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Body Surface Area in Clinical Practice

With Reference to Oral Glucose Tolerance Test, Blood Pressure and Ankle-Brachial Index

Samuel Palmu

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To my family

UNIVERSITY OF TURKU
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SAMUEL PALMU: Body Surface Area in Clinical Practice
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ABSTRACT

Primary health care is crucial when it comes to diagnosis and treatment of common diseases, and health counselling. Body height, body weight and waist circumference are easy to measure enabling calculation of body mass index, body surface area, waist-to-height ratio, and waist-to-hip ratio. However, in clinical practice and guidelines little attention has been paid to differences in body size among individuals except in relation to overweight and obesity. A difference between men and women that has received little attention is the smaller body size of women on average.

The aim of this thesis was to assess the association between body surface area and 24-hour ambulatory blood pressure monitoring in participants from the Helsinki Birth Cohort Study population (n = 534, mean age 61 years, 51% women), and plasma glucose concentrations in an oral glucose tolerance test (n = 2659, mean age 58 years, 56% women) and ankle brachial index (n = 972, mean age 59 years, 53% women) in participants from Harjavalta Risk Monitoring for Cardiovascular Disease Project population considering unexplained sex differences. BSA was calculated using the Mosteller formula $(\text{weight (kg)} \times \text{height (cm)} / 3600)^{0.5}$.

Body surface area was positively associated with blood pressure even after adjustment for confounding factors. However, blood pressure load per body surface area was significantly higher among women. Body surface area showed an inverse association with 2-hour post-load plasma glucose concentration in an oral glucose tolerance test. The smaller body surface area was the higher was proportion of new pre-diabetes or diabetes diagnoses. Body surface area also had a negative association with 2-hour post-load plasma glucose concentration in subjects with normal glucose tolerance. Body surface area had a positive association with ankle-brachial index and difference in ankle-brachial index between women and men was modified by body surface area. This partially explains why women have lower ankle-brachial index. In conclusion, body size should be considered in epidemiological studies especially when comparing glucose metabolism, blood pressure or ABI between men and women. Moreover, an OGTT may not be an appropriate diagnostic method to detect glucose disorders.

KEYWORDS: ankle-brachial index, blood pressure, body size, body surface area, BSA, oral glucose tolerance test

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Yleislääketiede
SAMUEL PALMU: Kehon pinta-ala kliinisessä työssä käsitellen glukoosirasituskoetta, verenpainetta ja nilkka-olkavarsipainesuhdetta
Väitöskirja, 171 s.
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TIIVISTELMÄ

Perusterveydenhuolto on keskeisessä asemassa väestön elintapaneuvonnan toteuttamisessa sekä kansansairauksien diagnostiikassa ja hoidossa. Helposti mitattavien kehon kokoa kuvaavien suureiden (pituus, paino ja vyötärönympärys) avulla voidaan laskea kehon painoindeksi, kehon pinta-ala, vyötärö-lantiosuhde sekä vyötärö-pituussuhde. Kuitenkin käytännön kliinisessä työssä kiinnitetään verrattain vähän huomiota ihmisten kokoeroon eikä toisaalta hoitosuosituksissakaan tätä yleensä huomioida muuten kuin ylipainon tai lihavuuden osalta. Vähälle huomiolle jäänyt ero miesten ja naisten välillä on se, että naiset ovat keskimäärin kooltaan miehiä pienempiä.

Tämän tutkimuksen tavoitteena oli selvittää kehon pinta-alan yhteyttä verenpaineen vuorokausirekisteröinnin tulokseen Helsingin syntymäkohorttitutkimuksen aineistolla (n = 534, ikä keskimäärin 61 vuotta, 51% naisia) sekä glukoosirasituskokeen tuloksiin (n = 2659, ikä keskimäärin 58 vuotta, 56% naisia) ja nilkka-olkavarsipainesuhteeseen (n = 972, ikä keskimäärin 59 vuotta, 53% naisia) Kokemäenjokilaakson valtimotautien ehkäisyprojektin (Harmonica Project) aineistolla huomioiden vielä tuntemattomasta syystä johtuvat eroavaisuudet miesten ja naisten välillä. Kehon pinta-ala laskettiin Mostellerin kaavalla (paino (kg) × pituus (cm) / 3600)^{0,5}.

Kehon pinta-alalla todettiin positiivinen yhteys verenpaineen vuorokausirekisteröinnin tuloksiin, vaikka sekoittavat tekijät huomioitiin. Kuitenkin suhteutettuna kehon pinta-alaan, naisilla verenpainekuorma oli merkittävästi korkeampi. Kehon pinta-alalla oli negatiivinen yhteys glukoosirasituskokeen kahden tunnin arvoon. Mitä pienempi henkilön kehon pinta-ala oli, sitä todennäköisemmin hänellä todettiin esidiabetes tai diabetes. Kehon pinta-alan todettiin olevan vaikutuksen muuntaja nilkka-olkavarsipainesuhteeseen siten, että suurempi kehon pinta-ala oli yhteydessä korkeampaan nilkka-olkavarsipainesuhteeseen, mikä osaltaan selittää naisilla todettua matalampaa nilkka-olkavarsipainesuhdetta. Kehon koko olisi suositeltavaa huomioida epidemiologisissa tutkimuksissa erityisesti vertailtaessa glukoosiaineenvaihduntaa, verenpainetta ja nilkka-olkavarsipainesuhdetta miesten ja naisten välillä. Lisäksi glukoosirasituskoe ei välttämättä ole soveltuva diagnostinen testi glukoosiaineenvaihdunnan häiriöiden tunnistamiseen.

AVAINSANAT: glukoosirasituskoe, kehon koko, kehon pinta-ala, nilkka–olkavarsipainesuhde, verenpaine

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Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ABPM	Ambulatory blood pressure monitoring
ADA	American Diabetes Association
β	Beta
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CAD	Coronary artery disease
CFA	Common femoral artery
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DALY	Disability-adjusted life-year
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FPG	Fasting plasma glucose
GBD	the Global Burden of Diseases, Injuries, and Risk Factors Study
GFR	Glomerular filtration rate
GP	General practitioner
HbA_{1c}	Glycated haemoglobin
HBPM	Home blood pressure measurement
HDL-C	High-density lipoprotein cholesterol
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction

HMOD	Hypertension-mediated organ damage
HR	Hazard ratio
IAS	International Atherosclerosis Society
ICCR	the International Chair on Cardiometabolic Risk
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
ISH	International Society of Hypertension
LDL-C	Low-density lipoprotein cholesterol
LEAD	Lower-extremity peripheral arterial disease
LTPA	Leisure-time physical activity
MAP	Mean arterial pressure
MET	Metabolic equivalent of task
MetS	Metabolic syndrome
MI	Myocardial infarction
mmHg	Millimetres of mercury
MRI	Magnetic resonance imaging
NHANES	the National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
OR	Odds ratio
PG	Plasma glucose
PNS	Parasympathetic nervous system
PP	Pulse pressure
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin–angiotensin system
RCT	Randomized controlled trial
RMSE	Root mean square error
RR	Relative risk
SBP	Systolic blood pressure
SCORE	Systematic coronary risk evaluation
SD	Standard deviation
SNP	Single-nucleotide polymorphism
SNS	Sympathetic nervous system
T2D	Type 2 diabetes
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
2hPG	2-hour post-load plasma glucose
3D	Three-dimensional

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 Korhonen, P. E., Palmu, S., Kautiainen, H., & Eriksson, J. G. Blood pressure load per body surface area is higher in women than in men. *Journal of Human Hypertension*, 2021; 35(4): 371–377. https://doi.org/10.1038/s41371-020-0339-z

II Palmu, S., Rehunen, S., 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; 157:107877. https://doi.org/10.1016/j.diabres.2019.107877

III Palmu, S., Kuneinen, S., Kautiainen, H., Eriksson, J. G., & Korhonen, P. E. Body surface area may explain sex differences in findings from the oral glucose tolerance test among subjects with normal glucose tolerance. *Nutrition, Metabolism and Cardiovascular Diseases*, 2021; 31(9): 2678–2684. https://doi.org/10.1016/j.numecd.2021.05.018

IV Palmu, S., Kautiainen, H., Eriksson, J. G., Hakovirta, H., & Korhonen, P. E. Body surface area is positively associated with ankle-brachial index. *Science Progress*, 2024; 107(2). https://doi.org/10.1177/00368504241251649

1 Introduction

High systolic blood pressure (SBP), high fasting plasma glucose, and high body mass index (BMI) are globally recognized as major risk factors for diseases and caused 223, 134, and 62 million disability-adjusted life-years (DALY) in 2021, respectively (Brauer et al., 2024). Obesity increases the risk of developing type 2 diabetes (T2D), cardiovascular diseases (CVD), various cancers, and musculoskeletal disorders (Bhaskaran et al., 2018).

Hypertension is one of the most extensively studied diseases due to its major contribution to CVD morbidity and mortality. However, questions remain regarding sex differences. Prevalence of hypertension is higher in men until approximately age 45, whereas after age 60, it is more prevalent in women across both high-income and low-income countries (Go et al., 2013; Prince et al., 2012; Robitaille et al., 2012). Several hypotheses explaining the sex differences have been proposed, including the influence of oestrogen. Although women exhibit greater awareness of their hypertension, they are less likely than men to achieve blood pressure (BP) treatment targets, particularly at older ages (Egan et al., 2010; Gee et al., 2012). Women are more likely to develop left ventricular hypertrophy (Piro et al., 2010) and heart failure with preserved ejection fraction (HFpEF) (Borlaug & Redfield, 2011). Regression of left ventricular hypertrophy with antihypertensive treatment is less common in women than in men (Okin et al., 2008). In older women, arterial stiffening is more pronounced (Rossi et al., 2011; Shim et al., 2011). However, one of the most obvious differences between men and women – body size – has been relatively little investigated.

Since 1980, the WHO has recommended using a standard 75-gram glucose load in the oral glucose tolerance test (OGTT) (World Health Organization, 1980). Height has been found to be inversely associated with the 2-hour post-load plasma glucose (2hPG) level in OGTT (Brown et al., 1991). Impaired glucose tolerance is more common in women than in men, but this difference disappears when height is adjusted for in analyses (Færch et al., 2010; Sicree et al., 2008).

Lower-extremity peripheral arterial disease (LEAD) is associated with reduced quality of life, increased cardiovascular event risk, and higher mortality. Diagnosis of LEAD is commonly based on the ankle-brachial index (ABI), with a threshold of ≤0.90 (Mazzolai et al., 2024). This cutoff has a sensitivity and specificity exceeding 90% compared to angiographic assessment (Aboyans et al., 2012). The non-invasive ABI measurement is well-suited for use in primary care settings. Sex differences in the ABI have been observed, but it remains uncertain whether these differences are attributable to atherosclerotic changes (Aboyans et al., 2007). Women have been reported to have lower ABI values than men, which has been attributed to differences in height (Kapoor et al., 2018).

Primary healthcare plays a crucial role in providing lifestyle counselling and managing the diagnosis and treatment of common chronic diseases. However, the measurement methods currently used in routine practice in relation of hypertension, diabetes mellitus (DM), or LEAD do not account for variations in patient body size. Commonly used and easily measurable anthropometric parameters include height, weight, and waist circumference (WC). These measurements allow for the easy calculation of BMI, body surface area (BSA), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). The aim of this thesis is to assess the association between BSA and BP, plasma glucose concentrations in an OGTT, and ABI measurement.

I have used generative pre-trained transformer models in the language editing and to enhance the readability of the text of my doctoral dissertation in accordance with the University of Turku and Finnish National Board on Research Integrity TENK recommendations and guidelines.

2 Review of the Literature

2.1 Cardiovascular Risk Factors and Diagnosis in Primary Care

2.1.1 Pre-diabetes and Type 2 Diabetes

2.1.1.1 Definition

DM is a group of metabolic disorders affecting carbohydrate metabolism, characterized by impaired glucose utilization for energy and excessive production of glucose due to inappropriate gluconeogenesis and glycogenolysis, leading to hyperglycaemia (Sacks et al., 2023). T2D has various causes, though its specific aetiology remains unclear. However, it is not associated with autoimmune destruction of β-cells, and affected individuals do not exhibit any of the other known causes of DM.(American Diabetes Association Professional Practice Committee, 2024) Abnormal glucose metabolism is classified into two clinical categories: pre-diabetes and T2D, both defined by biochemical criteria shown in **Table 1** (Marx et al., 2023).

2.1.1.2 Epidemiology

In 2021, the global DM prevalence among individuals aged 20–79 years was 10.5% (537 million people), and the prevalence is estimated to rise to 12.2% (783 million) by 2045. The prevalence was similar between men and women, with the highest rates observed in those aged 75–79 years.(Sun et al., 2022) T2D comprises 90–95% of all diagnosed cases of DM (American Diabetes Association Professional Practice Committee, 2024). According to The Healthy Finland Survey, prevalence of DM in Finland was 14% in men and 11% in women in 2022–2023 (Lindström et al., 2023).

2.1.1.3 Pathophysiology

T2D develops from insulin resistance, affecting especially the liver and muscles, and β-cell dysfunction in pancreas (Stumvoll et al., 2005). Genetic susceptibility, obesity, physical inactivity, and chronic low-grade inflammation contribute to insulin resistance reducing glucose uptake and increasing glucose production (DeFronzo, 2009; Galicia-Garcia et al., 2020; Stumvoll et al., 2005). Increased hepatic glucose production (hepatic insulin resistance), decreased glucose uptake in muscles (muscle insulin resistance) and impaired insulin secretion in pancreas (β-cell dysfunction) are the main underlying causes of hyperglycaemia in T2D. Moreover, excess lipolysis and release of free fatty acids due to adipose tissue dysfunction, deficiency in incretin hormones glucagon-like peptide 1 and gastric inhibitory polypeptide in the gastrointestinal tract, excess glucagon secretion in pancreatic α-cells, increased glucose reabsorption in kidneys, and impaired insulin action in appetite regulation in brain are recognized as contributors.(DeFronzo, 2009) Visceral fat secretes inflammatory molecules (tumor necrosis factor-alpha, interleukin 6) worsening insulin resistance (Galicia-Garcia et al., 2020). Gut microbiota dysbiosis contributes to insulin resistance and metabolic dysfunction (Galicia-Garcia et al., 2020).

2.1.1.4 Risk Factors

Non-modifiable risk factors for T2D include family history of T2D, and genome-wide association studies have identified genetic variants linked to insulin secretion and insulin resistance (Galicia-Garcia et al., 2020; Grarup et al., 2014). Certain ethnic groups (e.g., Japanese, Hispanic, Native American, African, and South Asian populations) have a higher genetic predisposition to T2D (Galicia-Garcia et al., 2020). The risk of T2D increases significantly with age, especially after 40–45 years (Zhang et al., 2024).

Obesity and overweight are the key risk factors for T2D, with visceral obesity being especially important (Schnurr et al., 2020). A BMI of 30 kg/m^2 or higher is associated with increased insulin resistance (Schnurr et al., 2020). A sedentary lifestyle is also strongly associated with both insulin resistance and obesity (Hamilton et al., 2014). Diets that are high in calories, sugar, and fat contribute to obesity and metabolic dysfunction (Galicia-Garcia et al., 2020). Excessive consumption of saturated fats, refined carbohydrates, and processed foods increases the risk of insulin resistance (Galicia-Garcia et al., 2020). Metabolic syndrome (MetS) increases the risk of developing T2D (Marott et al., 2016). Chronic stress promotes insulin resistance and fat accumulation (Kyrou et al., 2006). Poor sleep quality has been linked to poorer glycaemic control, indicating that sleep is important in metabolic function of T2D patients (S. W. H. Lee et al., 2017). Additionally, an inverse association between socioeconomic status and the occurrence of T2D has been observed, partly due to differences in health behaviours and other risk factors (Kumari et al., 2004).

2.1.1.5 Symptoms and Signs

T2D may be asymptomatic or cause symptoms such as polyuria, polydipsia, fatigue, blurred vision, weight loss, slow-healing wounds, and recurrent infections (Marx et al., 2023).

2.1.1.6 Diagnosis

In clinical practice, DM is diagnosed using biochemical tests such as fasting plasma glucose, 2-hour post-load plasma glucose (2hPG) in an OGTT, random plasma glucose, and glycated haemoglobin (HbA_{1c}) (Marx et al., 2023). Diagnostic criteria are summarized in **Table 1**.

Table 1. Diagnosis and classification of diabetes, impaired glucose tolerance, and impaired fasting glycaemia according to WHO 1999 (World Health Organization, 1999), WHO 2006 (World Health Organization, 2006), WHO 2011 (World Health Organization, 2011), ESC/EASD 2019 (Cosentino et al., 2020), ESC 2023 (Marx et al., 2023) and ADA 2024 (American Diabetes Association Professional Practice Committee, 2024)

	WHO 1999	**WHO 2006/2011**	**ESC/EASD 2019**	**ESC 2023**	**ADA 2024**
Diabetes Mellitus (DM)					
HbA_{1c}	-	Not recommended (2006). If measured, ≥48 mmol/mol (2011).	Recommended, ≥48 mmol/mol	Recommended, ≥48 mmol/mol	Recommended, ≥48 mmol/mol
FPG	≥7.0 mmol/L	≥7.0 mmol/L	≥7.0 mmol/L	≥7.0 mmol/L	≥7.0 mmol/L
2hPG	≥11.1 mmol/L	≥11.1 mmol/L	≥11.1 mmol/L	≥11.1 mmol/L	≥11.1 mmol/L
RPG	Symptoms plus ≥11.1 mmol/L	Symptoms plus ≥11.1 mmol/L	Symptoms plus ≥11.1 mmol/L	Symptoms plus ≥11.1 mmol/L	Symptoms plus ≥11.1 mmol/L
Impaired Glucose Tolerance (IGT) [1]					
FPG	<7.0 mmol/L	<7.0 mmol/L	<7.0 mmol/L	<7.0 mmol/L	<7.0 mmol/L
2hPG	≥7.8 to <11.1 mmol/L	≥7.8 to <11.1 mmol/L	7.8-11.0 mmol/L	7.8-11.0 mmol/L	7.8-11.0 mmol/L
Impaired Fasting Glycaemia (IFG) [1]					
FPG	≥6.1 to < 7.0 mmol/L	6.1–6.9 mmol/L	5.6–6.9 mmol/L	5.6–6.9 mmol/L	5.6–6.9 mmol/L
2hPG	<7.8 mmol/L (if measured)	<7.8 mmol/L	<7.8 mmol/L		

Abbreviations: 2hPG, 2-hour post-load plasma glucose in an oral glucose tolerance test; FPG, Fasting plasma glucose; HbA_{1c}, glycated haemoglobin; RPG, Random plasma glucose
[1] Pre-diabetes is defined as IGT and/or IFG and/or HbA1c 39–47 mmol/mol according to ADA and ESC.

2.1.1.7 Prognosis

A study investigated the relationship between the age of diagnosis of T2D and life expectancy in high-income countries. Analysing data from 1.5 million participants across 19 countries with a follow-up of 23 million person-years, a strong association was observed between earlier T2D diagnosis and higher mortality risk. Each decade earlier that T2D was diagnosed reduced life expectancy by approximately 3–4 years. Individuals diagnosed at age 30 died, on average, 14 years earlier than those without T2D, while diagnoses at ages 40 and 50 led to reductions of 10 and 6 years, respectively in the United States, and using EU death rates, the corresponding estimates were 13, 9, or 5 years earlier.(Kaptoge et al., 2023).

An observational study examined the impact of achieving multiple risk factor targets on mortality and life expectancy in individuals with T2D using data from the UK Biobank. Analysing 316,995 participants (14,162 with T2D) over a median follow-up of 13.8 years, the study found that higher adherence to seven risk factor targets (non-smoking, being physically active, healthy diet, guideline-recommended levels of HbA_{1c}, BMI, BP, and total cholesterol) was associated with significantly lower mortality risk. T2D patients who met 6–7 targets had no substantial excess mortality risk or life expectancy reduction compared to non-diabetic individuals, whereas those with 0–1 target achieved had a markedly higher risk of death and lost an average of 7.67 years of life expectancy at age 50.(Wang et al., 2024)

2.1.2 Hypertension

2.1.2.1 Definition

Hypertension is defined as a confirmed office SBP of ≥140 mmHg (millimetres of mercury) or diastolic blood pressure (DBP) of ≥90 mmHg and this definition is widely accepted in guidelines by ESH, ESC, ISH, and WHO (Mancia et al., 2023; McEvoy et al., 2024; Unger et al., 2020; World Health Organization, 2021). However, large body of evidence shows that there is no single threshold level for BP in relation to CVD risk but rather the risk increases progressively from SBP level 90 mmHg upward.(Arvanitis et al., 2021; McEvoy et al., 2024; Rapsomaniki et al., 2014).

An individual participant data meta-analysis investigated the effect of pharmacological BP lowering on CVD prevention. Data from 48 randomized controlled trials (RCT) were analysed, including 344,716 participants with and without pre-existing CVD. Reducing SBP by 5 mmHg lowered the risk of major CVD events by about 10%, irrespective of baseline BP level or prior CVD history. The study suggested that antihypertensive treatment should be viewed primarily as a tool for reducing CVD risk, rather than being restricted to individuals with hypertension. These results challenged guidelines and advocated for broader use of antihypertensive medications in individuals at elevated CVD risk, even at BP levels not traditionally considered for treatment.(Rahimi et al., 2021)

The present ESC Guidelines for the management of elevated blood pressure and hypertension (McEvoy et al., 2024) introduced a new classification of BP shown in **Table 2**. The BP classification according to ESH Guidelines for the management of arterial hypertension (Mancia et al., 2023), shown in **Table 3**, is in line with the previous ESC/ESH 2018 guidelines (Williams et al., 2018) with no significant adjustments in last decades (European Society of Hypertension-European Society of Cardiology Guidelines Committee, 2003). The BP classification in Finnish guidelines is in line with the ESH Guidelines (Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2020). In the ESC 2024 Guidelines, the category “non-elevated BP” is not labelled as ”optimal” or ”normal” due to the continuous CVD risk also at lower BP levels (McEvoy et al., 2024).

Table 2. Blood pressure categories according to ESC Guidelines for the management of elevated blood pressure and hypertension (McEvoy et al., 2024)

CATEGORY	OFFICE BLOOD PRESSURE (MMHG)	HOME BLOOD PRESSURE (MMHG)	24H AMBULATORY BLOOD PRESSURE MONITORING (MMHG)
Non-elevated blood pressure	<120/70	<120/70	<115/65
Elevated blood pressure	120/70 – <140/90	120/70 – <135/85	115/65 – <130/80
Hypertension	≥140/90	≥135/85	≥130/80

Table 3. Blood pressure categories according to 2023 ESH Guidelines for the management of arterial hypertension (Mancia et al., 2023).

CATEGORY	SYSTOLIC BLOOD PRESSURE (MMHG)	DIASTOLIC BLOOD PRESSURE (MMHG)
Optimal	<120	<80
Normal	120–129	80–84
High-normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110
Isolated systolic hypertension	≥140	<90
Isolated diastolic hypertension	<140	≥90

2.1.2.2 Epidemiology

In total, the estimated number of people aged 30–79 years with hypertension increased from 0.65 billion in 1990 to 1.3 billion in 2019 globally. The age-standardized average prevalence of hypertension was 34% (95% CI 32–37%) in men and 32% (95% CI 30–34%) in women in 2019.(B. Zhou et al., 2021) Globally, high SBP contributed 7.8% (95% CI 6.4–9.2) of total DALYs and was surpassed only by particulate matter air pollution as the leading contributor to the global disease burden in 2021. (Brauer et al., 2024). According to The Healthy Finland Survey, prevalence of hypertension in Finland was 52.4% in men and 46.1% in women in 2022–2023 (Laatikainen et al., 2023).

2.1.2.3 Pathophysiology

Hypertension research began in the late 19th century, with early studies linking kidneys to BP regulation (Goldblatt et al., 1934; Harrison et al., 2021). In 1897, a Finnish scientist Robert Tigerstedt and his assistant Per Bergman conducted experiments on rabbits, discovering that an extract from renal cortex increased BP. This led them to identify a hypothetical pressor substance, which they named renin.(Tigerstedt & Bergman, 1898) In the 1940s, Irvine Page and Braun-Menendez identified angiotensin (Braun-Menendez & Page, 1958), leading to the description of renin–angiotensin system (RAS) (Harrison et al., 2021). In 1949 Irvine Page presented the "Mosaic Theory" proposing that hypertension results from multiple interacting factors, including neural, renal, and vascular influences (Harrison et al., 2021). Modern research has expanded the original theory by introducing new mechanisms and providing strong evidence of reciprocal influences between cardiovascular (CV) control systems, where changes in one system can reinforce or promote changes in others (Mancia et al., 2023).

Most hypertensive patients have primary hypertension with no known underlying known cause, while about 10% have secondary hypertension, which originates from specific, identifiable causes (Mancia et al., 2023; McEvoy et al., 2024). The pathophysiology of hypertension involves complex interactions between BP regulation, genetic factors, lifestyle factors and environmental factors summarized in **Figure 1**.

BP is regulated by various CV parameters, including blood volume, cardiac output, and systemic vascular resistance, which is influenced by intravascular volume and neurohumoral systems (Oparil et al., 2003; Titze & Luft, 2017). Maintaining physiological BP levels requires a complex interaction between multiple components of the neurohumoral system, including the renin-angiotensin-aldosterone system (RAAS), natriuretic peptides, the endothelium, the sympathetic nervous system (SNS), and the immune system (Mancia et al., 2014; Oparil et al., 2003). Increased systemic vascular resistance is the hallmark hemodynamic abnormality responsible for BP elevation in almost all hypertensive people (Mancia et al., 2023). Primary hypertension is a polygenic disease influenced by environmental factors, with a heritability of 30%–50% (McEvoy et al., 2024;

Padmanabhan & Dominiczak, 2021). New environmental contributors such as air pollution and noise have been recognized causing vascular inflammation and endothelial dysfunction, which mediate the BP increasing effects. (Mancia et al., 2023; Shin et al., 2020). Gut microbiome dysbiosis and immune system activation (particularly inflammation and oxidative stress) are associated with development of hypertension (Griendling et al., 2021; Li et al., 2017). Disruptions or dysfunctions in any of these systems can lead to increased BP, BP variability, or both, ultimately contributing to target organ damage (Oparil et al., 2003). Strong evidence shows associations with BP and behavioral factors such as physical inactivity, smoking, excessive alcohol use, and an unhealthy diet high in sodium, and low in potassium (McEvoy et al., 2024). Sleep disorders, low socioeconomic status, stress, and psychosocial factors are also associated with elevated BP (McEvoy et al., 2024).

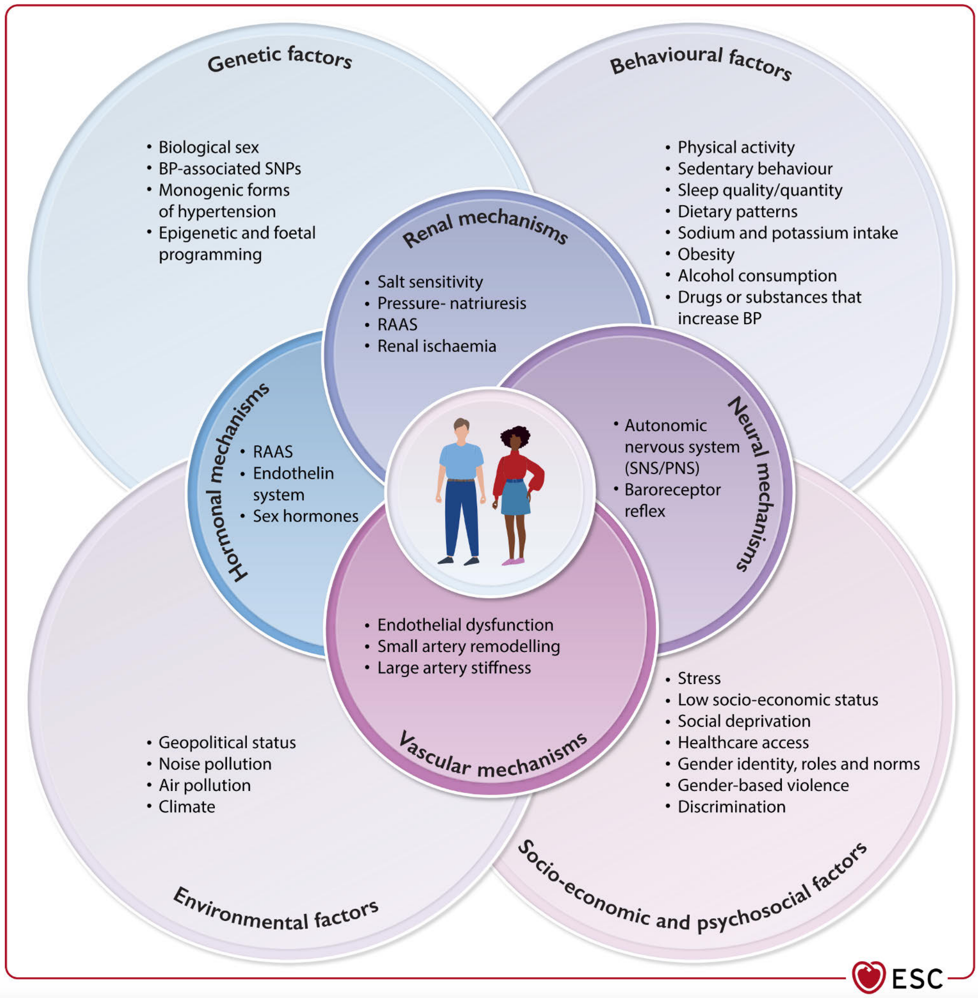


Figure 1. Pathophysiology of hypertension (McEvoy et al., 2024). Abbreviations: BP, blood pressure; PNS, parasympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; SNP, single-nucleotide polymorphism; SNS, sympathetic nervous system. Reprinted with permission conveyed through Copyright Clearance Center, Inc. Copyright © 2024 Oxford University Press

2.1.2.4 Risk Factors

The pathophysiological factors shown in **Figure 1** are also risk factors for elevated BP and hypertension. High sodium consumption is a significant risk factor in the development of hypertension and CVD (Filippini et al., 2021). Sodium contributes to elevated BP by impairing renal sodium excretion, leading to chronic activation of the RAAS and subsequent fluid retention (McEvoy et al., 2024). Obesity increases hypertension risk due to factors such as RAAS activation, insulin resistance, and inflammation (Deng et al., 2018; McEvoy et al., 2024). Chronic alcohol consumption raises BP incrementally with dosage (Roerecke et al., 2018). Both short sleep duration and poor sleep quality contribute to hypertension through neuroendocrine and pro-inflammatory pathway dysregulation (McEvoy et al., 2024).

Hypertension is one of the major CVD risk factors and a detailed approach to assess also other CVD risk factors is recommended in subjects with hypertension. CVD risk factors can be divided in four categories: high-risk conditions, traditional CVD risk factors, and non-traditional CVD risk modifiers further divided into sex-specific and shared risk modifiers (McEvoy et al., 2024). The CVD risk factors are summarized in **Table 4**. The risk evaluation is possible to refine by using additional risk assessment tools such as coronary artery calcium score, pulse wave velocity, high-sensitivity cardiac troponin, N-terminal pro-brain natriuretic peptide, and evaluation of carotid or femoral plaques if considered reasonable. Individuals with elevated BP (120–139/70–89 mmHg) should undergo a risk-based evaluation. For BP-lowering treatment decisions, individuals with elevated BP and a predicted 10-year CVD risk of 10% or higher according to SCORE-2 system (Hageman et al., 2021) are classified as sufficiently high-risk.(McEvoy et al., 2024)

Table 4. Summary of cardiovascular disease risk factors (McEvoy et al., 2024).

CATEGORY	RISK FACTORS
High-risk conditions	Chronic kidney disease, diabetes, familial hypercholesterolaemia, hypertension-mediated organ damage, established cardiovascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, heart failure)
Traditional risk factors	Age, sex, systolic blood pressure, cholesterol levels, and smoking evaluated by Systematic COronary Risk Evaluation 2 (SCORE2) (Hageman et al., 2021) or Systematic COronary Risk Evaluation 2–Older Persons (SCORE-OP) (de Vries et al., 2021)
Sex-specific non-traditional risk modifiers	Pregnancy-related conditions (gestational hypertension, pre-eclampsia, gestational diabetes, pre-term delivery, stillbirths, recurrent miscarriage), androgenic alopecia, erectile dysfunction
Shared non-traditional risk modifiers	High-risk ethnicity (South Asian populations), family history of premature atherosclerotic cardiovascular disease, socio-economic deprivation, autoimmune diseases (e.g. lupus, rheumatoid arthritis, severe psoriasis), severe mental illness (e.g. schizophrenia, bipolar disorder, major depressive disorder), human immunodeficiency virus infection

2.1.2.5 Symptoms and Signs

Hypertension is predominantly an asymptomatic condition (McEvoy et al., 2024). Hypertension-mediated organ damage (HMOD) or CVD may cause symptoms such as syncope, impaired vision, sensory or motor deficit, chest pain, shortness of breath, oedema, palpitations, arrhythmias, polyuria, nocturia, cold extremities, intermittent claudication or leg ulcers (McEvoy et al., 2024). Symptoms that may suggest secondary hypertension include episodes of muscle weakness and tetany, witnessed apnoea, heavy snoring, pulsatile tinnitus, and repetitive episodes of sweating, pallor, headache, anxiety or palpitations (McEvoy et al., 2024).

2.1.2.6 Diagnosis

It is recommended that all adult patients have their office and/or out-of-office BP measured opportunistically, recorded in their medical file, and informed of their current BP (McEvoy et al., 2024). The office blood pressure measurement (OBPM) protocol is described in **Table 5**. The summary of home BP measurement (HBPM) and ambulatory BP measurement (ABPM) is shown in **Table 6** and **Table 7**, respectively.

ESC 2024 guidelines represent a protocol for confirming hypertension diagnosis according to the OBPM categories shown in **Table 2**. Non-elevated BP should be screened opportunistically at least every 3 years (age <40) or yearly (age ≥40). Elevated BP should be confirmed preferably with HBPM or ABPM if CVD risk warrant BP-lowering therapy, or else opportunistically screened at least yearly. Hypertension in OBPM should be confirmed preferably with HBPM or ABPM. In the case of OBPM ≥160/100mmHg the confirming measurements should be performed promptly, and OBPM ≥180/110mmHg necessitates evaluation for hypertensive emergency.(McEvoy et al., 2024)

The clinical evaluation aims to diagnose hypertension, identify potentially contributing factors (**Figure 1**) and CVD risk factors (**Table 4**), assess comorbidities, screen for secondary hypertension when needed, and detect any signs of organ damage or existing heart, brain, or kidney disease (symptoms and signs in section 2.1.2.5).(McEvoy et al., 2024)

Table 5. A standardized method for office blood pressure measurement according to European Society of Cardiology guidelines (McEvoy et al., 2024).

	OFFICE BLOOD PRESSURE MEASUREMENT
1	Measure after 5 minutes of sitting comfortably in a quiet environment.
2	Use a validated device with a properly sized cuff, adjusted according to arm circumference.
3	Position the BP cuff at heart level, ensuring the patient's back and arm are properly supported.
4	Measure blood pressure three times, 1–2 minutes apart, and average the last two readings.
5	Take additional measurements if the readings vary by more than 10 mmHg.
6	Measure blood pressure in both arms during the first visit to identify any differences between them.
7	Record heart rate and check for arrhythmia through pulse palpation.
8	Evaluate for orthostatic hypotension during the first visit and monitor symptoms thereafter.

Table 6. Summary of home blood pressure measurement according to European Society of Cardiology guidelines (McEvoy et al., 2024).

	HOME BLOOD PRESSURE MEASUREMENT
1	Use a validated blood pressure device.
2	Measure blood pressure in a quiet room after 5 minutes of rest, ensuring the arm and back are supported.
3	Take two readings on each occasion, 1–2 minutes apart.
4	Take readings twice daily (morning and evening) for at least 3 days, ideally 7 days.
5	Record all readings, calculate the average, and present the results to the clinician.

Table 7. Summary of ambulatory blood pressure monitoring according to European Society of Cardiology guidelines (McEvoy et al., 2024).

	AMBULATORY BLOOD PRESSURE MONITORING
1	Use a validated blood pressure device.
2	The device typically measures blood pressure every 15–30 minutes during the day and every 30–60 minutes at night.
3	At least 70% of blood pressure recordings must be valid and usable.
4	The patient should maintain a diary documenting their activities, medication intake, and sleep times.

2.1.2.7 Prognosis

A study analysed linked electronic health records from 225 primary care practices covering 1.25 million UK subjects aged 30 and above, who were initially free of CVD, to examine how BP relates to 12 different CVD outcomes during a median follow-up of 5.2 years. Across all age groups, the lowest CVD risk was observed in individuals with a SBP of 90–114 mmHg and a DBP of 60–74 mmHg. There was no indication that lower BP levels would increase the CVD risk. Hypertension led to a loss of 5.0 CVD-free years by age 30, 3.4 years by age 60, and 1.6 years by age 80.(Rapsomaniki et al., 2014)

An individual participant meta-analysis of 61 prospective observational studies involving one million adults was conducted to determine the age-specific relationship between BP and vascular mortality. The study found that BP was strongly and directly related to CVD and overall mortality with no clear threshold down to at least 115/75 mmHg. A 20 mmHg reduction in SBP or a 10 mmHg reduction in DBP above BP level 115/75 mmHg was associated with reduced risk of stroke mortality [hazard ratio (HR) 0.30 (95% CI 0.23-0.40)], coronary artery disease (CAD) mortality [HR 0.42 (95% CI 0.38-0.47)], and other CVD mortality [HR 0.35 (95% CI 0.30-0.42)] in the age group of 40-49 years. The prognosis of hypertension significantly improved with BP reduction, and the benefits extend across all age groups.(Lewington et al., 2002)

For every 10 mmHg increase in SBP, the risk of CVD increased by 49%, CAD by 50%, and stroke by 44%, respectively (Malik et al., 2021). For every 5 mmHg increase in DBP, the risk of CVD increased by 35%, CAD by 36%, and stroke by 39%, respectively (Malik et al., 2021). The prognosis of hypertension is influenced by the presence of HMOD which is associated with a 2-3 times higher risk of CVD events at any BP category above normal (Vasan et al., 2022).

2.1.3 Lower-extremity Peripheral Arterial Disease

2.1.3.1 Definition

LEAD is defined as a stenosis or occlusion of the arteries that supply blood to the lower limbs (Aboyans et al., 2018; Golledge, 2022). Alternative terms peripheral artery disease, peripheral vascular disease, and lower-extremity peripheral arterial disease (Mazzolai et al., 2024) are also used. LEAD is a subtype of peripheral arterial diseases which encompass all arterial diseases other than coronary arteries and the aorta (Aboyans et al., 2018).

2.1.3.2 Epidemiology

In a systematic review of 118 articles and 33 countries concluded that the global prevalence of LEAD in people aged 25 years and older was 5.6% (95% CI 3.8–8.6) in 2015. The prevalence of LEAD was 8.0% (95% CI 5.1–13.4%) in the European Region and 8.0% (95% CI 4.8–14.4) in Finland.(Song et al., 2019) In a recent meta-analysis (Adou et al., 2024) including all population-based studies on LEAD epidemiology from 2000 to 2021 the prevalence of LEAD was globally 9.7% (95% CI: 7.1–12.4). The prevalence was higher in women than in men (10.2%, 95% CI: 7.0–13.5 vs. 8.8%, 95% CI: 6.3–11.3).

2.1.3.3 Pathophysiology

The main cause of LEAD is atherosclerosis. Atherosclerosis is a chronic intimal artery disease, which has several progressive stages involving accumulation of lipids, inflammatory cells, smooth muscle cells, necrosis, fibrosis, calcification and thrombosis in the wall of the artery (Golledge, 2022; Ross, 1993). Rare causes of LEAD include popliteal entrapment syndrome, cystic adventitial disease, arteritis and artery endofibrosis (Golledge, 2022).

2.1.3.4 Risk Factors

Cigarette smoking and DM are the most prominent modifiable risk factors for LEAD (American Diabetes Association, 2003; Ding et al., 2019). DM is associated with 2–3-fold and cigarette smoking with 2-fold increased risk of LEAD (Criqui et al., 2021).

Song et al. pooled ORs of 30 risk factors for LEAD in a meta-analysis using at least three individual studies that reported ORs based on a multivariable analysis (Song et al., 2019). Smoking was globally the most prominent risk factor (OR 2.8, 95% CI 2.0–3.4). Increasing age (OR 1.6 per 10-years increase, 95% CI 1.4–1.8), hypertension (OR 1.7, 95% CI 1.5–1.9), DM (OR 1.9, 95% CI 1.7–2.1), dyslipidaemia (OR 1.5, 95% CI 1.0–2.2), CVD (OR 2.3, 95% CI 1.9–2.8), stroke (OR 2.4, 95% CI 1.7–3.2), obesity (OR 1.6, 95% CI 1.2–2.0), chronic kidney disease in high-income countries (OR 1.8, 95% CI 1.0–3.1) and high circulating levels of the inflammatory marker high-sensitivity C-reactive protein >3.0 mg/l (OR 2.2, 95% CI 1.5–3.1) were also important risk factors.(Song et al., 2019)

According to Adou et al., the most prominent risk factor for LEAD is CVD, including CAD (OR 3.4, 95% CI 2.5-4.6) and stroke (OR 3.8, 95% CI 2.5-5.8). DM (OR 2.3 95% CI 2.0–2.8) and smoking (OR 1.9 95% CI 1.4–2.5) are important risk factors. Hypertension (OR 2.3, 95% CI 1.9–2.8), and hypercholesterolaemia (total cholesterol ≥5.2 mmol/l) (OR 1.9, 95% CI 1.3–2.8), chronic kidney disease (OR 2.0, 95% CI 1.3–3.2) and obesity (OR 1.5, 95% CI 1.2–1.8) show strong associations with LEAD. (Adou et al., 2024)

Table 8 summarizes the risk factors for LEAD identified in various meta-analyses along with their ORs. The ORs and confidence intervals for risk factors vary slightly between the meta-analyses, but all highlight the strong association of smoking, DM, and hypertension with LEAD. All meta-analyses report that aging is one of the most important risk factors for LEAD. The OR increases substantially with advancing age even though specific values are not provided by Adou et al. Obesity is a risk factor but has a more modest effect compared to other risk factors.

Table 8. Comparison of risk factors of lower extremity artery disease across different meta-analyses

RISK FACTOR	COMPARISON OF GLOBAL ESTIMATES OF PREVALENCE AND RISK FACTORS FOR PERIPHERAL ARTERY DISEASE IN 2000 AND 2010: A SYSTEMATIC REVIEW AND ANALYSIS (Fowkes et al., 2013)	GLOBAL, REGIONAL, AND NATIONAL PREVALENCE AND RISK FACTORS FOR PERIPHERAL ARTERY DISEASE IN 2015: AN UPDATED SYSTEMATIC REVIEW AND ANALYSIS (Song et al., 2019)	GLOBAL EPIDEMIOLOGY OF LOWER EXTREMITY ARTERY DISEASE IN THE 21ST CENTURY (2000–21): A SYSTEMATIC REVIEW AND META-ANALYSIS (Adou et al., 2024)
SMOKING	HIC: OR = 2.7 (2.0–3.7, current), OR = 2.0 (1.7–2.4, former) LMIC: OR = 1.4 (1.2–1.7, current), OR = 1.5 (1.3–1.6, former)	HIC: OR = 3.4 (2.6–4.6, current), OR = 1.9 (1.6-2.3, former) LMIC: OR = 2.2 (1.6–3.0, current), OR = 1.4 (1.0–1.8, former)	OR = 1.9 (1.4–2.5, current), OR = 1.6 (1.3–1.9, former)
DIABETES	HIC: OR = 1.9 (1.5–2.4), LMIC: OR = 1.5 (1.3–1.7)	HIC: OR = 2.0 (1.8–2.2), LMIC: OR = 1.8 (1.5–2.2)	OR = 2.3 (2.0–2.8)
HYPERTENSION	HIC: OR = 1.6 (1.4–1.7), LMIC: OR = 1.4 (1.2–1.5)	HIC: OR = 1.6 (1.5–1.7), LMIC: OR = 1.8 (1.4–2.2)	OR = 2.3 (1.9–2.8)
HYPERCHOLESTEROLAEMIA	HIC: OR = 1.2 (1.1–1.3), LMIC: OR = 1.1 (1.0–1.3)	HIC: OR = 1.4 (1.2–1.7), LMIC: OR = 1.2 (0.9–1.6)	OR = 1.9 (1.3–2.8)
CHRONIC KIDNEY DISEASE	Not specifically mentioned	HIC: OR = 1.8 (1.0–3.1)	OR = 2.0 (1.3–3.2)
CORONARY ARTERY DISEASE	Not specifically mentioned[1]	HIC: OR = 2.2 (1.7–2.9), LMIC: OR = 1.6 (1.3–1.9)	OR = 3.4 (2.5–4.6)
CEREBROVASCULAR DISEASE	Not specifically mentioned[1]	HIC: OR = 2.8 (1.5–5.2), LMIC: OR = 2.2 (1.6–3.1)	OR = 3.8 (2.5–5.8)
OBESITY	HIC: OR = 1.0 (0.8–1.1), LMIC: 0.7 (0.6–0.8) [2]	HIC: OR = 1.1 (0.6–1.8), LMIC: OR = 1.8 (1.4–2.2) [3]	OR = 1.5 (1.2–1.8) [3]
AGE (PER 10-YEAR INCREASE)	HIC: OR = 1.8 (1.6–1.9), LMIC: OR = 1.3 (1.2–1.3)	HIC: OR = 1.7 (1.4–2.0), LMIC: OR = 1.3 (1.2–1.4)	OR not reported

[1] History of other cardiovascular disease such as coronary artery disease or stroke HIC: OR = 2.6 (1.8–3.7), LMIC: OR = 1.8 (1.4–2.2)

[2] BMI >25 kg/m^2
[3] BMI ≥30 km/m^2
95% confidence intervals in parentheses
abbreviations: HIC, high-income countries; LMIC, low-income and middle-income countries; OR, odds ratio

2.1.3.5 Symptoms and Signs

Most people with LEAD are asymptomatic (Aboyans et al., 2018). Clinical stages of LEAD are classified according to Fontaine or Rutherford from asymptomatic to worsening claudication, ischemic rest pain, ulceration, tissue loss, and gangrene (Aboyans et al., 2018). Ischemic intermittent claudication is a classical symptom of LEAD (Aboyans et al., 2018). However, in community cohort studies, people with LEAD report this less often (6–9%) than exertional leg pain atypical for claudication (46–48%) (Khan et al., 2006).

2.1.3.6 Diagnosis

Personal and family clinical history is the first step in LEADs management. Lifestyle habits, dietary patterns, walking performance and physical ability need to be assessed and CVD risk factors and comorbidities evaluated (Aboyans et al., 2018). Risk factors for LEAD are listed in chapter 2.1.3.4. and symptoms and signs in chapter 2.1.3.5.

ABI is usually the first diagnostic test after clinical examination and pedal pulse palpation to diagnose LEAD (Aboyans et al., 2018). A randomized clinical trial involving all men aged 65–74 in Denmark's mid-Jutland Region, who were invited to vascular screening (n = 18,681) or assigned to an unscreened control group, reported that pedal pulse palpation had a sensitivity of 71.7% and a specificity of 72.3% for detecting LEAD when the test was considered positive if one or more pulses were absent. (Londero et al., 2016). Clinical examination findings should be interpreted in context with pre-test probability, as they are not independently sufficient to definitively confirm or exclude a diagnosis of LEAD (Khan et al., 2006). Measurement of ABI is a practical, reliable, and noninvasive tool to use in a primary health care setting (Stoffers et al., 1996). The optimal cutoff value of ABI to diagnose LEAD depends on the Bayesian pretest probability of LEAD based on medical history, symptoms and physical examination (Aboyans et al., 2012). An ABI ≤0.90 has 75% sensitivity and 86% specificity to diagnose LEAD (Xu et al., 2013). People with borderline ABI (0.90–1.00), and people with a normal ABI (1.00–1.40) and clinical suspicion of LEAD need further diagnostic tests (Aboyans et al., 2018). Sensitivity of ABI measurement is lower in patients with DM or end-stage chronic kidney disease due to medial calcification (Aboyans et al., 2018). In case of incompressible ankle arteries or ABI >1.40, alternative methods are indicated (Aboyans et al., 2018).

The American Heart Association published a guidance and a standardized method to measure ABI (Aboyans et al., 2012). This protocol is in line with the European Society of Cardiology (ESC) guidelines which is summarized in **Figure 2** (Aboyans et al., 2018). The subject should rest in the supine position for 5–10 minutes in a room with temperature between 19–22°C before and stay still during ABI measurement. Smoking should be avoided 2 hours before the ABI measurement. SBP should be measured using an 8- to 10-Mhz Doppler device from both arms and legs. The cuff size should be proper and the width at least 40% of the limb circumference. The ankle cuff should be placed 2 cm above the malleoli. The cuff should be gradually inflated to 20 mmHg above the point where the flow signal disappears and then slowly deflated to identify the pressure level at which the flow signal reappears. Limb pressures should be measured in a sequence of first arm, first posterior tibial artery, first dorsalis pedis artery, other posterior tibial artery, other dorsalis pedis artery and other arm. If the SBP of the first arm subtracted by the SBP of the other arm exceeds or equals 10 mmHg, the BP measurement of the first arm should be repeated.

ABI should be calculated in both legs separately by dividing the higher of the posterior tibial artery or dorsal pedis artery SBP by the higher of the right or left arm SBP (Aboyans, et al., 2012). If ABI is used to diagnose LEAD, the ABI should be reported separately for each leg. If the ABI is used as a prognostic marker for CVD event and mortality, the lower of the ABIs of the right and left leg should be used (Aboyans et al., 2012). Espinola-Klein et al. concluded that using the lower of the two ankle pressures of each leg to calculate ABI enables to find more patients at CVD risk (Espinola-Klein et al., 2008).

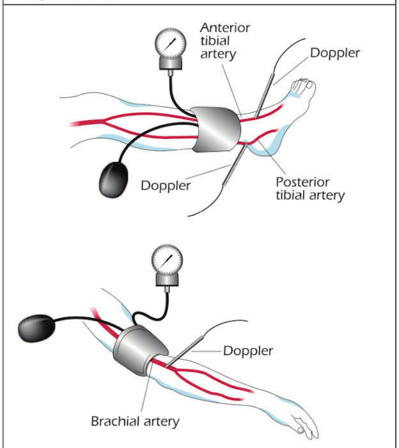
Table 3 The Ankle-Brachial Index

1. Who should have an ABI measurement in clinical practice?

- **Patients with clinical suspicion for LEAD:**
  - Lower extremities pulse abolition and/or arterial bruit
  - Typical intermittent claudication or symptoms suggestive for LEAD
  - Non-healing lower extremity wound
- **Patients at risk for LEAD because of the following clinical conditions:**
  - Atherosclerotic diseases: CAD, any PADs
  - Other conditions: AAA, CKD, heart failure
- **Asymptomatic individuals clinically-free but at-risk for LEAD:**
  - Men and women aged >65 years
  - Men and women aged <65 years classified at high CV risk according the ESC Guidelines[a]
  - Men and women aged >50 years with family history for LEAD

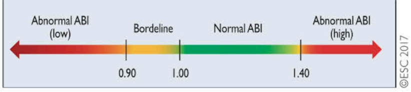
2. How to measure the ABI?

In supine position, with cuff placed just above the ankle, avoiding wounded zones. After a 5–10 minute rest, the SBP is measured by a Doppler probe (5–10 MHz) on the posterior and the anterior tibial (or dorsal pedis) arteries of each foot and on the brachial artery of each arm. Automated BP cuffs are mostly not valid for ankle pressure and may display overestimated results in case of low ankle pressure. The ABI of each leg is calculated by dividing the highest ankle SBP by the highest arm SBP.



3. How to interpret the ABI?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg).
- For the CV risk stratification: take the lowest ABI between the two legs.
- Interpretation:



AAA = abdominal aorta aneurysm; ABI = ankle-brachial index; BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; ESC = European Society of Cardiology; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; SBP = systolic blood pressure. [a]Subjects with: markedly elevated single risk factors; diabetes mellitus (except for young people with type 1 diabetes without other major risk factors); a calculated SCORE ≥5% and <10%.

Figure 2. The Ankle-Brachial Index according to ESC Guidelines reprinted from (Aboyans et al., 2018) with permission conveyed through Copyright Clearance Center, Inc. Copyright © 2018 Oxford University Press

2.1.3.7 Prognosis

People with LEAD, whether symptomatic or asymptomatic, have higher risk of mortality and CVD events such as myocardial infarction (MI) and stroke, even after accounting for conventional risk factors. An ABI ≤0.90 is associated with more than double the 10-year risk of coronary events, CVD mortality, and total mortality. Additionally, 20% of patients with intermittent claudication experience MI or stroke within 5 years, and mortality rates range between 10–15%. This emphasizes the need for comprehensive CVD prevention beyond site-specific disease management. (Aboyans et al., 2018)

2.2 Anthropometric Measurements

2.2.1 Adult Height

2.2.1.1 Overview

Adult height is an obvious and easily measurable anthropometric variable. Estimates of adult height in different populations are available from several thousand years ago (Hermanussen, 2003). However, adult height trends of men have been studied systematically for up to 250 years in Europe, in the United States, and in Japan using data mainly from conscripts, while historical data for women are more limited (NCD Risk Factor Collaboration (NCD-RisC), 2016). Over the last century, global trends in adult height have shown significant increases in many regions such as the Nordic countries, other European countries, North America, and Asia but despite substantial gains the height difference between the tallest and shortest populations has remained around 20 cm (Batty et al., 2009; NCD Risk Factor Collaboration (NCD-RisC), 2016; Silventoinen et al., 2000; Stefan et al., 2016).

In the late 19th century, the first observations were made about the inheritance of height from parents to children. Francis Galton demonstrated that the average of the two parents' height predicted the heights of their children with a tendency to regression to the population mean representing the influence by contributions from ancestors (Galton, 1886). Ronald Fisher established the theoretical foundation for understanding the genetic resemblance between relatives integrating Mendelian genetics with biometrical genetics (Fisher, 1919). At the beginning of the millennium, the human genome was sequenced (Lander et al., 2001). Adult height has been widely studied in genetic linkage analyses since then and its complex multifactorial and polygenic nature makes gene identification challenging (Perola et al., 2007). Adult height is among the most genetically inheritable human traits

(Aulchenko et al., 2009). Genome-wide association studies have identified hundreds of common genetic variants influencing adult height (Visscher et al., 2006).

Both genetic and environmental factors affect adult height. In modern Western countries, 80% variation of adult height is due to genetic factors and 20% due to environmental factors (Batty et al., 2009; Perola et al., 2007; Silventoinen, 2003; Visscher et al., 2006). Adult height is a polygenic trait influenced by numerous genes, including sex chromosomes, with the Y chromosome contributing to taller stature (Silventoinen, 2003). Gene-environment interactions affect adult height, where genetic predispositions determine how individuals respond to environmental influences like nutrition and diseases (Silventoinen, 2003).

Several environmental factors affect adult height. These include childhood nutrition, with adequate protein and nutrient intake being important for normal growth (Liu et al., 1998). Chronic illnesses and infections, such as diarrheal diseases and parasitic infections, can impede growth by causing malnutrition or reducing nutrient absorption (Batty et al., 2009). Psychosocial stress during childhood, including family instability or stressful living conditions, can reduce growth velocity (Montgomery et al., 1997). Living conditions, such as poor housing and sanitation, increase the risk of illness, further limiting growth (Batty et al., 2009). Additionally, maternal health and prenatal factors, such as maternal nutrition and smoking, play a role in determining a child's growth potential (Batty et al., 2009; Liu et al., 1998). These factors interact with socioeconomic status, as wealthier environments typically provide better access to nutrition, healthcare, and clean-living conditions, which promote better growth outcomes (Batty et al., 2009).

Adult height has a bidirectional association with disease risks. A large individual participant meta-analysis including 1,085,949 participants (mean age of 55 years at baseline, 48% women) from 121 prospective cohort studies assessed risk of cause-specific deaths and vascular morbidity in association with adult height. After adjusting for age, sex, smoking, and year of birth, a 6.5 cm increase in height was associated with a 3% lower risk of all-cause mortality (HR 0.97, 95% CI 0.96–0.99), a 6% lower risk of vascular mortality (HR 0.94, 95% CI 0.93–0.96), a 4% higher risk of cancer mortality (HR 1.04, 95% CI 1.03–1.06), and an 8% lower risk of mortality from other causes (HR 0.92, 95% CI 0.90–0.94). Height was inversely associated with mortality from coronary disease, stroke, heart failure, stomach and oral cancers, chronic obstructive pulmonary disease, mental disorders, liver disease, and external causes, while positively associated with deaths from ruptured aortic aneurysm, pulmonary embolism, melanoma, and cancers of the pancreas, endocrine and nervous systems, ovary, breast, prostate, colorectum, blood, and lung. These associations remained consistent after further adjusting for factors like adiposity, BP, lipids, inflammation markers, DM, alcohol use, and socio-economic status. (The Emerging Risk Factors Collaboration, 2012)

2.2.1.2 Adult Height and Pre-diabetes and Type 2 Diabetes

A study of 346 adults reported a significant inverse association between height and 2hPG levels in an OGTT, independently of age and BMI, particularly in males (Brown et al., 1991). According to the authors, this was the first study reporting an inverse association between OGTT and height.

A study of 11,247 subjects reported the relationship between height and the response to the OGTT as part of the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study (Sicree et al., 2008). Women showed higher 2hPG, and lower fasting plasma glucose (FPG) compared to men. The authors concluded that these differences could be largely explained by height, as shorter individuals had higher 2hPG levels when a fixed glucose load was used in the OGTT. This suggests that smaller body size may contribute to higher 2hPG levels, indicating that the current fixed glucose load in an OGTT might not account adequately for body size variations. Adjustments for height eliminated the observed sex differences in 2hPG levels, raising questions about the appropriateness of fixed glucose load in an OGTT.

In our study population, an inverse relationship between height and 2hPG, independently of adiposity, was observed in subjects with BMI <35 kg/m^2. (Rehunen et al., 2017). Indeed, adult height is reported to be inversely associated with 2hPG in an OGTT also in other studies and populations (Færch et al., 2010; Janghorbani & Amini, 2008; Rathmann et al., 2008).

A systematic review and meta-analysis concluded that taller women had lower risk of developing T2D compared to shorter women (RR 0.83, 95% CI 0.73–0.95). However, the same inverse association was not statistically significant in men (RR 0.87, 95% CI 0.71–1.07).(Janghorbani et al., 2012)

Another systematic review and meta-analysis examined the association between adult height and T2D. Data from 16 observational studies were analysed. Nine of the studies included were the same as in the previously mentioned meta-analysis (Janghorbani et al., 2012) and seven were new. An inverse relationship between height and T2D risk was found with no significant sex difference.(Shrestha et al., 2019)

A case-cohort study investigated the relationship between adult height and risk of T2D (Wittenbecher et al., 2019). Taller individuals, particularly those with longer leg lengths, had a significantly lower risk of developing T2D [HR per 10 cm, men 0.59 (95% CI 0.47-0.75) and women 0.67 (95% CI 0.51-0.88)].

A retrospective cohort study investigated the association between adult height and incidence of DM by analysing data from 783,029 outpatients followed in 816 GP practices in Germany. The main result was that shorter adult height was associated with an increased risk of T2D, and for every 10 cm decrease in height, the risk of developing T2D increased by 15% in women and 10% in men, even after adjusting for age and BMI. A correlation between height and HbA1c levels or type

1 DM was not found. The authors concluded that tall individuals have a lower risk of T2D than short individuals.(Loosen et al., 2023)

2.2.1.3 Adult Height and Hypertension

Relatively little is known about the relationship between adult height and hypertension, and the literature contains only a few studies addressing this topic. A recent systematic review of adult height in association with BP indicates the existence of an inverse relationship between adult height and BP (Cochran et al., 2021). In the Helsinki Birth Cohort Study, shorter individuals had higher BP than taller individuals in office BP measurements and 24-h ambulatory BP measurements (ABPM), even after adjusting for factors like age, physical activity, body fat percentage, and smoking (Korhonen et al., 2017).

2.2.1.4 Adult Height and Lower-extremity Peripheral Arterial Disease

Kapoor et al. found that females had a lower ABI (mean 1.09) compared to males (mean 1.13). The 3,052 participants were selected from 15 geographic locations in the United States to represent the general population. Shorter height was associated with a lower ABI value (OR 0.91 per 4 cm, 95% CI 0.86–0.96). The study suggests that the difference in ABI between sexes is partly due to height, as ABI values are correlated with body height. Even after adjusting for traditional CVD risk factors such as age, DM, and smoking, female sex remained correlated to a lower ABI, with females having ABI values about 0.03 lower than males. The authors concluded that lower ABI values in healthy females appear to be a normal occurrence rather than a result of undetected LEAD, with height contributing to this difference.(Kapoor et al., 2018)

In our CVD risk population, a positive linear relationship has previously been observed between height and ABI values in men, but not in women. Additionally, shorter stature in men showed an association with the prevalence of subclinical LEAD.(Heikkilä et al., 2016)

Fu et al. reported the relationship between height and the risk of LEAD among 4,528 Chinese patients with T2D. The authors concluded that shorter stature was associated with a higher risk of LEAD. Study subjects in the shortest height quartile had a 1.174 times higher risk among men and 1.143 times higher risk among women compared to those in the tallest quartile. These findings remained significant after adjusting for various confounding factors such as age, DM duration, hypertension, smoking, and other metabolic conditions. The study suggests that shorter individuals might have higher risk of LEAD independently of other known risk factors.(Fu et al., 2015)

2.2.2 Body Mass Index

2.2.2.1 Overview

Obesity is defined as an excessive deposition of fat within adipose tissue leading to possible deterioration of health (World Health Organization, 2000). BMI is considered the most practical, though somewhat simplistic, measure of obesity at the population level (World Health Organization, 2000). The classification of BMI is showed in **Table 9**. In year 2021, BMI over 25 kg/m^2 has been estimated to cause globally 62 million DALYs and 3.6 million deaths (Brauer et al., 2024; X. Zhou et al., 2024). According to The Healthy Finland Survey 2023, among men, 27%, and among women, 30% had a BMI of ≥30 kg/m^2, meeting the WHO criteria for obesity corresponding to approximately 1.2 million adults in Finland (Lehtoranta et al., 2023). According to WHO, 16% of adults were classified as obese in 2022, corresponding to 890 million individuals (World Health Organization, 2024).

Over the decades, various approaches have been used to define obesity, either based on reference values derived from population distributions of height and weight or by developing index measures combining weight and height (Kuczmarski & Flegal, 2000). BMI is calculated by dividing weight in kilograms by square of height in meters (Keys et al., 1972). The use of the equation of BMI began with contributions of Adolphe Quetelet (1796–1874), a Belgian mathematician. In 1832, Quetelet introduced the "Quetelet Index", observing that body weight increases proportionally to the square of height in the growth of humans apart from than the spurts of growth after birth and during puberty (Eknoyan, 2008). The term BMI was introduced by Keys et al. in 1972. Keys et al. evaluated various indices for measuring relative weight and obesity, emphasizing their effectiveness in reflecting body fatness and minimizing dependency on height. The BMI was a superior metric compared to alternatives like the ponderal index (the cube root of the body weight divided by the body height) and simple weight-to-height ratios. Using data from 7,426 men across 12 cohorts, the authors demonstrated that BMI had stronger correlation with body fat and lower dependency on height, making it a reliable and universal measure of relative obesity. The authors concluded that BMI is the most practical and accurate tool for assessing relative weight and obesity across diverse populations and time periods.(Keys et al., 1972)

However, over the past decades, criticism has been raised regarding the use of BMI for assessing obesity emphasizing its limitations as an indirect indicator of body fat (Gallagher et al., 1996; Rothman, 2008). Even though BMI is a useful population-level measure of obesity it has limitations in distinguishing between fat and muscle, accounting for age, sex, ethnic differences, body proportions, and individual health risks (World Health Organization, 2000). Moreover, BMI fails to account for variations in muscle mass, bone density, and fat distribution, as well as changes in body composition with age, leading to misclassification of individuals (Rothman, 2008).

In healthcare, lifestyle counselling for weight loss is routinely initiated when BMI exceeds 25.0 kg/m^2. However, a 2013 meta-analysis demonstrated that overweight (BMI 25.0–29.9 kg/m^2) was associated with reduced mortality risk, and class I obesity (BMI 30.0–34.9 kg/m^2) was not associated with a significantly increased mortality risk compared to normal weight individuals (Flegal et al., 2013). Although obesity is a well-established risk factor for morbidity and mortality, the obesity paradox has been observed in middle-aged, elderly, and chronically ill individuals, where overweight and mild obesity appear to be associated with lower mortality risk compared to normal weight (Flegal et al., 2013; Hainer & Aldhoon-Hainerová, 2013). The findings have prompted discussion on whether weight loss recommendations are warranted for individuals with a BMI of 25–30 kg/m^2.

A study, using data from the PARADIGM-HF trial, challenges the obesity paradox in heart failure with reduced ejection fraction (HFrEF) by comparing BMI with newer indices like WHtR (Butt et al., 2023). The authors reported that adjusting for prognostic factors like natriuretic peptides eliminates the obesity paradox observed with BMI. Alternative measures, better reflecting adiposity, consistently show that greater adiposity increases the risk of adverse outcomes, suggesting that the use of BMI has limitations in assessing the impact of obesity on HFrEF (Butt et al., 2023). Indeed, mortality risk in the relationship between general adiposity (measured by BMI) and abdominal adiposity (measured by WC and WHR) was assessed in a large European cohort of 359,387 participants from nine countries, followed for a mean of 9.7 years (Pischon et al., 2008). The lowest mortality risks were associated with a BMI of 25.3 kg/m^2 for men and 24.3 kg/m^2 for women, with both low and high BMI linked to increased mortality risks. Additionally, WC and WHR were strongly associated with higher mortality risk, independent of BMI, with particularly elevating risk of death in participants with a lower BMI. In conclusion, abdominal adiposity was an independent predictor of mortality and WC, or WHR can be used alongside BMI for a more comprehensive assessment of mortality risk.

Table 9. Classification of body mass index (NHLBI Obesity Education Initiative Task Force, 1998).

CLASSIFICATION	BODY MASS INDEX (KG/M²)
Underweight	<18.5
Normal range	18.5-24.9
Overweight	25.0-29.9
Obesity class I	30.0-34.9
Obesity class II	35.0-39.9
Obesity class III	≥40.0

2.2.2.2 Body Mass Index and Pre-diabetes and Type 2 Diabetes

A large body of evidence shows that higher BMI is associated with increased risk of glucose disorders. A systematic review and dose-response meta-analysis, involving 182 cohort studies with over 5.5 million participants, demonstrated a strong linear association between BMI and T2D risk. A 5-unit increase in BMI was associated with a 72% higher RR of developing T2D (RR 1.7, 95% CI 1.7–1.8). This association was consistent across ethnicities with no sex difference, with slightly stronger effects observed in European populations. A significant positive linear relationship was identified between BMI and the risk of developing T2D with no specific cut-off value.(Jayedi et al., 2022)

A collaborative analysis of 57 prospective studies examined the relationship between BMI and cause-specific mortality through an analysis of nearly 900,000 adults. Mortality was lowest at a BMI of 22.5–25 kg/m^2 and increased substantially with higher BMI. For every 5 kg/m^2 increase in BMI above 25 kg/m^2, the HR for DM mortality was 2.2 (95% CI 1.9–2.5), indicating a 116% higher risk of death from DM. This made DM one of the most strongly associated causes of mortality linked to elevated BMI in the study.(Prospective Studies Collaboration, 2009)

A systematic review and meta-analysis examined the association between BMI categories and the risks of pre-diabetes and T2D across 84 prospective cohort studies involving over 2.69 million participants from 20 countries. The study found that overweight (BMI 25–30 kg/m^2 for non-Asians or 23–25 kg/m^2 for Asians) and obesity (BMI ≥30 kg/m^2 for non-Asians or ≥25 kg/m^2 for Asians) significantly increased the risks of pre-diabetes and T2D, with RRs of 2.2 (95% CI 2.0–2.6) for overweight, 4.6 (95% CI 3.7–5.6) for obesity, and 23.0 (95% CI 13.6–38.9) for severe obesity (BMI ≥35 kg/m^2) compared to normal weight. Underweight individuals (BMI <18.5 kg/m^2) showed an unclear relationship with T2D, acting as a protective factor in non-Asians (RR 0.7, 95% CI 0.4–1.0) but with inconsistent results in Asians.(H.-J. Yu et al., 2022)

2.2.2.3 Body Mass Index and Hypertension

A prospective cohort study with 21,630 subjects investigated the relationship between BMI and physical activity with the risk of developing hypertension in Finland. Over an average follow-up period of 11 years, 1,600 new cases of drug-treated hypertension were recorded. The multivariate-adjusted HRs for hypertension across BMI categories (<25 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2) were 1.00, 1.18, and 1.66 for men (p for trend <0.001) and 1.00, 1.24, and 1.32 for women (p for trend <0.007), respectively.(Hu et al., 2004)

A prospective cohort study investigated the relationship between BMI and the risk of developing hypertension over the life course, using data from The Johns Hopkins Precursors Study. Over a 46-year median follow-up of 1,132 white men, obesity (BMI ≥30 kg/m^2) in young adulthood was associated with incident hypertension, with a HR of 4.2 (95% CI 2.3–7.4), and overweight (BMI 25–30 kg/m^2) with a HR of 1.6 (95% CI 1.3–2.0). Men who transitioned from normal weight to overweight or obesity by midlife had a HR of 1.6 (95% CI 1.2–2.1) of hypertension compared to those who maintained a normal weight, while weight loss from overweight or obesity to normal weight reduced the risk (HR 0.91, 95% CI 0.4–1.9). BMI changes, regardless of baseline BMI, were an independent predictor of hypertension risk. In conclusion, both higher weight and weight gain, even in later life stages, significantly increased hypertension risk. Thus, maintaining a healthy weight across the life course was recommended.(Shihab et al., 2012)

A systematic review and dose–response meta-analysis of 57 prospective cohort studies involving over 2.3 million participants examined the relationship between BMI, WC, WHR, WHtR, and the risk of developing hypertension. In conclusion, hypertension risk increased linearly with all anthropometric measures summarized in **Table 10.**(Jayedi et al., 2018)

In summary, the association between obesity and hypertension is well established, with increases in BMI leading to higher SBP and DBP (World Health Organization, 2000). Current ESC hypertension guidelines recommend maintaining a stable and healthy BMI (20–25 kg/m^2) to lower the risk for developing hypertension and CVD (McEvoy et al., 2024).

Table 10. Relative risk of hypertension according to increment in adiposity measures (Jayedi et al., 2018).

MEASURE	INCREMENT	RELATIVE RISK (RR)
Body Mass Index (BMI)	5-unit increase	1.5 (95% CI 1.4–1.6)
Waist Circumference (WC)	10-cm increase	1.3 (95% CI 1.2–1.4)
Waist-to-Hip Ratio (WHR)	0.1-unit increase	1.4 (95% CI 1.2–1.5)
Waist-to-Height Ratio (WHtR)	0.1-unit increase	1.7 (95% CI 1.4–2.1)

abbreviations: CI, confidence interval

2.2.2.4 Body Mass Index and Lower-extremity Peripheral Arterial Disease

The relationship between BMI and LEAD is not well-established and remains a subject of controversy (Heffron et al., 2020; Lempesis et al., 2023). Lempesis et al. explored the "obesity paradox" in LEAD, where higher BMI may protect against LEAD complications, despite being a CVD risk factor (Lempesis et al., 2023). Conflicting findings arouse due to factors such as body fat distribution, genetic and ethnic variations, frailty in underweight individuals, and methodological issues such as reliance on BMI and inadequate confounder adjustments (Lempesis et al., 2023).

A study investigated the relationship between BMI and LEAD in a large population of over 3 million self-referred individuals who paid out-of-pocket for vascular screening tests including ABI screenings. The overall prevalence of LEAD in the study was 4.1%. A J-shaped relationship between BMI and LEAD prevalence was observed and overweight individuals (BMI 25–29.9 kg/m^2) showed the lowest prevalence of LEAD. In women, LEAD risk increased significantly with obesity, whereas in men, the association was weaker and only prominent in severe obesity (BMI ≥40 kg/m^2).(Heffron et al., 2020)

A systematic review and meta-analysis examined the relationship between BMI and mortality among over 5.7 million people with LEAD. A U-shaped association was observed, where the lowest mortality risk was in the BMI category of 33–34 kg/m^2, highlighting the "obesity paradox", where higher BMI correlates with better long-term survival despite being a CVD risk factor.(Lin et al., 2022)

A Mendelian randomization analysis investigated a causal relationship between BMI and LEAD. Conducted on 11,477 adults in China, the study used a BMI-Genetic Risk Score derived from 14 genetic variants associated with BMI. The analysis demonstrated that higher BMI increased the risk of LEAD, with each 1 kg/m^2 increase in BMI associated with a 44% greater LEAD risk (OR 1.4 per BMI-unit, 95% CI: 1.2–1.8; $p < 0.0003$). The findings remained robust after adjusting for confounding factors, such as BP, plasma glucose and lipid levels, highlighting the causal role of obesity in LEAD. While the study provided evidence for this association, the association of genetic variants with BMI was validated in an East Asian population, which may limit generalisation to other populations .(Huang, Xu, et al., 2016)

A Mendelian randomization study investigated the associations of BMI with 14 CVDs, including LEAD, utilizing the UK Biobank database of 367,703 individuals. Per 1 kg/m increase in BMI, the OR for LEAD was 1.1 (95% CI 1.0–1.1).(Larsson et al., 2020)

A Mendelian randomization analysis investigated the relationship between BMI and LEAD using data from 6,707 subjects from the National Health and Nutrition Examination Survey (NHANES). Higher BMI was positively associated with an increased risk of LEAD, especially in females and individuals with obesity class 2 and 3 (BMI ≥35 kg/m^2).(Bai et al., 2025)

According to the latest European guidelines recommended treatment target for a patient with LEAD is BMI 20–25 kg/m^2 (Mazzolai et al., 2024).

2.2.3 Body Surface Area

2.2.3.1 Overview

Body surface area (BSA) is a measure of the total external surface area of the human body, commonly expressed in square meters (m^2). Efforts to estimate human surface area began in 1793 when John Abernethy used cut paper to measure the surface area of the head, hand, and foot, while other body parts were approximated using cylinder-like calculations (Abernethy, 1793; Gehan & George, 1970). Although techniques have significantly improved since then, there is still no simple and accurate method for directly determining BSA (Gehan & George, 1970). Indeed, BSA is cumbersome to measure and several formulas to estimate BSA according to weight and height has been published (Faisal et al., 2016). Early interest on BSA arose in the late 19th century from observations that an animal's metabolism appeared to be proportional to its BSA (Rubner, 1883). The initial research focus on BSA was in relation to understanding heat production and exploring the potential to predict metabolic rates based on body size measurements (Krovetz, 1965). **Figure 3** illustrates the relationship between height, BMI, and BSA.

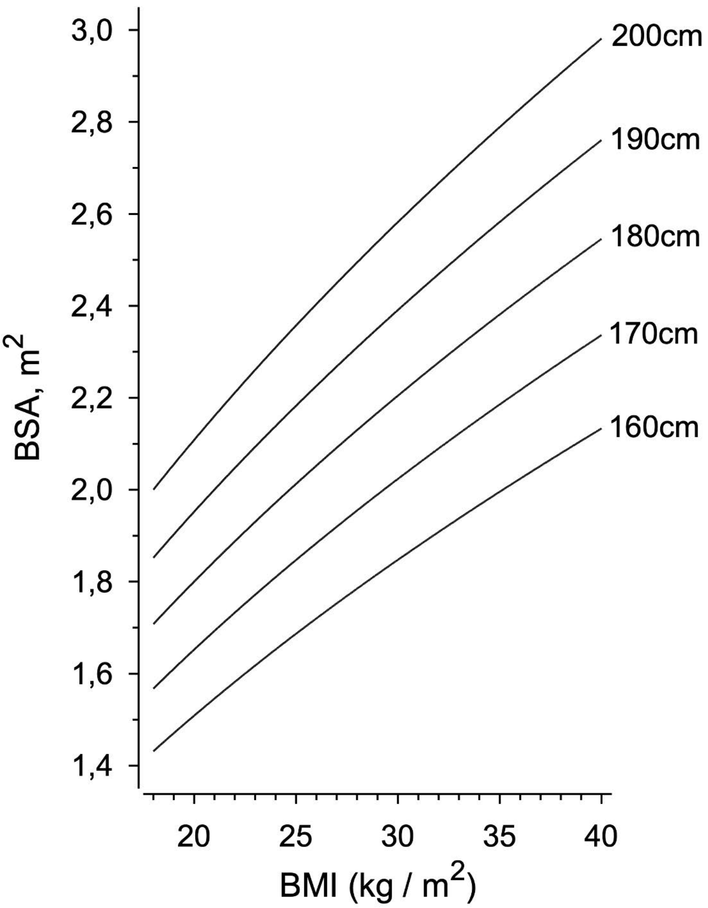


Figure 3. Association between height, body mass index (BMI), and body surface area (BSA). Reprinted from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

2.2.3.2 Body Surface Area in Clinical Practice

The indexing of physiological parameters, such as glomerular filtration rate (GFR), to BSA is undertaken with two principal objectives: enabling the direct comparability of these metrics independently of body size and establishing standardized reference values regarded as normal (Delanaye et al., 2005). BSA is commonly used in clinical practice for assessing physiological and metabolic parameters such as cardiac output and renal function (Heaf, 2007; Soldin et al., 2011). BSA is also a reliable predictor of liver volume (Vauthey et al., 2002).

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (Levey et al., 2009) standardize estimated GFR to a BSA of 1.73 m^2, based on the average BSA of 25-year-old Americans in the 1920s (McIntosh et al., 1928). However, since then, average body size has increased; for instance, the mean height of adult Finnish men was 177 cm and the mean weight 87 kg in 2017 (Koponen et al., 2018), corresponding a BSA of 2.07 m^2. Using a fixed BSA of 1.73 m^2 for larger individuals can underestimate their estimated GFR. To address this, the US National Institutes of Health (NIH) recommends adjusting estimated GFR by multiplying it by the individual's BSA and dividing by 1.73 m^2 for more accurate drug dosing (the US National Institutes of Health (NIH), 2024). Indeed, a study investigated the relationship between kidney volume, kidney function, body composition, and physical performance using MRI data from 38,526 participants in the UK Biobank (Cho et al., 2024). Higher BSA-adjusted kidney volume was associated with better kidney function (higher estimated GFR), increased muscle volume, better physical performance, and reduced CKD risk regardless of the GFR calculation method used (Cho et al., 2024). Moreover, in our study population, an above-normal estimated GFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was associated with all-cause mortality when indexed to 1.73 m^2 but not when adjusted for an individual's actual BSA (Korhonen et al., 2023).

BSA is used to determine chemotherapy drug doses in cancer treatment to individualize drug dosages based on a patient's body size (Faisal et al., 2016). BSA is recommended to use for drug dose calculations when there is a proven correlation between BSA and pharmacokinetic parameters, such as clearance, particularly for drugs with high serum protein binding or those confined to the blood compartment (Fabre et al., 2010). BSA calculations are commonly used in oncology for cytotoxic drugs with narrow therapeutic ranges to optimize efficacy and minimize toxicity, as well as in paediatrics where drug metabolism and distribution align with BSA (Fabre et al., 2010).

BSA is used to standardize reference ranges for cardiac and aortic measures, aiding in the differentiation between normal and pathological findings. Aortic valve area, and the cross-sectional areas of cardiac structures, such as left ventricle and pulmonary arteries have a linear correlation with BSA (Gutgesell & Rembold, 1990). Fung et al. investigated an optimal method for indexing echocardiographic measurements to body size, focusing on the accuracy of BSA compared to other metrics such as lean body mass, height, and weight raised to various powers (Fung et al., 2023). Using data from the National Echocardiography Database Australia, the authors evaluated the prognostic value of these indexed measures in predicting 5-year CVD mortality across different BMI categories. Indexing left ventricular mass, left atrial volume, right atrial area, aortic sinus diameter, and right ventricular diameter by BSA enhanced the prognostic value of these measurements (Fung et al., 2023). Zafrir et al. investigated the prognostic significance of BSA in chronic heart failure patients and reported an inverse relationship between BSA and all-cause and CVD mortality, establishing low BSA as a significant predictor of 1-year mortality (Zafrir et al., 2015). ESC 2024 guidelines for the management of peripheral arterial and aortic diseases recommend aortic diameter indexing to BSA, along with nomograms or z-scores, which provides a more accurate assessment, particularly for smaller body sizes (Mazzolai et al., 2024). The anatomy of aorta and upper limits of normal dimensions are shown in **Figure 4**.

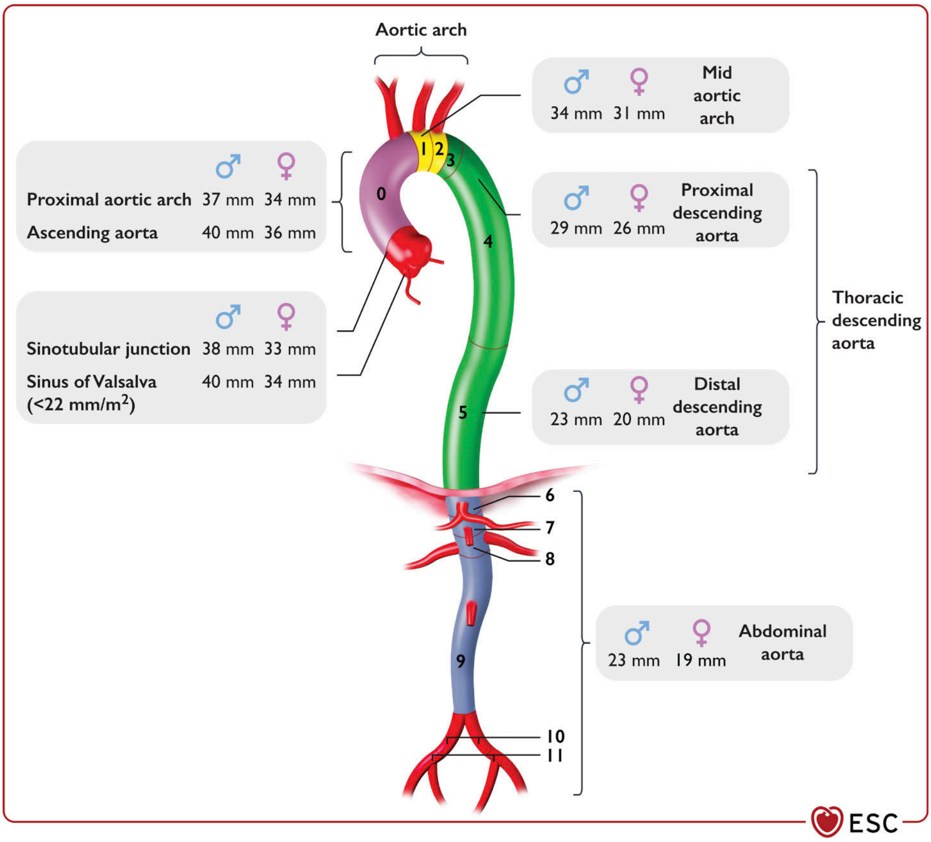


Figure 4. Anatomy and upper normal diameters of aorta according to ESC guidelines for the management of peripheral arterial and aortic diseases (Mazzolai et al., 2024). Reprinted with permission conveyed through Copyright Clearance Center, Inc. Copyright © 2024 Oxford University Press.

2.2.3.3 Body Surface Area Formulas

The efforts to formulate an accurate BSA formula began with the work of Karl Meeh, a German physiologist who conducted studies on animal thermoregulation in the late 19th century (Meeh, 1879). Meeh developed a mathematical formula to estimate BSA based on body weight. His work was grounded in the observation that BSA correlates more closely with metabolic processes than body mass alone (Meeh, 1879). Over the past century, several dozen new formulas and improvements to the original formula have been proposed. The following paragraphs present the key findings.

The Du Bois brothers estimated that Meeh's formula (Meeh, 1879), which was based solely on body weight, had error rates of up to 15–30%, especially for individuals with unusual body shapes. This prompted the Du Bois brothers to develop a formula that incorporates both height and weight (D. Du Bois & Du Bois, 1916). The article describes a linear method requiring 19 precise measurements across various body parts, but it is laborious and impractical for routine use and the error level does not differ compared with the height-weight formula (1.5-5%) (D. Du Bois & Du Bois, 1916).

Edith Boyd published a book titled *The Growth of the Surface Area of the Human Body* in 1935. The original publication is not available, but according to a book review by E. Du Bois, the book included comprehensive analysis of methods to measure and estimate BSA, based on data from 1114 subjects. According to the book review, Boyd evaluated 36 formulas, finding recent height-weight-based formulas reasonably accurate, and introduced improved equations incorporating weight and height.(E. Du Bois, 1936)

Gehan and George presented an updated model for calculating BSA using height and weight. The formula, based on the earlier work of DuBois and DuBois, is refined using a dataset of 401 directly measured cases, significantly larger than the original nine. The model explains over 99% of the variation in BSA and offers improved accuracy without requiring separate formulas for different age groups. The authors compare their results with the original DuBois and DuBois model and Boyd's formula, concluding that their model provides greater accuracy without requiring additional complexity.(Gehan & George, 1970)

Sendroy and Cecchini described a graphical method to estimate BSA by combining height and weight measurements with weight-to-height ratio to account for body shape. The dataset used in the study included 252 individuals at least partly gathered from previously published data from studies by Du Bois and Boyd. The study population or statistical methods were not clearly described.(Sendroy & Cecchini, 1954)

Heycock at al. introduced a new height-weight formula for estimating BSA based on data from 81 individuals, including infants, children, and adults. The formula was derived geometrically, treating the body as a combination of cylinders and spheres, and validated against previously established methods. The study concludes that while the Du Bois formula is acceptable for adults, it is unsuitable for infants and young children, and the new formula was recommended as a reliable alternative for clinical and physiological applications.(Haycock et al., 1978)

A study evaluated different BSA formulas for estimating the BSA of newborns by analysing BSA estimates in 589 full-term newborns using Boyd, Meban, Mosteller, and Du Bois formulas along with a computed mean of these four formulas. Authors concluded that the Meban formula (Meban, 1983) most closely approximated the mean of BSA formulas, making it suitable for newborns, followed closely by the Mosteller formula. The Boyd and Du Bois formulas demonstrated systematic overestimation and underestimation, respectively, making them less reliable for neonatal use.(Ahn & Garruto, 2008)

Mosteller introduced a simplified formula for calculating BSA derived from Gehan and George formula. According to Mosteller, the new formula was slightly less accurate (deviation <2%) than more complex methods but it has proven clinically effective and practical in routine calculations.(Mosteller, 1987)

Shutter and Aslani critically examined the Du Bois and Du Bois formula for estimating BSA, highlighting its reliance on data from only nine subjects, which is insufficient for general application. By re-analysing Du Bois brothers' data, including measurements from 42 individuals (ten subjects were encased in moulds and 32 had body linear measurements only), and applying modern statistical methods, the authors derived updated constants that improve the formula's accuracy. While the original formula remains adequate for adults, the study recommends using more robust and validated alternatives, such as Haycock's formula, particularly for paediatric applications.(Shuter & Aslani, 2000)

Yu et al. introduced a BSA estimation formula, derived from three-dimensional (3D) scans of 3951 subjects. According to the authors, the new formula demonstrated superior accuracy and reliability compared to widely used models at least in an adult Chinese population. The authors emphasized the advantages of 3D scanning in terms of speed, accuracy, and versatility.(C. Y. Yu et al., 2003)

Verbraecken et al evaluated accuracy and applicability of the Mosteller's formula in comparison with six other BSA formulas to identify the most accurate and practical BSA formula for clinical and research usage. The study involved 1868 adults categorized into normal-weight (BMI 20–24.9; 397 participants), overweight (BMI 25–29.9 kg/m^2; 714 participants), and obese (BMI ≥30; 757 participants) groups. Anthropometric measurements included height (139–200 cm, mean 172 ± 9 cm) and weight (44–196 kg, mean 88 ± 19 kg). BSA was calculated using nine formulas: Mosteller, Du Bois and Du Bois, Boyd, Gehan and George, EPA's BSA formula (US Environmental Protection Agency (EPA), 1985), Haycock, Mattar, Livingston and Scott, and Yu. Statistical comparisons of these formulas were made using Spearman correlations, Bland-Altman analyses, and root mean square error (RMSE). Additionally, the mean BSA across all formulas was calculated as a reference. The main result was that BSA values varied significantly between the formulas, with Mosteller's formula showing strong correlations (≥0.97) with other methods but producing slightly higher estimates in obese individuals compared to DuBois and DuBois formula, which underestimated BSA by up to 4.47% in women and 2.74% in men. The authors concluded that Mosteller's formula was accurate, simple, and suitable for clinical use in normal-weight, overweight, and obese individuals.(Verbraecken et al., 2006)

Redlarski et al. simulated computationally results of different BSA formulas. The aim of the study was to evaluate the accuracy and reliability of 25 BSA formulas by comparing computationally their results across a broad range of body weights and heights, with a focus on identifying discrepancies and their clinical implications. Using Python-based computational simulations, the authors calculated BSA values for each formula over a range of 0–200 kg for weight and 0–210 cm for height. These values were visualized through 3D plots and analysed to identify patterns of agreement or divergence. The study found significant variability among the 25 BSA formulas, even within standard adult physiques with anecdotal example cases.(Redlarski et al., 2016)

A study was conducted to improve the accuracy of BSA estimation methods by optimizing existing formulas and developing new models that account for a broader range of anthropometric parameters. The authors analysed BSA using data from 179 adult participants with diverse anthropometric profiles, including variations in age, sex, BMI, and WC. Participants underwent 3D body scanning which captured detailed body measurements. Additional anthropometric data, such as circumferences of the neck, chest, waist, hips, arms, and legs, as well as height, weight, and other anatomical features, were collected using traditional measuring tools. The data were processed using statistical and computational methods to optimize the coefficients of existing BSA formulas and to develop new models. The authors concluded that existing BSA formulas are limited in their accuracy, particularly for individuals with atypical body size, and more anthropometric parameters than weight and height should be used to calculate BSA for greater precision.(Redlarski et al., 2024)

Table 11. Body surface area (BSA) formulas

AUTHOR (YEAR)	FORMULA	REFERENCE
Meeh (1879)	$BSA = 0.1053 \cdot W^{2/3}$	(Meeh, 1879)
Du Bois and Du Bois (1916)	$BSA = 0.007184 \cdot \mathrm{H}^{0.725} \cdot \mathrm{W}^{0.425}$	(D. Du Bois & Du Bois, 1916)
Boyd (1935)*	$BSA = 0.0003207 \cdot (\mathrm{W} \cdot 1000)^{0.7285-0.0188\log_{10}(\mathrm{W}\cdot 1000)} \cdot \mathrm{H}^{0.3}$	(Redlarski et al., 2016) (E. Du Bois, 1936)
Sendroy & Cecchini (1954)	$BSA = 0.0097 \cdot (W + H) - 0.545$	(Sendroy & Cecchini, 1954)
Gehan and George (1970)	$BSA = 0.0235 \cdot \mathrm{H}^{0.42246} \cdot \mathrm{W}^{0.51456}$	(Gehan & George, 1970)
Haycock (1978)	$BSA = 0.024265 \cdot \mathrm{H}^{0.3964} \cdot \mathrm{W}^{0.5378}$	(Haycock et al., 1978)
Meban (1983)**	$\mathrm{BSA} = 6.4954 \cdot H^{0.320} \cdot (\mathrm{W} \cdot 1000)^{0.562}$	(Meban, 1983)
Mosteller (1987)	$\mathrm{BSA} = \sqrt{\frac{\mathrm{W} \cdot \mathrm{H}}{3600}}$	(Mosteller, 1987)
Shuter and Aslani (2000)	$BSA = 0.00949 \cdot \mathrm{H}^{0.655} \cdot \mathrm{W}^{0.441}$	(Shuter & Aslani, 2000)
Yu et al (2003)	$BSA = 0.015925 \cdot (\mathrm{H} \cdot \mathrm{W})^{0.5}$	(C. Y. Yu et al., 2003)

abbreviations: H, height (cm); W, weight (kg)
* Original full text publication was not accessible
** Meban BSA formula results BSA at birth in cm^2

2.2.3.4 Body Surface Area and Pre-diabetes and Type 2 Diabetes

The Committee on Statistics of the American Diabetes Association (ADA) recommended standardization of the OGTT by recommending the glucose load of 40 grams per square meter of BSA in 1968.(Klimt et al., 1969) According to the committee, this approach ensures to challenge adequately the capacity to handle glucose, accounting for differences in body size and the mass utilizing glucose ensuring that the test accounted for physiological differences rather than applying a fixed dose.

In 1970 a study was conducted to analyse the effects of varying carbohydrate loads in OGTT. Blood glucose responses were evaluated according to different carbohydrate loads in OGTT for different body sizes. The larger glucose load (45 g/m^2) resulted in significantly higher two-hour and three-hour blood glucose levels compared to the smaller load (30 g/m^2). (Chandalia & Boshell, 1970)

In Baltimore Longitudinal Study of Aging (BLSA), the glucose load used in the OGTT was 40 g/m^2 of BSA corresponding to an average glucose dose of 78 g in men and 68 g in women. The aim of the study was to evaluate the effect on abnormal

2hPG values to the prevalence of MetS. Including 2hPG in MetS criteria significantly increased the prevalence of MetS across all age groups and in both sexes, overall, from 24.7% to 32.6% in men (32% increase) and from 15.0% to 21.1% in women (41% increase), both statistically significant (p <0.001).(Rodriguez et al., 2005)

2.2.3.5 Body Surface Area and Hypertension

Evans et al. conducted a study aimed to investigate how body size parameters, including BSA, height, weight, and BMI, influence on BP regulation and its underlying CV components (stroke volume, cardiac output, and total peripheral resistance) in healthy young adults. The authors hypothesized that inter-individual variability in BP could be partially explained by these body size factors. The study population consist of 34 young adults (19 men, 15 women) who underwent BP, cardiac, and vascular resistance measurements while supine and during a standing test. Data collection included manual and continuous BP monitoring, Doppler ultrasound for stroke volume and cardiac output, and calculations of peripheral vascular resistance. According to the article SBP correlates positively with BSA both in supine and standing positions, while DBP shows a significant correlation with BSA only in the standing position. The relationship between BSA and BP was mediated by underlying CV components: stroke volume and cardiac output were positively correlated with BSA, whereas total peripheral vascular resistance was inversely correlated at rest but increases with BSA upon standing. In conclusion, BSA seemed to be a more reliable scaling factor for CV variables compared to BMI, suggesting its potential for more accurate assessments of BP variability and regulation.(Evans et al., 2017)

Field et al. investigated whether BP targets for secondary prevention of lacunar strokes should vary by body size, using data from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial of 3020 subjects. By analysing anthropometric metrics like BSA, BMI, height, and weight, the authors found no significant interactions between BP targets and body size for outcomes like recurrent strokes or death. The reduction in BP and recurrence risk was consistent across all body sizes, suggesting that current BP treatment thresholds are effective regardless of body size. In conclusion, body size-based modifications to BP targets were not recommended, though further research on this topic was encouraged. (Field et al., 2015)

2.2.3.6 Body Surface Area and Lower-extremity Peripheral Arterial Disease

According to a literature search on 7th December 2024 in PubMed, Embase and Web of Science little is known about BSA in relation to LEAD. When using search query “(BSA OR "Body surface area") AND (ABI OR "Ankle-brachial index" OR "Ankle brachial index" OR LEAD OR "Lower extremity artery disease" OR PAD OR "Peripheral Arterial Disease")” the only relevant article is our Study IV. Two relevant abstracts with no full text available were gathered. However, studies on BSA and dimensions of aorta and lower extremity arteries are summarized in the following paragraphs.

Biaggi et al. studied the correlation of BSA, sex, and age on the normal dimensions of the ascending aorta and sinus of Valsalva using transthoracic echocardiography. Data from 1799 individuals with normal cardiac findings were gathered. The authors concluded that BSA, sex, and age significantly correlated with dimensions of ascending aorta and sinus of Valsalva.(Biaggi et al., 2009)

Dietenbeck et al. performed 3D magnetic resonance imaging (MRI) to measure aortic morphology such as length, diameter, volume, curvature, and tortuosity in 119 healthy controls and 82 hypertensive subjects. The aim of the study was to provide normative age-related values for 3D aortic measurements and to analyse changes associated with aging and hypertension. Age, sex, and BSA were identified as the major determinants of aortic morphology. Hypertension influenced morphological parameters, such as curvature, higher diameters, length, and volumes in older individuals. Women had smaller aorta measured by length, diameter, and volume. After indexing for BSA, no significant differences in aortic volumes were observed between sexes.(Dietenbeck et al., 2021)

Jones et al. conducted a cohort study to analyse the prevalence of abdominal aortic aneurysm (AAA) in population at elevated CVD risk. According to the article, AAA has traditionally been diagnosed using a fixed threshold of 30 mm for aortic diameter, derived from male populations, which fails to account for differences in body size between sexes. Moreover, this approach has led to an underestimation of AAA prevalence in women, as their smaller average body size results in lower absolute aortic diameters even when the relative enlargement is significant. Authors described the Aortic Size Index (ASI) which is calculated as the maximum aortic diameter divided by BSA. The study revealed that the prevalence of AAA in women is nearly double when ASI-based criteria (≥ 1.5) are used, compared to the fixed 30 mm threshold. The findings suggest that the perceived male predominance in AAA prevalence is largely a result of size-related bias in diagnostic thresholds. The authors concluded that sex-specifics or BSA-adjusted thresholds should be used to ensure accurate detection of AAA for both men and women.(Jones et al., 2018)

Sandgren et al. examined the diameter of the common femoral artery (CFA) in 122 healthy subjects aged 8 to 81 years and analysed the influence of age, sex, and body metrics such as BSA, weight and height on CFA. The authors reported that CFA diameter increases steadily with age, with adult men generally exhibiting larger diameters than women. Furthermore, among body metrics, BSA demonstrated the strongest correlation with CFA diameter ($r = 0.60$ for males, $r = 0.62$ for females, $p < 0.0001$), enabling the development of predictive models and nomograms for normal CFA size to distinguish normal variations from pathological dilations. In conclusion, the authors emphasized the importance of age, sex, and BSA in predicting CFA diameter.(Sandgren et al., 1999)

Sandgren et al. measured the diameter of the popliteal artery in 121 healthy subjects aged 8 to 81 years and analysed its relationship to age, body size, and sex. The authors reported that the popliteal artery diameter increases with age, both during growth and adulthood, and that males generally have larger popliteal arteries than females. BSA and age were identified as the most important for these findings. The study provides nomograms to predict normal artery diameters, aiding in the evaluation of pathological dilations. The authors concluded that the diameter of the popliteal artery is related to age, sex, and BSA.(Sandgren et al., 1998)

2.2.4 Other Anthropometric Measurements

2.2.4.1 Waist Circumference

In the 1980s, accumulating evidence established a causality between abdominal obesity and increased risks of CVD and premature mortality. Moreover, the distribution of fat, particularly visceral adipose tissue, was more predictive of metabolic and CVD complications than overall obesity.(Krotkiewski et al., 1983; Pouliot et al., 1994) Abdominal fat mass can vary significantly even within a narrow range of total body fat or BMI (World Health Organization, 2000). Thus, additional methods beyond BMI measurement were considered important for identifying individuals at heightened risk of obesity-related illnesses caused by abdominal fat accumulation (World Health Organization, 2000).

A study assessed 81 men and 70 women using anthropometric measurements (WC and hip circumference, WHR), hydrostatic weighing, and computed tomography (CT) scans to measure abdominal fat distribution. Metabolic profiles were evaluated with an OGTT and cholesterol values. WC correlated strongly with visceral adiposity, which was associated to metabolic disturbances like insulin resistance and dyslipidaemia. In conclusion, WC values exceeding 100 cm in men and women were likely indicative of significant metabolic and CVD risks.(Pouliot et al., 1994)

A study conducted in Glasgow, showed that WC thresholds 94 cm for men and 80 cm for women could help identify individuals at risk and in need of weight management interventions and WC over 102 cm for men and 88 cm for women was associated significant health risks and weight loss should be urged. The authors emphasized WC as a practical alternative to BMI for public health programs, considering its simplicity and strong correlation with metabolic and CVD risks. In conclusion, incorporating WC measurements in health promotion strategies could enhance early detection and targeted interventions for obesity-related health risks.(Lean et al., 1995)

A pooled analysis study of 650,386 adults examined the relationship between WC and mortality across varying BMI categories with a median follow-up of 9 years (Cerhan et al., 2014). Larger WC was significantly associated with higher all-cause mortality, independently of BMI. Each 5 cm increase in WC raised mortality risk by 7% in men and by 9% in women, with the greatest risks seen at the extremes of BMI. Higher WC associated strongly with CVD and respiratory disease mortality. Estimated life expectancy reductions were approximately three years for men and five years for women with the highest WC category compared to the lowest. In conclusion, the assessment of WC alongside BMI was recommended for evaluation of obesity-related mortality risk even in the normal range of BMI.

Measuring WC is straightforward and practical. According to the International Diabetes Federation, central obesity is defined in Caucasian populations as WC ≥ 94 cm in men and ≥ 80 cm in women (The International Diabetes Federation, 2006). According to the US National Cholesterol Education Program: Adult Treatment Panel III WC ≥ 102 cm in men and ≥ 88 cm in women is considered as central obesity (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002). WHO has discussed the previously mentioned threshold values as possible levels of increased and substantially increased risk of metabolic complications, respectively (World Health Organization, 2000). In a consensus statement, International Atherosclerosis Society (IAS) and the International Chair on Cardiometabolic Risk (ICCR) have recently emphasized the importance of incorporating WC as a vital sign in clinical practice for better assessment and management of cardiometabolic risks associated with obesity (Ross et al., 2020). The consensus advocates for routine measurement of WC alongside BMI to classify obesity more accurately and identify high-risk phenotypes of obesity. Moreover, the consensus questions a single WC threshold for all BMI categories which is considered as inadequate for identifying individuals at higher health risk and proposes new WC thresholds according to BMI categories (Ross et al., 2020).

2.2.4.2 Waist-to-hip ratio

A case-control study examined the relationship between WHR and MI risk using data from the INTERHEART study, which included over 27,000 participants from 52 countries. WHR was a stronger predictor of MI risk than BMI. The OR of MI risk for every SD increase in a specific measure of obesity was 1.37 (95% CI 1.34–1.41) for WHR, and 1.10 (95% CI 1.07–1.13) for BMI after adjusting for age, sex, region, and smoking. Using WHR instead of BMI significantly increased the estimated proportion of MIs attributable to obesity, suggesting that abdominal fat distribution plays a more crucial role in MI risk than overall body weight.(Yusuf et al., 2005)

A 0.1-unit increase in WHR was associated with a 34% higher risk of death in men (OR 1.34, 95% CI, 1.28–1.39) and a 24% higher risk in women (OR 1.24, 95% CI, 1.20–1.29) in a study discussed in paragraph 4 in chapter 2.2.2.1 (Pischon et al., 2008). Relative risk (RR) of hypertension in association with WHR is shown in **Table 10**.

A collaborative analysis of 58 prospective studies involving 221,934 participants, analysed the associations between BMI, WC, and WHR with the risk of first-onset CVD. All three adiposity measures were associated to an increased risk of CVD, with WHR showing a slightly stronger association after adjusting for age, sex, and smoking. However, when further adjusted for conventional risk factors such as BP, DM history, and cholesterol levels, the predictive value of BMI, WC, and WHR was significantly reduced. The authors concluded that these adiposity measures, whether used alone or in combination, do not substantially improve CVD risk prediction when traditional risk factors are already accounted for.(Emerging Risk Factors Collaboration et al., 2011)

A meta-regression analysis of 15 prospective studies investigated the association between WC and WHR with the risk of CVD events. Analysing data from 258,114 participants and 4,355 CVD events, the study found that a 1 cm increase in WC increases the RR of a CVD event by 2% (95% CI 1–3%), while a 0.01 unit increase in WHR raises the risk by 5% (95% CI 4–7%). Although both measures are significantly associated with CVD risk, WHR appears to be a slightly stronger predictor than WC. The study suggests incorporating these simple anthropometric measures into CVD risk assessments, emphasizing their potential utility in identifying high-risk individuals.(De Koning et al., 2007)

2.2.4.3 Waist-to-height ratio

In a systematic review and dose-response meta-analysis of cohort studies encompassing 2.3 million individuals, WHtR was a strong predictor of T2D, with a 0.1-unit increase associated with a 73% higher risk (RR: 1.73, 95% CI: 1.51–1.98). This positive monotonic association persisted across subgroups, including men, women, and various regions such as the United States, Europe, and Asia. WHtR was found to outperform other measures such as BMI and WC in predicting T2D risk.(Jayedi et al., 2022)

In a systematic review and meta-analysis of over 300,000 individuals across diverse ethnicities, WHtR was a better screening tool for CVD risk factors compared to WC and BMI. WHtR consistently demonstrated higher accuracy in predicting T2D, hypertension, dyslipidaemia, MetS, and CVD outcomes. WHtR outperformed BMI and WC by 4–5% and 1–2% respectively in terms of discrimination power, supporting its efficacy in detecting risks associated with abdominal obesity. The study recommends a simple "keep your waist circumference to less than half your height" guideline as a practical public health tool.(Ashwell et al., 2012)

A study analysed data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort in Germany including 27,548 participants with 176,780 person-years of follow-up. The predictive power of different anthropometric measures in relation of T2D was assessed using Cox proportional hazards analysis and Receiver Operating Characteristic curves. WHtR emerged as an effective anthropometric indicator for predicting the risk of T2D. Particularly among men, WHtR demonstrated the highest predictive capability compared to other measures, including WC and BMI. In women, both WHtR and WC exhibited comparable predictive strength, surpassing BMI and WHR in their ability to assess T2D risk. While WC alone was a robust predictor, incorporating WHtR further enhanced the predictive accuracy for T2D risk.(Schulze et al., 2006)

3 Aims

This thesis aimed to investigate BSA in association with BP, OGTT and ABI to gain knowledge about the significance of body size in clinical practice. The specific aims were:

1. To assess the relationship between BSA and sex differences in ambulatory BP levels.
2. To assess the relationship between BSA and 2hPG in an OGTT.
3. To assess the relationship between BSA and sex differences in an OGTT.
4. To assess the relationship between BSA and ABI.

4 Materials and Methods

4.1 Study Population

4.1.1 Study I

The Helsinki Birth Cohort Study includes 8,760 men and women born at Helsinki University Central Hospital between 1934 and 1944. For the clinical study, a subset of individuals from the original epidemiological cohort was selected using random-number tables, including only those who were still alive and residing in Finland in 1971. A subset of 2,691 individuals were invited to participate, and 2,003 attended clinic visits between 2001 and 2004. The study population includes 534 individuals who had no history of using medication that affects the CV system. The selection of the study population is shown in **Figure 5**.

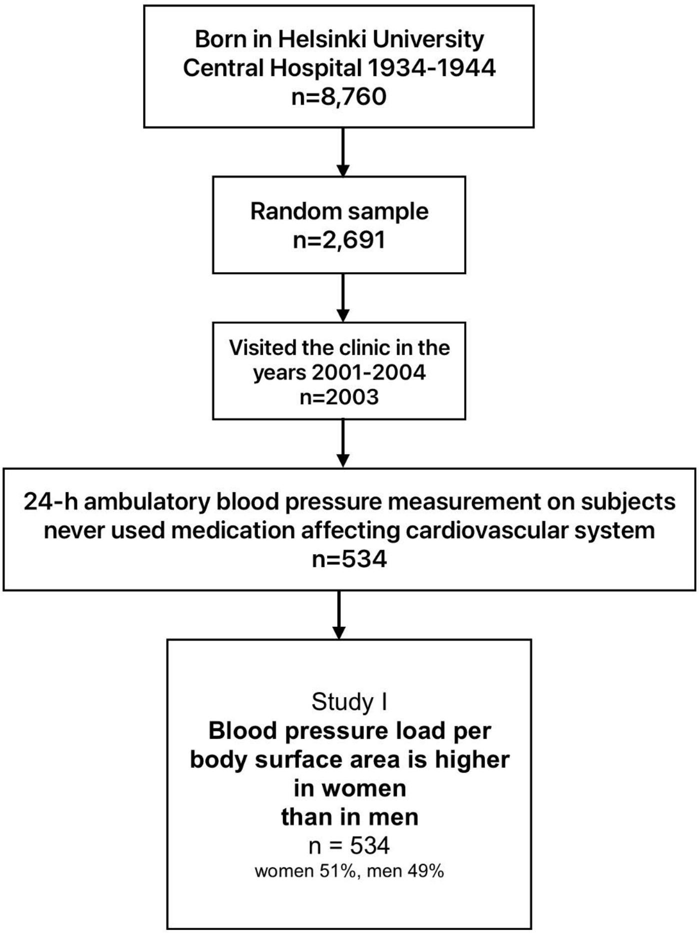


Figure 5. Selection of the study population.

4.1.2 Study II-IV

Study data were gathered in a population survey, the Harmonica (Harjavalta Risk Monitoring for Cardiovascular Disease) project which was conducted in south-western Finland in the rural towns of Harjavalta and Kokemäki in 2005–2007. The selection of the study population is shown in **Figure 6**. An invitation letter was mailed to the home-resident individuals aged 45 to 70 years, including a risk factor survey (**Table 12**), a validated T2D risk assessment form (The Finnish Diabetes Risk Score questionnaire, FINDRISC) (Lindström & Tuomilehto, 2003), and a measuring tape for WC measurement. Participants were invited to complete and return the risk factor survey and the validated T2D risk assessment form to the healthcare centre if they agreed to take part in the project. Participation, including all tests, was free of charge. The participation rate was 74% (4,450/6,013). Subjects with previously diagnosed CKD, DM, or CVD were excluded (n = 274). At least one risk factor was reported by 3,027 participants, and of those 2,752 were willing to participate further examination was performed by a trained study nurse.

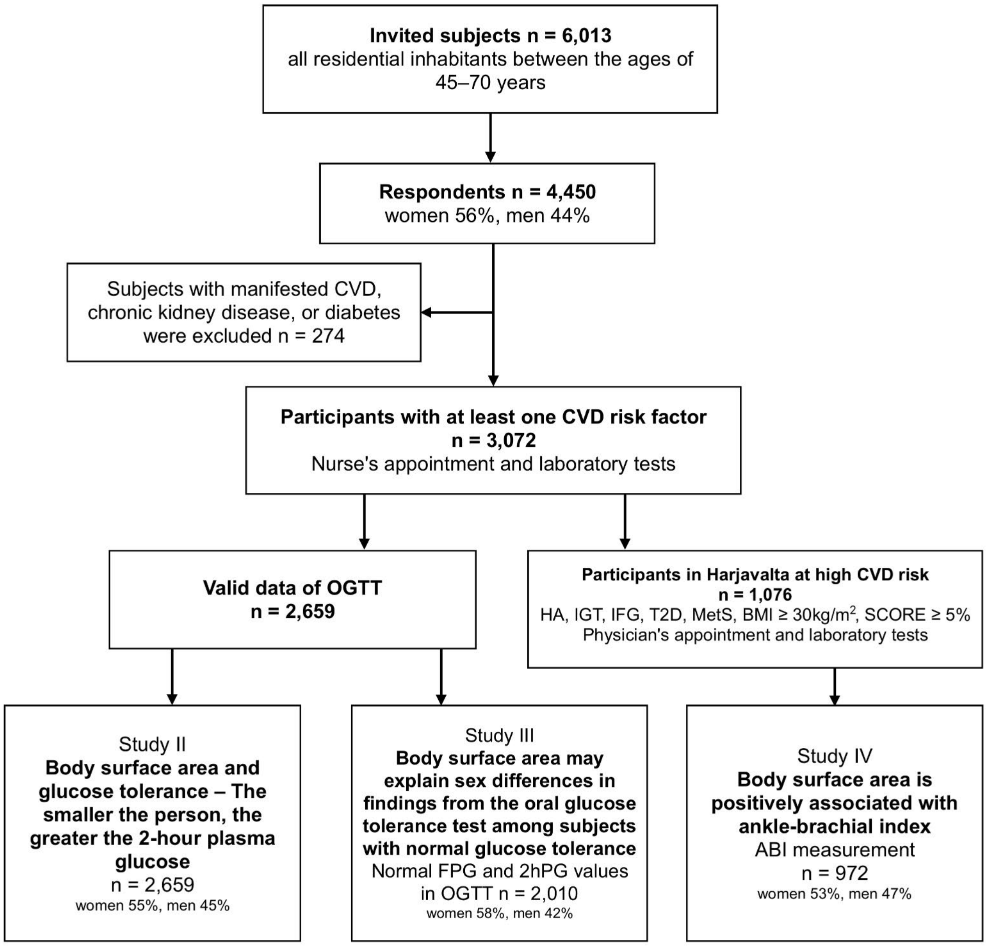


Figure 6. Selection of the study population. Abbreviations: 2hPG, 2-hour post-load plasma glucose in an oral glucose tolerance test; ABI, ankle-brachial index; BMI, body mass index CVD, Cardiovascular disease; FPG, Fasting plasma glucose; HA, hypertension arterialis; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MetS, metabolic syndrome; OGTT, Oral glucose tolerance test; SCORE, Systematic coronary risk evaluation; T2D, type 2 diabetes

Table 12. The risk factor survey of the Harmonica (Harjavalta Risk Monitoring for Cardiovascular Disease) project.

VARIABLE	DEFINITION OF RISK FACTOR
The latest measure of blood pressure	≥140/90 mmHg
Use of antihypertensive medication	Yes
History of gestational diabetes	Yes
History of gestational hypertension	Yes
Self-measured waist circumference	≥80 cm in women or ≥94 cm in men
Family history (parents/siblings) of	
myocardial infarction	yes
coronary artery disease	yes
stroke	yes
FINDRISC score (Lindström & Tuomilehto, 2003)	≥12 in Harjavalta or ≥15 in Kokemäki

4.2 Methods

4.2.1 Questionnaires

Before the appointment with the nurse, the participants completed self-administered questionnaires on their health, lifestyle habits, sociodemographic factors, and medication use.

4.2.1.1 Sociodemographic Factors

The sociodemographic factors included age, sex, and years of education. Participants were asked to report their total years of education.

4.2.1.2 Lifestyle Associated Factors

In studies II–IV, leisure-time physical activity (LTPA), smoking status (current or not current), and the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 1989) were assessed at the clinic with self-administered questionnaires. LTPA was classified as high if it lasted at least 30 minutes per session and was performed six or more times per week, moderate if it lasted at least 30 minutes per session and occurred four to five times per week, and low if it lasted at least 30 minutes per session and occurred three or less times per week.

In study I, LTPA was assessed with the validated 12-month Kuopio Ischemic Heart Disease questionnaire (Lakka et al., 1994). Data on the type, average duration per month, and average frequency per month of LTPA were collected. A specific metabolic equivalent of task (MET) was assessed to each reported activity (n=47) to determine its absolute intensity, using the standard definition of 1 MET as 3.5 ml O2/kg/min or 1 kcal/kg/h. LTPA was expressed as a time-weighted average intensity (TWA-MET) (Wasenius et al., 2014).

4.2.2 Baseline Medication

Data on regularly used medications were collected from both the questionnaire and medical records.

4.2.3 Physical Examination

4.2.3.1 Blood Pressure

BP was measured by a trained nurse using a mercury sphygmomanometer while participants were seated, following a rest period of at least five minutes the cuff was placed on the arm. A larger cuff was used for big arms when necessary. SBP and DBP were determined based on Korotkoff sounds I and V. For each participant, the mean of two readings taken at intervals of at least two minutes was used.

In study I, for 24-hour ABPM, Spacelabs 90207 oscillometric monitors (Spacelabs Healthcare, Issaquah, Washington) were used, with appropriately sized cuffs placed on the nondominant arm. Measurements were taken every 30 minutes throughout the day, except between 10 p.m. and 7 a.m., when readings were recorded once per hour. Pulse pressure (PP) was defined as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated as DBP + (SBP− DBP)/3.

4.2.3.2 Anthropometric Measurements

Height and weight were measured with the participants in standing position, wearing indoor clothing without shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.1 kg using digital scales (in study I Seca® Alpha 770, and in studies II–IV Seca® 861, Germany), which were regularly calibrated. WC was measured at the midpoint between the lowest rib margin and the iliac crest. BMI (Keys et al., 1972) was calculated as weight (kg) divided by square of height (m^2). BSA was calculated using the Mosteller formula (**Table 11**), and in study I BSA at birth was calculated using Meban BSA formula (**Table 11**). Body fat percentage was calculated by the relative fat mass (RFM) equation as follows: 76 − [20 ×

(height/WC)] for women, and 64 − [20 × (height/WC)] for men (Woolcott & Bergman, 2018).

4.2.3.3 Ankle-Brachial Index

BP measurements were taken by a physician using a Doppler instrument (UltraTec® PD1v with a 5 MHz vascular probe; Medema T/A Omega Medical Supplies Ltd, UK). BP measurements were taken with the subject in a supine position using an appropriately sized cuff. SBP in the brachial artery was measured in both upper arms at the antecubital fossa. SBP in both lower limbs were measured at the dorsalis pedis artery. The posterior tibial was artery used if the dorsalis pedis pulse was not detectable. The cuff was placed just above the malleoli for ankle measurements. ABI was calculated by dividing the lower ankle SBP by the higher brachial SBP.

4.2.4 Laboratory Measurements

Laboratory tests were obtained following a minimum fasting period of 12 hours. In study I, plasma glucose concentrations were determined using the hexokinase method. In studies II–IV, the OGTT involved measuring capillary whole blood glucose levels before and two hours after ingestion of 75 g of anhydrous glucose dissolved in water. These values were then converted to capillary plasma glucose concentrations using the HemoCue Glucose 201+ system (Ängelholm, Sweden). Glucose regulation was classified based on the WHO 1999 criteria (World Health Organization, 1999).

In study I, serum total cholesterol and triglyceride concentrations were measured with the use of standard enzymatic methods (Barker et al., 2005). In studies II–IV, high-density lipoprotein cholesterol (HDL-C), triglycerides, and total plasma cholesterol were determined enzymatically using the Olympus AU604 system, while low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula (Friedewald et al., 1972).

4.2.5 Statistical Analyses

The characteristics of the study population and descriptive statistics are presented as means with standard deviations (SDs) or as counts with percentages.

In study I, statistical significances for the hypothesis of linearity of daytime and night-time ambulatory BP components across categories of BSA (I≤1.81, II=1.81–2.00, and III≥2.00) tertiles were evaluated by using the analysis of variance to determine overall differences between BSA groups, and an orthogonal polynomial contrast to test for a linear trend. Multivariate linear regression analysis was conducted to examine the relationship between BSA, treated as a continuous variable, and ambulatory BP components, using the standardized regression coefficient beta (β). The β coefficient quantifies the strength of the predictor variable (BSA) in influencing the outcome variable, measured in SD units. According to Cohen's standards, β values exceeding 0.10, 0.30, and 0.50 indicate small, moderate, and large association, respectively. Sex differences in BSA, BMI, and BP components were assessed using a t-test or analysis of covariance. The adjusted models included age, smoking, LTPA, and body fat percentage as covariates. If the assumptions were violated (e.g., non-normality), a bootstrap-based test with 10,000 replications was applied. BSA distributions between sexes were compared using the Epps–Singleton two-sample empirical characteristic function test. The Epps–Singleton test evaluates whether the distribution functions of two independent samples are identical. The normality of the variables was assessed using the Shapiro–Wilk W test. All analyses were performed using Stata 15.0 (StataCorp LP; College Station, Texas, USA).

In study II, study 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. Statistical significance for the unadjusted hypothesis of linearity across BSA categories was assessed using the Cochran-Armitage trend test, logistic regression models, and analysis of variance with an appropriate contrast. If the assumptions were violated (e.g., non-normality), a bootstrap-based test was applied. The relationship between DM and BSA was modeled using a logistic regression model with restricted cubic splines, incorporating four knots placed according to Harrell's recommended percentiles (Harrell, 2001). Regression analyses were conducted to assess the relative effects of height and weight as predictors of FPG and 2hPG, using standardized regression coefficients β. The β coefficient quantifies the strength of each predictor's influence on the dependent variable, measured in units of SD. Correlation coefficients were determined using the Pearson method. The normality of the variables was tested by using the Shapiro–Wilk W test. Stata 15.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

In study III, men and women were separately classified into five sex-specific BSA levels, with each level representing 12.5%, 25%, 25%, 25%, and 12.5% of the total distribution. Statistical significance for the hypothesis of linearity across sex-specific BSA levels was assessed using the Cochrane-Armitage test for trend and analysis of variance with an appropriate orthogonal contrast. The main and interactive effects of sex and BSA levels were analysed by including sex, BSA, and their interaction as independent variables in the models. Age, WC, LTPA, and smoking were included as covariates. Linear regression analyses were conducted to determine the association between BSA levels and the OGTT results, using both crude and adjusted standardized regression coefficients β. The β coefficient quantifies the strength of each predictor variable's influence on the dependent variable. A potential nonlinear relationship between the OGTT and sex-specific BSA was evaluated using 4-knot restricted cubic spline regression. The knot locations were determined based on Harrell's recommended percentiles (Harrell, 2001). The bootstrap method was applied when the theoretical distribution of the test statistics was unknown or when assumptions, such as normality, were violated. The normality of the variables was assessed both graphically and using the Shapiro-Wilk W test. Stata 16.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

In study IV, subjects were divided into five BSA levels according to total BSA distribution percentiles: I≤1.71 m^2 (12.5^{th}), II 1.72–1.89 m^2 (25^{th}), III 1.90–2.03 m^2 (25^{th}), IV 2.04–2.22 m^2 (25^{th}), and V>2.22 m^2 (12.5^{th}). Linearity across the five BSA levels was assessed using the Cochran–Armitage test (Chi-square test for trend), logistic regression models, and analysis of variance with an appropriate orthogonal contrast. The possible non-linear relationship between BSA and ABI values was modeled using restricted cubic spline regression with four knots positioned at the 5th, 35th, 65th, and 95th percentiles, following Harrell's recommended percentiles (Harrell, 2001). Effect modification by BSA on the relationship between ABI and sex, as a function of BSA, along with the estimation of the inflection point, was derived using a four-knot restricted cubic spline regression model. Generalized linear models were used to examine the relationship between weight and height as continuous variables and ABI values, using the standardized regression coefficient β. The β value quantifies the strength of the predictor variable's influence on the outcome variable and is expressed in SD units. According to Cohen's standard (Cohen, 1988), β values above 0.10, 0.30, and 0.50 indicate small, moderate, and large relationships, respectively. The models were adjusted for sex, pulse pressure, age, glucose regulation, AUDIT score, smoking status, WC, LTPA, and medication, as appropriate. All analyses were performed using STATA software, version 17.0 (StataCorp LP, College Station, TX).

4.2.6 Ethical approvals

The Ethics Committee for Epidemiology of Helsinki and Uusimaa Hospital District approved Study I. The Ethics Committee of Satakunta Hospital District reviewed and approved the study protocol and consent forms for the Studies II–IV. All participants provided written informed consent for the project and subsequent research.

5 Results

5.1 Body Surface Area and Blood Pressure (Study I)

The study included 534 individuals who had never used medication affecting the CV system. The mean age of the study population was 61 years (SD 3), with 51% being female. **Table 13** presents the characteristics of the study participants. On average, men had higher BSA, height, and weight also at birth than women. In contrast, women had a higher mean body fat percentage, total cholesterol, and HDL-C levels. Men exhibited higher FPG and triglyceride concentration, as well as higher office DBP measurements and MAP. Additionally, they reported greater levels of LTPA and were more likely to be current smokers than women.

Table 13. Characteristics of the study population by sex. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

	WOMEN (N=274)	MEN (N=260)	P-VALUE
Body surface area, m^2	1.79 (0.15)	2.03 (0.17)	<0.001
Height, cm	163 (6)	177 (6)	<0.001
Weight, kg	71 (11)	84 (12)	<0.001
Body mass index, kg/m^2	26.8 (4.2)	26.9 (3.5)	0.84
Body fat percentage	32.6 (6.4)	23.0 (5.5)	<0.001
Age, years	61 (3)	61 (3)	0.49
Education years	11.8 (3.4)	12.4 (3.8)	0.034
Length at birth, cm	50.0 (1.9)	50.8 (2.0)	<0.001
Weight at birth, g	3369 (483)	3517 (499)	<0.001
Body surface area at birth, cm^2	2159 (190)	2224 (197)	<0.001
Fasting plasma glucose, mmol/l	5.44 (0.80)	5.97 (1.22)	<0.001
Total cholesterol, mmol/l	6.18 (1.02)	5.92 (1.05)	0.003
HDL cholesterol, mmol/l	1.79 (0.45)	1.50 (0.41)	<0.001
Triglycerides, mmol/l	1.34 (0.74)	1.50 (0.82)	0.015
Systolic blood pressure, mmHg	145 (21)	146 (19)	0.41
Diastolic blood pressure, mmHg	87 (10)	91 (11)	<0.001
Pulse pressure, mmHg	70 (10)	70 (13)	0.71
Mean arterial pressure, mmHg	107 (12)	109 (12)	0.011
Current smoker, n (%)	45 (16)	66 (25)	0.011
Leisure-time physical activity, TWA-MET	4.4 (0.9)	4.8 (1.4)	<0.001

Data are presented as mean (SD) except where indicated.
Abbreviations: BSA, body surface area; HDL, high-density lipoprotein; TWA-MET, time-weighted average intensity in MET-values

Figure 7 illustrates the distribution of BSA in men and women (p <0.001 for equality of BSA distributions). While the mean BMI values did not differ significantly between sexes (p = 0.40), the mean BSA was notably higher in men than in women (p <0.001, **Figure 8**). The mean ratio between men and women was 1.01 (95% CI: 0.98–1.04) for BMI and 1.13 (95% CI: 1.12–1.15) for BSA.

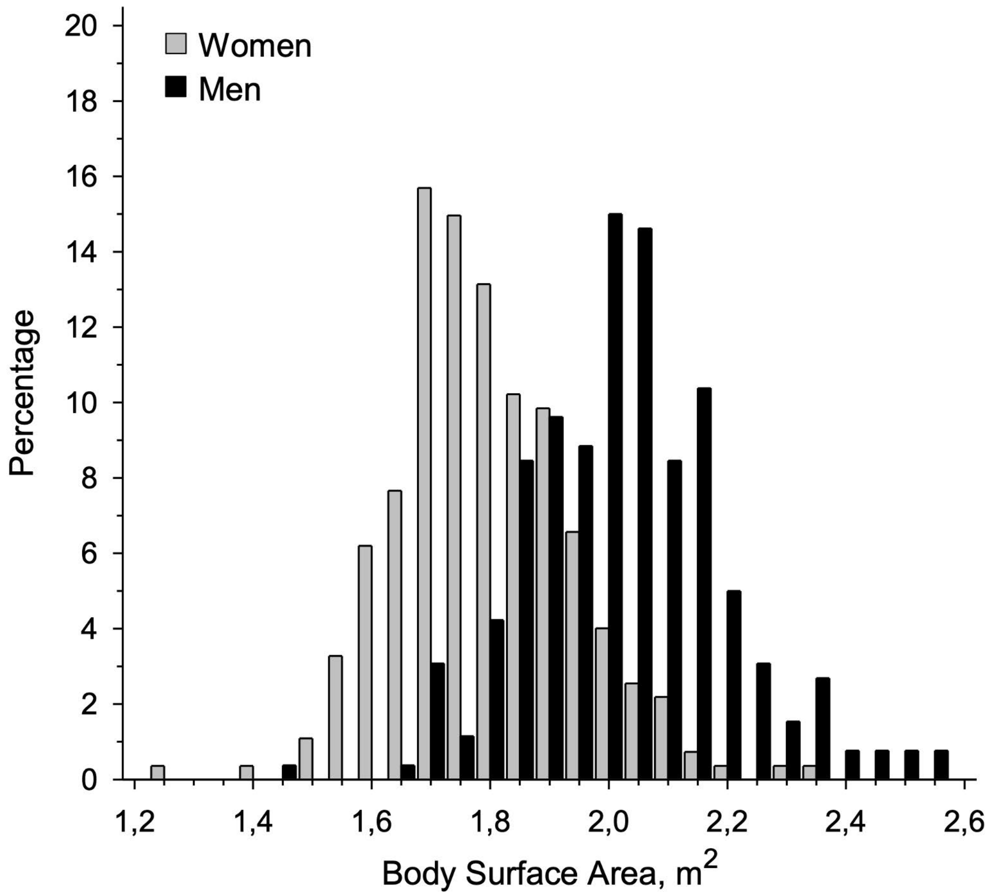


Figure 7. Distribution of body surface area by sex. Grey bars represent women, while black bars represent men. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

Ambulatory daytime and nighttime SBP, DBP, and MAP showed a positive association with BSA, which remained statistically significant even after adjusting for age, smoking, LTPA, and body fat percentage. Additionally, adjusted nighttime PP showed a linear increase with BSA (**Table 14**).

Table 14. Ambulatory blood pressure findings by tertiles of body surface area. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

	I N=178	II N=178	III N=178	P FOR LINEARITY	
				Crude	Adjusted[a]
Daytime BP, mmHg					
Systolic	127 (14)	129 (13)	132 (13)	<0.001	<0.001
Diastolic	77 (9)	81 (8)	83 (9)	<0.001	<0.001
PP	49 (10)	48 (8)	49 (8)	0.71	0.87
MAP	95 (10)	98 (9)	100 (10)	<0.001	<0.001
Daytime heart rate, beats/min	75 (9)	75 (10)	75 (11)	0.49	0.75
Night-time BP, mmHg					
Systolic	114 (13)	116 (13)	119 (13)	<0.001	<0.001
Diastolic	66 (8)	69 (8)	71 (8)	<0.001	<0.001
PP	47 (9)	47 (8)	48 (8)	0.49	0.19
MAP	83 (9)	86 (9)	88 (10)	<0.001	<0.001
Night-time heart rate, beats/min	65 (8)	65 (9)	66 (11)	0.88	0.44

Values are mean (SD).
Abbreviations: BP, blood pressure; PP, pulse pressure; MAP, mean arterial blood pressure.
[a]Adjusted for age, smoking, leisure-time physical activity, and body fat percentage.

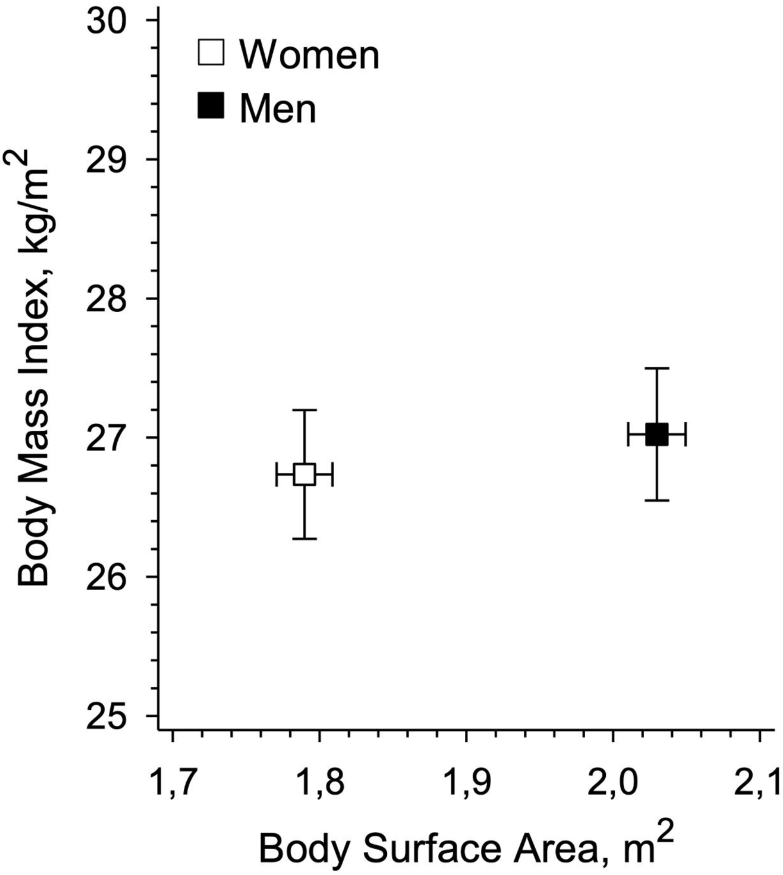


Figure 8. Mean body mass index and body surface area in men and women, adjusted for age, smoking, and leisure-time physical activity. Whiskers represent 95% confidence intervals. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

When ambulatory BP values were stratified by sex, males had higher SBP and DBP, as well as MAP, compared to females. However, divided by BSA, all BP components were significantly higher in females ($p < 0.001$ for all comparisons), as shown in **Table 15** and **Figure 9**.

Table 15. Mean ambulatory blood pressure values in mmHg and mmHg per body surface area by sex. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited.

	MMHG			**MMHG / BSA**			
	Women	Men		Women	Men	p[a]	
						mmHg	mmHg / BSA
Daytime BP, mmHg							
Systolic	127 (13)	131 (13)		71 (10)	65 (8)	<0.001	<0.001
Diastolic	78 (8)	83 (9)		44 (6)	41 (5)	<0.001	<0.001
PP	49 (10)	48 (8)		28 (6)	24 (5)	0.98	<0.001
MAP	96 (9)	100 (10)		54 (7)	49 (6)	<0.001	<0.001
Night-time BP, mmHg							
Systolic	115 (13)	117 (12)		64 (9)	58 (7)	<0.001	<0.001
Diastolic	67 (8)	71 (8)		37 (5)	35 (5)	<0.001	<0.001
PP	48 (9)	46 (8)		27 (6)	23 (4)	0.99	<0.001
MAP	84 (9)	87 (9)		47 (6)	43 (6)	<0.001	<0.001

Values are mean (SD).
Abbreviations: BP, blood pressure; PP, pulse pressure; MAP, mean arterial blood pressure.
[a]Adjusted for age, smoking, leisure-time physical activity, and body fat percentage.

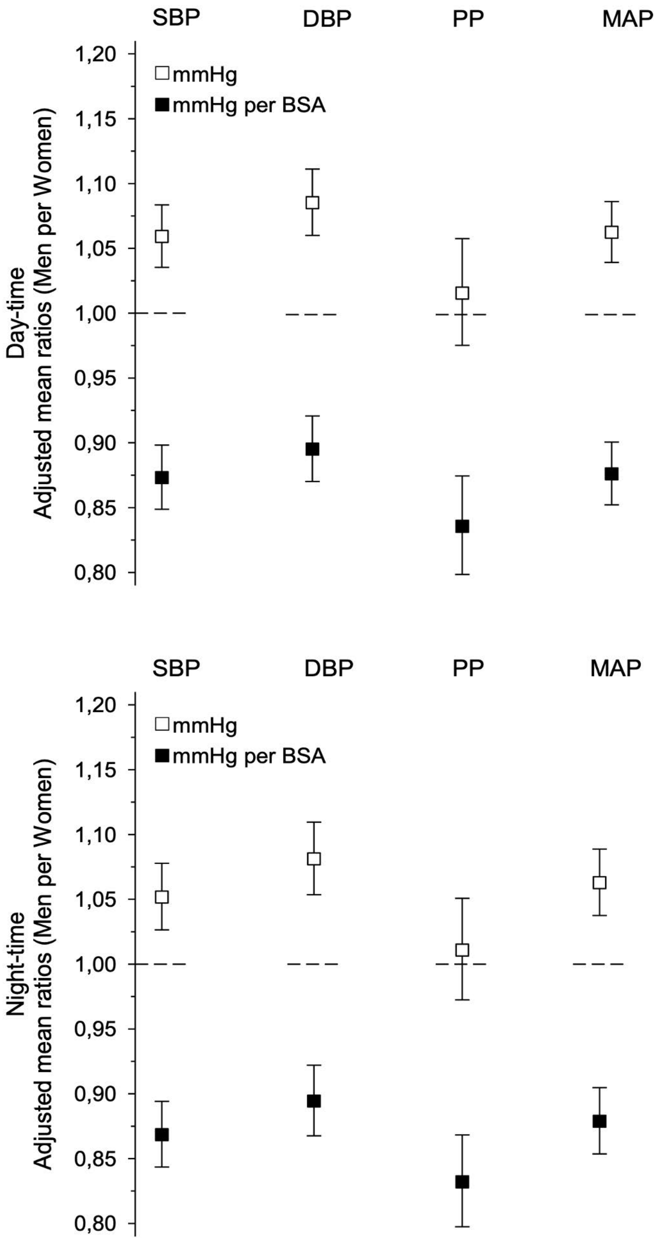


Figure 9. Mean ratio between men and women for different daytime and nighttime ambulatory blood pressure components, adjusted for age, smoking, leisure-time physical activity, and body fat percentage. Whiskers represent 95% confidence intervals. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

In multiple regression analysis, BSA showed a positive association with ambulatory measurements of SBP, DBP, and MAP (**Figure 10**).

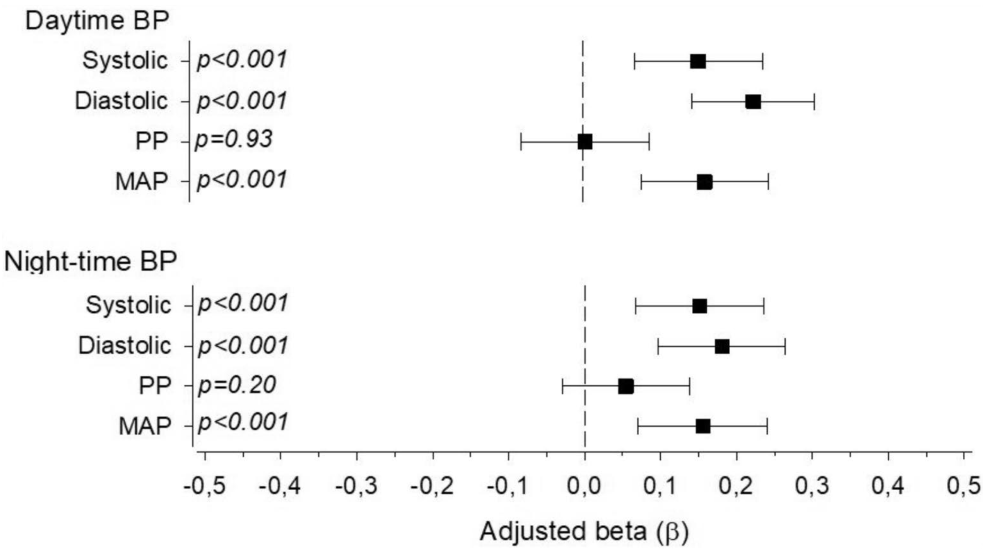


Figure 10. Magnitude of the effect of body surface area as a continuous variable on ambulatory blood pressure components. Beta (β) values with 95% confidence intervals were adjusted for age, smoking, leisure-time physical activity, and body fat percentage. From Study I (Korhonen et al., 2021) with permission from Springer Nature Limited. © The Author(s), under exclusive licence to Springer Nature Limited 2020.

5.2 Body Surface Area and Glucose Tolerance (Study II)

The study included 2,659 participants at increased cardiovascular risk, with a mean age of 58 years (SD 7), of whom 56% were women. **Table 16** presents the characteristics of participants across five BSA level groups. The two lowest BSA categories were predominantly composed of women, while the two highest included mainly men. Participants with higher BSA tended to be younger and exhibited higher SBP and DBP, elevated plasma glucose and triglyceride levels, and lower HDL and total cholesterol levels. BSA showed a positive association with other anthropometric measures, AUDIT score, and the use of statins and antihypertensive medication but was inversely related to LTPA.

The prevalence of impaired glucose regulation increased linearly with rising BSA levels. Among individuals with normal glucose tolerance, FPG showed a positive association with BSA, while the 2hPG/FPG ratio was negatively associated.

In subjects with newly diagnosed T2D, the 2hPG/FPG ratio was inversely related to BSA.(**Table 17**)

Table 16. The clinical and anthropometric characteristics of participants across different body surface area (BSA) levels. Modified from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

	BODY SURFACE AREA LEVEL					
	I N=332	II N=674	III N=668	IV N=662	V N=323	P for linearity
BSA, m^2	1.63	1.79	1.95	2.11	2.35	..
Range, m^2	<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
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

Abbreviations: BSA, body surface area; BMI, body mass index; WC, waist circumference; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity. Data are expressed as mean (SD), except where indicated.

Table 17. Prevalence of glucose tolerance categories and plasma glucose levels by body surface area levels. Modified from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

	BODY SURFACE AREA LEVEL					
	I N=332	II N=674	III N=668	IV N=662	V N=323	P for linearity
Glucose tolerance						<0.001
NGT, n (%)	281 (85)	554 (82)	532 (80)	487 (74)	201 (62)	
IH, n (%)	29 (9)	92 (14)	91 (14)	106 (16)	62 (19)	
T2D, n (%)	22 (7)	28 (4)	45 (7)	69 (10)	60 (19)	
NGT, mean (SD)						
FPG, mmol/l	5.11 (0.51)	5.18 (0.49)	5.25 (0.46)	5.32 (0.48)	5.31 (0.41)	<0.001
2hPG, mmol/l	6.94 (1.49)	6.91 (1.43)	6.92 (1.63)	6.86 (1.70)	7.02 (1.91)	0.95
2hPG/FPG ratio	1.37 (0.30)	1.34 (0.29)	1.32 (0.32)	1.30 (0.33)	1.33 (0.36)	0.018
IH, mean (SD)						
FPG, mmol/l	6.23 (0.52)	6.29 (0.44)	6.37 (0.36)	6.34 (0.25)	6.34 (0.39)	0.21
2hPG, mmol/l	8.36 (1.85)	7.95 (1.87)	8.07 (1.97)	7.61 (1.88)	8.16 (1.93)	0.43
2hPG/FPG ratio	1.35 (0.33)	1.27 (0.33)	1.28 (0.33)	1.20 (0.30)	1.29 (0.32)	0.21
T2D, mean (SD)						
FPG, mmol/l	7.68 (3.71)	7.08 (1.66)	7.97 (2.22)	7.87 (2.10)	8.51 (2.48)	0.076
2hPG, mmol/l	13.08 (3.63)	12.70 (2.80)	12.71 (3.35)	12.41 (3.47)	12.45 (3.26)	0.48
2hPG/FPG ratio	2.11 (0.74)	2.05 (0.59)	1.84 (0.57)	1.75 (0.53)	1.66 (0.45)	<0.001

Abbreviations: NGT, normal glucose tolerance; IH, intermediate hyperglycaemia (pre-diabetes, defined as IFG or IGT); IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; T2D, type 2 diabetes; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose

In the study population, body weight was closely related to BMI [(r=0.82 (95% CI: 0.80 to 0.83)] and even more to BSA [r=0.97 (95% CI: 0.96 to 0.98)]. Height of the study subjects was related to BSA [r=0.68 (95% CI: 0.66 to 0.70)], but only minimally to BMI [r=-0.08 (95% CI: -0.12 to -0.04)]. (**Figure 11**)

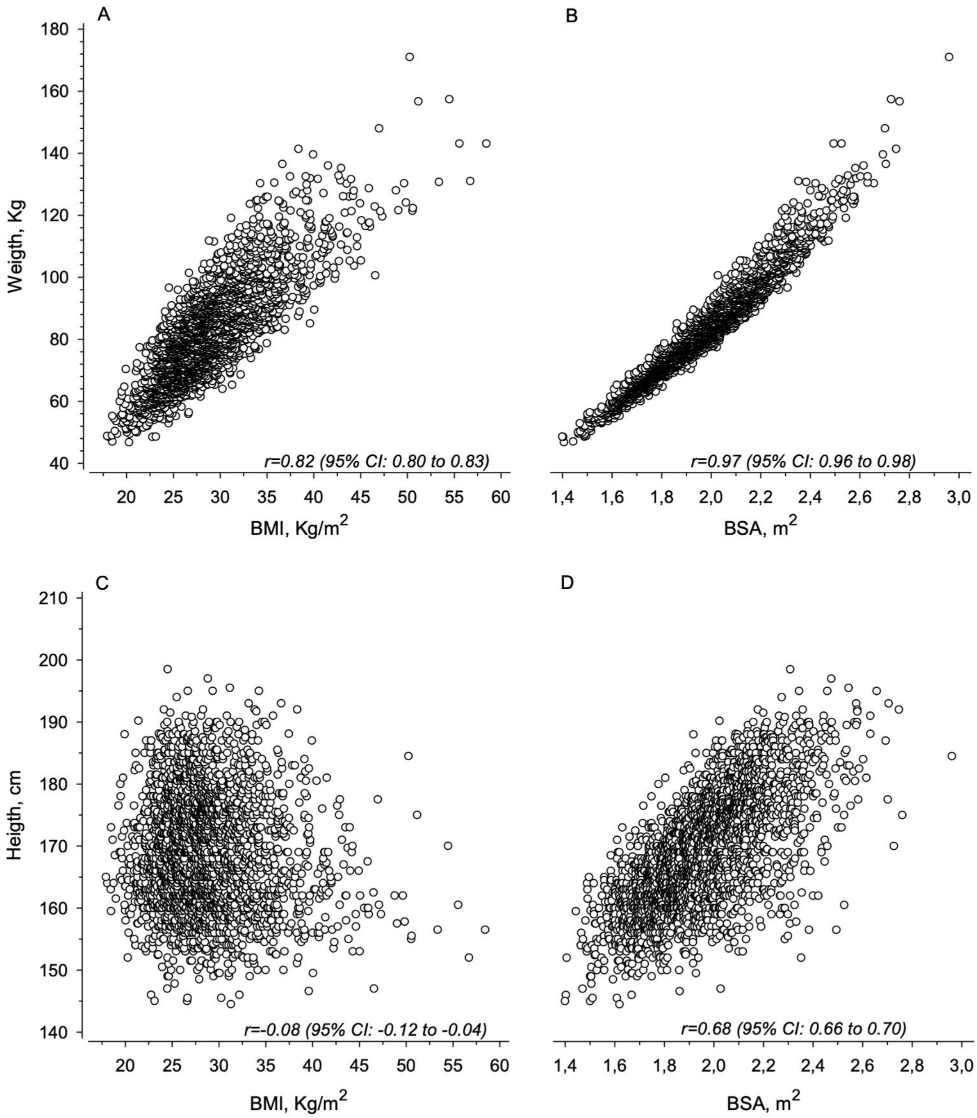


Figure 11. Relation of body weight to body mass index (Panel A) and to body surface area (Panel B), and relation of height to body mass index (Panel C) and to body surface area (Panel D).

After adjusting for age, sex, WC, alcohol intake, current smoking, and LTPA, BSA exhibited an inverse linear relationship with both 2hPG and the 2hPG/FPG ratio across all categories of glucose tolerance (p for linearity < 0.001). Among individuals with normal glucose tolerance, the 2hPG/FPG ratio declined from 1.47 (95% CI: 1.42–1.52) to 1.23 (95% CI: 1.17–1.29) as BSA increased. Similarly, in participants with newly diagnosed T2D, the ratio decreased from 2.08 (95% CI:

1.91–2.24) to 1.51 (95% CI: 1.40–1.62). A significant interaction was observed between BSA and the 2hPG/FPG ratio (p <0.001), while no interaction was found between BSA and 2hPG (p = 0.70) (**Figure 12**).

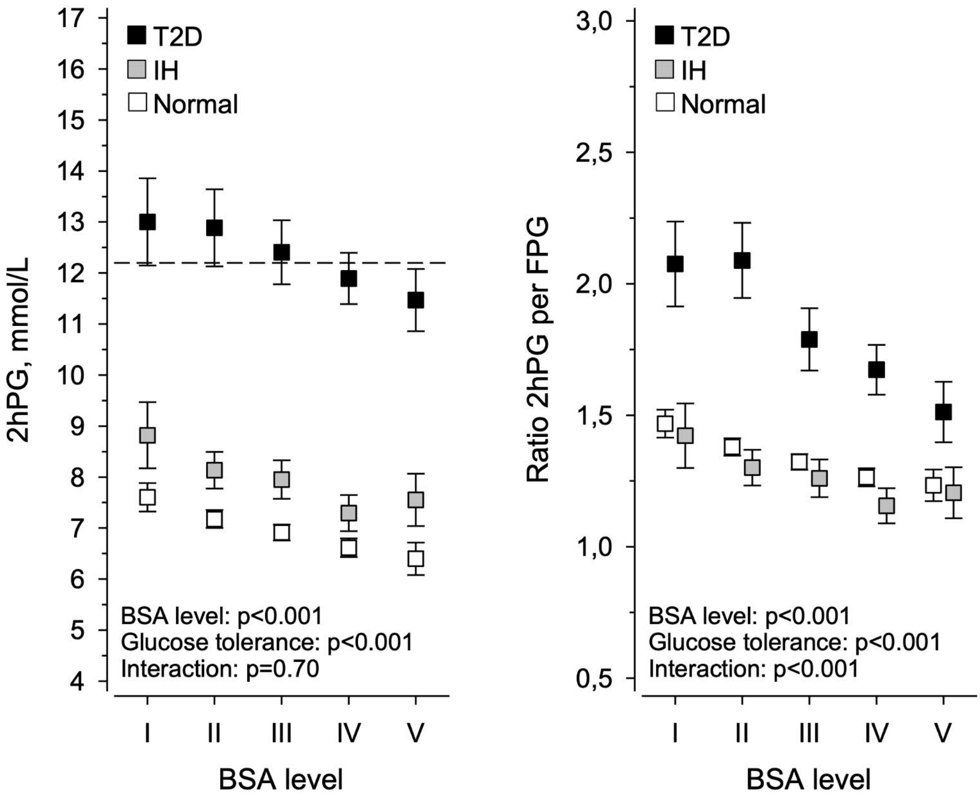


Figure 12. Mean 2-hour plasma glucose (2hPG) and the 2hPG-to-fasting plasma glucose (FPG) ratio across body surface area (BSA) levels and glucose tolerance categories. Adjusted for age, smoking status, leisure-time physical activity, alcohol intake, waist circumference, and sex. Error bars represent 95% confidence intervals. The dashed line denotes the 2hPG diagnostic cut-off value for type 2 diabetes. Reprinted from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

Figure 13 presents the adjusted proportion of new T2D diagnoses based on the OGTT. BSA demonstrated an inverse association with new T2D diagnoses (p for linearity <0.001). In univariate regression analysis, both height and weight were positively associated with FPG, with weight exhibiting a stronger effect. While weight showed a positive relationship with 2hPG, height was inversely associated with 2hPG (**Figure 14**).

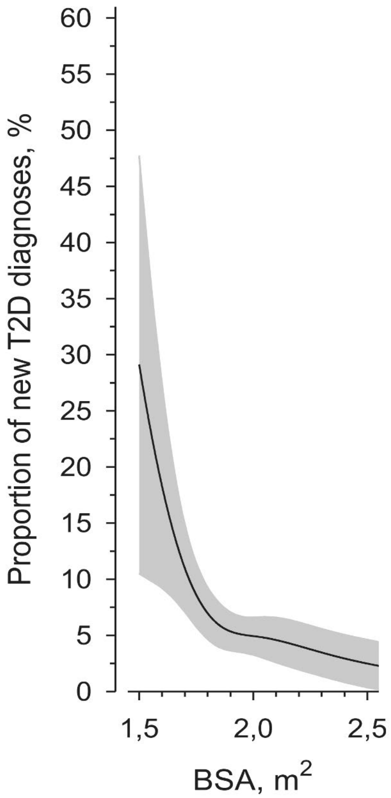


Figure 13. Proportion of new type 2 diabetes diagnoses based on 2hPG values across BSA levels. The curves were generated using four-knot restricted cubic splines logistic regression models, adjusted for age, sex, smoking status, leisure-time physical activity, alcohol intake, and waist circumference. The grey area represents the 95% confidence intervals. Reprinted from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

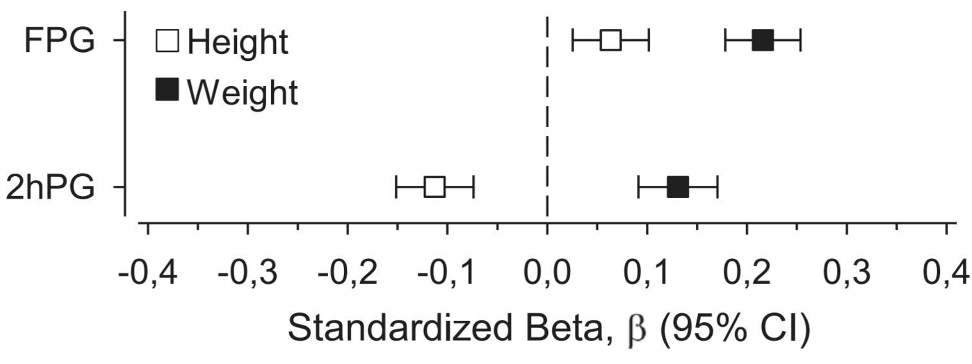


Figure 14. Univariate associations between body size predictive variables (height and weight) and diagnostic variables (FPG and 2hPG). Standardized beta coefficients (β) with 95% confidence intervals. Reprinted from Study II (Palmu et al., 2019) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

5.3 Body Surface Area and Sex Differences in the Oral Glucose Tolerance Test (Study III)

The study included 2,010 participants (841 men and 1,169 women) with normal glucose tolerance. The mean age was 57 years (SD 7) for men and 58 years (SD 7) for women, with women comprising 58% of the total study population. **Table 18** and **Table 19** present the characteristics of the participants according to sex and five BSA levels. In both men and women, a higher BSA was associated with lower HDL-C and higher triglyceride concentrations, higher DBP, and increased use of antihypertensive medication. Participants with larger BSA were also less engaged in LTPA compared to those with smaller BSA (p for linearity <0.001). Among men, those with a larger BSA were younger (p for linearity <0.001) and more educated (p for linearity 0.002) than those with a smaller BSA. In women, LDL-C levels increased with higher BSA (p for linearity 0.031).

Table 18. The clinical and anthropometric characteristics of male participants across different body surface area levels. Modified from Study III (Palmu et al., 2021). © The Author(s) 2021. Published by Elsevier. Distributed under the terms of the Creative Commons Attribution 4.0 License (https://creativecommons.org/licenses/by/4.0/).

	BODY SURFACE AREA LEVEL					
	I N=105	II N=210	III N=211	IV N=210	V N=105	P for linearity
BSA m^2	1.82 (0.07)	1.96 (0.03)	2.06 (0.03)	2.18 (0.04)	2.39 (0.11)	
Range, m^2	<1.89	1.89–2.01	2.02–2.11	2.12–2.26	≥2.27	
Age, years	59.0 (6.8)	57.6 (7.0)	58.3 (6.6)	56.3 (6.7)	55.9 (6.4)	<0.001
Education years	9.6 (2.2)	10.2 (2.5)	9.8 (2.3)	10.9 (2.8)	10.2 (2.3)	0.002
Height, cm	170 (5)	174 (5)	177 (6)	180 (5)	184 (6)	<0.001
Weigh, kg	70 (5)	80 (3)	87 (4)	95 (4)	112 (10)	<0.001
BMI, kg/m^2	24.4 (2.3)	26.3 (2.3)	27.8 (2.8)	29.6 (2.8)	33.2 (4.1)	<0.001
WC, cm	88.2 (6.8)	94.3 (5.9)	99.4 (6.6)	104.2 (6.5)	114.6 (9.9)	<0.001
FPG, mmol/l	5.28 (0.53)	5.22 (0.47)	5.30 (0.48)	5.36 (0.48)	5.28 (0.39)	0.077
2hPG, mmol/l	7.03 (1.46)	6.95 (1.68)	6.83 (1.83)	6.78 (1.70)	6.75 (1.76)	0.12
TC, mmol/l	5.36 (0.93)	5.40 (0.95)	5.24 (0.88)	5.34 (1.03)	5.37 (0.99)	0.78
HDL-C, mmol/l	1.56 (0.39)	1.52 (0.47)	1.40 (0.36)	1.39 (0.47)	1.21 (0.30)	<0.001
LDL-C, mmol/l	3.28 (0.80)	3.31 (0.86)	3.25 (0.85)	3.29 (0.94)	3.39 (0.88)	0.52
Triglycerides, mmol/l	1.19 (0.64)	1.33 (0.67)	1.40 (0.74)	1.56 (0.76)	1.72 (0.73)	<0.001
Blood Pressure, mmHg						
Systolic	140 (20)	140 (16)	141 (17)	139 (18)	143 (19)	0.34
Diastolic	83 (10)	85 (10)	87 (10)	87 (9)	91 (10)	<0.001
Current smoker, n (%)	28 (27)	37 (18)	45 (22)	40 (19)	14 (13)	0.075
AUDIT score	6.8 (5.6)	6.6 (5.5)	6.8 (5.2)	6.6(5.2)	7.0 (5.1)	0.82
LTPA, n (%)						<0.001
Low	12 (12)	34 (17)	47 (23)	49 (24)	36 (35)	
Moderate	55 (55)	111 (54)	96 (47)	98 (48)	48 (47)	
High	33 (33)	59 (29)	63 (31)	56 (28)	19 (18)	
Current medication, n (%)						
Statins	7 (7)	22 (10)	34 (16)	25 (12)	10 (10)	0.43
Antihypertensives	21 (20)	48 (23)	71 (34)	68 (32)	46 (44)	<0.001

Abbreviations: BSA, body surface area; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; 2hPG, 2-hour post-load plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AUDIT, Alcohol Use

Disorders Identification Test; LTPA, leisure-time physical activity. Data are expressed as mean (SD), except where indicated.

Table 19. The clinical and anthropometric characteristics of female participants across different body surface area levels. Modified from Study III (Palmu et al., 2021).

	BODY SURFACE AREA LEVEL					
	I N=146	II N=292	III N=293	IV N=291	V N=147	P for linearity
BSA m^2	1.58 (0.06)	1.71 (0.03)	1.81 (0.03)	1.94 (0.05)	2.16 (0.11)	
Range m^2	≤1.64	1.65–1.75]	1.76–1.85	1.86–2.03	>2.03	
Age, years	58.2 (7.6)	58.5 (7.1)	57.8 (6.9)	57.7 (6.8)	57.3 (7.3)	0.11
Education years	10.9 (2.8)	10.7 (2.9)	10.8 (2.9)	10.6 (2.8)	11.1 (2.9)	0.83
Height, cm	158 (5)	161 (5)	163 (5)	164 (6)	167 (6)	<0.001
Weight, kg	57 (4)	65 (3)	73 (3)	83 (5)	101 (11)	<0.001
BMI, kg/m^2	22.9 (2.4)	25.3 (2.3)	27.4 (2.5)	30.8 (3.6)	36.6 (5.5)	<0.001
WC, cm	76 (6)	82 (6)	89 (6)	97 (8)	109 (10)	<0.001
FPG, mmol/l	5.04 (0.48)	5.16 (0.51)	5.17 (0.49)	5.28 (0.43)	5.29 (0.44)	<0.001
2hPG, mmol/l	6.89 (1.44)	6.85 (1.51)	6.97 (1.43)	6.90 (1.55)	7.30 (1.72)	0.034
TC, mmol/l	5.46 (0.91)	5.57 (0.97)	5.55 (0.93)	5.55 (0.94)	5.54 (0.90)	0.63
HDL-C, mmol/l	1.84 (0.46)	1.82 (0.41)	1.72 (0.42)	1.61 (0.40)	1.48 (0.34)	<0.001
LDL-C, mmol/l	3.15 (0.79)	3.26 (0.92)	3.26 (0.85)	3.34 (0.89)	3.34 (0.87)	0.031
Triglycerides, mmol/l	1.09 (0.65)	1.12 (0.63)	1.28 (0.65)	1.35 (0.59)	1.64 (0.81)	<0.001
Blood Pressure, mmHg						
Systolic	136 (19)	139 (18)	136 (17)	138 (18)	141 (15)	0.12
Diastolic	80 (10)	81 (9)	82 (9)	84 (9)	86 (9)	<0.001
Current smoker, n (%)	24 (17)	40 (14)	35 (12)	33 (11)	18 (12)	0.16
AUDIT score	2.8 (3.2)	2.7 (2.8)	2.9 (3.1)	2.9 (2.8)	2.6 (3.4)	0.88
LTPA, n (%)						<0.001
Low	16 (11)	23 (8)	32 (11)	46 (16)	34 (24)	
Moderate	61 (42)	149 (52)	148 (52)	143 (51)	80 (56)	
High	67 (47)	115 (40)	104 (37)	94 (33)	28 (20)	
Current medication, n (%)						
Statins	9 (6)	27 (9)	21 (7)	35 (12)	16 (11)	0.071
Antihypertensives	24 16)	65 (22)	63 (22)	97 (33)	77 (52)	<0.001

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

Although all anthropometric measures increased linearly across BSA categories in both sexes (**Table 18** and **Table 19**), women had a lower BSA than men at every BMI level (**Figure 15**). In linear regression analysis, BSA exhibited a negative linear association with 2hPG in both men and women, independent of age, WC, LTPA, and smoking. In women, BSA showed a positive linear relationship with FPG, but this association disappeared after adjusting for confounding variables (**Table 20)**.

Table 20. Regression models for the relationship between body surface area (BSA) levels and diagnostic variables fasting plasma glucose (FPG) and 2-hour post-load plasma glucose (2hPG) in men and women. From Study III (Palmu et al., 2021). © The Author(s) 2021. Published by Elsevier. Distributed under the terms of the Creative Commons Attribution 4.0 License (https://creativecommons.org/licenses/by/4.0/).

BSA LEVEL	GLUCOSE, MMOL/L					
	FPG			2hPG		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Women						
I	Reference	Reference	Reference	Reference	Reference	Reference
II	0.11(0.02 to 0.19)	0.08 (-0.01 to 0.17)	0.08 (-0.01 to 0.17)	-0.01 (-0.10 to 0.07)	-0.09 (-0.17 to -0.00)	-0.09 (-0.18 to -0.01)
III	0.12 (0.03 to 0.20)	0.06 (-0.03 to 0.16)	0.06 (-0.03 to 0.16)	0.02 (-0.06 to 0.11)	-0.12 (-0.21 to -0.03)	-0.14 (-0.23 to -0.05)
IV	0.22 (0.14 to 0.30)	0.13 (0.02 to 0.24)	0.13 (0.02 to 0.24)	0.00 (-0.08 to 0.09)	-0.23 (-0.33 to -0.12)	-0.24 (-0.35 to -0.13)
V	0.17 (0.10 to 0.25)	0.07 (-0.04 to 0.18)	0.06 (-0.05 to 0.17)	0.09 (0.01 to 0.16)	-0.18 (-0.29 to -0.07)	-0.20 (-0.30 to -0.09)
	p<0.001*	p=0.15	p=0.22	p=0.034	p<0.001	p<0.001
Men						
I	Reference	Reference	Reference	Reference	Reference	Reference
II	-0.05 (-0.15 to 0.05)	-0.08 (-0.18 to 0.03)	-0.08 (-0.19 to 0.02)	-0.02 (-0.12 to 0.08)	-0.05 (-0.15 to 0.05)	-0.05 (-0.16 to 0.05)
III	0.02 (-0.08 to 0.12)	-0.03 (-0.14 to 0.08)	-0.05 (-0.16 to 0.07)	-0.05 (-0.15 to 0.05)	-0.15 (-0.25 to -0.04)	-0.14 (-0.25 to -0.03)
IV	0.07 (-0.03 to 0.17)	-0.01 (-0.13 to 0.13)	-0.01 (-0.14 to 0.11)	-0.06 (-0.16 to 0.04)	-0.17 (-0.29 to -0.05)	-0.17 (-0.28 to -0.05)
V	0.00 (-0.09 to 0.09)	-0.09 (-0.22 to 0.04)	-0.10 (-0.23 to 0.03)	-0.05 (-0.14 to 0.04)	-0.21 (-0.32 to -0.09)	-0.22 (-0.34 to -0.10)
	p=0.082	p=0.70	p=0.59	p=0.12	p<0.001	p<0.001

*P for linearity
Model 1: crude
Model 2: adjusted for age and waist circumference
Model 3: adjusted for age, waist circumference, leisure time physical activity, and smoking

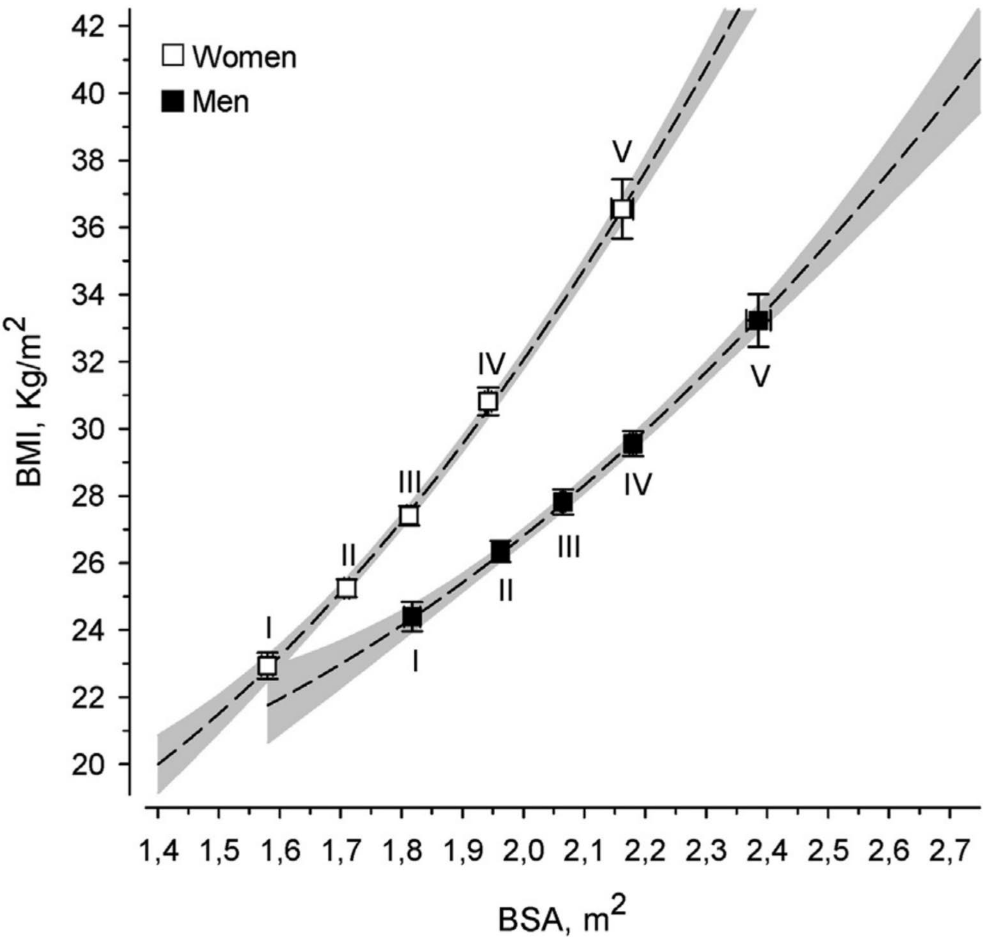


Figure 15. The relationship between body surface area (BSA) and body mass index (BMI) levels in men and women, with grey areas indicating 95% confidence intervals. From Study III (Palmu et al., 2021).

Figure 16 illustrates the mean FPG concentrations by sex and BSA levels. The difference between men and women was statistically significant (p = 0.038) and was specifically observed in the smallest BSA category, where the FPG difference was 0.18 mmol/L (95% CI: 0.06 to 0.31, p = 0.004). However, no linear relationship was found between FPG concentrations and BSA levels (p = 0.61), nor was there a significant interaction effect (p = 0.11). The continuous BSA spline curve indicates that men with below-average BSA had higher FPG concentrations than women, whereas no sex-related differences were observed at larger BSA levels (**Figure 16**).

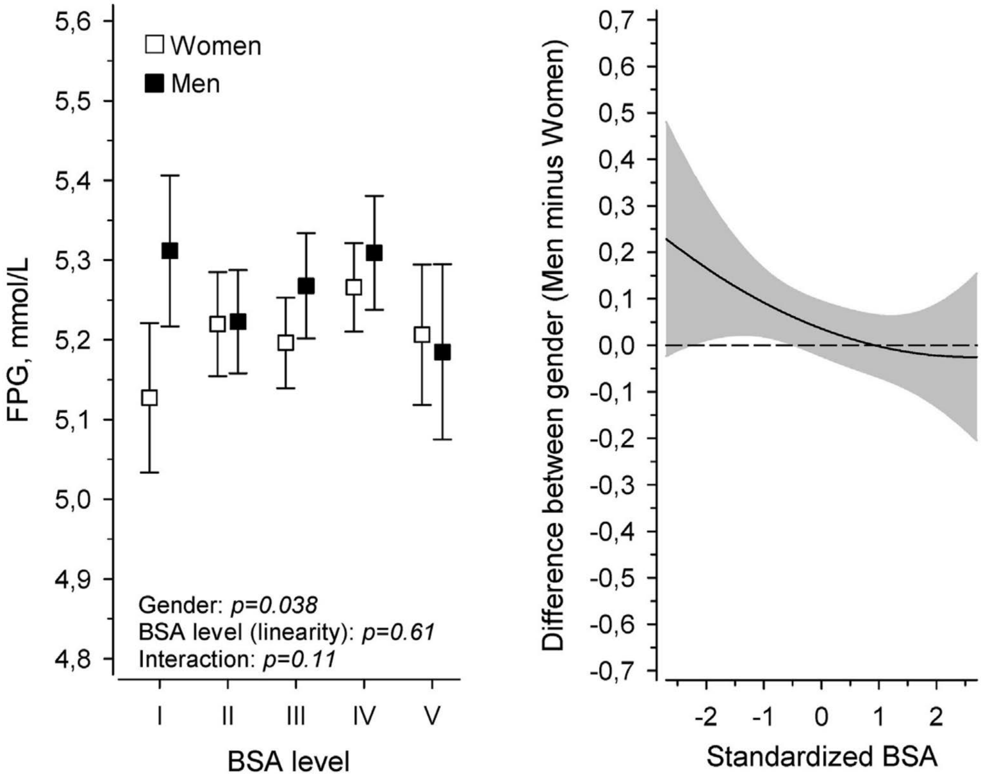


Figure 16. Mean fasting plasma glucose (FPG) by sex-specific body surface area (BSA) level and sex, adjusted for age, waist circumference, leisure-time physical activity, and smoking. Error bars indicate 95% confidence intervals. Differences in continuous FPG between men and women were estimated using a 4-knot restricted cubic spline regression model. The grey area represents the 95% confidence interval. From Study III (Palmu et al., 2021). © The Author(s) 2021. Published by Elsevier. Distributed under the terms of the Creative Commons Attribution 4.0 License (https://creativecommons.org/licenses/by/4.0/).

Women consistently had higher mean 2hPG concentrations than men across all BSA levels (p <0.001). In both sexes, 2hPG concentrations demonstrated a negative linear relationship with BSA levels (p for linearity <0.001), with no significant interaction effect (p = 0.36). The difference in 2hPG concentrations between men and women was most pronounced at the largest BSA level, measuring 0.76 mmol/L (95% CI: 1.15 to 0.37, p <0.001).(**Figure 17**)

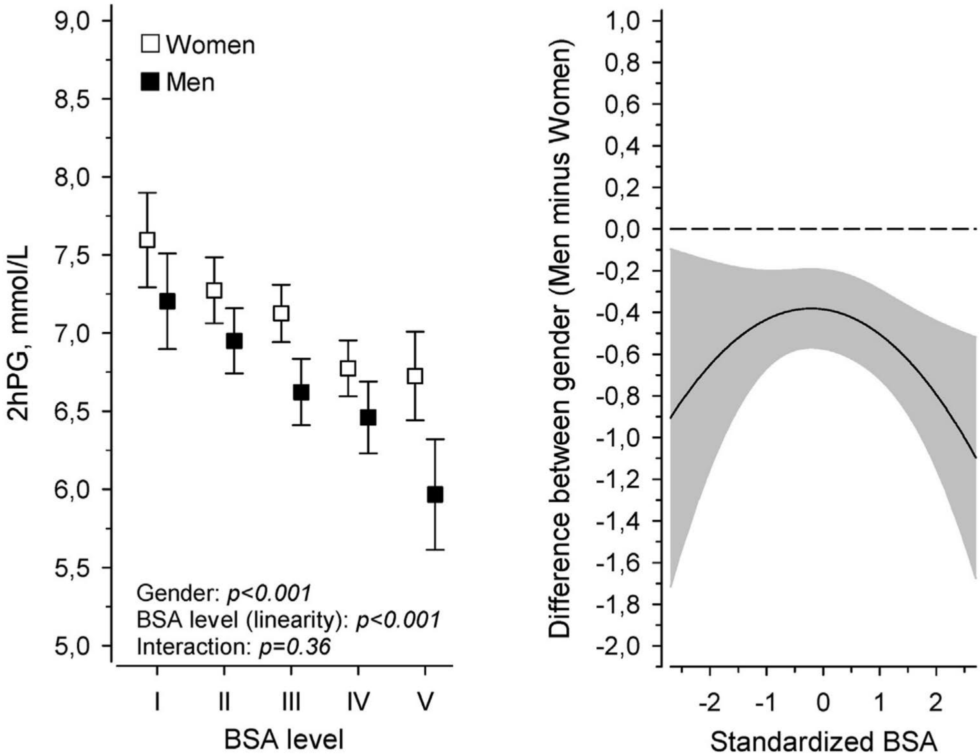


Figure 17. Mean 2-hour plasma glucose (2hPG) by sex-specific body surface area (BSA) level and sex, adjusted for age, waist circumference, leisure-time physical activity, and smoking. Error bars indicate 95% confidence intervals. Differences in continuous 2hPG between men and women were estimated using a 4-knot restricted cubic spline regression model. The grey area represents the 95% confidence interval.

5.4 Body Surface Area and Ankle-Brachial Index (Study IV)

In Study IV, we evaluated 972 subjects at high CVD risk. Their mean age was 59 years (SD 7), 53% being women. Characteristics of the study subjects according to BSA levels are shown in **Table 21**. The mean BSA was 1.98 m^2 (SD 0.22), with an average of 1.88 m^2 (SD 0.20) in women and 2.09 m^2 (SD 0.19) in men. The mean ABI was 1.08 (SD 0.12), with values of 1.08 (SD 0.12) in women and 1.09 (SD 0.12) in men. Subjects with lower BSA were, on average, older and more frequently female compared to those with higher BSA. A larger BSA showed a positive linear association with anthropometric measures, DBP, FPG, triglyceride levels, MetS prevalence, AUDIT score, and vasodilator use. Conversely, BSA was negatively associated with pulse pressure and HDL-C concentration.

Table 21. Characteristics of the study subjects according to body surface area level.

	BODY SURFACE AREA LEVEL					
	I N=121	II N=243	III N=244	IV N=243	V N=121	P-value
BSA	≤1.71	1.72–1.89	1.90–2.03	2.04–2.22	>2.22	
Demographic:						
Number of women, n (%)	115 (95)	188 (77)	113 (46)	72 (30)	29 (24)	<0.001[a]
Age, years, mean (SD)	61 (7)	60 (7)	58 (7)	58 (7)	56 (6)	<0.001[a]
Weight, kg, mean (SD)	61 (5)	73 (4)	83 (4)	93 (5)	113 (12)	<0.001[a]
Height, cm, mean (SD)	158 (6)	163 (6)	169 (7)	174 (8)	179 (9)	<0.001[a]
Waist, cm, mean (SD)	81 (7)	91 (7)	98 (7)	104 (7)	116 (10)	<0.001[a]
Body Mass Index, kg/m^2 mean (SD)	24.4 (2.9)	27.5 (3.1)	29.3 (3.9)	30.8 (4.0)	35.6 (6.6)	<0.001[a]
Clinical:						
Blood pressure, mmHg, mean (SD)						
Systolic	153 (18)	149 (18)	148 (18)	148 (17)	148 (16)	0.082[a]
Diastolic	88 (8)	87 (8)	89 (9)	89 (8)	92 (9)	<0.001[a]
Pulse pressure	65 (15)	61 (14)	59 (14)	59 (13)	56 (12)	<0.001[a]
Fasting glucose, mmol/l, mean (SD)	5.51 (1.77)	5.56 (0.93)	5.74 (1.10)	5.73 (0.82)	6.01 (1.27)	<0.001[a]
Total cholesterol, mmol/l, mean (SD)	5.33 (0.96)	5.40 (1.01)	5.32 (0.94)	5.25 (0.88)	5.18 (0.91)	0.037[a]
HDL-C, mmol/l, mean (SD)	1.72 (0.43)	1.57 (0.38)	1.49 (0.42)	1.39 (0.36)	1.24 (0.31)	<0.001[a]
LDL-C, mmol/l, mean (SD)	3.12 (0.86)	3.23 (0.93)	3.18 (0.83)	3.21 (0.78)	3.19 (0.83)	0.76[a]
Triglycerides, mmol/l, mean (SD)	1.12 (0.51)	1.35 (0.62)	1.41 (0.64)	1.45 (0.76)	1.67 (0.76)	<0.001[a]
Metabolic syndrome present (ATPIII), n (%)	23 (19)	87 (36)	116 (48)	128 (53)	97 (78)	<0.001[a]
Glucose homeostasis, n (%)						<0.001[b]
Normal	70 (58)	123 (51)	111 (45)	117 (48)	54 (45)	
Impaired glucose tolerance	17 (14)	63 (26)	70 (29)	86 (35)	37 (31)	

Impaired fasting plasma glucose	28 (23)	48 (20)	48 (20)	25 (10)	17 (14)	
Type 2 diabetes	6 (5)	9 (4)	15 (6)	15 (6)	13 (11)	
Health behaviors						
Current smokers, n (%)	21 (17)	32 (13)	45 (18)	50 (21)	22 (18)	0.17[a]
AUDIT, mean (SD)	2.7 (2.9)	4.2 (5.1)	5.8 (5.4)	5.4 (5.1)	6.0 (5.4)	<0.001[a]
LTPA, n (%)						0.079[a]
Low	20 (17)	35 (14)	30 (12)	34 (14)	13 (11)	
Moderate	81 (67)	159 (65)	179 (73)	157 (65)	78 (64)	
High	20 (17)	49 (20)	34 (14)	52 (21)	30 (25)	
Current medication, n (%)						
Vasodilatators	30 (25)	66 (27)	74 (30)	73 (30)	44 (36)	0.044[a]
Beta-blockers	22 (18)	57 (23)	47 (19)	55 (23)	24 (20)	0.90[a]
Diuretics	11 (9)	24 (10)	17 (7)	30 (12)	18 (15)	0.084[a]
Statins	21 (17)	35 (14)	41 (17)	34 (14)	9 (7)	0.062[a]
ABI, n (%)						
≤0.90	9(7)	9(4)	16(7)	9(4)	6(5)	0.47[a]
≤1.00	37(31)	71(29)	61(25)	45(19)	27(22)	0.005[a]

[a] Linearity across BSA levels; [b] differences between BSA levels. Modified (units in mmol/l added in the table) from Study IV (Palmu et al., 2024).
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Figure 18 illustrates the distribution of BSA and ABI among men and women. After adjusting for age, sex, pulse pressure, glucose regulation, AUDIT score, LTPA, smoking status, and WC, BSA level exhibited a positive linear relationship with ABI (**Figure 19**a). Additionally, the continuous BSA spline curve demonstrated a positive association with ABI (**Figure 19**b). **Figure 20** illustrates the difference in ABI between sexes (males minus females) as a function of BSA. When BSA was below 2.0 m^2 (the estimated inflection point), no significant difference was observed between sexes. However, for BSA values exceeding 2.0 m^2, men exhibited higher ABI than women. In the regression analysis, height was positively associated with ABI in men (**Figure 21**). When both sexes were analysed together, both weight and height demonstrated a positive relationship with ABI.

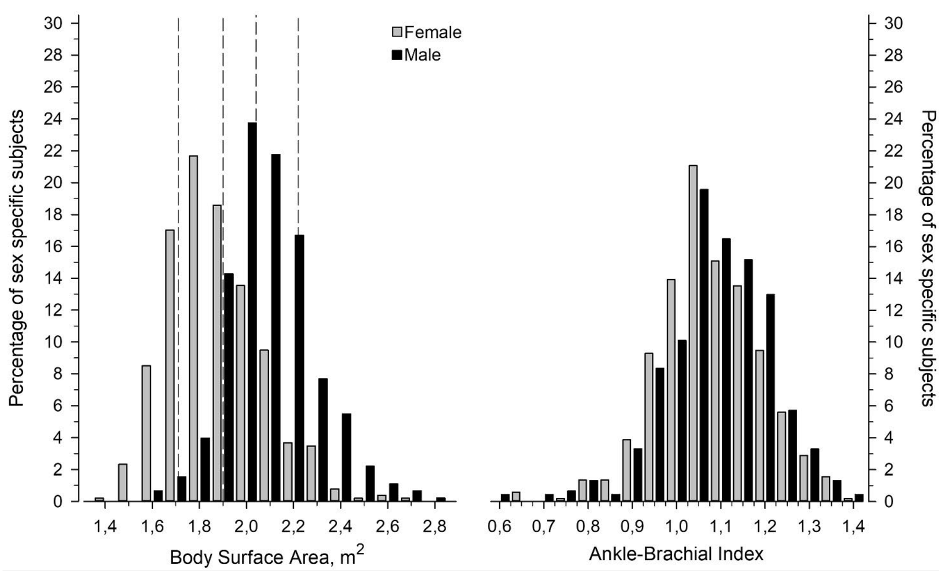


Figure 18. Distribution of body surface area and ankle-brachial index in male and female subjects. The dotted vertical lines indicate BSA values categorized into five levels, corresponding to the 12.5th, 25th, 25th, 25th, and 12.5th percentiles of the total distribution. From Study IV (Palmu et al., 2024).

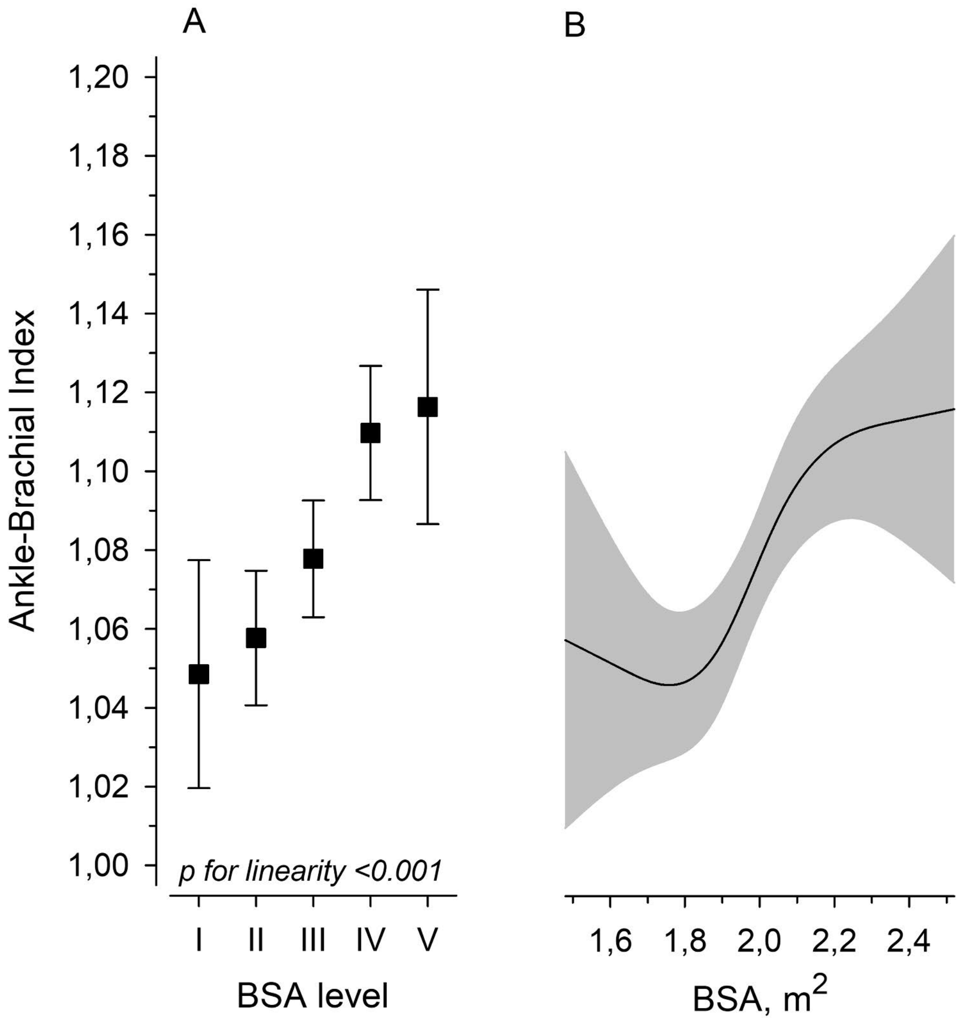


Figure 19. Mean ankle-brachial index (ABI) values across different levels of body surface area (BSA). Error bars indicate the 95% confidence intervals. (a) Continuous ABI values by BSA were estimated using a four-knot restricted cubic splines regression model, with the grey area representing the 95% confidence interval. (b) Models were adjusted for sex, pulse pressure, age, glucose regulation, waist circumference, AUDIT score, smoking status, leisure-time physical activity, and medication use. From Study IV (Palmu et al., 2024). © The Author(s) 2024. Published by Sage Publications. Distributed under the terms of the Creative Commons Attribution 4.0 License (https://creativecommons.org/licenses/by/4.0/).

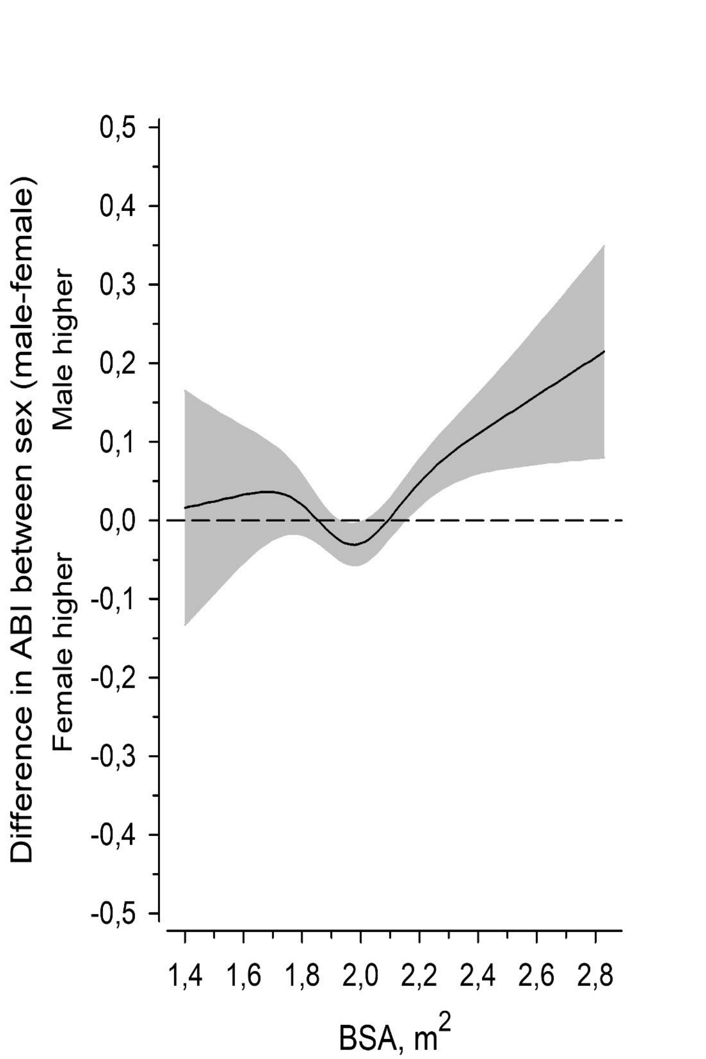


Figure 20. Effect modification of the ankle-brachial index (ABI) by body size between sexes (male–female) as a function of body surface area (BSA), estimated using a four-knot restricted cubic splines regression model. The grey area represents the 95% confidence interval. Adjusted for pulse pressure, age, glucose regulation, waist circumference, AUDIT score, smoking status, leisure-time physical activity, and cardiovascular medication. From Study IV (Palmu et al., 2024).

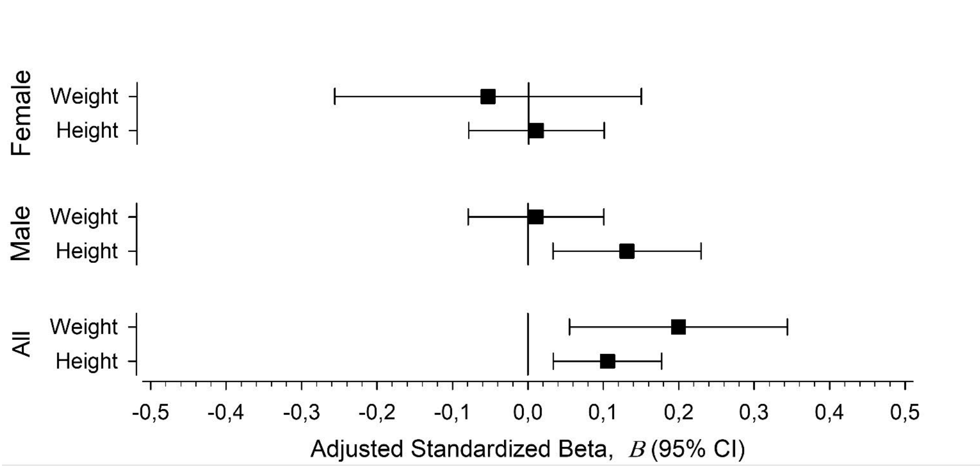


Figure 21. Univariate associations between continuous body size predictive variables (height and weight) and ankle-brachial index (ABI). Adjusted standardized beta coefficients (β) with 95% confidence intervals. Models were adjusted for pulse pressure, age, AUDIT score, smoking status, waist circumference, leisure-time physical activity, glucose regulation, and cardiovascular medication. From Study IV (Palmu et al., 2024).

6 Discussion

6.1 Study Population

The Helsinki Birth Cohort Study included 8,760 men and women born at Helsinki University Central Hospital between 1934 and 1944. For the clinical study, a subset of individuals from the original epidemiological cohort was selected using random-number tables, including only those who were still alive and residing in Finland in 1971, when a unique personal identifier was given to the Finnish population. A subset of 2,691 individuals was invited to participate, and 2,003 attended clinic visits between 2001 and 2004. The study I population included 534 individuals (mean age 61 years, SD 3 years) who had no history of using medication that affects the CV system. The cohort is a globally unique birth cohort. However, as participants were born in Helsinki, and the clinical cohort was drawn from the Helsinki metropolitan area, this may affect generalisability to the entire Finnish population.

Study II–IV data of the Harmonica project were gathered in a population survey which was conducted in south-western Finland in the rural towns of Harjavalta and Kokemäki in 2005–2007. The study population was 45–70 years old home-dwelling citizen at the time of the enrolment. The participation rate was 74% (4,450/6,013). Each of 2,752 participants had at least one CVD risk factor but no prior diagnosis of DM, CVD, or CKD. A response rate of at least 70% is representative for population surveys (Tolonen et al., 2006) and 74% was above the average response rate in the beginning of the millennium. The respondents consisted of 56% women and 44% men. Women were slightly overrepresented compared to sex-distribution of the Finnish population in 2007 (51% women, 49% men) (Official Statistics of Finland (OSF), 2007), which is normal in population surveys (Tolonen et al., 2006). Thus, the study population was representative of the middle-aged Finnish population at risk for CVD.

6.2 Methods

6.2.1 Questionnaires

Questionnaires are an easy and cost-effective method to collect data on health behaviour. It is well documented that undesired health behaviour such as tobacco smoking may be underestimated when self-reported (Gorber et al., 2009). However, self-reported drinking demonstrated sufficient reliability and validity when assessed structured to reduce bias (Babor et al., 1989; Del Boca & Darkes, 2003).

6.2.2 Physical Examination

BP was measured by a trained study nurse using a calibrated device and a proper sized cuff. In study I ABPM was also performed with an appropriate device. Height, weight, and WC were measured by a trained study nurse with calibrated devices. The average difference between self-measured and nurse-measured WC was -3.76 cm ± 6.59 in women and -2.41 cm ± 4.49 in men ($p < 0.001$) in studies II–IV (Korhonen et al., 2009). The professionally measured WC was used in analyses.

SBP measurements for ABI calculation were taken by a single physician. This is a strength since measurements were thus performed consistently. ABI measurements were taken according to the guidelines. However, for logistic reasons, the posterior tibial artery was used if the dorsalis pedis pulse was not detectable. It is possible that ABI values could have been higher in some subjects if also the posterior tibial artery had been used. ABI was calculated by dividing the lower ankle SBP by the higher brachial SBP. This is a proper procedure (compared to using higher ankle SBP) for a CVD prevention program since this method for calculating ABI has been demonstrated to identify a greater number of subjects at increased risk of CVD (Espinola-Klein et al., 2008).

6.2.3 Laboratory Measurements

In studies II–IV, FPG and 2hPG concentrations were measured from capillary whole blood using an analyzer that converts the results to PG values and glucose disorders were classified according to the WHO guidelines (World Health Organization, 1999). Current guidelines recommend use of venous PG samples though WHO accepts measurement of glucose in capillary blood (Sacks et al., 2023; World Health Organization, 2006). In study I, FPG concentrations were determined using the hexokinase method. Cholesterol values were measured using proper devices and values are reliable. In studies II–IV LDL-C was calculated using Friedewald's formula (Friedewald et al., 1972).

6.3 Results

6.3.1 Body Surface Area and Blood Pressure (Study I)

In study I, BSA was positively associated with ambulatory daytime and nighttime BP values even after adjusting for age, smoking, LTPA, and body fat percentage. Although men have higher absolute BP values, when BP was indexed to BSA, women exhibit a significantly higher BP load per BSA. This may help explain reported sex differences in BP-related morbidity.

Hypertension prevalence is higher in men until the age of 45 years, but the prevalence surpasses in women after age of 60 years both in developed and developing countries (Go et al., 2013; Prince et al., 2012; Robitaille et al., 2012). Several hypotheses have been proposed to explain this age-related sex disparity. Some studies suggest that while women are more likely to be aware of their hypertension, they are less likely than men to achieve adequate BP control, particularly beyond the age of 60 years (Egan et al., 2010; Gee et al., 2012). Hypertensive women are more prone to developing concentric left ventricular hypertrophy (Piro et al., 2010) and have more frequently HFpEF compared to men (Borlaug & Redfield, 2011). Arterial stiffness is more pronounced in older women (Rossi et al., 2011; Shim et al., 2011). Pulse pressure amplification, characterized by higher BP in peripheral compared to central arteries, is notably elevated in postmenopausal women (Benetos et al., 2010). Although the mechanisms underlying these BP-related sex differences remain unclear, the research on body size difference between women and men is quite limited.

Aortic valve area, and the cross-sectional areas of cardiac structures, such as left ventricle and pulmonary arteries show a linear correlation with BSA (Gutgesell & Rembold, 1990). Diameter of arteries from ascending aorta to popliteal artery also are proportional to BSA (Biaggi et al., 2009; Dietenbeck et al., 2021; Jones et al., 2018; Sandgren et al., 1998, 1999). Given that blood vessels are organs of tubular shape, and the size of several arteries shows linear association with BSA, it is reasonable to explore the relationship between BSA and BP. According to Poiseuille's law (Pfitzner, 1976) a wider pipe is associated with lower flow resistance and higher volume flow rate. Since radius affects flow to the fourth power, even

$$F = (P_A - P_B) \times \left(\frac{\pi}{8}\right) \times \left(\frac{1}{\eta}\right) \times \left(\frac{r^4}{L}\right)$$

Figure 22. Poiseuille-Hagen formula (Ganong, 2003). F = flow, P_A-P_B = pressure difference between the two ends of the tube, η = viscosity, r = radius of tube, L = length of tube

small changes in the calibre of the vessel can significantly impact blood flow (Ganong, 2003). **Figure 22** shows Poiseuille-Hagen formula.

Current BP guidelines (McEvoy et al., 2024) do not account for sex or body size, applying the same normal BP ranges to both adult men and women. In nonhuman mammals, BP is well recognized to vary with body size (Paton et al., 2009). Our findings confirm that, in humans, BP load per unit of BSA is higher in smaller individuals compared to larger ones. Therefore, adjusting BP values for body size, such as BSA, could help explain why women experience higher rates of uncontrolled hypertension (Egan et al., 2010; Gee et al., 2012), left ventricular hypertrophy (Piro et al., 2010), HFpEF (Borlaug & Redfield, 2011), poorer outcomes after stroke (Reeves et al., 2008), and worse prognoses following percutaneous coronary intervention or coronary bypass surgery (Stramba-Badiale et al., 2006). Indexing BP to BSA may also enhance CVD risk prediction across individuals of varying body sizes. Notably, BSA has already been inversely associated with total and CVD mortality in patients with chronic heart failure (Futter et al., 2011; Zafrir et al., 2015). However, it remains uncertain whether BSA-based BP indexing is the optimal method for adjusting BP to body size.

6.3.2 Body Surface Area and the Oral Glucose Tolerance Test (Study II and III)

In Study II, we analysed the relationship between BSA and plasma glucose (PG) concentrations in an OGTT in apparently healthy individuals who were at risk for CVD. The main finding was that the proportion of newly diagnosed T2D based on 2hPG values adjusted for age, sex, smoking status, LTPA, alcohol intake, and WC, was significantly higher when BSA was smaller. Thus, there is a possibility that an OGTT-based T2D diagnosis may cause a false positive result in a relatively smaller individual and a false negative result in a relatively larger individual considering the ingestion of the uniform 75 g glucose dose in an OGTT.

We utilized the 2hPG/FPG ratio to assess the extent to which the 75 g glucose dose increased 2hPG concentration relative to FPG levels. Regardless of glucose tolerance category, 2hPG was lower in relation to FPG as BSA increased. This suggests that the uniform 75 g glucose dose has a smaller impact on 2hPG levels in individuals with larger body size, even when FPG concentration taken into account.

Adjusted BSA may be considered to represent the body's structural framework, housing organs involved in glucose absorption, utilization, and production. A larger framework may likely correspond to larger internal organs and muscle mass. Indeed, a larger BSA has been shown to predict higher total liver volume (Vauthey et al., 2002) and diameter of arteries from ascending aorta to popliteal artery (Biaggi et al., 2009; Dietenbeck et al., 2021; Jones et al., 2018; Sandgren et al., 1998, 1999).

Moreover, the glucose uptake by brain, skeletal muscle, and heart per unit of time is proportional to BSA (Zierler, 1999). Men have significantly more skeletal muscle than women, both in absolute terms and relative to body mass, and height is positively associated with muscle mass in both sexes, indicating that taller individuals generally have more muscle (Janssen et al., 2000).

Although we suggest that 2hPG values may be influenced by body size, it is important to note that, according to a meta-analysis by Huang et al., 2hPG demonstrated a stronger predictive value for all-cause mortality than elevated FPG (Huang, Cai, et al., 2016). In the studies included in the meta-analysis on individuals with impaired glucose regulation, adjustments for body height or BSA were not made. Moreover, in a pooled analysis of 96 population-based studies, the global prevalence of DM estimated using FPG alone was 2–6 percentage points lower than prevalence estimates based on either FPG or 2hPG. (Danaei et al., 2015). Our findings indicate that higher 2hPG concentrations during a 75 g OGTT characterize individuals with generally smaller body size. Shorter body height is a well-established risk factor for both CVD and all-cause mortality (C. M. Y. Lee et al., 2009; Schmidt et al., 2014; The Emerging Risk Factors Collaboration, 2012). Therefore, after adjusting for body size-related factors such as body height or BSA, the association between 2hPG concentrations and increased mortality risk may no longer be significant.

In Study III, we analysed the relationship between BSA, sex, and PG concentrations in an OGTT in apparently healthy individuals who were at risk for CVD and had normal glucose regulation in an OGTT (FPG concentrations were <6.1 mmol/l and 2hPG concentrations were <8.9 mmol/l) according to the WHO 1999 criteria (World Health Organization, 1999).

Within the normal PG range, apparently healthy women had higher mean 2hPG levels than men in an OGTT across all sex-specific BSA levels. In both sexes, higher BSA was associated with lower 2hPG levels, even when adjusted for age, WC, LTPA, and smoking. This suggests a physiological phenomenon associated to body size. Unlike BMI, BSA accounts for body size differences between men and women. Apparently healthy men had slightly higher mean FPG than women, with no interaction with BSA. This may be due to fundamental sex differences in the metabolism of carbohydrates and lipids as energy sources (Mauvais-Jarvis, 2015). At rest and in the post-absorptive state, the female body preferentially promotes energy storage (Kautzky-Willer et al., 2016). This may help to explain why women exhibit lower fasting endogenous glucose production (Anderwald et al., 2011).

Adult height is influenced by both genetic and environmental factors (Silventoinen, 2003). On average, women have a higher proportion of adipose tissue and lower skeletal muscle mass than men, along with a greater tendency for fat accumulation (Mauvais-Jarvis, 2015). The relationship between weight and height differs between sexes, and BMI is not independent of height, often showing an inverse correlation in most populations (Diverse Populations Collaborative Group, 2005). At the same BMI, women typically have a higher percentage of body fat than men (Rothman, 2008). Despite these differences, height or BSA is rarely considered in epidemiological studies (Richter et al., 2018).

In conclusion, study II shows that the OGTT detects more cases of T2D and IGT in subjects with relatively smaller body sizes. In study III, we focused on the normoglycaemic range and analysed men and women separately. In both sexes, BSA was negatively associated with 2hPG, and women exhibited higher mean 2hPG concentrations than men after adjustment with age, abdominal obesity, LTPA, and smoking. This finding suggests a physiological relationship between body size and glucose metabolism. Sex and body size are important factors to consider when evaluating glucose metabolism using an OGTT.

6.3.3 Body Surface Area and Ankle-Brachial Index (Study IV)

A larger BSA was associated to a higher ABI in our CVD risk population, even after adjustment for sex, pulse pressure, age, glucose regulation, AUDIT score, smoking status, WC, LTPA, and medication. The difference in ABI between men and women can largely be attributed to effect modification by BSA, with the disparity becoming more pronounced when BSA exceeds 2.0 m^2. This means that sex differences in ABI can be explained by the fact that men have on average larger BSA than women.

An abnormal ABI is a reliable indicator of CVD risk, generalized atherosclerosis, and all-cause mortality (Aboyans et al., 2018; Ankle Brachial Index Collaboration, 2008; Resnick et al., 2004). Adou et al. reported that the overall prevalence of LEAD was 9.7% in a population with an average age of 60 years. Prevalence varied by sex, with 10.2% in women and 8.8% in men, and this difference could not be explained by age differences. According to Adou et al, this disparity may partly result from the naturally lower ABI values in women, even in the absence of traditional risk factors. The "J-shaped" curve observed in the prevalence of LEAD across age groups in women suggested that LEAD prevalence in younger women may be overestimated due to lower ABI values not associated with occlusive disease. This limits the use of ABI as the sole diagnostic criterion across different sexes and age groups.(Adou et al., 2024)

Healthy women have been reported to have lower ABI compared to men which was considered as a normal phenomenon with some contribution of height (Kapoor et al., 2018). In a low CVD risk population, women had lower ABI than men, though the relationship between height and ABI was minor (Aboyans et al., 2007). Height in men in univariate analysis showed a positive association with ABI (as previously reported (Heikkilä et al., 2016)) while height in women or weight in both sexes did not in our study population. However, when both sexes were analysed together, height and weight showed a positive relationship with ABI. This is in line with the finding in this study that BSA functions as an effect modifier on ABI. The difference in ABI between men and women is influenced by BSA and becomes notable when BSA exceeds 2.0 m^2. Effect modification by body size should be considered in epidemiological studies comparing ABI between men and women. Adjusting ABI values for the actual BSA of a subject may serve as a practical approach to account for sex- and body size-specific variations in ABI interpretation.

6.4 Strengths and Limitations

The major strengths of this study include a representative study population and a comprehensive evaluation of participants. We also accounted for multiple potential confounding variables, including sex, age, anthropometric measures, educational attainment, and lifestyle factors.

In Studies II and III, participants represent a typical primary care population at increased CVD risk, where OGTT is commonly used to detect glucose regulation disorders. The exclusion of individuals with established CVD, CKD, and DM further minimized confounding by comorbidities. Dividing participants into five BSA groups enables comparison with other populations, as BSA follows a normal distribution. However, the findings may not be directly generalisable to populations with different ethnic backgrounds. A strength of Study I is the extensive phenotypic data, including anthropometric measurements at birth.

Another strength of our study is the standardised approach to ABI measurements, all conducted by the same physician, ensuring consistency. Additionally, comprehensive data on risk factors and medical history were collected.

While lifestyle-related factors were assessed using self-administered questionnaires and dietary habits were not recorded, anthropometric measurements were performed by trained medical staff. Despite the robust data collection, the primary limitation of our study is its cross-sectional design, which prevents the assessment of causality in the relationship between BSA and BP, OGTT, or ABI.

6.5 Implications for Future Research

This study presents implications for future research. Individuals with relatively smaller body sizes may benefit from earlier initiation of antihypertensive medication and targeting lower BP levels compared to those with larger body sizes. Further research is needed to establish a threshold for body size that would justify a more aggressive therapeutic approach.

Body size affects OGTT results, and therefore, different glucose doses according to body size would be necessary in order to obtain accurate results, which is cumbersome. HbA_{1c} was not measured in this study, and its relationship with body size would be a subject of future research.

The difference in ABI between men and women is modified by BSA. A prospective study could help confirm the relationship between BSA and ABI in relation to the development of LEAD, mortality, and the potential need to adjust diagnostic ABI thresholds.

7 Conclusion

BSA is positively associated with ambulatory daytime and nighttime BP values even when the effect of adiposity is accounted for. BP load per unit of BSA is significantly higher in women than in men, potentially contributing to observed sex differences in CVD morbidity. BSA significantly influences the outcome of an OGTT, with smaller individuals being more likely to be diagnosed with pre-diabetes or T2D than larger individuals. BSA is inversely related to 2hPG concentration in both sexes, with women exhibiting higher 2hPG levels than men in an OGTT, even within the physiological PG range. This may lead to an underestimation of glucose disorders in individuals with larger BSA and an overestimation in those with smaller BSA when using OGTT. Effect modification by BSA should be considered in epidemiological studies comparing ABI between men and women. Adjusting ABI values for the actual BSA of a subject may serve as a practical approach to account for sex- and body size-specific variations in ABI interpretation.

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