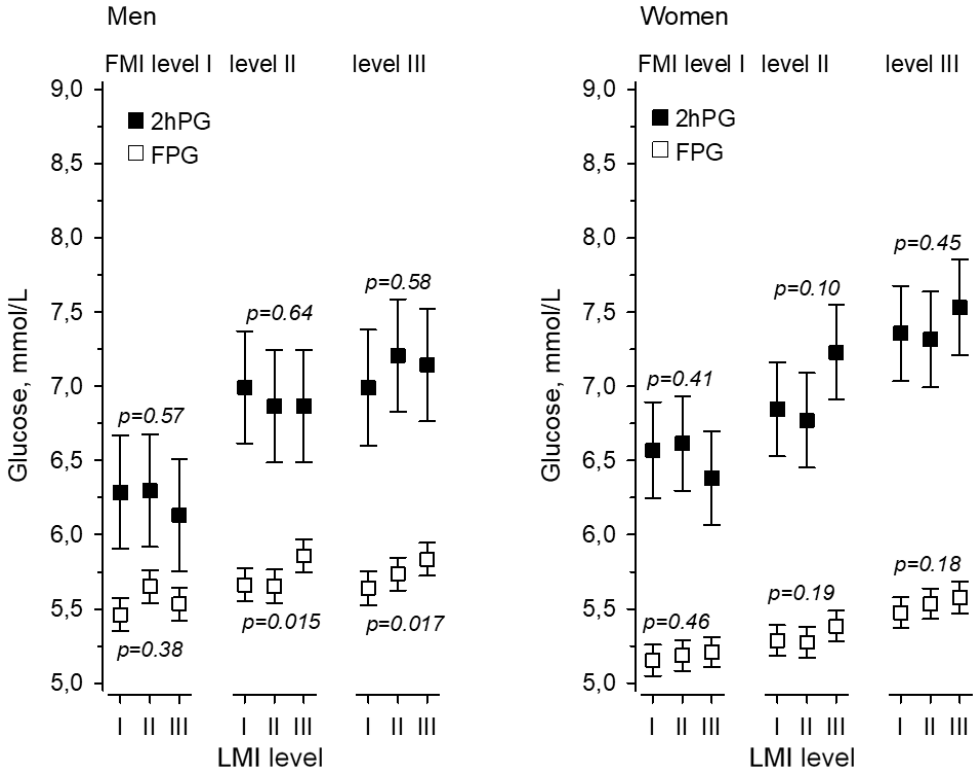


Figure 13. Mean fasting plasma glucose (FPG) and 2-h plasma glucose (PG) by fat mass index (FMI) and lean mass index (LMI) level and gender adjusted for age, smoking status and leisure-time physical activity. Error bars are for 95% CIs. P values indicate the significance for linearity.

Figure 14 presents the association between the FMI and LMI levels with HOMA-IR, adjusted for age, smoking status, and LTPA. Among men, a positive association between LMI and HOMA-IR was found in the middle and high FMI levels with significant interaction between FMI and LMI (p < 0.0001). In both men and women, increased FMI was associated with increased HOMA-IR (p for linearity < 0.001 in both genders).

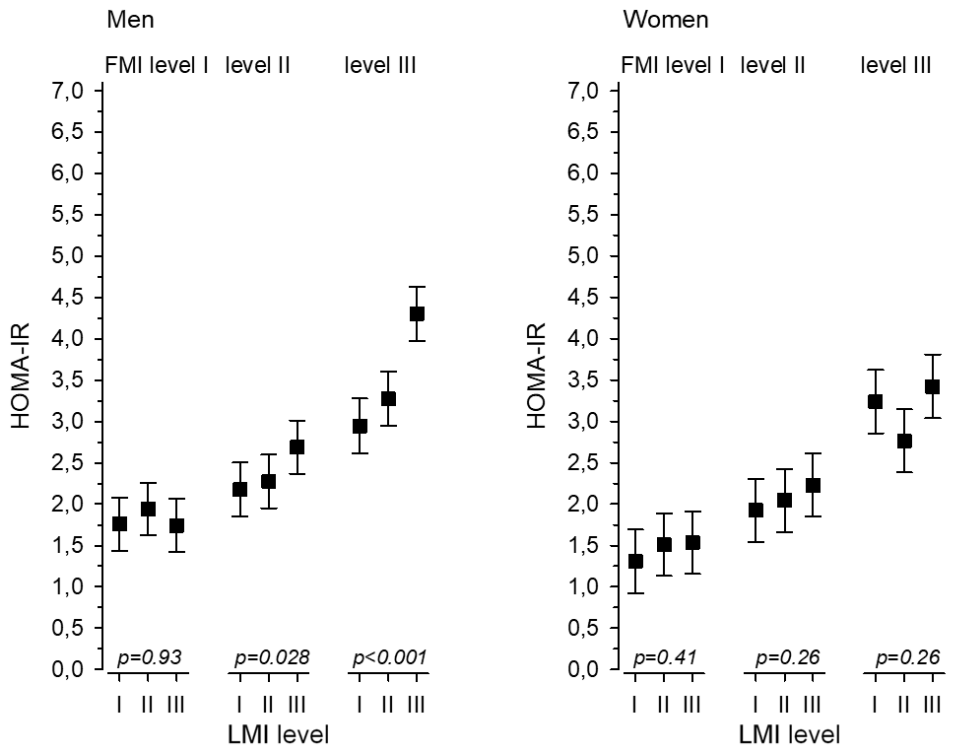


Figure 14. Mean HOMA-IR by fat mass index (FMI) and lean mass index (LMI) level and gender adjusted for age, smoking status and leisure-time physical activity. Error bars are for 95% CIs. P values indicate the significance for linearity.

Figure 15 presents the association of FMI and LMI levels with prevalence of prediabetes, adjusted for age, smoking status, and LTPA. In men prevalence increased with increasing LMI (p for linearity 0.003). A positive association between LMI and prevalence was found in high FMI level without significant interaction between FMI and LMI (p = 0.15). Among both men and women, increased FMI was associated with increased the prevalence of prediabetes (p for linearity 0.002 and < 0.001, respectively).

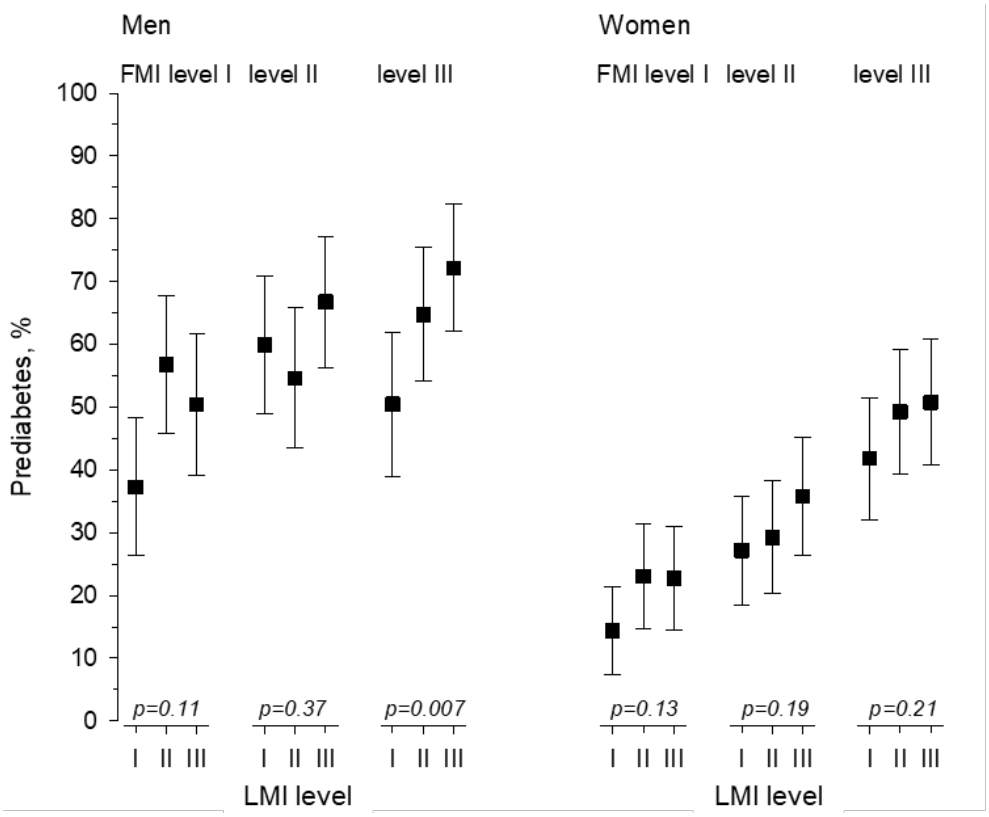


Figure 15. Mean prevalence of prediabetes by fat mass index (FMI) and lean mass index (LMI) level and gender adjusted for age, smoking status and leisure-time physical activity. Error bars are for 95% CIs. P values indicate the significance for linearity.

5.4 Body composition and risk of type 2 diabetes (IV)

The study included 704 participants (mean age 61 ± 3 years at baseline, 58% women) without diabetes at baseline. The relationships between FMI and LMI and the median-split categories of body composition in women and men are shown in Figure 16.

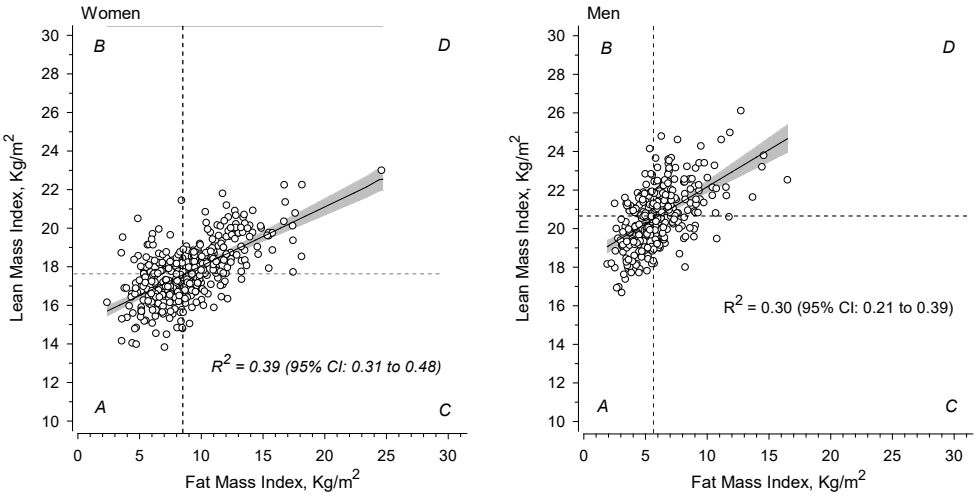


Figure 16. The relationship between fat mass index (FMI) and lean mass index (LMI) in women and men at baseline. The line shows estimated linear regression with 95% confidence intervals. The dashed lines indicate medians of FMI and LMI.

The characteristics of the participants at baseline are presented in Table 8 according to gender-specific categorization as having low or high FMI or LMI. The four body composition categories (LFLL, LFHL, HFLL, HFHL) did not differ with respect to sex, LTPA, smoking and total cholesterol. BMI and WC increased with increasing FMI and LMI. Persons with high FMI had higher body fat percentage, higher concentrations of 2hPG, fasting and 2-h plasma insulin, and triglycerides than persons with low FMI. Participants in the HFHL category had the highest FPG and LDL concentrations, systolic and diastolic BP and the lowest HDL concentrations.

Median follow-up time was 14.8 years, during which incident T2D occurred in 8.9% in the LFLL category (n = 22), 10.5% in the LFHL category (n = 11), 10.5% in the HFLL category (n = 11), and 26.6% in the HFHL category (n = 66), respectively.

Table 8. The characteristics of study participants at baseline according to gender-specific categorization as having low or high fat mass index (FMI) or lean mass index (LMI).

	FMI LOW		FMI HIGH		P-VALUE*
	LMI low (A)	LMI high (B)	LMI low (C)	LMI high (D)	
Women, n (%)	147 (60)	56 (53)	56 (53)	148 (60)	0.48
Age, years	61 (3)	61 (2)	62 (3)	61 (3)	0.045 [B/C]
Education years	12.7 (3.5)	12.1 (3.2)	12.2 (3.6)	11.6 (3.0)	<0.001 [A/D]
BMI, kg/m^2	23.3 (1.7)	25.7 (1.3)	26.9 (1.5)	30.7 (3.1)	<0.001 [All]
Fat %	24.1 (6.2)	22.5 (5.4)	31.8 (6.2)	33.2 (7.2)	<0.001 [A/C, A/D, B/C, B/D]
Waist, cm					
women	79 (6)	85 (6)	89 (6)	98 (9)	<0.001 [All]
men	89 (6)	95 (5)	100 (5)	107 (9)	<0.001 [All]
METhours per week	40.9 (24.3)	39.2 (25.6)	35.8 (23.1)	37.0 (27.3)	0.20
Current smoker, % (n)	15 (38)	23 (24)	18 (19)	13 (33)	0.15
Fasting plasma glucose, mmol/l	5.31 (0.53)	5.33 (0.47)	5.48 (0.51)	5.59 (0.54)	<0.001 [A/C, A/D, B/D]
2-h plasma glucose, mmol/l	6.33 (1.62)	6.34 (1.68)	7.19 (1.64)	7.02 (1.57)	<0.001 [A/C, A/D, B/C, B/D]
Fasting plasma insulin, mU/l	6.32 (3.51)	7.26 (4.22)	10.75 (16.00)	12.13 (12.71)	<0.001 [A/C, A/D, B/C, B/D]
2-h plasma insulin, mU/l	48.6 (33.6)	51.9 (49.2)	79.1 (48.2)	87.8 (69.2)	<0.001 [A/C, A/D, B/C, B/D]
Homa-β, %	72 (38)	85 (58)	117 (179)	125 (150)	<0.001 [A/D, B/D]
Homa-IR	1.52 (0.93)	1.72 (0.99)	2.62 (3.79)	3.02 (3.04)	<0.001 [A/C, A/D,B/D]
Cholesterol, mmol/l					
Total	5.83 (0.97)	5.97 (0.87)	5.98 (1.10)	6.05 (1.10)	0.13
HDL	1.79 (0.43)	1.72 (0.46)	1.63 (0.40)	1.54 (0.39)	<0.001 [A/C,A/D, B/D]
LDL	3.52 (0.81)	3.71 (0.78)	3.70 (0.94)	3.78 (0.89)	0.011 [A/D]
Triglycerides, mmol/l	1.17 (0.60)	1.21 (0.55)	1.46 (0.77)	1.64 (0.82)	<0.001 [A/C, A/D, B/C, B/D]
Blood pressure, mmHg					
Systolic	137 (19)	139 (20)	143 (21)	148 (17)	<0.001 [A/C, A/D, B/D]
Diastolic	85 (10)	85 (9)	89 (10)	91 (10)	<0.001 [A/C, A/D, B/D]

Data are mean (SD), except where indicated.
*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p<0.05$).

In the HFHL category, concentrations of HbA_{1C} and FPG at follow-up, number of subjects diagnosed with T2D by a physician and the composite incidence of T2D were significantly higher than in all other categories (for all, $p < 0.001$) (Figure 17).

After adjustment of sex, LTPA, education years and BMI at baseline, HFHL was associated with an increased risk of T2D compared to the other categories (LFLL: odds ratio (OR) 0.41, 95% CI 0.19–0.91; LFHL: OR 0.44, 95% CI 0.20–0.98; HFLL: OR 0.39, 95% CI 0.19–0.83). There was no difference between LFLL, LFHL and HFLL categories in relation to the risk of developing T2D ($p = 0.97$).

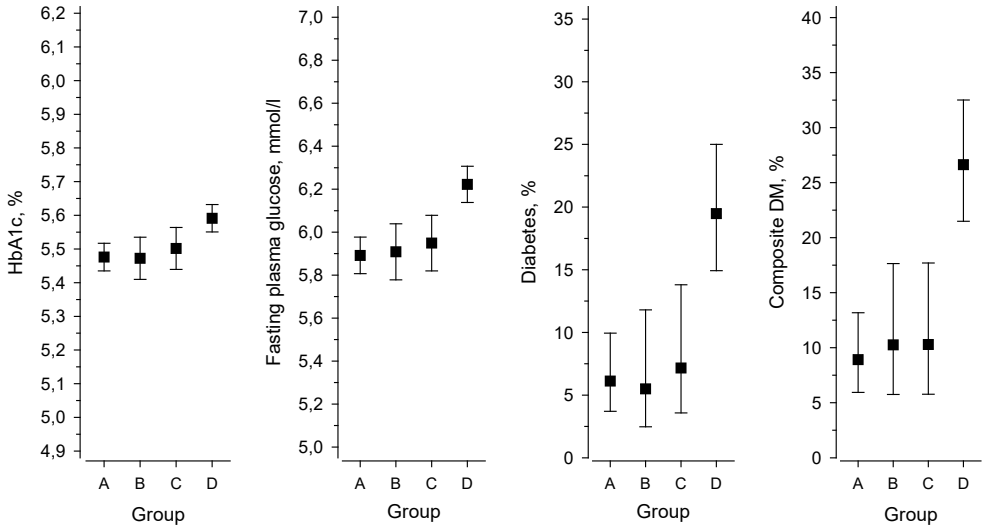


Figure 17. Mean hemoglobin A1c (HbA_{1C}) and fasting plasma glucose, percentage of subjects with type 2 diabetes diagnosed by a physician and the composite incidence of type 2 diabetes (DM) at follow-up according to body composition category at baseline: A low fat mass index (FMI) and low lean mass index (LMI), B low FMI and high LMI, C high FMI and low LMI, D high FMI and high LMI (HFHL). There were no gender difference nor interactions between FMI and LMI on these variables. Error bars are for 95% CIs. Comparison of the HFHL category to the other categories $p < 0.001$, for all.

6 Discussion

6.1 Study population

The HARMONICA Project is a population-based survey conducted in two rural Finnish towns, Harjavalta and Kokemäki in 2005–2007. The study population consisted of apparently healthy middle-aged persons (45–70 years of age). Each participant had at least one traditional CVD risk factor but no previously diagnosed diabetes, CVD or renal disease. Thus, with a reasonably high participation rate of 74%, the sample can be considered as representative of the Finnish general middle-aged population at risk for CVD and T2D.

HBCS is globally a unique birth cohort study including 13,345 subjects in the epidemiological part of the cohort and over 2000 randomly selected participants in the clinical part. The clinical study cohort is longitudinal with data throughout the life course including prenatal life, early childhood and later life. The study cohort has been followed up clinically and comprehensive data have been collected including metabolic and body composition data. Altogether, 2003 individuals participated in the baseline clinical examination in 2001-2004. The age range of the participants was 56–69 years (mean 61 years). Follow-up examinations considering this thesis were performed in 2017–2018 when the participants were 72–84 years old (mean 75 years). For the Study III, participants with prevalent diabetes diagnosis were exluded to verify diabetes-free cohort sample. Thus, 1617 participants (56% women) with sufficient data were identified in Study III. Of those 704 individuals participated in the follow-up examination for Study IV.

The limitations of HBSC include that cohort members may not represent all citizens in Finland as they were both born and attended child-welfare clinics in the city of Helsinki, the capital of Finland. In addition, the study population of the clinical part of the cohort lived in the surroundings of Helsinki and may not be fully representative of all people in Finland. Also, a characteristic feature of prospective studies consisting of older adults, including the Study IV, is that there is a considerable loss of participants in the follow-up.

Due to the cross-sectional nature of Studies I-III, the direction of causality is uncertain. A prospective study design was used in Study IV, with an extensive average follow-up time of 15 years. However, there might be a selection bias. In

study IV, only those who were in better health might have attended the follow-up examination.

6.2 Methods

6.2.1 Anthropometric measurements

Trained study nurses performed anthropometric measurements, which is a more accurate method than self-report. Self-reported height tends to be overestimated and weight to be underestimated especially among overweight and obese individuals (Maukonen et al., 2018). Measurements were carried out following the standard WHO MONICA procedures (The World Health Organization MONICA Project, 1988). The mean heights for both women and men in Study I were equal to the mean heights of Finns in 2007, i.e., 163cm in women and 177cm in men (Peltonen et al., 2007).

6.2.2 Laboratory measurements

In Study I and II, for logistic reasons glucose values were measured from capillary whole blood with an analyzer which converts the result to plasma glucose values. According to the Finnish Current Care Guidelines on Diabetes, the more preferable method to perform OGTT is to use venous plasma glucose values (Type 2 Diabetes: Current Care Guideline, 2020). However, the current WHO criteria states reference values also for capillary glucose measurement, and in Studies I and II glucose disorders were classified according to these WHO criteria (World Health Organization, 2006).

In Study IV, one measurement of FPG was used to define T2D. Finnish Current Care Guidelines on Diabetes recommend to control abnormal FPG values another day (Type 2 Diabetes: Current Care Guideline, 2020). This was not possible in this study setting.

6.2.3 Body composition

BIA method was chosen because of its practicality in large epidemiologic studies (Bedogni et al., 2002, Malavolti et al., 2003). Between-day precision of InBody 3.0 has been reported to be 2.7% (Malavolti et al., 2003). Morbid obese individuals have a relatively high amount of extracellular water and total body water, which may overestimate lean body mass and underestimate fat mass (Coppini et al., 2005) Use of DXA in assessing body composition would have ensured better validity.

When compared to DXA lean body mass, percent root mean square error of InBody 3.0 was 6% (Malavolti et al., 2003).

6.2.4 Questionnaires

Questionnaires are commonly used in epidemiological studies as being low-cost and convenient. A great amount of information on sociodemographic and lifestyle factors was obtained using a self-adminitered questionnaire at baseline. Their variation over time could not be considered in the prospective setting as in Study IV. Self-reports of smoking habits, alcohol intake, and LTPA may be biased (Del Boca & Darkes, 2003; Connor Gorber et al., 2009; Tucker et al., 2011). Compared to accelerometer-measured LTPA self-reported LTPA tend to overestimate physical activity levels (Boon et al., 2010).

6.3 Results

6.3.1 Adult height, body mass index, body surface area and glucose tolerance (I & II)

Study I shows that adult height has an inverse relationship with 2hPG concentration during an OGTT independently of adiposity for people with a BMI up to 35 kg/m^2. Study II indicates that the smaller the adjusted BSA of a population, the higher the proportion of new T2D cases diagnosed by 2hPG in an OGTT is. Thus, there is a possibility that the diagnosis of T2D made by an OGTT is a false positive result in a relatively smaller individual, and a false negative result in a relatively larger individual.

In people with a BMI up to 35 kg/m^2, the results support previous reports associating shorter stature with higher 2hPG levels, but not with FPG levels (Janghorbani & Amini, 2008; Sicree et al., 2008; Faerch et al., 2010). Previous studies have reported that men have higher FPG levels than women, whilst IGT is more prevalent in women (Sicree et al., 2008; Faerch et al., 2010; Vistisen et al., 2014). We found no significant gender difference in FPG concentrations. This is not surprising, because endogenous glucose production is positively related to FPG only in diabetic patients with markedly increased insulin resistance, but not in persons without diabetes, such as the study participants in the study of Williams et al. (Williams et al., 2003). There were no sex differences in the mean 2hPG concentrations in the present study either. This finding is in accordance with the Whitehall II study, in which 2hPG glucose did not differ between men and women (Vistisen et al., 2014). Additionally, in studies presenting adjustment for height, women did not have higher 2hPG levels than men (Rathmann et al., 2008; Sicree et

al., 2008; Faerch et al., 2010). Therefore, we agree with the conclusion of Faerch et al. (Faerch et al., 2010) that previously documented (Williams et al., 2003; Sicree et al., 2008) sex differences in 2hPG and in the prevalence of IGT are not related to sex-specific differences in the physiology of glucose regulation but rather are an artefact caused by giving individuals of different body size and body composition the same amount of glucose during an OGTT. Additionally, in the recent meta-analysis no sex differences were found in the associations between adult height and T2D (Shrestha et al., 2019).

In Study II, higher BSA was associated with higher levels of several cardiometabolic risk factors. Nevertheless, after adjustment for confounding factors increasing BSA was associated with decreasing 2hPG and 2hPG/FPG ratio in all categories of glucose tolerance. Ratio of 2hPG and FPG was used to assess to what extent the 75 g glucose dose increased PG concentration in relation to FPG concentrations. Higher BSA was associated with lower 2hPG concentration in relation to FPG. This indicates that when body size is smaller, the uniform 75 g glucose dose has greater impact on 2hPG level even if FPG level has been taken into account. Moreover, as a consequence of their smaller body size, women may be more often diagnosed with IGT or T2D than men.

Adjusted BSA may be regarded as the framework of the human body in which the organs responsible for glucose homeastasis function. It is reasonable to assume that the larger the framework, the larger the internal organs, e.g. liver (Vauthey et al., 2003) and lean mass (LM). Further, it may be hypothesized that the more LM, the more vasculature, the larger absorptive capillary area, the lower 2hPG. Considering the inverse association between height and glucose regulation Sicree et al. (Sicree et al., 2008) have postulated that this association is due to fact that taller persons have more LM (Hansen et al., 1999), which is the predominant site for insulin-stimulated glucose disposal (DeFronzo & Tripathy, 2009). This hypothesis was supported by the KORA Survey 2000 (Rathmann et al., 2008) and the Inter99 study (Faerch et al., 2013) showing that 2hPG levels could be explained by differences in the absolute amount of LM, and that faster glucose absorption was related to greater height and LM. Moreover, gut glucose half-life shows an inverse relationship with body height and LM (Anderwald et al., 2011; Faerch et al., 2013). It is also worth noting that blood volume is demonstrated to associate positively with height, weight, BSA and LM (Feldschuh & Enson, 1977; Boer, 1984; Raes et al., 2006). Thus, it may be assumed that a fixed glucose load given in OGTT dilutes more in larger individual, resulting in lower 2hPG concentrations.

In Study I, 2hPG values increased along with an increase in BMI supporting the association between the severity of insulin resistance and adiposity (Bogardus et al., 1984, Kahn & Flier, 2000). Recent studies focusing upon the association between height and glucose tolerance also reported that BMI is positively related to

2hPG *per se* (Janghorbani & Amini, 2008; Faerch et al., 2010). However, to our knowledge, we are the first to study the combined effect of height and BMI on 2hPG and to demonstrate that height is not associated with 2hPG among persons with BMI ≥ 35 kg/m^2. Thus, the present findings may indicate that the response to OGTT transforms gradually along with increased adiposity into a physiological response, meaning that eventually no "height-related response" remains, and an "obesity-related physiological response" over-rides this. This may be due to adipose tissue, the largest "organ" in human body, becoming dysfunctional in obesity (Kahn & Flier, 2000; Lee et al., 2013).

The findings of Studies I & II have many clinical implications. First, adjustment of BSA or height and BMI is required to better interpret the results of an OGTT. Second, a uniform oral glucose load may be inadequate to accurately assess glucose tolerance. Sicree et al. suggested that varying the glucose load (as is done in children) may improve measurements of glucose tolerance as an alternative to anthropometric adjustments (Sicree et al., 2008). Third, any given elevation of 2hPG may represent a more severe metabolic disturbance in relatively taller or larger person than in relatively shorter or smaller one.

Simplicity and convenience are needed for diagnostic testing in clinical practice. These considerations apply to the choice of the 75 g glucose load as the official standard for the diagnosis of T2D (World Health Organization, 1980). It is therefore questionable whether OGTT, which is so strongly associated with height, BMI and BSA, has such a clinical importance without taking them into consideration. Unfortunately, such an adjusted OGTT would encounter practical difficulties and would no longer be simple nor convenient. In addition, it is not known whether the prognostic value of the OGTT also differs according to height, BMI and BSA. There might be a risk that smaller people receive a diagnosis of T2D or IGT without being at increased risk of diabetic complications.

Furthermore, in obese individuals (BMI ≥ 35 kg/m^2) there may be no additive value for testing glucose tolerance, because they seem to be already glucose intolerant. Thus, primary prevention should focus on obesity prevention and weight loss rather than screening abnormal glucose metabolism by OGTT. Potentially screening with FPG and HbA_{1C} would be sufficient.

In Studies I & II, taller stature in those with a BMI < 35 kg/m^2 and larger body size "protected" participants from OGTT-induced glucose increases. It is noteworthy that 2hPG predicted all-cause mortality better than elevated fasting glucose in a meta-analyses performed by Huang et al. (Huang et al., 2016). However, in eleven studies included in the meta-analysis focusing upon individuals with impaired glucose regulation, findings were not adjusted for height or BSA. Importantly, it is well known that short adult stature is a risk factor for CV and all-cause mortality (Lee et al., 2009; Emerging Risk Factors Collaboration, 2012;

Schmidt et al., 2014). Thus, it is possible that after controlling for height-related confounders, such as body height or BSA, 2hPG values might not be associated with increased risk of mortality.

Studies I & II demonstrated that higher 2hPG concentration during standard OGTT identifies individuals with on average smaller body height and size: Smaller persons are more likely to be diagnosed as glucose intolerant or diabetics than relatively larger sized individuals. Given that OGTT is a time and effort consuming method and the glucose values during OGTT are substantially affected by body size, the standard use of OGTT should be abandoned.

6.3.2 Body composition and glucose regulation and type 2 diabetes (III & IV)

Studies III & IV suggest that persons with high FMI and high LMI have the most unfavorable cardiometabolic risk profile. Study III shows that LMI has a positive relationship with FPG and insulin resistance as assessed by HOMA-IR in men, whereas in women no relationship between LMI and glucose tolerance was found. As for the other component of BMI, FMI showed a positive association with HOMA-IR, FPG, and 2hPG in both men and women. In Study IV, the combination of high FMI and high LMI among community-living 60-year-old adults is associated with an elevated risk of developing T2D during a 15-year follow-up period. Contrary to a general belief that greater muscle mass – the predominant part of LM – is protective against T2D is not supported by our findings. Our results indicate, that a high LM accompanied with fatness may be detrimental for glucose regulation and may predict subsequent development of T2D.

Previous studies addressing the association between lean or muscle mass indexed to body height and insulin resistance are sparse. In a study by Lee et al. they reported that appendicular skeletal muscle (ASM, sum of muscle mass of arms and legs) assessed by BIA and ASM/height^2 were positively correlated with HOMA-IR in Korean men and women aged 70 years (Lee et al., 2015). However, based on their finding of the inverse association between ASM indexed to body weight and HOMA-IR, they assumed that lower skeletal muscle mass is associated with glucose intolerance imitating surmises of similar studies dealing with the association between lean or muscle mass indexed to body weight and glucose tolerance (Srikanthan et al., 2010; Srikanthan & Karlamangla, 2011; Moon, 2014). Nevertheless, participants with low relative LM may have high relative FM, and the latter may be the cause of their worse glucose tolerance. This potential confounder is of concern when LM is indexed to body weight, because increases in FM translate to reductions in the LM fraction of body weight. To obviate such

difficulty, this confounder is less relevant, as LM or FM is divided by the square of height analogously to BMI, the approach we adopted in Studies III & IV.

Furthermore, in a Japanese study of Sakai et al. they postulated that reduced muscle mass is associated with decreased β-cell function based on a positive association between ASM/height^2 and HOMA-β albeit they likewise found positive relationship between ASM/height^2 and HOMA-IR (Sakai et al., 2016). This one-dimensional approach is also of concern, because one might conclude erroneously that a person has failing β-cells, as opposed to appropriately low secretion because of good insulin sensitivity (Wallace et al., 2004).

Exceptionally, in a study including 99 postmenopausal women, Lebon et al. found a positive correlation between muscle mass indexed to height and assessed by DXA and HOMA-IR even after adjusting for visceral fat mass (Lebon et al., 2012). In Study III, we found no statistically significant association between LMI and glucose regulation in women.

To the best of our knowledge, the combined effect of LM and FM indexed to body height on development of T2D has not been previously investigated. Similar to our findings in Study IV, in a substudy of the Look AHEAD trial, participants with T2D had more LM and more truncal FM, yet, less total FM, than healthy controls (Heshka et al., 2008). Further, in the Health ABC study, muscle and abdominal adipose tissue areas were larger in persons with T2D than in persons with normal glucose tolerance (Goodpaster et al., 2003). Maiolo et al. reported non-significantly more LM and less FM in women with T2D compared to women with normal glucose tolerance (Maiolo et al., 2002). Svendsen and Hassager detected more total FM in premenopausal but not in postmenopausal women with T2D compared to healthy controls. Additionally, they found no difference in total LM irrespective of age, menopausal or diabetes status (Svendsen & Hassager, 1998). Furthermore, Poynten et al. observed no difference in either LM or FM between weight and BMI-matched controls and persons with T2D (Poynten et al., 2003).

Both in the longitudinal Health ABC Study and in the Danish Diet, Cancer and Health cohort study, total LM was positively associated with a higher incidence of T2D (Larsen et al., 2016; Baker et al., 2019). This association appeared to be largely explained by the fact that those with more muscle mass also generally have more body fat because no association remained significant after adjusting for body size and body composition. Kalyani et al. observed in the Baltimore Longitudinal Study of Aging, that higher total LM was associated with a higher risk of T2D even after accounting for total FM (Kalyani et al., 2020). Hong et al. reported a positive relationship between body fat percentage and incident T2D in Korean men and women with a median age of 39 years (Hong et al., 2017). However, both in the study by Kalyani et al. and in the study by Hong, et al. opposite findings were

observed. In other words, relative LM, i.e. LM indexed to body weight, was inversely associated with the incidence of T2D in men in the study of Kalyani et al. and in both genders in the study of Hong et al. (Hong et al., 2017; Kalyani et al., 2020). Nevertheless, as described previously, participants with low relative LM may have high relative FM, and the latter may be the cause of their higher incidence of T2D. Undoubtedly that might be the case in the Korean study in which body fat percentage was calculated (Hong et al., 2017).

Study III showed that all studied markers of glucose regulation (FPG, 2hPG, HOMA-IR) increased with an increase in FMI supporting the association between the severity of insulin resistance and adiposity (Bogardus et al., 1984, Kahn & Flier, 2000). To the best of our knowledge, we are the first to split BMI and study the combined effect of LMI and FMI on glucose tolerance and to show that in men LMI was significantly and positively related with FPG and HOMA-IR in the middle and high FMI tertiles.

In Study IV markers of glucose regulation were the highest in the HFHL category also at baseline indicating a disturbance in glucose metabolism among persons in the HFHL category even before overt hyperglycemia develops. Considering underlying pathophysiological mechanisms increased skeletal muscle lipid infiltration has been shown to impair the normal physiological function of skeletal muscle and to be an independent risk factor for insulin resistance and T2D (Yim et al., 2007; Carobbio et al., 2011; Miljkovic et al., 2013; Hausman et al., 2014). A greater muscle lipid content was also observed to be a characteristic feature of older adults with T2D (Goodpaster et al., 2003). Additionally, in Study III we studied adipocytokines associated with adiposity, i.e. anti-inflammatory adiponectin and proinflammatory leptin. Lower adiponectin concentration has been associated with insulin resistance, whereas higher leptin levels have been associated with obesity; subcutaneous fat being a major determinant of circulating leptin levels (Yadav et al., 2013). The leptin/adiponectin ratio is an efficacious parameter of insulin resistance (Inoue et al., 2006; Finucane et al., 2009; Bravo et al., 2017). We found that the leptin/adiponectin ratio increased with increasing FMI and LMI.

In respect of metabolomics, that is, determination of small particles in serum related to metabolism, circulating amino acids, especially BCAAs, have been linked to obesity, insulin resistance, and T2D (Newgard et al., 2009; Wang et al., 2011; Guillet et al., 2012). BCAAs have been introduced to be indicators of metabolic disturbances rather than that of obesity (Newgard et al., 2009; Batch et al., 2013). BCAA overload may even have a causal role in developing insulin resistance and T2D (Newgard et al., 2009; Manders et al., 2012). In our study population, both FMI and LMI have been shown to associate positively with BCAAs in both genders regardless glucose concentrations (Mikkola et al., 2020).

The findings in Studies III & IV have several clinical implications. Our results challenge the general assumption that more skeletal muscle mass is beneficial for glucose homeostasis. Instead, we showed that obese people are not protected against insulin resistance and the risk of developing T2D by having a high LM - quite the opposite. Our findings indicate that among people without excess body fat the size of LM, which is mostly composed of skeletal muscle tissue, is not crucial for glucose regulation, whereas having more adipose tissue together with higher LM contribute to development of T2D. Hence, adiposity, which is a major contributor to the increasing incidence of cardiometabolic diseases (Hunter & Reddy, 2013; Bauer et al., 2014) and disease-related mortality (Pischon et al., 2008), is undoubtedly the key factor of insulin resistance and T2D. Some researchers have called for a shift in the public health focus away from markers of adiposity (Hunger & Tomiyama, 2015). We could not disagree more with this assertion. Furthermore, since obese individuals seem to be already glucose intolerant, there may be no additive value for testing glucose tolerance. Thus, we pave the way to question, whether OGTT has any longer such a clinical importance. Additionally, in obese people higher amount of LM might be a natural consequence: more muscle mass is needed to carry the excess body fat. Our findings could help direct public health resources toward programs that target weight management among people, who might benefit most. Preventive strategies should focus on obesity prevention and weight loss through exercise and dietary changes in order to reduce the risk of T2D (Tuomilehto et al., 2001, Knowler et al., 2002). Such approaches may indeed be the most appropriate for overweight/obese individuals, who would likely benefit more from losing excess fat than gaining more muscle.

In Study III we found that among men high LM accompanied with fatness may be detrimental for glucose regulation, whereas among women the size of LM has no effect on glucose regulation. Fatness is the major determinant of glucose intolerance. As a consequence, greater amount of both FM and LM was found to be associated with development of T2D in Study IV.

6.4 Strengths and limitations

The main strengths of this study/these studies/this thesis are representative population-based study samples with a comprehensive data and a high response rate (74% for both). Study samples consisted of apparently healthy middle-aged individuals at elevated CVD risk and 60 years old individuals without diabetes - typical populations to undergo health examinations in primary care. The exclusion of subjects with previously diagnosed diabetes and established CVD ensured more

homogenous and comorbid-free cohorts. Therefore, our results are well generalizable to primary care population.

Furthermore, we took into consideration several possible confounding variables including gender, age, other anthropometry, educational attainment, and lifestyle factors. Also, all clinical measurements were carried out by trained medical staff. Additionally, assigning participants in Studies I & II into five groups of height and BSA makes the results comparable to other populations based on the fact that height and BSA are normally distributed in the general population.

Above all, to our knowledge, we are the first to study the combined effect of height and BMI on glucose tolerance, as well as to split BMI and take simultaneously into account both FM and LM and their interaction on glucose tolerance and subsequent development of T2D during a notable 15-year follow-up period - by far the longest follow-up duration in this field. Hence, these findings bring the importance of body size and body composition on glucose regulation into daylight.

Nevertheless, limitations are also acknowledged. Major limitations of Studies I-III include their cross-sectional design, which does not allow us to assess causal relationship of anthropometrics on glucose regulation or to evaluate the role of genetic and environmental factors between body size, body composition and glucose metabolism. Use of DXA in assessing body composition would have ensured better validity. However, the BIA method has been validated against DXA and is acceptably reliable for body composition measurements (Ling et al., 2011). Additionally, measuring body composition does not take into account metabolism of fat nor muscle tissue. Insulin clamp technique would have been more accurate to assess insulin resistance, but this technique is impossible to use in a primary care setting. A characteristic feature of longitudinal studies consisting of older adults, including Study IV, is that there is a considerable loss of participants in the follow-up. Further, part of the data was gathered by self-evaluation forms in which compliance and correct responses are not possible to verify. These factors may have influenced our results.

6.5 Future research prospectives

This study offers several implications for future research. Longitudinal study designs are needed to draw conclusions about the causality whether adult height adjusted for adiposity estimates and body surface area are associated with development of T2D and cardiometabolic events. Due to considerable impact of height and body surface area on glucose tolerance, reanalysis of the previously presented association between 2-hour plasma glucose and mortality (Huang et al., 2016) would be interesting and recommended with adjustment for height-related

confounders. In addition, longitudinal studies should clarify whether body composition, lean mass and fat mass taken simultaneously into account, is associated with cardiovascular morbidity and mortality. Future studies are also needed to determine whether changes in body composition in later life alter and especially could prevent the risk of developing T2D and diabetic complications.

7 Conclusions

Body size and body composition have a considerable impact on glucose regulation among middle-aged Finnish adults. Taller people have lower 2-hour plasma glucose than shorter people, up to a BMI of 35 kg/m^2. The smaller the adjusted body surface area of the person, the higher the proportion of newly diagnosed T2D based on 2-hour plasma glucose in the OGTT. Persons with high fat mass index and high lean mass index, defined as lean/fat mass divided by the square of height analogously to BMI, have the most unfavorable cardiometabolic risk profile. Among 60-year-old men high lean mass index accompanied with high fat mass index was associated with insulin resistance, whereas in women lean mass index had little influence on glucose tolerance. Higher adiposity increased 2-hour plasma glucose values. The combination of high fat mass index and high lean mass index was associated with an elevated risk of developing T2D during a 15-year follow-up period.

Based upon these findings, the following conclusions can be drawn:

- There is a possibility that the diagnosis of T2D made by an OGTT is a false positive finding in a relatively smaller individual, and a false negative finding in a relatively larger individual. Thus, is it time to dispense with the standard use of the OGTT, and as Elsa in Disney's Frozen sings, "let it go"?
- Contrary to a general belief a greater muscle mass is not protective against T2D. On the contrary a high muscle mass accompanied with fatness seems to be detrimental for glucose homeostasis and predict subsequent development of T2D.
- Fatness is one of the major determinants of glucose intolerance.

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