UiT The Arctic University of Norway

Faculty of Health Sciences

Prevalence of obesity and its associations with other cardiovascular risk factors in Russia

Insights from the Know Your Heart Study

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The cover photo is made by K. Kholmatova

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Abbreviations

AO	abdominal obesity
ApoB	apolipoprotein B
ATC	WHO Anatomical Therapeutic Chemical Classification System
AUC	area under the receiver operating characteristic curve
AUDIT	Alcohol Use Disorders Identification Test
BIA	biological impedance analysis
BFP	body fat percentage
BMI	body mass index
CHD	coronary heart disease
CT	computed tomography
CVD	cardiovascular diseases
DALYs	disability-adjusted life years
DBP	diastolic blood pressure
DQS	Dietary Quality Score
DXA	dual-energy X-ray absorptiometry
EPIC	European Prospective Investigation into Cancer and Nutrition
ESP2013	European Standard Population 2013
FMI	fat mass index
GAD-7	General Anxiety Disorder-7
GO	general obesity
HbA1c	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IPCDR	International Project on Cardiovascular Disease in Russia

kg	kilogram
KYH	Know Your Heart study
LDL-C	low-density lipoprotein cholesterol
MetS	metabolic syndrome
mmHg	millimeter of mercury
mmol/L	millimole per liter
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
non-HDL-C	non high-density lipoprotein cholesterol
OR	odds ratio
PHQ-9	Patient Health Questionnaire-9
PR	prevalence ratio
ROC	receiver operating characteristic
SBP	systolic blood pressure
SEP	socio-economic position
T2D	type 2 diabetes mellitus
TC	total cholesterol
Tromsø 7	Tromsø 7 Study
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
WHtR	waist-to-height ratio

List of papers

Paper I

Kholmatova K., Krettek A., Leon D.A., Malyutina S., Cook, S., Hopstock L.A., Løvsletten O., Kudryavtsev A.V.
Obesity Prevalence and Associated Socio-Demographic Characteristics and Health Behaviors in Russia and Norway.
International Journal of Environmental Research and Public Health 2022, 19 (15): 9428.
https://doi.org/10.3390/ijerph19159428

Paper II

Kholmatova K., Krettek A., Dvoryashina I.V., Malyutina S., Kudryavtsev A.V.
Assessing the prevalence of obesity in a Russian adult population by six indices and their associations with hypertension, diabetes mellitus and hypercholesterolaemia.
International Journal of Circumpolar Health 2024, 83 (1): 2386783
https://doi.org/10.1080/22423982.2024.2386783

Paper III

Kholmatova K., Krettek A., Dvoryashina I.V., Malyutina S., Cook S., Avdeeva E., Kudryavtsev A.V.
Waist-to-height ratio – reference values and associations with cardiovascular risk factors in a Russian adult population.
Diabetes, Metabolic Syndrome and Obesity [Submitted]

Summary

Background. The prevalence of obesity has reached epidemic proportions worldwide. Obesity is a risk factor for the development of cardiovascular disease (CVD) and predisposes to hypertension, type 2 diabetes mellitus (T2D) and dyslipidemia. The simultaneous presence of visceral adiposity and these cardiometabolic disorders, also known as the metabolic syndrome, accelerates atherosclerotic development and the onset of CVD. There are various methods to assess obesity, but the metric that best defines cardiometabolic risk has not yet been determined.

Aims. The specific aims of this thesis were to: (1) compare the prevalence of obesity and its possible associations with socio-demographic characteristics and health behaviours in Russia and Norway; (2) assess the prevalence of obesity using six indices and compare their associations with hypertension, hypercholesterolemia and T2D in a Russian adult population; (3) establish reference values for waist-to-height ratio (WHtR) and investigate its associations with socio-demographic, lifestyle and clinical characteristics in Russian adults.

Methods. This thesis is based on data from the population-based cross-sectional Know Your Heart study (KYH, Novosibirsk and Arkhangelsk, Russia, age 35-69 years, N=4495) and from the Tromsø Study 7 (Tromsø 7, Tromsø, Norway, age ≥40 years, N=17646). In Paper I, men and women aged 40-69 years from KYH and Tromsø 7 were compared on the associations of general obesity (GO; body mass index (BMI) ≥30 kg/m^2) and abdominal obesity (AO; waist-to-hip ratio (WHR) ≥0.90/0.85 for men/women) with socio-demographic, economic and behavioural characteristics. In Paper II, the KYH data were used to assess obesity prevalence according to BMI, waist circumference, WHR, WHtR, body fat percentage, and fat mass index (FMI). The predictive values of the six indices for detecting the presence of hypertension, T2D, hypercholesterolemia, and a combination of at least two of these disorders were assessed by calculating the areas under the receiver operating characteristic curves (AUCs). In the KYH-based Paper III, WHtR reference values for Russian men and women were defined. These values were derived as marginal 5th-95th percentiles (P5-P95) from age-adjusted quantile regressions. The associations between WHtR and CVD risk factors and biomarkers were also analysed.

Main results. In KYH women, the age-standardised prevalence of GO (36.7%) and AO (44.2%) were higher compared to Tromsø 7 women (22.0% and 18.4%, respectively). Men in KYH and Tromsø 7 exhibited similar age-standardised prevalence of GO (26.0% vs. 25.7%) and AO (74.8% vs. 72.2%). In KYH women, the growth of GO and AO odds with age was

steeper compared to Tromsø 7 women. In men, on the contrary, there was a steeper growth of AO odds with age in Tromsø 7. Living with spouse or partner had a stronger association with GO in KYH men compared to Tromsø 7 men. Current smoking was negatively associated with GO in both studies (except for KYH women), but positively associated with AO (except for KYH men). Frequent drinking had a negative association with both obesity types in Tromsø 7 men and women, but a positive association with GO in KYH men. As evidenced by the KYH data, the age-standardised prevalence of obesity in Russian adults varies substantially depending on the index used. It was the highest when assessed according to WHtR (75.8% in men and 65.0% women) and the lowest according to FMI (17.2% and 23.6%, respectively). In women, WHtR demonstrated the strongest association with hypertension (AUC = 0.784) and with a combination of at least two cardiometabolic disorders (AUC = 0.779) compared to all other indices. In men, WHtR exhibited the largest AUCs for T2D, hypertension and a combination of cardiometabolic disorders, although this was not significantly different from that of other indices. Based on the KYH data, the P50 value for WHtR was 0.55 in men and 0.54 in women, and the conventional WHtR cutoff for obesity of 0.5 was the value of P25 for both sexes taken together. In terms of socio-demographic characteristics, WHtR was associated with older age, lower education and the city of residence (higher in Novosibirsk vs. Arkhangelsk) in both sexes. In women, WHtR was also associated with a poor financial situation and low physical activity, while in men – with being married and non-smoking. Among the studied clinical parameters, C-reactive protein demonstrated the strongest positive association with WHtR both in men and women (standardised β coefficients 0.435 and 0.321, respectively) and the strongest negative association with high-density lipoprotein (HDL) cholesterol (standardised β coefficients -0.334 and -0.297). The association between WHtR and age, higher education, levels of blood pressure, C-reactive protein and HDL cholesterol was stronger in women than in men.

Conclusion. The prevalence of obesity was comparable between Russian and Norwegian men, but higher in Russian women because of a more pronounced increase with age. Among the six analysed obesity indices, WHtR demonstrated the closest association with hypertension and a combination of at least two cardiometabolic disorders in Russian women, while being non-inferior in men. Three quarters of Russian men and women in KYH had WHtR values exceeding the conventional cutoff for abdominal obesity. The strength of WHtR associations with socio-demographic and clinical parameters differed between KYH men and women. WHtR is therefore recommended as a valuable tool for AO screening and CVD risk identification in clinical practice.

Sammendrag

Bakgrunn. Utbredelsen av fedme har nådd epidemiske proporsjoner over hele verden. Overvekt er en risikofaktor for utvikling av hjerte- og karsykdommer (CVD), og disponerer for hypertensjon, type 2 diabetes (T2D) og dyslipidemi. Visceralt fett kombinert med disse kardiometabolske lidelsene, også kjent som det metabolske syndromet, akselererer aterosklerotisk utvikling som kan føre til CVD. Det finnes ulike metoder for å vurdere fedme, men beregningen som best definerer kardiometabolsk risiko er ennå ikke bestemt.

Mål. De spesifikke målene med denne avhandling var å: (1) sammenligne forekomsten av fedme og dens mulige assosiasjoner med sosiodemografi og helseatferd i Russland og Norge; (2) vurdere forekomsten av fedme ved å bruke seks indekser og sammenligne deres assosiasjoner med hypertensjon, hyperkolesterolemi og T2D i en russisk befolkning; (3) etablere referanseverdier for midje-til-høyde-forhold (WHtR) og undersøke dets assosiasjoner til sosiodemografiske, livsstils- og kliniske egenskaper hos voksne russere.

Metoder. Denne oppgaven er basert på data fra den populasjonsbaserte tverrsnittsundersøkelsen Know Your Heart (KYH, Novosibirsk og Arkhangelsk, Russland, alder 35-69 år, N=4495) og fra Tromsø-studien 7 (Tromsø 7, Tromsø, Norge, alder ≥40 år, N=17646). I Paper I ble menn og kvinner i alderen 40-69 år fra KYH og Tromsø7 sammenlignet for generell fedme (GO; kroppsmasseindeks (BMI) ≥30 kg/m 2) og abdominal fedme (AO); midje-til-hofte-forhold (WHR) ≥0,90/0,85 for menn/kvinner) i forhold til sosiodemografi, økonomi og adferd. I Paper II ble KYH-dataene brukt til å vurdere fedmeprevalens i henhold til BMI, midjeomkrets, WHR, WHtR, kroppsfettprosent og fettmasseindeks (FMI). De prediktive verdiene for de seks indeksene for å påvise tilstedeværelsen av hypertensjon, T2D, hyperkolesterolemi og en kombinasjon av minst to av disse lidelsene ble vurdert ved å beregne arealene under ROC-kurven (AUC). I det KYH-baserte Paper III ble WHtR-referanseverdier for russiske menn og kvinner definert. Disse verdiene ble utledet som marginale 5.-95. persentiler (P5-P95) fra aldersjusterte kvantile regresjoner. Assosiasjonene mellom WHtR og CVD risikofaktorer ble også analysert.

Hovedresultater. Hos KYH-kvinner var aldersstandardisert prevalens av GO (36,7 %) og AO (44,2 %) høyere sammenlignet med kvinner i Tromsø 7 (henholdsvis 22,0 % og 18,4 %). Menn i KYH og Tromsø 7 viste relativt like verdier av GO (26,0 % vs. 25,7 %) og AO (74,8 % vs. 72,2 %). Hos KYH-kvinner økte GO og AO odds med alderen brattere enn hos kvinner i Tromsø 7. Hos menn var det tvert imot en brattere vekst av AO-odds med alderen i Tromsø 7. Samboer med ektefelle eller partner hadde en sterkere tilknytning til GO hos menn i KYH

sammenlignet med Tromsø 7. Nåværende røyking var negativt assosiert med GO i begge studiene (unntatt for KYH-kvinner), men positivt assosiert med AO (unntatt for KYH-menn). Hyppig alkoholdrikking var negativt assosiert med fedme i Tromsø 7 hos menn og kvinner, men positivt assosiert med GO hos KYH-menn. Som det fremgår,av KYH-dataene, varierer den aldersstandardiserte forekomsten av fedme hos russiske voksne betydelig avhengig av indeksen som brukes. Den var høyest ved vurdering i henhold til WHtR (75,8 % hos menn og 65,0 % kvinner) og lavest ifølge FMI (henholdsvis 17,2 % og 23,6 %). Hos kvinner viste WHtR den sterkeste assosiasjonen med hypertensjon (AUC = 0,784) og med en kombinasjon av minst to kardiometabolske lidelser (AUC = 0,779) sammenlignet med alle andre indekser. Hos menn var WHtR størst med AUC-ene for T2D, hypertensjon og en kombinasjon av kardiometabolske lidelser, selv om dette ikke var signifikant forskjellig fra andre indekser. Basert på KYH-dataene var P50-verdien for WHtR 0,55 hos menn og 0,54 hos kvinner, og den konvensjonelle WHtR-grensen for fedme på 0,5 var verdien av P25 for begge kjønn tatt sammen. Når det gjelder sosiodemografi var WHtR assosiert med høyere alder, lavere utdanning og bostedsby (høyere i Novosibirsk vs. Arkhangelsk) hos begge kjønn. Hos kvinner var WHtR også assosiert med dårlig økonomi og lav fysisk aktivitet, mens hos menn – med å være gift og ikke røyke. Blant de studerte kliniske parameterne viste C-reaktivt protein den sterkeste positive assosiasjonen med WHtR både hos menn og kvinner (standardiserte β-koeffisienter henholdsvis 0,435 og 0,321) og den sterkeste negative assosiasjonen med høydensitetslipoprotein (HDL) kolesterol (standardiserte β-koeffisienter -0,334 og -0,297). Sammenhengen mellom WHtR og alder, høyere utdanning, blodtrykk, C-reaktivt protein og HDL kolesterol var sterkere hos kvinner enn hos menn.

Konklusjon. Forekomsten av fedme ble funnet å være sammenlignbar hos russiske og norske menn, men høyere hos russiske kvinner på grunn av en mer uttalt økning med alderen. Blant de seks analyserte fedmeindeksene, visteWHtR den nærmeste assosiasjonen med hypertensjon og en kombinasjon av minst to kardiometabolske lidelser hos russiske kvinner, mens den var ikke-underlegen hos menn. Tre fjerdedeler av russiske menn og kvinner i KYH hadde WHtR-verdier som oversteg den konvensjonelle grensen for fedme. Styrken til WHtR-assosiasjoner med sosiodemografiske og kliniske parametere var forskjellig mellom KYH menn og kvinner. WHtR anbefales derfor som et verdifullt verktøy for AO-screening og CVD-risikoidentifikasjon i klinisk praksis.

1 Introduction

1.1 Epidemiology of obesity

Obesity is a chronic disease characterized by the excessive accumulation of adipose tissue in the body, which presents a threat to health (1). In addition, obesity is a major risk factor for the development of a number of other chronic diseases (1, 2).

Adipose tissue, also known as body fat, is a loose connective tissue, that is composed primarily of adipocytes. It also contains the stromal vascular fraction of cells, including adipose stem cells, preadipocytes, fibroblasts, vascular endothelial cells and a variety of immune cells (3). Adipose tissue plays an important role in the human body, serving as the primary storage depot for energy and water. Furthermore, adipose tissue participates in thermogenesis, in the regulation of phosphorus-calcium metabolism and the metabolism of steroid hormones, in addition to its involvement in the production of hormones and biologically active substances (4, 5). However, an increase in the amount of adipose tissue is associated with a number of adverse effects on the human body. The negative impact of being overweight on human health has been known since the time of Ancient Greece (6). Nevertheless, modern ideas about normal body weight began to form only from the thirties of the 19th century. Prior to this period, medicine mostly struggled with infectious diseases. It was only after an increase in life expectancy that the negative effects of excessive body fat accumulation began to manifest themselves, and obesity became the subject of scientific research.

1.1.1 Prevalence of obesity

The World Health Organization (WHO) has recognized obesity as a non-communicable epidemic of the 21st century due to its high prevalence. Since 1990, the prevalence of obesity among adults has more than doubled worldwide, and among adolescents has quadrupled (1). The most commonly used indicator of general obesity (GO) in epidemiological studies is body mass index (BMI), which is calculated using weight and height (7, 8). In 2022, the WHO reported a gradual increase in the number of overweight and obese adults aged 18 years and over compared to 2016. The number of overweight individuals (BMI $\geq$ 25 kg/m^2) increased from 2.5 billion to 3.1 billion, while the number of obese individuals (BMI $\geq$ 30 kg/m^2) increased from 890 million to 940 million. Consequently, in 2022, 16% of adults worldwide were obese. It is projected that by 2030, 60% of the global population may be either overweight (2.2 billion) or obese (1.1 billion) if the current trends in the incidence of obesity persist (2).

The prevalence of obesity varies by region and country. In the European region, it was 23% (21.8% in men and 24.5% in women) (2). Obesity prevalence ranged from 19.7% in Denmark to 27.8% in the United Kingdom (2, 9-12). In Russia, compared to European indicators, the prevalence of obesity is higher in women (26.9%), but lower in men (18.1%) (2). The growth rate of obesity in Russia has increased in recent years. The annual growth in the prevalence of obesity ranged between 0.1-0.2% in 1998-2004 and 0.2-0.3% in 2005-2016 (7).

1.1.2 Aetiology of obesity

Adipose tissue is present in varying amounts in all organs of the body, and its physiological distribution depends on many modifiable and non-modifiable factors, including age, gender, ethnicity, genetic characteristics and lifestyle (5). The heritability of BMI has been estimated to range from 40 to 70%, and several genes have been identified that regulate body weight and metabolism (2, 5).

Extensive accumulation of adipose tissue can be caused by various factors. Obesity can be an independent disease or a syndrome that develops in conjunction with other diseases. In the latter case, excess body weight can be eliminated after the cure or compensation of the underlying disease (5). In accordance with the aetiological principle, obesity is classified into primary and secondary types (5, 13). Primary obesity is referred to as exogenous constitutional or alimentary obesity. Secondary or symptomatic obesity is caused by other diseases. Obesity caused by an established genetic defect includes monogenic disorders (melanocortin-4 receptor mutation, leptin deficiency, proopiomlanocortin deficiency) or known genetic syndromes (Pechkraans-Babinsky-Frilik's, Cohen, Bardet-Biedl, etc.). Neurologic obesity is a result of brain tumors or injuries, dissemination of systemic lesions and infectious diseases or consequences of cranial irradiation. Endocrinopathies associated with obesity include diseases of the hypothalamic-pituitary system, adrenal glands, pseodohypoparathyroidism and hypothyroidism. Psychological obesity is caused by depression or eating disorders. Iatrogenic obesity occurs when medications that contribute to weight gain are taken (tricyclic antidepressants, oral contraceptives, antipsychotics, glucocorticoids, etc.).

Primary obesity is the most common form (14). This type of obesity is multifactorial in nature, involving lifestyle, various neurohumoral mechanisms and environmental factors (5). In 95% of cases, obesity is based on a neurochemical defect in the cerebral systems that regulate eating behavior and hormonal status (15).

The key aetiological mechanism of obesity is an imbalance between energy intake and expenditure. To ensure energy balance, the energy consumed must be equal to the energy expended. An individual's energy intake depends on three factors. The first factor is the basal metabolic rate, measured in proportion to body weight (excluding fat) and body surface area. It represents the expenditure of energy to maintain basic physiological functions under standard conditions. The second factor is the thermogenic effect (specific dynamic effect of food), which accounts for about 5-10% of the total energy expenditure (in people with high physical activity - up to 15%) and is associated with additional energy costs for digestion and stimulation of metabolism due to the influx of a new substrate. The third factor of energy expenditure is physical activity, which leads to the greatest and significantly different energy expenditure (16).

Despite the hereditary predisposition, the high rates of obesity over the past 30 years have been mainly due to cultural and environmental changes. The main factors contributing to the development of obesity are: high-calorie diets, increased portion sizes, disturbed daily eating rhythm, sedentary lifestyles and chronic stress (5). However, these factors are modifiable, while the hereditary predisposition to develop obesity is manifested in the phenotype under the influence of these factors.

Additionally, there are a number of other non-modifiable and modifiable factors associated with obesity. Positive associations of obesity with age have been described previously (8, 15, 17-24). The association of obesity with sex varies across socioeconomic position (SEP) and cultural values (15, 25, 26). In high-income countries, people with lower income and education levels have higher obesity prevalence, whereas in low-income countries obesity is associated with higher SE (25, 27-29). While smoking is associated with lower obesity prevalence (30-32), the role of alcohol consumption in weight gain is controversial and may have large individual variability (33). Alcohol calories count more in non-daily consumers of moderate amounts of alcohol, than in daily or heavy alcohol consumers (34).

Obesity is associated with urbanization and market environment (15). The increasing importance of urban lifestyle in the development of modern society and the associated chronodisruption (changes in the circadian rhythms) and prolonged use of modern communication devices play an important role in the development and progression of obesity. Besides, digital food marketing, food transition and increasing sale of cheaper, more energy-dense and less nutritionally beneficial foods contribute to the growth in the prevalence of obesity (2, 5, 13, 15, 35).

1.1.3 Pathogenesis of obesity

Both the type and distribution of adipose tissue largely determine its function and effects in addition to its direct amount (36). There are two major types of adipose tissue: white adipose tissue and brown adipose tissue (3, 36). The main function of white adipose tissue is to store excess energy as triglycerides. The main function of brown adipose tissue is thermogenesis, the dissipation of energy through the production of heat (3, 36). Brown adipose tissue is most developed in newborns, but its amount regresses with age (4, 36). White adipose tissue is located subcutaneously, especially in the lower part of the abdominal wall, on the buttocks and thighs. It is also found in intraabdominal area: in the omentum, mesentery and retroperitoneal area (35-38).

There are also so-called gynoid (female type, pear shape) and android, or visceral (abdominal, male type, apple shape) obesity (39). Gynoid obesity is characterised by fat deposition mainly subcutaneously, in the hips and buttocks. The android type of obesity is characterised by the localization of fat in the abdominal area (40). Abdominal obesity (AO) is also referred to as central or visceral obesity (8). An abdominal adipose tissue is represented by two components: subcutaneous and visceral (41). Currently, the visceral fat depot is considered from the position of an organ with an independent endocrine function that produces many highly active substances, including free fatty acids, adipokines, interleukin-6, tumor necrosis factor-α and others (42, 43). Gradually, structural changes, such as hypertrophy and hyperplasia of adipocytes, are observed in adipose tissue. They lead to the development of chronic inflammation of adipose tissue and changes in its secretory function. Chronic adipose tissue inflammation, in turn, underlies the pathogenesis of insulin resistance (42, 43). It is the central type of obesity with visceral fat deposition that leads to the obesity-related metabolic and cardiovascular diseases (CVD) (44-49).

1.2 Health consequences of obesity

The clinical picture of obesity is not specific. It is determined by the actual increased body weight and the presence of concomitant diseases, the course of which is directly dependent on body weight. For this reason, obese people often do not seek medical help until they develop obesity-related diseases.

1.2.1 Metabolic disorders

A variety of metabolic disorders have been linked to abdominal adipose tissue (8). These include decreased glucose tolerance, reduced insulin sensitivity, hypertension and an unfavorable lipid profile (44, 50). The relationship between obesity and metabolic disorders is based on the development of secondary insulin resistance. Compensatory hyperinsulinemia, which inevitably develops in the presence of insulin resistance, leads to additional increase in body weight, creating a vicious circle that causes a number of other pathophysiological complications, including an impact on systemic glucose homoeostasis (50, 51). In individuals with obesity, a dysfunction of adipose tissue results in an imbalance in adipokine production, infiltration of immune cells and secretion of inflammatory cytokines. This results in an inflammatory process in the adipose tissue and a systemic low-grade chronic inflammation (52, 53). Low-grade inflammation influences metabolic homeostasis and contributes to CVD development (54-56). Visceral adiposity activates endothelial dysfunction and oxidative stress, thereby exacerbating insulin resistance (42, 43).

Obesity is the main factor causing the development of type 2 diabetes mellitus (T2D); up to 90% of patients with T2D are obese (1, 4). T2D is characterized by insufficient insulin secretion and peripheral insulin resistance in adipose, muscle and liver tissues (42, 57). T2D accounts for 90% of all diabetes forms, and has a worldwide prevalence of 10.5% (9, 57). Decreased insulin sensitivity results in chronic hyperglycemia, leading to damage of blood cells and the vascular intima (57). Hyperglycemia also exacerbates endothelial dysfunction (42, 43). However, this condition may remain undiagnosed for an extended period (57). The main complications of T2D are damage to the heart and blood vessels, kidneys, retina, joints, peripheral and central nerves (42, 57).

Weight gain is commonly accompanied by an increase in blood pressure associated with activation of the sympathetic nervous system (44). Activation of the sympathoadrenal system in obesity is mainly a consequence of insulin resistance, which is caused by decreased insulin receptor density on enlarged adipocytes. An increase in the tone of the sympathoadrenal system is accompanied by activation of the renin-angiotensin-aldosterone system, which together lead to an increase in blood pressure (58, 59). Worldwide, approximately 1.3 billion adults aged 30-79 years have hypertension (60). Obesity and hypertension have a causal relationship (61). Hypertension can also cause damage to blood vessels and the heart, leading to stroke, acute coronary syndrome or heart failure. Hypertension may also cause kidney damage, which leads to renal failure (44).

In hypertensive individuals, the plasma lipid levels are changed towards atherogenic dyslipidemia. In the presence of obesity, this condition had additional adverse effects on the vascular wall (44).

The dysregulation of lipid metabolism in obesity leads to an increase in triglycerides, elevated or normal low-density lipoprotein cholesterol (LDL-C) with an increased proportion of small dense LDL particles. Conversely, there is a decrease in high-density lipoprotein cholesterol (HDL-C) with small HDL and their dysfunction (62, 63). Furthermore, there is a postprandial increase in blood lipid concentrations with the accumulation of atherogenic remnants (64). Overproduction of lipoproteins containing apolipoprotein B (apoB) by the liver results in a high blood concentrations of apoB (63, 64). These obesity-related lipid disorders lead to earlier onset and progression of atherosrclerosis (55, 65).

Abnormal accumulation of body fat, particularly visceral adiposity, shows a strong association with risk of CVD, hyperinsulinemia, hypertension and hyperlipidemia (66-68). The metabolic syndrome (MetS) is a cluster of metabolic disorders, including insulin resistance and hyperglycemia, hypertension and dyslipidemia based on AO (44, 46). Population-based data on MetS are lacking due to different diagnostic criteria (44, 65, 69). However, the prevalence of MetS is approximately three times higher than that of T2D. Thus, more than one billion people, or a quarter of the total worldwide population has MetS (65). This coexistence of CVD risk factors significantly accelerates early atherosclerotic changes and the onset of CVD (55, 65, 69, 70). Thus, obesity is a prevalent driver of metabolic and cardiovascular risk factors that can be prevented by lifestyle modification and pharmacological treatment (62).

1.2.2 Cardiovascular diseases

CVD is the leading cause of death in developed and many developing countries (1, 71). A number of large epidemiological studies, including the Framingham Heart Study, have identified major, or traditional, CVD risk factors (72-74). These include age, sex, high blood pressure, blood lipids, obesity, diabetes and smoking. These traditional risk factors can explain more than 80% of the excess risk of coronary heart disease (CHD) at the population level (75). In addition, obesity may precipitate and exacerbate other major CVD risk factors included in MetS (35).

Cardiovascular dysfunction is one of the factors underlying CVD in the presence of obesity (76). Endothelial dysfunction is one of the earliest vascular changes observed in obesity. This condition is accompanied by a decrease in the synthesis and availability of nitric oxide, which leads to a dysregulation of the arterial wall elasticity and the subsequent development of arterial stiffness (76-78). At the same time, endothelial cells undergo modification, activation and acquire a proatherosclerotic phenotype (76). Metabolic disorders associated with obesity also eventually lead to a gradual thickening of the arterial wall. Arterial stiffness leads to chronic vascular damage and contributes itself to the CVD progression (44).

Obesity increases the risk of CHD and stroke, two leading causes of CVD mortality (2). Obesity has a causal effect on the CHD development (68, 79). Obese people have more frequent and more advanced atherosclerotic vascular lesions compared to normal weight individuals (79). The risk of developing coronary artery atherosclerosis increases by 12% with obesity (80). The risk of ischemic and hemorrhagic stroke increases by 4% and 6%, respectively, for each unit increase in BMI (81, 82).

Excessive fat accumulation adversely affects the left atrium and increases the risk of atrial fibrillation independant of the factors included in the CHA2DS2-VASc score (56). Atrial fibrillation is an arrhythmia that can be complicated by blood clotting, leading to stroke or other thrombosis and heart failure (80). The main mechanism of the unfavourable influence of obesity on atrial fibrillation is structural and electrical atrial remodeling, leading to the creation of a proarrhythmic substrate (56, 83). Moreover, an increased electrical sensitivity may lead to more frequent, complex and severe ventricular arrhythmias (84).

Obesity is associated with a risk of developing and complicating all forms of heart failure, but especially in heart failure with preserved ejection fraction (35, 55). Approximately half of patients have heart failure with preserved ejection fraction, although its evidence-based treatment is limited (85). Thus, the prevention of this form of heart failure is crucial. Among participants in the Framingham Heart Study, the incidence of heart failure increased by 5% in men and 7% in women for each unit increase in BMI (86).

1.2.3 Other diseases and quality of life

Obesity predisposes to a number of noncommunicable diseases. Severe complications of obesity include pulmonary diseases, osteoarthrosis, non-alcoholic fatty liver and gallbladder diseases, autoimmune, neurogenerative and oncological diseases (13, 35). Obesity is the major cause of alveolar hypoventilation and obstructive sleep apnea syndrome (55, 87). Obesity correlates with the development of dementia and specific neurodegenerative diseases, including Alzheimer’s and Parkinson’s diseases (35). In addition, overweight and obesity can kickstart the development of various types of neurodegenerative diseases (35).

Adiposity is associated with an increased risk of developing several types of cancer. Approximately 40% of all types of cancers can be attributed to overweight and obesity (88). To date, there is a sufficient level of evidence to suggest an association between excessive fat accumulation and 11-13 types of cancer (13, 89). The most prevalent obesity-related cancers are colorectal, endometrial and postmenopausal breast cancers (90). Individuals with AO are at an elevated risk of developing hormone-dependent cancers (2). In women, obesity is also associated with a high frequency of anovulation, menstrual cycle disorders, infertility, endometrial hyperplasia and polyposis associated with impaired production of sex hormones (91, 92). In men, obesity increases the risk of various prostate diseases, including prostatic hyperplasia and prostate cancer (13, 35). Overweight and obesity are responsible for 4.2-14.2% of deaths from cancer in men and 14.3-19.8% in women (13).

Excessive fat accumulation has an adverse effect on the onset and progression of various immune-mediated diseases, including thyroid autoimmunity, especially Hashimoto’s thyroiditis, psoriasis and psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and type 1 diabetes mellitus (35, 93). Recent data show that obesity exacerbates the severity of COVID-19 infection (94-96). Individuals with obesity are at a higher risk of COVID-19 positive status, severe course of disease, hospitalisation and mortality (95, 96).

Several studies also suggest that obesity can lead to fair or poor quality of life and frailty (13, 66, 97-99). There is an inverse relationship between increasing weight status and decreasing quality of life (97, 100). The decline in quality of life attributed to obesity is similar to having schizophrenia, kidney disease or heart failure and greater than that associated with myocardial infarction, diabetes or cancer (100).

1.2.4 Disability and mortality

Obesity is one of the leading causes of disability and mortality worldwide (35). The populations of Central and Eastern Europe have the highest age-standardised CVD mortality rates attributable to combined effects of high blood pressure, cholesterol, BMI and plasma glucose in the world (75). As reported by the Global Burden of Disease group, high BMI was responsible for four million deaths in 2015 (101). Obesity increases mortality rates from many chronic diseases and infections (35), however, two thirds of these deaths are attributed to CVD (101). Heart disease is the most common cause of death in patients with morbid obesity (BMI 40.0-59.9 kg/m^2) (13). Annually, overweight and obesity cause approximately 1.2 million deaths across the WHO European Region, representing 13% of total deaths (1, 2). Consequently, is the fourth leading cause of mortality, ranking behind high blood pressure, an unhealthy diet and tobacco use (2).

Previous data have shown a phenomenon called the "obesity paradox", wherein people with obesity exhibit a better prognosis for preexisting disease, especially in acute situations, compared to those with normal or lower BMI (79, 85). These diseases include CHD, coronary revascularisation, acute and chronic heart failure, hypertension, stroke and atrial fibrillation (53, 55, 79, 85, 102). However, this beneficial effect of obesity appears to be lost in individuals with severe obesity (82, 103, 104).

Disability-adjusted life years (DALYs) are a measure of the disease or disability burden in populations (105). DALYs are calculated as the sum of the years of life lost due to premature mortality and the years lived with a disability due to condition or disease in a population (105). Between 1990 and 2015, the global DALYs attributable to high BMI increased by 35.8% (from 1200 per 100000 to 1630 per 100000) (101). Over the same period, mortality associated with high BMI increased by 28.3% (from 41.9 per 100000 to 53.7 per 100000), yet these changes became insignificant after standardisation by age (101). In recent decades, the prevalence of overweight and obesity has exhibited one of the highest growth trends among other health risk factors, despite the implementation of preventive measures (101, 106).

Excess adiposity is also linked to decreased life expectancy (2). Individuals with obesity have a life expectancy that is, on average, five years shorter than individuals with a normal weight (107, 108). Overweight and obesity account for 7% of total years of healthy life lost due to disability or ill-health in the WHO European Region (2). However, the WHO committee suggests that obesity-related disability and mortality may be substantially underestimated due to different links of obesity with other risk factors (2).

1.2.5 Economic impact of obesity

The economic impact of overweight and obesity is significant, irrespective of the geographical location and economic status of the country (109). Obesity leads to more frequent use of healthcare services, higher rates of visits to outpatient departments, hospitalisation, including bariatric surgery and the need for medication and rehabilitation (101). An analysis of 161 countries found that the impact of excess adiposity averaged 2.19% of gross domestic product (109). In 2014, obesity was responsible for 8% of healthcare costs in the European Union (2) The economic impact of obesity is projected to increase by approximately 50% by 2060 (109).

If one takes into account the costs of treating diseases caused by obesity, the amount of economic damage increases several times compared to direct obesity costs (2). The costs of major obesity-related diseases (T2D, acute myocardial infarction and stroke) were calculated in an assessment of the economic costs of obesity in Russia (110). The term "cost of the disease" refers exclusively to the expenses associated with the direct treatment of the disease (emergency care, outpatient, inpatient treatment and rehabilitation). Annually, the direct costs of treating patients with T2D are about 407 billion rubles (6.3 billion USD), with myocardial infarction – about 36 billion rubles (554 million USD), and with stroke – about 71 billion rubles (1.1 billion USD). Taking into account the population risk of developing these conditions in the presence of obesity, the contribution of obesity to the total cost of treatment and management of patients with T2D is approximately 85%, with myocardial infarction 35% and with stroke 15% (110).

1.3 Methods of obesity measurements

Despite the high prevalence, as well as the causal associations of obesity with serious concomitant diseases, a unified method for obesity measurement has not yet been established. Several variants of obesity indicators have been proposed.

1.3.1 Anthropometric measurements of obesity

1.3.1.1 Body mass index

To date, the classification of body weight by BMI, recommended by WHO in 1997, is the most widely used in practice. BMI was proposed by Adolphus Quetelet in 1842 (111). It is calculated by dividing the weight, expressed in kilograms, by the square of the height, expressed in meters. All categories of body weight according to BMI are presented in Table 1. The degree of risk of diseases associated with overweight or obesity classes varies (8). Cutoff values for BMI are unique for both sexes, but may vary depending on ethnicity (112, 113). In adults, BMI > 25 kg/m^2 indicates overweight, and BMI > 30 kg/m^2 indicates obesity, although lower thresholds have been proposed for Asian populations (113). A WHO expert consultation stated that cutoff points for observed risk of developing T2D and CVD (identified overweight) ranged from 22 kg/m^2 to 25 kg/m^2; for high risk (identified obesity) they ranged from 26 kg/m^2 to 31 kg/m^2 in different Asian populations (112).

Although BMI is highly correlated with the total amount of adipose tissue and total fat percentage, the main disadvantage of BMI is its inability to estimate the amount of lean and fat mass (111, 114). Due to significant variability at the individual level, BMI has good specificity but a low sensitivity for diagnosing GO (111). Despite the heterogeneity of regional body fat deposition, health professionals using BMI must therefore rely on the assumption that adipose tissue is evenly distributed throughout the body (63). Moreover, in cases where a person’s musculature is overdeveloped (for example, in professional athletes) or atrophied (in the elderly), BMI does not accurately reflect the content of body fat. As obesity is a heterogeneous condition, health professionals may significantly underestimate the magnitude of the obesity epidemic by using BMI as the sole marker of obesity (63, 111). The 1997 WHO Expert Consultation on Obesity emphasised the need to use other obesity indicators in addition to BMI measurements (8). Thus, in 2008 the WHO stated that not only BMI, but also an indicator of AO should be used in practice for proper assessment of the obesity-related health risks (8).

Table 1. BMI categories and associated disease risk (T2D, CVD) (8)

BMI (KG/M^2)	CATEGORY	DISEASE RISK (RELATIVE TO NORMAL WEIGHT)
<18.5	Underweight	
18.5-24.9	Normal weight	
25.0-29.9	Overweight	High
30.0-34.9	Obesity class Ⅰ	Very high
35.0-39.9	Obesity class Ⅱ	Very high
≥40	Obesity class Ⅲ	Extremely high

1.3.1.2 Waist circumference

In 1997, the WHO Expert Consultation on Obesity recognized the importance of measuring abdominal fat mass as an indicator of cardiometabolic risk (Table 2) (8). AO can vary significantly within a narrow range of BMI and total body fat (8, 62). There are several anthropometric parameters used to determine the amount and distribution of adipose tissue in the body. The most common in clinical practice are those that require little time and provide quick results.

To assess the deposition of fat in the abdominal region, the WHO recommends measuring waist circumference (WC) using a stretch-resistant measuring tape around the abdomen (8). It is an indirect indicator of visceral obesity, well correlated not only with the body fat percentage (BFP) and the amount of visceral fat measured by computed tomography (115), but also with cardiometabolic risk (8, 41, 116, 117). A sex-specific increase in the WC index indicates the presence of excess abdominal fat and can be used to determine the risk of T2D and CVD (Table 2).

In recent decades, there has been a greater increase in the values of WC compared to BMI, which resulted in a shift toward higher WC values within the same BMI categories. Normal and overweight individuals have the same characteristics (118). WC has an independent (after adjustment for BMI) and stronger association with the risk of T2D and CVD compared to BMI (8).

Table 2. WC values and associated disease risk (T2D, CVD) (8)

SEX	WC (CM)	DISEASE RISK
MEN	> 94	Increased
MEN	> 102	High
WOMEN	> 80	Increased
WOMEN	> 88	High

However, several different options have been proposed for the exact placement of the tape for WC measurement (8). It should be measured at the end of several consecutive natural breaths, at a level parallel to the ground, approximately halfway between the lower edge of the last palpable rib and the top of the iliac crest in the midaxillary line according to the criteria of the International Obesity Group and the WHO (8). While other official documents instruct that the measurement should be made at the level of the umbilicus or navel, at the top of the iliac crest or at the minimum waist point (8). In addition, different ethnicity-specific cutoff values for increased disease risk have been proposed for the populations of South Asia, China and Japan: for men > 90 cm, for women > 80 cm (8). However, WC does not take into account the type of fat deposition and does not provide information on the predominance of subcutaneous or visceral components of adipose tissue. (45).

1.3.1.3 Waist-to-hip ratio

Waist-to-hip ratio (WHR) is one of the anthropometric indices that is preferred over WC. WHR makes an adjustment for the distribution of subcutaneous fat at the hip level and, thereby, is therefore a surrogate indicator of peripheral (gluteofemoral or gynoid) adiposity (45, 113, 119). Accumulation of fat in the lower body is considered safer in terms of metabolic abnormalities (63). WHR is calculated as WC in centimeters divided by hip circumference (HC) in centimeters. HC is measured at the widest part of the hips. According to the WHO (1997), AO is defined as a WHR ≥ 0.90 for men and ≥ 0.85 for women (Table 3) (8). Individuals with WHR obesity have a substantially increased cardiometabolic risk. Compared to WC, the between-country variation of cutoff values for WHR is lower (8).

Table 3. WHR values and associated disease risk (T2D, CVD) (8)

SEX	WC (UNITS)	DISEASE RISK
MEN	≥ 0.9	Substantially increased
WOMEN	≥ 0.85	Substantially increased

However, as indices reflecting AO, WC and WHR do not take into account the variation in body height. The amount of abdominal fat varies with height and the proportion of abdominal fat reflected by WC may be physiologically different. Within the same WC strata, the cardiometabolic risk is substantially higher in shorter individuals, compared to taller ones (120, 121).

1.3.1.4 Waist-to-height ratio

Waist-to-height ratio (WHtR) is an anthropometric index of AO that avoids the limitations of WC and WHR (121, 122). WHtR assumes that a certain amount of abdominal adipose tissue is acceptable for an individual of a certain height of individual (121). WHtR is calculated as WC divided by height, both in centimeters. Ashwell et al. suggest using a cutoff value of 0.5 to define obesity for both sexes (Table 4) (113, 123).

Table 4. WHtR values and associated disease risk (T2D, CVD) (123)

WHTR (UNITS)	OBESITY	DISEASE RISK
< 0.5	No	Normal
0.5 - < 0.6	Yes	Increased
≥ 0.6	Yes	Substantially increased

Individuals with normal WC but WHtR ≥ 0.5 are more prone to hypertension, CVD and especially T2D (120). In addition, WHtR may be an indicator of “early health risk” as it has a higher predictive value for CVD risk factors than using a combination of BMI and WC (123). WHtR may be a better screening tool than BMI, WC, and their combination in identifying people with hypertension, diabetes and CVD risk (120, 123). WHtR, being an easy-to-measure index, is a proxy estimator of visceral fat accumulation (123). WHtR, like all other anthropometric indices of AO, does not provide a distribution between skeletal muscle mass and fat (67).

1.3.1.5 Other anthropometric indices

A variety of anthropometric indices have been proposed based on the above anthropometric measurements. The abdominal volume index is based on WC and HC, while the weight-adjusted-waist-index includes WC and weight (124, 125). The body shape index uses BMI, height and WC; the conicity index uses WC, weight, and height; while the body roundness index and the body adiposity index are based on WC and height. All these indices are calculated according to complicated formulas (126-129). The hip index was proposed as an HC measurement normalized to standard height and weight (130). Sagittal diameter, calculated as the height of the patient's abdomen in the supine position, is an additional indicator of AO (45).

All anthropometric indices of AO are indicators of abdominal fat accumulation, but they do not allow its quantification (45, 119). The advantages of all anthropometric methods include their simplicity of implementation and wide accessibility. Nevertheless, they may all have significant measurement errors (45). Therefore, more accurate methods are needed to estimate the amount of fat mass and visceral fat.

1.3.2 Body composition analysis

Body composition analysis can be performed using multifrequency biological impedance analysis (BIA) or with dual-energy X-ray absorptiometry (DXA).

The study of the electrical properties of different tissues began at the end of the 18th century (131, 132). BIA is an electro-physical method based on the different behavior of biological tissues in response to an applied electric current (133). It measures the electrical resistance of tissues of the whole body and its individual parts (132). First, the total amount of water in the body is calculated, then the amount of lean mass, and finally the amount of fat mass is obtained by subtracting the fat-free mass from the total body weight (67, 132). This method is easy to use, non-invasive, relatively inexpensive, does not use radiation and allows for dynamic assessment of body composition (133). However, compared to DXA, BIA shows 2-6% lower values of fat mass percentage (133). Furthermore, the reproducibility of the results is low, and the consistency of BIA results is BMI-dependent (134). The phase angle decreases with increasing BMI, which leads to a significant shift of the resulting BIA vector (134-136).

DXA is a radiographic technique used to assess bone mass and body composition (37, 134). Fat mass, fat-free mass, bone mineral component, and non-bone lean mass are assessed in 2-, 3- or multi-compartment models (37, 134). Although DXA is the "gold standard" method for assessing bone mass, it is not yet the standard for assessing body composition (134, 137). DXA demonstrates higher accuracy and consistency of results compared to BIA in a variety of populations, although it is more expensive, requires complex analysis and is limited in frequency by the low radiation doses (133, 134).

Thus, both methods can differentiate between muscle and adipose tissue and assess the distribution of fat mass between the trunk and extremities (67). Two indicators of body composition analysis can reflect true body fatness: BFP and fat mass index (FMI).

A BFP is calculated using the formula: BFP = [(weight – free fat mass) / weight] * 100 (111). A BFP of $\geq 25\%$ in men and $\geq 35\%$ in women is considered to indicate obesity (Table 5) (111). There is an overall good correlation between BFP and BMI, although it is better in women, than in men (111).

Table 5. Adiposity categories according to BFP (113)

BFP (%)	**ADIPOSITY CATEGORY**
MEN	
< 10	Underweight
10 - < 20	Normal weight
20 - < 25	Overweight
≥ 25	Obesity
WOMEN	
< 20	Underweight
20 - < 30	Normal weight
30 - < 35	Overweight
≥ 35	Obesity

FMI is calculated as total fat mass in kilograms divided by the square of height in meters. Obesity is defined as FMI > 9 kg/m^2 in men and > 13 kg/m^2 in women (Table 6) (37, 137).

Table 6. Adiposity categories according to FMI (37)

FMI (KG/M^2)	ADIPOSITY CATEGORY
MEN	
< 3	Fat deficit
3 - 6	Normal
> 6 - 9	Excess fat
> 9 - 12	Obesity class Ⅰ
> 12 - 15	Obesity class Ⅱ
> 15	Obesity class Ⅲ
WOMEN	
< 5	Fat deficit
5 - 9	Normal
> 9 - 13	Excess fat
> 13 - 17	Obesity class Ⅰ
> 17 - 21	Obesity class Ⅱ
> 21	Obesity class Ⅲ

In terms of its ability to estimate the amount of body fat, body composition analysis is significantly superior to anthropometric methods, but inferior to other high-resolution techniques (37). Although body composition indices are positively correlated with MetS components, studies suggest that they are not superior to classic anthropometric indices (38, 67, 138). Like anthropometric methods, body composition analysis does not directly estimate the amount of subcutaneous and visceral fat in the abdominal area (37, 139).

1.3.3 High-resolution imaging technologies

With the development of new high-resolution imaging technologies, it has become possible to assess both the total amount of adipose tissue in the body and the topographic features of its distribution. In addition to simple methods, there are technologically advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI) that allow direct visualisation of adipose tissue and its quantification (140).

1.3.3.1 Computed tomography

The advent of a method of tomographic scanning of the body, with the ability to clearly differentiate body tissues based on different values of X-ray density, gave impetus to the use of CT as a method for verifying visceral obesity. Visceral adipose tissue can be distinguished from other tissues according to the tissue-specific gray tone on CT scans (140). In fact, the capabilities of CT have made this method one of the best techniques for verification and quantitative assessment of adipose tissue of any ectopic depot. It allows its use in research aimed at studying the role of visceral obesity in cardiometabolic risk stratification (45, 141). However, radiation exposure is a significant limitation to the widespread use of CT as a screening tool for visceral obesity, especially in longitudinal observations and in specific populations such as pediatric, obstetric or geriatric ones (45, 142).

1.3.3.2 Magnetic resonance imaging

MRI is a technique that uses magnetism and radio waves to produce cross-sectional images of the body (45). To assess the degree of visceral obesity, the property of adipose tissue to change the relaxation time when pulse sequences are applied is used. The MRI method is not inferior to CT in the verification and quantitative assessment of visceral fat tissue. In addition, MR images may have a better resolution of soft tissues compared to CT images (142). Moreover, MRI obviously has advantages over CT since the patient is not exposed to radiation and contrast agent. To date, MRI is the gold standard for body fat content and distribution (142). However, the visualization of ectopic fat depots in the pericoronary and paraaortic compartments has not received sufficient evidence [30]. Furthermore, these high-tech methods are time-consuming and expensive, which limits their widespread use in clinical practice.

Thus, all methods described have their advantages and disadvantages. The ideal method for assessing obesity should be simple, convenient, cost-effective and demonstrate strong associations with cardiometabolic risk factors and CVD. The ideal methods should be used not only to detect obesity, but also to guide early preventive measures.

1.4 Rationale of the thesis

The rationale for this PhD thesis was the observed lack of a unified approach to assess obesity as a risk factor for metabolic diseases and CVD. Currently, the concept of risk factors as possible causes for the onset and progression of cardiometabolic diseases is a fundamental aspect of health promotion approaches, preventive medicine and therapeutic strategies. Obesity is a modifiable risk factor and predisposes to the development of other CVD risk factors such as T2D, hypertension, dyslipidemia and kidney disease. Thus, successful control of obesity can also prevent the development of other undesirable health outcomes.

The key to successful CVD prevention is to find an indicator that reflects the presence of obesity, is most closely associated with the cardiometabolic complications of obesity, and allows for the earliest possible start of prevention in individuals at increased risk. A large number of different indicators reflecting obesity are being developed, and data are available to assess the relationship of these indicators with complications and CVD. However, for routine clinical practice, it is desirable that the indicator of obesity is easy to measure and does not require the use of additional equipment. Preferably, it should also have a single threshold value despite differences in personal, demographic and ethnic characteristics. Finally, there has been a paucity of published studies that directly compare the existing obesity indices with respect to their links to cardiometabolic disorders, particularly in Russia.

Thus, the present thesis is based on the assessment of obesity and associated CVD risk factors in a Russian adult population. Figure 1 shows the logical structure of the three papers that compose this thesis.

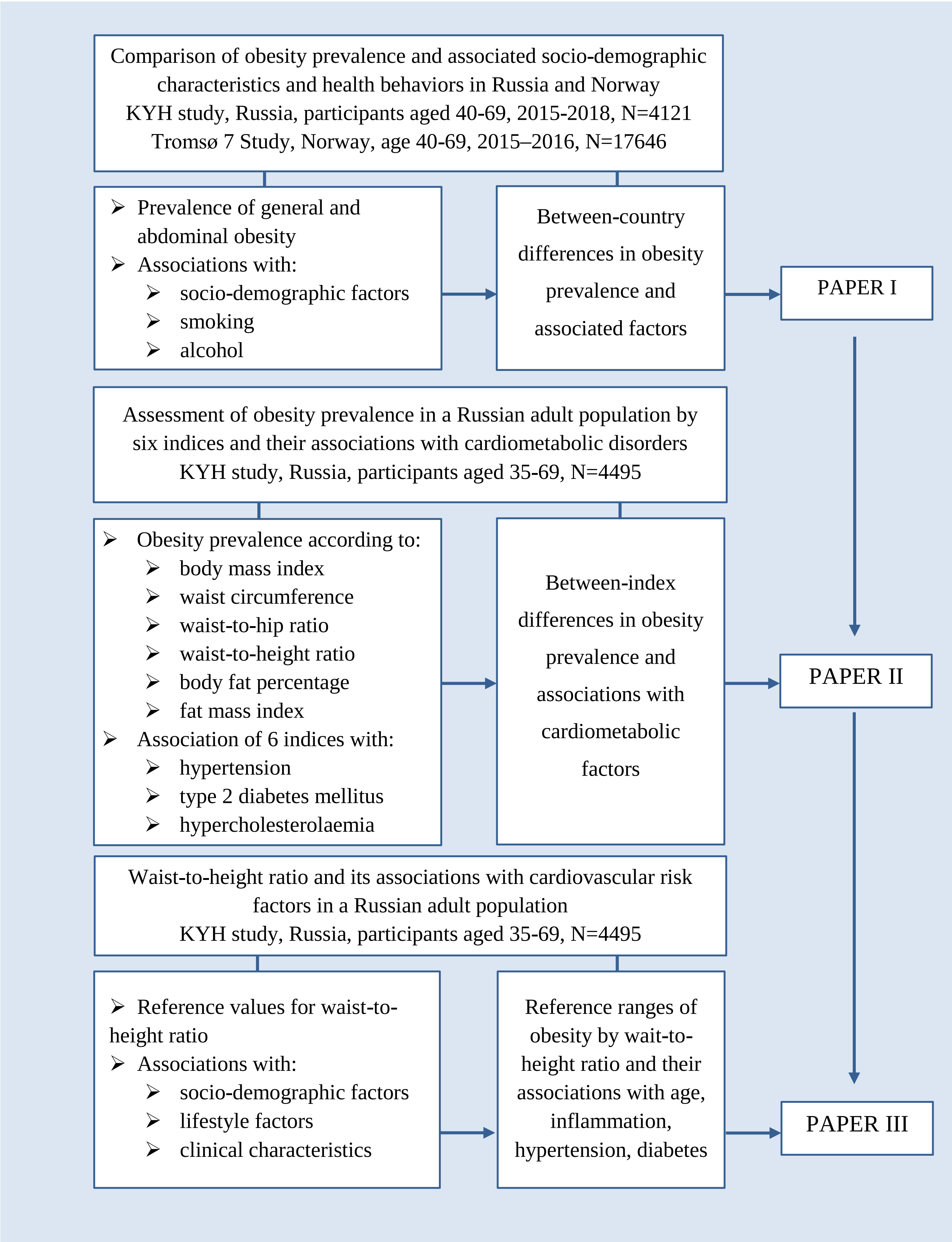

Figure 1 Structure of this thesis and of Papers I-III

2 Aims of the Thesis

The overall aim of this thesis was to assess the prevalence, determinants, and cardiometabolic correlates of obesity in a Russian adult population

The specific objectives were:

1. To compare the prevalence of obesity and its possible associations with socio-demographic characteristics and health behaviors in Russia and Norway (Paper I)

2. To assess the prevalence of obesity using six indices and compare their associations with hypertension, hypercholesterolaemia and T2D in a Russian adult population (Paper II).

3. To establish reference values for WHtR and to investigate its associations with characteristics of socio-demographic status, lifestyle and clinical characteristics in Russian adults (Paper III).

3 Materials and Methods

3.1 Study design and population

3.1.1 The Know Your Heart Study (Russia)

The Know Your Heart study (KYH), a cross-sectional study of CVD, was conducted in 2015-2018 as part of the International Project on Cardiovascular Disease in Russia (IPCDR). The aim was to characterize the nature and causes of CVD in Russia. The KYH study included the population of the two Russian cities, Arkhangelsk in Northwestern Russia and Novosibirsk in Siberia (Fig. 2), with a random population sample aged 35-69 years (143). Within each city, four districts were selected for the recruitment of participants. Potential participants at both sites were included based on address, age and sex data obtained from the Territorial Health Insurance Funds and were stratified with a target to obtain equal 5-year age and sex groups. The selected addresses were visited and persons of specified age and sex were invited to complete an interviewer-administered baseline questionnaire collecting information on lifestyle CVD risk factors. The interview was completed by 5089 participants (2480 participants from Arkhangelsk and 2609 participants from Novosibirsk). The response rate for the interviews at home was 68.2% in Arkhangelsk and 41.1% in Novosibirsk.

Figure 2 Location of Arkhangelsk, Novosibirsk and Tromsø (143). Reprinted with permission of the author

At the end of the interview, each participant was invited to attend a health check at a polyclinic where trained staff administered a questionnaire on the lifestyle, alcohol consumption, symptoms, medical history, medication use, and performed a medical examination. Of those who were invited to the second part of the study, 2381 participants from Arkhangelsk and 2161 participants from Novosibirsk attended the health check. This examination included the collection of a blood sample with a four hour fasting period. The participants were asked to fast for at least four hours prior to attending the polyclinic. A set of instrumental and functional measurements included blood pressure, pulse, pulse oximetry, anthropometry (height, weight, WC and HC), body composition, physical function tests (grip strength, 10 chair stands, one-legged balance with eyes open and closed), pulse wave velocity, 12-lead electrocardiogram, vascular ultrasound examination and echocardiography. Participants were also asked to provide urine and faecal samples. Spirometry and 5-day monitoring of physical activity using the Actiheart device were performed in a subsample of participants.

To find the features of obesity in Russia, data from the KYH study were compared with the data from the Tromsø 7 Study (Tromsø 7), which is based on the population of Tromsø in northern Norway.

3.1.2 The Tromsø 7 Study (Norway)

The Tromsø Study was initiated in 1974 by the University of Tromsø in northern Norway. The aim was to combat the high cardiovascular mortality among middle-aged men of working age in Norway, which was even higher in the northern parts of the country (144). It is a large population-based longitudinal study conducted in the municipality of Tromsø, the largest city in northern Norway. Initially focused on CVD, the study was later expanded to include a wide range of chronic diseases. Since 1974, seven surveys of the Tromsø Study have been conducted: Tromsø 1 (the Tromsø Heart Study, based on men only, 1974), Tromsø 2 (1979-1980), Tromsø 3 (1986-1987), Tromsø 4 (1994-1995), Tromsø 5 (2001-2002), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016). Data from the seventh survey of the Tromsø Study were used for this thesis.

In Tromsø 7, all citizens of Tromsø aged 40 years and older (32591) were invited to participate (a total of 21083 participants, 65% response rate) (145). They were invited to the examination by mail. The first questionnaire with questions about ethnicity, personal and family history of CVD, smoking and physical activity was sent via mail together with the invitation. This questionnaire could be completed electronically or on paper and returned during the examination. The examination was performed by trained personnel. It included the second questionnaire, physical examination and collection of blood samples. The second questionnaire collected information on dietary habits, alcohol consumption, lifestyle, social status, symptoms, medical history of illness, medication use and psychological status. Participants underwent a medical examination, including anthropometry (height, weight, WC and HC), measurement of blood pressure, pulse, pulse oximetry and pain sensitivity tests. Laboratory analyses included blood, urine, faecal and saliva sampling and nasal and throat swabs. Participants were asked not to eat within 4 hours before the examination. A subsample of participants underwent a dental examination. A subsample of 13 028 participants was also invited to a second visit for an extended medical examination of cardiovascular (electrocardiogram, vascular ultrasound examination and echocardiography) and other systems.

3.1.3 Study sample used in the papers

For Paper I, the KYH population consisted of 4121 participants aged 40–69 years (2129 from Arkhangelsk and 1992 from Novosibirsk), who underwent the health check and had anthropometric data. The Tromsø 7 population was restricted to those aged 40-69 years with anthropometric data, with a total of 17646 participants.

Based on the results of the Paper I, I focused on a Russian sample with a higher prevalence of obesity in women compared to Russian men and Norwegians of both sexes. Thus, Papers II and III were based on 4495 participants of the KYH aged 35-69 years (2352 from Arkhangelsk and 2143 participants from Novosibirsk) with available anthropometric data.

3.2 Variables

3.2.1 The Know Your Heart Study

3.2.1.1 Anthropometric variables

Anthropometric measurements were taken at the health check by trained personnel according to a standard protocol. Participants wore light clothes and no shoes. Height was measured to the nearest millimeter using a Seca® 217 portable stadiometer (Seca limited). Body weight, total fat mass and BFP were measured using a TANITA BC 418 body composition analyser (TANITA, Europe GmbH). WC was measured at the narrowest part of the trunk, while HC was measured at the widest part of the hips using a centimeter tape measure. WC and HC were measured twice to the nearest millimeter (143).

The parameters used to assess obesity were BMI, WC, WHR, WHtR, BFP and FMI. BMI was calculated as weight (kilograms) divided by the square of height (meters). GO was defined as BMI ≥ 30.0 kg/m^2 according to the WHO classification (1997) (146). BMI categories were used to describe the degree of adiposity: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity class I (BMI 30.0-34.9 kg/m^2), obesity class II (BMI 35.0-39.9 kg/m^2) and obesity class III (BMI ≥ 40.0 kg/m^2) (146).

AO was assessed by WC, WHR and WHtR. Obesity according to WC was determined in the presence of WC > 88 cm for women and > 102 cm for men, as we applied the definition of high disease risk comparable to BMI ≥ 30 kg/m^2 (8). As two measurements of WC and HC were obtained during the examination, WHR was calculated as the mean of two WC measurements divided by the mean of two HC measurements. According to WHR, we defined obesity as > 0.85 for women and > 0.9 for men (8). WHtR was calculated as the mean of two WC measurements in centimeters divided by height in centimeters. Obesity was defined as WHtR > 0.5 for both sexes (147).

Based on BIA data obesity by BFP was defined in the presence of BFP ≥ 35% for women and ≥ 25% for men (111). FMI was calculated as total fat mass in kg divided by the square of height in meters. Obesity according to FMI was considered as FMI > 13 kg/m^2 in women and > 9 kg/m^2 in men (37, 137).

3.2.1.2 Socio-demographic variables

The following socio-demographic characteristics were assessed: age (years), sex (female/male), marital status, education and financial situation of the household. Marital status was assessed as living together with a spouse in a registered marriage; living together with partner but not in a registered marriage; divorced or separated; widowed or never married. The question on education had the following variants: incomplete secondary; complete secondary; professional no secondary; professional and secondary; specialized secondary (college, three years); incomplete higher or higher education. The self-perceived financial situation of the household was measured using a categorical scale with six options:

not even enough money for food; it is difficult to make ends meet; enough money for food, but difficult to afford clothes and other items; enough money for food and clothes, but difficult to buy large domestic appliances; can afford to buy large domestic appliances, but difficult to buy a large new car; can afford to buy a large new car, but difficult to buy a flat or a house or no financial constraints, can afford to buy a flat or a house (143).

3.2.1.3 Health behaviours

Data on diet, physical activity, cigarette smoking and alcohol consumption were analysed. Diet quality was assessed by the Dietary Quality Score (DQS) questionnaire and used categorical variable (unhealthy diet (1-3 points); average diet (4-6 points) or healthy diet (7-9 points)) or dichotomous variable (unhealthy diet (yes/no)) (148).

Physical activity was assessed using the Total Physical Activity Index from the European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire, which is based on four questions about physical activity during the past year: physical activity at work, indoor and outdoor recreational activities, intensity of recreational activities and stair climbing (149). The following levels of physical activity were used: inactive: sedentary job and no recreational activity; moderately inactive: sedentary job with < 0.5 hours of recreational activity per day or standing job with no recreational activity; moderately active: sedentary job with 0.5-1.0 hour recreational activity per day or standing job with 0.5 hour recreational activity per day or physical job with no recreational activity); active: sedentary job with > 1 hour recreational activity per day or standing job with > 0.5 hour recreational activity per day or physical job with at least some recreational activity or heavy manual job. Dichotomous variable: presence or absence of low physical activity (sedentary job with < 0.5 hours of recreational activity per day or standing job with no recreational activity) (150).

Daily tobacco/cigarette smoking was assessed as a categorical variable (never, ex-smoking, or current smoking) or as dichotomous variable (current smoking (yes/no)). The Alcohol Use Disorders Identification Test (AUDIT) was used to study alcohol consumption (151). Frequency of alcohol use was categorised as “2 or more times per week” (frequent drinking) or less frequent. The number of standard alcohol units usually consumed per drinking occasion was categorised as “5 or more” (binge drinking) or less. Hazardous drinking was defined as ≥ 8 points on the AUDIT.

3.2.1.4 Clinical variables

Clinical parameters were assessed during the medical examination. As the health checks were performed during the day, participants were asked not to eat and to drink only water for at least four hours prior to the beginning of the examination at the policlinic.

The OMRON 705 IT automatic blood pressure monitor (OMRON Healthcare) was used for measuring systolic and diastolic blood pressure (SBP and DBP, mmHg) at the brachial artery. Three measurements were taken at two-minute intervals. The means of the second and third BP measurements were used in the analyses.

Levels of total cholesterol (TC, mmol/L), HDL-C (mmol/L) and LDL-C (mmol/L) in blood serum were analysed using enzymatic colorimetric assays (AU 680 Chemistry System Beckman Coulter) (143). Non-high-density lipoprotein cholesterol (non-HDL-C), which estimated the total amount of proatherogenic ApoB-containing lipoproteins, was calculated as TC minus HDL-C (71). High-sensitivity C-reactive protein (hs-CRP, mg/L) and glycated hemoglobin (HbA1c, %) in serum were assessed using immuno-turbidimetric tests (AU 680; Chemistry System Beckman Coulter).

Information on medication use was collected during the interview at the health check. The interviews recorded the commercial names, indications, doses and frequency of use of up to seven medicines. The international WHO anatomical therapeutic chemical (ATC) classification system (2016) was used to code the names of medicines according to the following codes: antihypertensive medication (ATC classes C02, C03, C07, C08 or C09); antidiabetic medication (ATC class A10); lipid-lowering medication (ATC class C10); heart rate lowering (HR-lowering) medication (ATC classes C01A, C01BC03, C01BD or C01EB17) (152, 153).

Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) (154). Based on the questionnaire data, participants were categorised as having no depression (< 5 points), mild (≥ 5-9 points), moderate (10-14 points), moderately severe (15-19 points) or severe depression (≥ 20 points). Anxiety was assessed using the General Anxiety Disorder-7 (GAD-7) questionnaire with levels of no anxiety (< 5 points), mild (5-9 points), moderate (10-14 points) or severe (≥15 points) anxiety (155).

Three cardiometabolic disorders were analysed according to the data from the questionnaires and the health check. Hypertension was defined as SBP > 140 mmHg and/or DBP > 90 mmHg at the medical examination (according to the average of the 2nd and the 3rd measurements) and/or self-reported daily use of anti-hypertensive medicines. Hypercholesterolaemia was defined as TC ≥ 5.2 mmol/L and/or LDL-C of > 3.0 mmol/L and/or self-reported daily intake of lipid-lowering medication. Diabetes was defined as HbA1C ≥ 6.5% and/or self-reported daily use of antidiabetic medicines.

3.2.2 The Tromsø 7 Study

The Tromsø 7 data were used only for the Paper I, so the amount of the analysed variables was limited to selected anthropometric, socio-demographic and behavioural variables.

3.2.2.1 Anthropometric variables

Anthropometry included measurements of weight, height, WC and HC (145). Weight was measured using an electronic digital scale (DS-B02, Dongsahn JENIX Co. Ltd., Seoul, Korea). Height was measured to the nearest millimeter using an electronic stadiometer (DS-103, Dongsahn JENIX Co. Ltd.). WC was measured to the nearest millimeter at the level of the umbilicus using a centimeter tape measure. HC was measured to the nearest millimeter at the widest part of the hips using a centimeter tape measure.

3.2.2.2 Socio-demographic variables

The assessed socio-demographic variables were: age (years), sex (female/male), living with a spouse/partner (yes/no), education (primary/partly secondary education (up to 10 years of schooling); upper secondary education (a minimum of 3 years); tertiary education, short (college/university less than 4 years); tertiary education, long (college/university 4 years or more)) and total annual income of the household (less than NOK 150000; NOK 150000-250000; NOK 251000-350000; NOK 351000-450000; NOK 451000-550000; NOK 551000-750000; NOK 751000-1000000; more than NOK 1000000).

3.2.2.3 Health behaviours

Questions on health behaviors were similar to KYH: daily tobacco/cigarette smoking (never, ex-smoker, current smoker) and data on the frequency of alcohol consumption (“2 or more times per week” or less often) and the number of standard units of alcohol consumed per drinking occasion according to AUDIT score (“5 or more” or less).

3.2.3 Harmonization of variables between studies

Paper I compared the prevalence of GO according to BMI ≥ 30.0 kg/m^2 and described the patterns of GO according to different BMI categories in the two countries (146). The definitions of AO according to WHR used the following criteria: > 0.85 for women and > 0.9 for men (8). WC and HC were used in the formula to calculate WHR. There were differences in the measurement of WC between study protocols. While WC was measured at the narrowest part of the trunk in KYH, it was measured at the level of the umbilicus in Tromsø 7. To harmonize WC, the conversion equation proposed by Mason and Katzmarzyk for this variable was used in Tromsø 7: for men: narrowest = –1.19141 + 0.09503 (age) + 0.94491 (umbilicus); for women: narrowest = –1.02517 + 0.03207 (age) + 0.90184 (umbilicus) (156).

Due to the differences in questionnaires between studies concerning socio-demographic variables, they were harmonised by recoding them into a uniform format: age (40-69 years and 5-year age groups); marital status: living with spouse or partner (KYH: living with a spouse in a registered marriage; living with partner but not in a registered marriage). Education was divided into primary/secondary education (KYH: incomplete secondary, complete secondary, professional no secondary and professional and secondary education; Tromsø 7: primary/partly secondary education and upper secondary education) and college/university education (KYH: specialized secondary, incomplete higher and higher education; Tromsø 7: short and long tertiary education). The household financial situation was divided into three levels: level 1 (KYH: not enough/enough money for food but difficult to afford clothes in; Tromsø 7: NOK ≤ 350000), level 2 (KYH: enough money for food and clothes but difficult to buy large domestic appliances; Tromsø 7: NOK 351000-1000000 NOK) and level 3 (enough money for large domestic appliances and higher categories in KYH; Tromsø 7: > NOK 1000000).

3.3 Data analysis

Methods of descriptive statistics were used in Papers I-III. Data were presented as mean values and standard deviations or medians with interquartile range for continuous variables and absolute numbers and proportions for categorical variables. Groups were compared using two-sample t-test or Wilcoxon rank-sum test for continuous variables, using Pearson's chi-squared test for categorical variables. All analyses were stratified by sex (Papers I-III).

3.3.1 Paper I

In Paper I, the age-standardised prevalence of GO and AO in Russia and Norway, assessed by BMI and WHR, respectively, was estimated based on the European Standard Population 2013 (ESP2013) with 5-year bands. Associations of obesity with socio-demographic and lifestyle characteristics were analysed separately for each study and sex. Logistic regression with stepwise entry of variables was used. First, the associations of all socio-demographic and behavioral factors with GO and AO were analysed with adjustments for age only. Next, SEP variables were simultaneously added in the models. In the third step, health behavior variables, which were limited to current smoking and alcohol consumption, were added to the previous model. Participants with missing values for any of the covariates were excluded from the logistic regressions. Finally, we made between-study comparisons of the strength of associations of GO and AO with the variables of interest in Models 3 by repeating the regressions with the pooled KYH and Tromsø7 dataset and adding the "study" variable. Interactions of the "study" variable with all other entered characteristics were assessed using likelihood ratio tests to compare models with and without interaction terms. All models were repeated for the pooled dataset to assess the effects of SEP and behavioral factors on the between-study differences in GO and AO.

3.3.2 Paper II

Paper II was based on KYH data. Sex- and age-stratified proportions of participants with obesity were assessed according to six indices (BMI, WC, WHR, WHtR, BFP and FMI). Sex-specific obesity prevalence estimates were presented age-standardised according to ESP2013 with 5-year age intervals (157). Receiver operating characteristic (ROC) analysis and the areas under the ROC-curve (AUC) were used to assess and compare the predictive abilities of the six indices for the presence of cardiometabolic disorders (hypertension, hypercholesterolaemia, diabetes and a combination of at least two of these disorders). The DeLong test was used for a simultaneous comparisons of the AUCs for six indices (158). Bonferroni correction was used for multiple pairwise comparisons. Optimal cutoff values in the adiposity indices to distinguish between participants with and without cardiometabolic disorders were identified by the Liu method, which maximises the product of sensitivity and specificity (159, 160). Finally, age-adjusted prevalence ratios (PRs) were calculated to examine the associations of cardiometabolic disorders with the presence of obesity defined by the six indices.

3.3.3 Paper III

Paper III was based on KYH data. Reference values for WHtR were estimated for the total study population, for women and men separately, and for 5-year age groups within each sex. Multivariable linear regression analyses with calculation of marginal means were used to estimate age-adjusted mean values for each sex, and age- and sex-adjusted WHtR means for both sexes. Similar regressions were used for estimating means for 5-year age bands in women and men.

Quantile regressions with age in years and sex as covariates were used to calculate age- and sex-adjusted percentile values (5th, 10th, 25th, 50th, 75th, 90th and 95th) of WHtR for both sexes and age-adjusted percentiles for women and men separately as marginal percentile values. Differences between women and men in mean and percentile values of WHtR were marked when the coefficients for the sex variable in regressions were significant.

Linear regression analysis was used to identify associations of WHtR with socio-demographic, lifestyle, and clinical parameters. First, the associations of all factors with WHtR were analysed with the adjustments for age only. In the second step, all socio-demographic and lifestyle factors were included in the regression model simultaneously. When analysing clinical factors, separate models were constructed for each clinical factor with adjustments for socio-demographic and lifestyle factors that were significantly associated with WHtR in either women or men. In all models, for BP variables additional adjustments were made for BP medication, for lipid profile variables – for lipid lowering medication, for diabetes (HbA1c) – for antidiabetic medication and for resting HR – for HR-lowering medication.

The strength of associations between WHtR and all independent factors was compared between women and men in multivariable models repeated on the pooled data for both sexes, assessing the interactions of each covariate with sex. Continuous variables were categorised into pentiles for interaction tests. Likelihood ratio tests for comparing regression models with and without interaction terms were used to study interactions.

Results were considered statistically significant with p-values < 5%, except for p-values < 0.003 for multiple pairwise comparisons with the Bonferroni correction in Paper II. Statistical analyses for all papers were performed using STATA V.16-18 (StataCorp, College Station, TX, USA).

3.4 Ethical aspects

3.4.1 Ethical approval for the KYH study

Ethical approval for KYH was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (approval number 8808; 24 May 2015), Novosibirsk State Medical University (approval number 75; 21 May 2015), the Institute of Preventative Medicine, Novosibirsk (no approval number; 26 December 2014) and the Northern State Medical University, Arkhangelsk (approval number 01/01-15; 27 January 2015).

3.4.2 Ethical approval for the Tromsø 7 study

Ethical approval for Tromsø 7 was obtained from the Regional Committee of Medical and Health Research Ethics (REC North, approval number 2014/940) and the Norwegian Data Protection Authority. The KYH - Tromsø 7 comparisons in this PhD project were a part of the Heart to Heart subproject included in the REC application (and approval) for Tromsø 7.

3.4.3 Ethical considerations

Both, KYH and Tromsø 7, were conducted in accordance with the principles of the Declaration of Helsinki (161). All participants in both studies signed an informed consent form. Participants could withdraw from the study at any time and without having to provide the reason of withdrawal.

Within 2-4 weeks after enrolment, participants in both studies received the values of the main parameters assessed during the health check. Participants with abnormal results were advised to contact a physician for a follow-up. The health check data were not transferred to a physician directly, thus relying on the participant's own initiative for follow-up.

There was no discrimination, as any resident of the required age could be included in the list of possible participants. The staff of both studies were bound to confidentiality. Each participant had a unique code. The datasets received for analysis contained neither personal identifiers nor unique anonymised codes, so all data were anonymised.

4 Main results

4.1 Paper I "Obesity prevalence and associated socio-demographic characteristics and health behaviours in Russia and Norway"

4.1.1 Age-standardised prevalence of obesity

The age-standardised prevalence of GO (BMI ≥ 30 kg/m^2) was higher in KYH women (36.7%) compared to women in Tromsø 7 (22.0%) and did not differ among men (26.0% vs. 25.7%). Apart from GO, 44.2% of KYH and 50.9% of Tromsø 7 men as well as 31.8% and 36.3% of KYH and Tromsø 7 women were overweight. The age-standardised prevalence of AO (WHR > 0.9 for men and > 0.85 for women) was also higher in KYH women compared to Tromsø 7 (44.2% vs. 18.4%, respectively) with no differences among men (74.8% vs. 72.2%). Although in both studies men had a higher age-standardised AO prevalence compared to women.

4.1.2 Associations of obesity with socio-demographic factors

In KYH women, GO showed a steep increase with age (especially after the age of 45-50 years), which was not present in Tromsø 7 women or men in either study. The prevalence of AO increased with age in both sexes and studies. In Tromsø 7 men, the odds ratios (ORs) of GO decreased with age in the age-adjusted model after adjustment for SEP covariates and health behaviors (p-trend = 0.049). In men, there was no significant association of age with GO in KYH and no between-study difference. The odds of AO were higher in Tromsø 7 men compared with KYH men, and there was a steeper growth of the difference with increasing age, regardless of adjustment for other SEP and behavioral factors (p for interaction < 0.001). The age-adjusted odds of GO in KYH women increased with age (p for trend < 0.001) both before and after adjustment. Tromsø 7 women had a downward trend in the ORs of GO after adjustment for SEP (p for trend < 0.001) and health behaviors (p for trend = 0.026). The odds of having AO increased with age in women in both studies, but the trend was steeper among KYH women when comparing the SEP- and lifestyle-adjusted models (p for interaction < 0.001).

In KYH, there was a higher proportion of men (70.0%) and women (78.3%) with a college or university education than in Tromsø 7 (50.5% vs. 55.7%, respectively). Among Tromsø 7 men and women in both studies, lack of university education significantly increased the odds of GO and AO before and after adjustment for other variables. However, there were no between-study differences in the associations of GO and AO with education in men.

The proportion of those living with spouse or partner among men was higher in KYH (84.8% vs. 81.8%) and among women in Tromsø 7 (75.4% vs. 56.9%). Men in KYH, but not in Tromsø 7, living with spouse or partner had higher odds of GO, and this persisted after all adjustments (p for interaction = 0.005).

The majority of participants in both studies had a medium financial level, but the proportion of participants of both sexes with a lower financial level was 2.5 times higher in KYH (17.8% vs. 6.5% in men and 22.7% vs. 10.8% in women). In Tromsø 7, men with medium and lower levels of income had higher odds of GO compared to men with an upper income level, but only in age-adjusted Model 1. Middle-income men in Tromsø 7 also had higher odds of AO in all models. In KYH men, financial situation was not associated with GO or AO, but this did not lead to a difference in the strength of the association between studies. Women in the lower financial level both in KYH and Tromsø 7 and in the medium financial level in Tromsø 7 had higher odds of GO and AO compared to those in the upper financial level, regrardless of the adjustments.

4.1.3 Associations of obesity with health behaviours

The proportion of current smokers among men was higher in KYH (35.7 vs. 13.8%) and did not differ between women in KYH and Tromsø 7 (15.0 vs. 15.3%). In Tromsø 7, the prevalence of current smoking was higher among women than among men (p=0.001). Current smoking decreased the odds of having GO in KYH and Tromsø 7 men, while ex-smoking increased the GO odds in Tromsø 7 men compared to non-smokers after adjustment for all covariates. In Tromsø 7 women, current smoking decreased, while ex-smoking increased the odds of GO after adjustment for SEP and behavioral factors. The odds of having AO were higher in current smoking KYH women and Tromsø 7 men and women. Ex-smoking was also positively associated with AO in Tromsø 7, regardless of sex. Although smoking was not associated with GO in KYH women, there were no between-study differences in the strength of the associations of smoking with obesity.

The proportion of frequent drinkers (≥ 2 times per week) was higher in Tromsø 7 for both men (34.2% vs. 20.7%) and women (27.3% vs. 2.8%). However, the rates of binge drinking

(≥ 5 drinks per occasion) were higher in KYH men (35.7% vs. 14.8%) and women (8.2% vs. 4.2%). While frequent drinking was positively associated with GO in KYH men, it was negatively associated with GO and AO in men and women in Tromsø 7. In the fully adjusted models, binge drinking was positively associated with GO and AO in all groups, except for GO in KYH women and AO in Tromsø 7 women. There were significant between-study differences in the strength of the association of frequent drinking with GO in both sexes and with AO in men. The associations of binge drinking were different only for AO in KYH and Tromsø 7 men.

Thus, we found a higher prevalence of obesity according to BMI and AO in KYH women compared to women in Tromsø 7 and men in both studies. Therefore, we decided to focus on Russian women as a high-risk group for obesity and find a valuable index to measure obesity and identify associations with CVD risk factors.

4.2 Paper II "Assessing the prevalence of obesity in a Russian adult population by six indices and their associations with hypertension, diabetes mellitus and hypercholesterolaemia"

4.2.1 Prevalence of obesity by six indices

A total of 2611 women and 1884 men of the KYH study, aged 35-69 years, were included in the analysis. Six indices of obesity (BMI, WC, WHR, WHtR, BFP and FMI) were analysed for each sex. Women had higher mean values of BMI, BFP and FMI, whereas WC and WHR were higher in men. The estimated proportions of participants with obesity by all indices were significantly different between the sexes. The proportions of obese participants by all indices increased with age in both sexes, except for obesity defined by BMI in men. Women, but not men, exhibited a steep increase in all indices in the age group of 45-49 years and older. Among cardiometabolic disorders, diabetes was more prevalent in women (9.1% vs. 7.4%), while men had higher proportion of hypertension (63.3% vs. 53.4%). Hypercholesterolemia was highly prevalent in both women and men (84.1% vs. 84.2%, respectively).

The age-standardised (to ESP2013) prevalence of obesity varied significantly depending on the measurement index used and was highest according to WHtR in both sexes. In women, it was 65.0% if determined by WHtR, 54.0% by BFP, 46,9% by WC, 41.0% by WHR, 33.6% by BMI and 23.6% when measured by FMI. In men, it was 75.8% if assessed by WHtR, 73.3% by WHR, 38.4% by BFP, 30.5% by WC, 25.8% by BMI and 17.2% if determined by FMI. Men had a 30-40% difference in obesity prevalence between WHtR and WHR and all other indices in all age groups.

Of those who had no obesity according to BMI, but were classified as overweight (BMI = 25.0-29.9 kg/m^2), obesity was found in 45.4-87.0% of women and in 20.7-94.6% of men according to other indices. Using WHtR index led to the highest obesity proportions among the overweight individuals of both sexes. Among participants with BMI < 25.0 kg/m^2, the proportions of those categorised as obese according to other indices (except FMI) ranged from 2.4% measured by WC to 16.2% by WHtR in women and from 0.18% by WC to 40.0% by WHR in men.

4.2.2 Associations of obesity with cardiometabolic disorders

When assessing the associations of the six obesity indices with cardiometabolic disorders (hypertension, hypercholesterolemia, diabetes and a combination of at least two disorders), WHtR had the strongest association with hypertension (AUC = 0.784; $p < 0.001$) and with a combination of disorders (AUC = 0.779; $p < 0.001$) in women. The AUCs for WHtR were also the largest compared to other indices for hypercholesterolemia in women and for hypertension, diabetes and a combination of disorders in men, although not all between-index differences reached significance.

The optimal empirically defined cutoff points in the six indices were the lowest for detecting hypercholesterolaemia and the highest for detecting diabetes in both men and women. In both sexes, the calculated cutoffs for detecting all analysed disorders were lower than conventionally used for FMI (> 9 kg/m^2) and for BMI (> 30 kg/m^2), except for diabetes in women. Additionally, in men, the calculated cutoffs were lower than what is conventionally used for WC (> 102 cm) and BFP (> 25%), both except for diabetes.

When assessing the age-adjusted PRs of cardiometabolic disorders in the presence of obesity, the prevalence of all disorders was higher in participants with obesity measured by all indices, except the FMI and hypercholesterolemia for both sexes. The associations of obesity defined using WHtR with hypertension (PR 2.16) and a combination of disorders (PR 2.24) were significantly stronger compared to other indices, but only in women. Among men, the prevalence of at least two disorders according to WHtR (PR 1.70) was significantly different from all other indices, except only that according to WHR (PR 1.51).

Thus, the age-standardised prevalence of obesity according to WHtR was the highest compared to the other indices. Besides, WHtR showed the strongest associations with hypertension and a combination of disorders in women and was non-inferior to other indices in men. As WHtR data on population level are limited in Russia, we decided to define the reference values of WHtR for Russian adults and further investigate associations of WHtR with a wide range of CVD risk factors and clinical biomarkers.

4.3 Paper III "Waist-to-height ratio – reference values and associations with cardiovascular risk factors in a Russian adult population"

4.3.1 Reference values of WHtR in a Russian adult population

A total of 2611 women and 1884 men aged 35-69 years of KYH were included in the analysis. Compared to men, higher proportions of women adhered to healthy diet, had higher education, but poorer financial situation, as well as higher proportions of depression and anxiety. Women also had lower levels of SBP and DBP, LDL-C and triglycerides.

Mean and median WHtR values for women (0.56 and 0.54) and men (0.55 and 0.55) had no significant between-sex differences. However, in the age 35-49 years, mean and P5-P50 WHtR values were higher in men. Conversely, in the age 60-69 years, P25-P95 WHtR values were higher in women. The conventional WHtR threshold for obesity of 0.5 was the value of the 25th percentile for both men and women, suggesting that 75% of the studied population had AO.

4.3.2 Associations of WHtR with CVD risk factors

In both sexes, WHtR was positively associated with age, residence in Novosibirsk (vs. Arkhangelsk), lack of higher education and low physical activity. In women, WHtR had positive associations with poor financial situation in both models, while it was positively associated with current smoking and negatively associated with diet quality only before adjustment for other socio-demographic and lifestyle factors. In men, being married and hazardous alcohol consumption were positively associated with WHtR, whereas current smoking was negatively associated with WHtR. According to the interaction analysis, the strengths of the adjusted WHtR associations with socio-demographic factors, except for the city of residence, were significantly stronger in women and with smoking in men.

For clinical parameters, the adjustments were made for age only in Model 1 and for all socio-demographic and lifestyle factors significant for both sexes in Model 2. In both sexes, hs-CRP was a correlate with the strongest association with WHtR (standardised β coefficient 0.435 in women and 0.321 in men). The second strongest correlate was HDL-C (standardised β coefficient -0.334 and -0.297, respectively). The third strongest correlate was DBP (standardised β = 0.219) in women and HbA1c (standardised β = 0.246) in men. Compared to men, women had stronger WHtR associations with SBP, DPB, HDL-C, and hs-CRP. Men had stronger WHtR associations with LDL-C and HbA1c.

5 Discussion

5.1 Methodological considerations

In designing and interpreting the results of my research, I have encountered methodological challenges that needed to be addressed or discussed. The first is the relevance of the study design to the research questions. The second, I have been concerned with the issues of internal and external validity. Internal validity may be affected by random or systematic error (162). The issue of random error, caused by random multidirectional deviations of the results from the true values, is resolved by increasing the sample size (163). Systematic error, also known as bias, is a non-random unidirectional deviation of the results from the true values, which can lead to incorrect conclusions. Systematic errors can be mainly related to selection bias, information bias and confounding bias (162, 164). I have discussed all the corresponding considerations in the following sections.

5.1.1 Study design and sample size

KYH aimed to characterise the nature and causes of CVD in Russia and was organised as a cross-sectional study. In such studies, all data are collected at one specific point in time. This approach is cost-effective and allows results to be obtained in a short time (165). A cross-sectional design allows the prevalence of a condition or disease to be studied and is therefore suitable for studying the burden of chronic diseases, but not usually for acute conditions or incidence. It is also unsuitable for investigating rare risk factors and outcomes, as their low prevalence in the population would require a too large sample size.

Since one of the objectives of my research was to study the prevalence of obesity, a chronic condition that is widespread in the population, a cross-sectional design was preferable. Cross-sectional studies can collect information on a variety of risk factors and outcomes. In addition, this study design is used to make inferences about possible associations between different risk factors and outcomes (164). Various potential factors leading to obesity and their associations with several cardiometabolic outcomes were studied in this thesis. However, as the data on risk factors and outcomes were collected simultaneously, it was not possible to establish cause-effect relationships (164, 165). Therefore, a cross-sectional study does not allow to establish the sequence of events, i.e., which came first (unhealthy diet and physical inactivity or obesity?). Therefore, it was only possible to identify associations between risk factors and obesity or obesity and cardiometabolic disorders, but not any causal relationships.

The samples for both KYH and Tromsø 7 were selected for several purposes, including the obesity research conducted (143, 145). Samples of 17646 Tromsø 7 participants and of 4495 (4121 for Paper I) KYH participants were used, which made it possible to keep the random error and confidence limits at an acceptable level.

5.1.2 Selection bias

Selection bias is an error caused by systematic differences between those who participate in the study and those who do not participate in it (163). When the aim is to study the associations between factors and outcomes, selection bias occurs when the participants of the study differ from the population from which the study participants are recruited regarding exposure factors and/or outcomes of interest (162).

Participants in KYH were randomly selected from the datasets of addresses provided by the regional health insurance funds. The response rate was calculated as a response percentage with denominator restricted to addresses where the interviewers determined that an eligible participant of the correct sex and age lived (143). The response rate for the home interview was significantly lower in Novosibirsk (41.1%) than in Arkhangelsk (68.2%). In addition, response proportions were higher for women than for men, and for older participants than for younger ones (143). The second part of the study (health check) was attended by 96.1% of the interviewed in Arkhangelsk and 82.8% in Novosibirsk.

There may be several explanations for the lower response rate in Novosibirsk. Novosibirsk is the third largest city in Russia. People in large cities may be more suspicious of various free programmes, including health screening. Besides, Novosibirsk covers a much larger area, so reaching a clinic for a health check can be difficult. In Arkhangelsk, there was a more effective campaign to inform the public about the study (143).

The response rate in Tromsø 7 was 64.7% of all adult inhabitants of Tromsø at the first visit and 90% of those who had participated in the first examination at the second visit (145). Response proportions were higher among women than among men, among older participants than among younger participants, among participants from previous waves of the Tromsø Study and among people born in Norway (145).

This may have led to self-selection of women, older people and people with higher education both in KYH and Tromsø 7. Those who agreed to participate in both studies may have been more interested in their health status or already had health problems due to their older age compared to those who did not participate. The overall rates of non-response were comparable in KYH and Tromsø 7, so the effect of the non-response bias on the data comparisons were unlikely substantial.

5.1.3 Information bias

Information bias is an error that occurs due to the way data are measured, collected, recalled, recorded, classified or handled (163). Although questionnaires remain the most common means of collecting socio-demographic, lifestyle and family history data, self-reporting may lead to inaccuracies in these data due to under- or over-reporting.

Self-reported data on socially reprehensible behaviour are prone to social desirability bias (166, 167), and, for example, alcohol consumption is often underreported (166). In my studies the AUDIT questionnaire was used. It allows for the simultaneous assessment of quantity and frequency of alcohol consumption. Questionnaires that assess both quantity and frequency of consumption of different beverages (beer, wine and liquor) separately result in 20% increase in alcohol intake estimates. These methods are more likely to reveal the most realistic levels of alcohol consumption (168). Nevertheless, the alcohol data used in this thesis could underestimate the true drinking volumes.

Self-reported smoking status is also commonly underreported (167). Daily cigarette smoking was assessed as a categorical variable with three options: never, ex-smoking or current smoking. The associations of ex-smoking with obesity could not be estimated sufficiently because the intensity of smoking among former smokers was not taken into account. Smoking intensity is assessed by calculating the number of pack-years, but these data were not available. Determination of cotinine levels in biological fluids (blood, urine or saliva) could provide an objective identification of smoking status (167), but these methods were not used in KYH or Tromsø 7.

Although the methods used may underestimate the strength of the association between smoking and alcohol and obesity, the questionnaires are most commonly used method of health behaviour assessment in population-based studies. The questionnaires used in KYH and Tromsø 7 have been previously validated for use in such studies.

I used self-reported medical history and medication use to assess diagnosis and treatment of hypertension, T2D and hypercholesterolaemia. I did not have access to the medical records of participants in either study, so information about medical history and prevalence of chronic diseases may be subject to recall and reporting bias. Although self-reporting of hypertension and diabetes has overall high levels of specificity and sensitivity compared with medical records, the validity of hypercholesterolaemia reporting is the lowest compared with both of the above-mentioned conditions (169, 170).

Data on medication use were also self-reported. However, in addition to questions about the name, dosage, indication and frequency of use of prescribed medications, participants were asked to show these medications (143). Daily use of medications for T2D, hypertension and hypercholesterolaemia shows good agreement between self-reported data and medical records (171, 172). Therefore, in the definitions of hypertension, T2D and hypercholesterolaemia, I used a combination of self-reported data on medications for these conditions and objective measurements of the blood pressure, HbA1c, TC and LDL-C levels. Such combinations of self-reported information and objectively measured variables increase the validity of the data used.

The data collected with DQS was used in KYH to assess diet. DQS assessed the overall quality of the food and drinks consumed and the variety of the diet in the 7 days prior to the interview. The questionnaire categorised the diet as unhealthy, average or healthy based on a variety of parameters. This is a simple, quick, but rough classification of diet quality (148). However, in obesity, the total calorie intake and the consumption of high-calorie products are crucial (173, 174). Although DQS has been validated and shown to be associated with certain indices of obesity and CVD risk factors (148, 175), the information collected may not be sufficient to fully answer the research questions posed in Paper III. In addition, one of the features of the diet in Russia is the consumption of a large amount of traditional Russian salty home-cooked dishes (176). Salt is associated with both weight and clinical parameters, especially blood pressure (71, 177, 178). However, the DQS does not specifically ask about salt consumption in DQS. The described deficits of the available data on participants' diet was an important limitation of my papers on obesity topic.

The period of fasting before blood collection in KYH was at least four hours, which allowed the study to be conducted throughout the day (143). Therefore, blood samples were collected without a 12-hour fast, which is the usual period required before laboratory testing (179).

Since the fasting period was rather short, this may have resulted in incorrect measurements of blood lipids. In particular, mainly TG levels rise due to recent food intake, while TC and LDL-C are reduced to fasting levels over a 4-hour period (179).

For this reason, I was unable to include hypertriglyceridaemia, a component of MetS, in the analysis of the association between obesity and cardiometabolic disorders in Paper II. In Paper III, non-HDL-C was used instead of the TG variable. Non-HDL-C allows estimation of the cholesterol content of the atherogenic apoB-containing lipoproteins (180). Measurement of non-HDL-C is recommended with a recommendation class of 1C for individuals with obesity, T2D or high TG levels according to the guidelines for the management of dyslipidaemias of the European Society of Cardiology (2019) (181).

5.1.4 Confounding and interaction

A confounder is a factor that affects the association between an exposure factor and the outcome of interest (163). A factor must meet three criteria simultaneously to be determined as confounder. First, this factor should be associated with the outcome. Second, it should be associated with the exposure factor. Third, the factor should not be an intermediate stage in the causal pathway between exposure and outcome (182).

If the distribution of a confounding factor is unequal between exposed and unexposed individuals, and the effect of this factor is not adjusted for during the analysis, the true association between exposure and outcome may be under- or overestimated (163). Randomisation, restriction and matching are used to control for confounders at the design stage. At the analysis stage, confounders can be controlled using stratification or statistical multivariable regression modelling (163). I used both stratification by sex and multivariable modelling to control for confounders in Papers I and III.

In Paper I, I examined associations of demographic, socio-economic and behavioural characteristics with obesity. A potential limitation of Paper I is that only socio-demographic and a limited range of behavioural characteristics (smoking and alcohol consumption) were included in the analysis as both potential associates and confounders. Despite the fact that excessive calorie intake and insufficient physical activity play a leading role in the development of obesity, it was not possible to analyse the impact of these factors on between-study differences in obesity. The KYH and Tromsø 7 studies included questions about diet and physical activity, but numerous attempts to harmonise them were not successful. Thus, an unaddressed confounding from these factors (183) was a major limitation in Paper I.

In Papers I and III, multi-stage models were used to assess the associations of obesity with various parameters. The multilevel adjustment approach makes it possible to see the differences in the strength of the association of the studied exposure with an outcome of interest before and after controlling for specific factors, or their groups. A change in the association after the adjustment will reflect a confounding effect of the extra variable entered into a regression model for the purposes of confounding control.

In Paper I, in the first step, only the adjustments for age were made for each factor separately. This gave a possibility to see what characteristics were more commonly observed in obese people independently of age. At the second step, all SEP characteristics, including age, education, living with a spouse or partner and financial level, were simultaneously added to the models in order to assess which among them were the obesity correlates, regardless of possible confounding from the others. For example, in Tromsø 7 men, the reduced odd of GO associated with living with a spouse or partner was attenuated to non-significance after controlling for other SEP factors. This meant living with a spouse was not an independent correlate of obesity, but part of a cluster of socio-economic characteristics that collectively determine the increased of odds of obesity.

Paper III examined the associations of WHtR with socio-demographic, lifestyle, and clinical parameters. The first step included age-adjusted analysis of the associations between each parameter and WHtR. In the second step, all socio-demographic and lifestyle factors were simultaneously entered into regression models. In the third step, the association between WHtR and each clinical parameter of interest was analysed in a separate model. In these analyses, multivariate models included adjustments for all socio-demographic and lifestyle factors that were significantly associated with WHtR in either women or men at the second step. No models with clinical characteristics entered simultaneously were built. The reason for the latter was the irrelevance of adjusting a mixture of various clinical parameters for each other because of interpretation difficulties. For example, there would be little rationale in adjusting LDL levels for the use of antidiabetic drugs. Besides, the intention was to show the associations of WHtR with a series of CVD biomarkers, where WHtR was considered an exposure rather than an outcome. Therefore, the associations of WHtR with clinical parameters were only adjusted for the socio-economic and behavioural characteristics, which could be considered as potential confounders in the studied associations.

One of the contradictory results of Paper III was that diet was not associated with WHtR in all models in men and in the multivariate model in women. This may be explained by residual confounding. Residual confounding is the effect of a confounder that remains even after adjustment (184). This may be due to the above-described deficits of DQS, which probably contained insufficient information for the correct assessment of the association between diet and obesity.

An interaction, also called an effect modification, is a phenomenon in which the effect of an exposure on an outcome depends on the presence or absence of another exposure (163). As sex was considered a potential modifier of the obesity's associations with socio-economic and lifestyle characteristics and cardiometabolic disorders, these associations were assessed separately in men and women. Therefore, analyses in Papers I-III were stratified by sex.

The assessment of the interactions of each covariate with the variable 'sex' was used in Paper III to investigate the differences between men and women in the strength of the associations between WHtR and the studied covariates. This allowed demonstrating that women had stronger associations of WHtR with age, absence of higher education, levels of hs-CRP, blood pressure and HDL-C.

One hypothesis was that a country of residence could modify the effects of socio-demographic and behavioural characteristics on obesity. For this reason, in Paper I the assessments of associations between obesity and studied characteristics were performed separately for KYH and Tromsø 7. Furthermore, between-study comparisons of the strength of obesity's associations with characteristics of interest were repeated with the pooled KYH and Tromsø 7 datasets and an additional "study" variable. Interactions of the "study" variable with each of these characteristics were assessed in separate multivariable regressions. As a result, it was, for example, demonstrated that living with a spouse or partner in KYH men had significantly stronger association with GO than in Tromsø 7 men.

5.1.5 Comparisons between the KYH and Tromsø 7 studies

In Paper I, the main methodological issues concerned the comparison of two studies with only partially harmonised data collection protocols. Therefore, some of the compared variables in the KYH and Tromsø 7 studies were approximated but assumed to be sufficiently comparable.

Regarding anthropometric measurements, WC was measured using different approaches, so the conversion equation proposed and validated by Mason and Katzmarzyk was used to ensure comparability of WC values in the studies (156). Socio-demographic variables also had to be adjusted for comparability. For example, in KYH, marital status was assessed according to five categories, but was recoded into a binary variable (living with a spouse or partner, yes/no) to match that of Tromsø 7, although separate information on divorced or widowed individuals was lost for analysis.

Russia and Norway have different education systems, so harmonising the education variable between KYH and Tromsø 7 was a challenge. To achieve comparability, education was categorised as primary/secondary or college/university in both datasets. The studies assessed the financial well-being of families in different ways. KYH assessed the family's ability to purchase certain goods. Tromsø 7 measured annual household income in monetary terms. A unified variable assessed financial well-being at three levels in order of increasing income.

Because of the imperfect harmonisation of the described variables, their associations with obesity may have been assessed differently in the two studies, and comparisons of their strengths may be biased by the incompletely accounted for differences in measurement.

Several variables of interest were not examined because they could not be harmonised. Data on body composition were assessed using the TANITA BC 418 body composition analyser (TANITA, Europe GmbH) in KYH and the GE Lunar Prodigy DXA (GE Healthcare, Norway) in Tromsø 7 (143, 145). These two methods have been compared previously, and comparability has not been achieved in several studies (134, 185-187). The study teams of KYH and Tromsø 7 attempted to develop an equation for direct comparison, but could not find a single conversion coefficient. The degree of difference between TANITA and DXA measurements depended on the sex and age of the participants.

The same situation was observed with data from two instruments for objective measurement of physical activity. Energy expenditure over five days was measured by Actiheart (CamNtech Ltd, Cambridge, UK) in a subsample of KYH participants (143). In Tromsø 7, physical activity was measured with an ActiGraph wGT3X-BT accelerometer (ActiGraph, LLC, Pensacola, USA) worn for eight full days (145). Actiheart allows the assessment of total, resting and exercise energy expenditure (188). Using ActiGraph, accelerometry variables are expressed as volume and as minutes per day of sedentary, light, moderate and vigorous physical activity (189).

Questions about diet were also worded differently. While KYH used DQS to assess dietary intake, Tromsø 7 applied the food frequency questionnaires, that were developed at the University of Oslo (190). Therefore, direct and indirect comparisons were not elaborated for all these factors. For this reason, comparisons between studies were not made for all the variables originally planned. Thus, if I had the opportunity to participate in the preparation of the protocols of the two studies at the planning stage of their comparison, I would use similar questionnaires and instrumental methods to increase the comparability of their data.

According to non-response pattern analysis, KYH and Tromsø 7 had differential inclusion of older, female and more educated individuals (143). As the inclusion biases were similar in the both studies, this suggests that differential selection is unlikely to negatively influence the results in Paper I. with regard to between-study differences in the associations of demographic, socio-economic and behavioural factors with obesity.

5.1.6 Generalisability

External validity, also called generalisability, is the extent to which the results of a study apply to other individuals or populations (163). Internal validity is an important prerequisite for external validity. Internal quality control is one way of ensuring external validity (163). During KYH, reports on data quality were produced on a monthly basis and included key variables to be monitored (143).

The KYH study included participants from the two Russian cities, Arkhangelsk and Novosibirsk. The populations of both cities had age distributions comparable to the Russian urban population as a whole. While the educational distribution in Arkhangelsk was also comparable with Russia, the proportion of people with higher education was larger in Novosibirsk (143). Mortality from diseases of the circulatory system in the age group 35-69 years was analysed in both cities and in Russia. Mortality in the Arkhangelsk region was higher than the Russian average, while in Novosibirsk it was lower than the national average (143). Thus, sampling from the two cities was expected to yield a study population with demographic characteristics and CVD mortality rates close to those of the for the Russia as a whole. However, the low response rate in Novosibirsk is a threat to generalisability and comparability with other settings.

Tromsø 7 was based on data from the municipality of Tromsø (145). The municipality of Tromsø, the largest municipality in northern Norway, has similar demographical and economic characteristics to the rest of Norway (191, 192). However, the study participants represented only the population of the northern part of Norway and the proportion of the population with a higher education is larger in Tromsø than the national average (193).

Therefore, the participants in both studies should not have major socio-demographic or lifestyle differences compared to the total Russian and Norwegian populations. However, it would be too ambitious to assume that the KYH and the Tromsø 7 data can be generalised to the entire populations of both countries, as they have different climate zones, varying levels of economic development of its regions, different ethnic composition with variations in cultural traditions. As KYH included a Caucasian population of urban settings, the generalisability of the results may be limited to populations with similar ethnic and socio-demographic characteristics.

5.2 Discussion of the main results

The main findings of my research have been discussed in detail in the three included papers (Papers I-III). The following sections will present a broader overview of the obesity problem, including the possibilities of early obesity detection and its associations with metabolic consequences, as well as the potential for practical applications of the findings obtained.

5.2.1 Comparisons of obesity between Russia and Norway

Nowadays obesity is a serious healthcare problem in most countries. Despite the ongoing efforts of healthcare professionals, the prevalence of obesity continues to rise. The COVID-19 pandemic worsened obesity statistics and contributed to the weight gains due to the decrease in physical activity, increase in the amount of food consumed and a rise in the prevalence of psychological disorders during the lockdown period (194, 195).

In 2022, more than one billion people worldwide had obesity (196). In recent decades, Russia has exhibited the same trend of increasing obesity observed worldwide and in the European region (7). In 2016, the prevalence of obesity according to BMI in Russian adults was 23.1%

(2). The collapse of the Union of Soviet Socialist Republics (USSR) in 1991 in a short period of time led to considerable changes in socio-economic characteristics and lifestyle of the Russian population within a short period of time. There were several economic crises until the situation stabilised in the mid-2000s (197, 198). Thus, after the collapse of the USSR, the Russian population developed a socio-economic environment that predisposes to an increase in obesity prevalence.

In 2016, according to the official statistics, 26.9% of women and 18.1% of men in Russia were obese (2). Several earlier studies that assessed obesity in the Russian population have also shown that its prevalence depends on sex, indicating possible differences between men and women in obesity determinants and associated characteristics (18, 29, 199-202). For this reason, I initially planned to study obesity and its associations with other factors for KYH women and men separately.

The features of obesity in the Russian population could be detected and better understood if investigated in comparison with those of other populations. Norway is a neighbouring country with a similar geographic location and climate. However, the cultures, socio-economic backgrounds and lifestyles in Russia and Norway are different (143, 203). Moreover, despite the improvement in overall health indicators in both countries over recent decades, significant between-country differences remain (204). In 2021, the life expectancy at birth in Russia was 70.0 years, while in Norway it was 82.9 years. Although ischaemic heart disease was the leading cause of death in both countries in 2019, mortality from this disease was almost four-fold in Russia compared to Norway (385 versus 98.9 per 100000) (204).

In 2016, the prevalence of obesity was 23.1% in both countries (7, 205). There has also been an upward trend in obesity in Norway. In 1990-2017, the growth rate of obesity in Norway exceeded that observed in Russia (196). However, despite the continued gradual increase in the prevalence of obesity in Russia since 2018, a decrease has been observed in Norway. In 2022, 24.2% of the adult population in Russia was obese, compared with 19.1% in Norway (204). This highlights the need to identify differences between countries and find obesity risk factors in Russia. Norway is therefore a suitable country for comparison with Russia regarding obesity.

In Paper I, the prevalence of GO and AO was higher among KYH women than among those in the Tromsø 7 cohort. However, the age-specific proportions in women differed significantly, with the greatest discrepancy observed in the age of 45-49 years. The only factor that demonstrated a significant between-study difference in associations with GO and AO in the KYH and Tromsø 7 female populations was age. Numerous studies have shown a positive association between GO and age, with the strongest association at the age of 50-65 years (8, 17, 19-24, 206). This may be because perimenopause women experience hormonal changes that affect metabolism and predispose to weight gain (8, 68, 207). In addition, the retirement age for women in the northern regions of Russia is 50. Due to the more pronounced traditional female gender role and the associated conditions of daily life in Russia, the lifestyle of retired women is typically characterised by a low level of physical activity and the consumption of home-prepared foods that are high in salt, sugar and fat (176, 208, 209). These cultural characteristics in Russia may possibly explain the higher obesity prevalence in KYH versus Tromsø 7 women.

In Tromsø 7 participants, the prevalence of GO did not increase with age. Young Tromsø 7 men had a higher GO prevalence compared to older participants, which may reflect a higher GO prevalence among men aged <40 years in the Tromsø 7 population (210-212). While there was no difference in GO obesity between men, the odds of AO increased with age for men in both studies, with the trend being more pronounced in Tromsø7 men.

The higher GO prevalence in KYH women compared to men was consistent with data from previous Russian studies (29, 200, 201). In contrast, Tromsø 7 men had higher rates of GO than women. Sex differences in the prevalence of obesity depend on SEP. In high-income countries, men and women have comparable levels of obesity prevalence, and women are more likely to be of normal weight if they have a higher income (25, 26, 28). Moreover, the association between obesity and SEP is reversed as a developing country moves to a higher income level (25, 27). The theory of obesity transition includes four stages, depending on the SEP and the sex-related patterns of obesity. The transition of obesity begins with an increase in its prevalence and a positive association with SEP in the first stage, and ends with a decrease in its prevalence in the fourth stage While the first stage is characterised by a higher prevalence of obesity in women than in men, the narrowing of the gap between sexes is observed in the second stage. In the fourth stage, the plateaus in obesity prevalence can be observed in women with high SEP (27).

As for the analysed countries, Norway is a high-income country, while Russia is an upper-middle income country according to the World Bank classification (204). The position of

Russia has not changed since 2007, when SK Huffman and M Rizov analysed the determinants of obesity in Russia (68). I assume that Russia is in the second stage of the obesity transition, since the prevalence of obesity among KYH women was almost twice as high as among KYH men. SEP was significantly and inversely related to GO only in KYH women.

In the studied period, Norway was in the third stage of the obesity transition similar to other European countries (27). In Tromsø 7, there were no differences in the prevalence of GO between men and women, which is similar to previous data (7). In Tromsø 7, a high SEP was associated with a lower GO prevalence in both men and women. According to recent data on obesity prevalence (204), Norway may have reached the end of the third stage and moved on to the fourth stage, as obesity prevalence has decreased over the last five years. However, longer follow-up is required to ensure that the decline in obesity prevalence is sustained over time.

In high-income countries, the level of education is also closely correlated with the income level, especially among women (19). In Tromsø 7 participants of both sexes, lower education and financial levels were associated with GO, but associations with AO were significant only in women. In KYH, associations of no university education and lower financial level with GO and AO were observed only in women. While 78.3% of KYH women and 70% of KYH men had college or university education, only 4.7% of women and 6.2% of men reported high income. In Russia, especially among men, there is not always a direct correlation between high education and income, since low-skilled manual labour can be better paid than highly-skilled labour (213). Higher education is associated with better knowledge about a healthy lifestyle, the consequences of obesity and effective methods of obesity prevention (19, 23, 213). However, the differences in obesity-related knowledge and behaviour among KYH men who differed on SEP and educational level were not as pronounced as among Tromsø 7 men.

In KYH men, the only socio-demographic factor associated with GO was living with a spouse or partner, whereas no such associations were found in Tromsø 7 men. Several studies show that marital status associates with obesity only in men (20, 213, 214), others found the same associations in both sexes (19, 215) or no associations (22). A possible explanation may be that married men in KYH have a different dietary pattern compared with unmarried men. This pattern may include regularly meals, a greater number of meals or eating home-prepared foods with high salt, sugar and fat content (176, 214, 216).

Both smoking and alcohol consumption show associations with obesity. Current smoking has an inverse association with obesity, since current smokers have lower body weight and BMI compared to ex-smokers and never-smokers (30-32). The higher risk of obesity among ex-smokers may be mainly due to weight gain after smoking cessation, which may be one of the main barriers to quitting smoking (30). Studies on alcohol consumption and obesity show conflicting results, which may be related to the variety of alcohol beverages, different patterns of alcohol consumption and different patterns of food intake associated with alcohol consumption (33, 217-224).

Since smoking and alcohol consumption could have mediating effects in the associations between SEP and obesity, I analysed them in univariate and multivariate models assessing their interaction with other characteristics. In both studies, current smoking was negatively associated with GO (except for KYH women), but positively associated with AO (except for KYH men). While ex-smoking was positively associated with GO and AO in Tromsø 7 participants, it was only associated with AO in KYH men. These differences may be explained by the higher prevalence of current smoking in KYH men (35.7%) with more widespread health effects of smoking in the KYH male population, as well as the lower prevalence of current and ex-smoking (15.0% and 12.9%) and the closer relationship between obesity and age in KYH women. However, there may be lifestyle differences between smoker and non-smokers.

Between-study differences were also found in obesity associations with the frequency and amount of alcohol intake in men and women. Frequent drinking showed a negative association with GO and AO in Tromsø 7 participants, but was positively associated with GO in KYH men. Tromsø7 men had a stronger positive association between binge drinking and AO compared to KYH men. The different associations of obesity with alcohol consumption may reflect the different alcohol consumption patterns between the two populations. However, the relatively rough classification of alcohol consumption may have underestimated the differences in associations between obesity and alcohol. In addition, data on alcohol consumption may have been underreported, which has been shown to be more common among Russian women than among women from both Norway and Finland (225, 226).

Modest attenuations of the GO and AO odds for education and financial level after adjustment for health behaviours were observed in Tromsø 7 participants, but not in KYH men. This may also support the hypothesis that health behaviours do not differ by SEP level in KYN men compared with Tromsø 7 men. However, the comparison of the associations of obesity with education and SEP in KYH and Tromsø 7 may have been affected by the overall difference in levels of income between Russia and Norway (203). Moreover, any of the above assumptions about between-country differences in the associations of obesity with SEP and behavioural factors may be limited by the lack of opportunities to compare genetics, diet, physical activity and neighbourhood between studies.

5.2.2 Comparison of obesity prevalence estimated by different indices

There are different ways of measuring obesity. However, there has not yet been a consensus on the best method. Existing approaches can be divided into anthropometric indices, methods of measuring the total amount of fat based on body composition analysis and high-resolution imaging techniques (8, 37, 121, 140). Imaging techniques such as CT and MRI allow the direct visualisation of the location of adipose tissue and determination of the volume of adipose tissue in the body, but are expensive and time-consuming, and thus are not recommended for screening (140). Body composition analysis also requires specialised equipment. A suitable practical indicator for assessing obesity is likely to be based on the measurement of individual anthropometric data

In Paper II, based on KYH participants aged 35-69 years, I included in the analysis anthropometric indices that allow the identification of GO (BMI) or AO (WC, WHR and WHtR). In addition, two indices of the direct assessment of fat volume based on BIA (BFP, FMI) were analysed. The comparison of obesity according to the studied indices has been discussed in detail in Paper II, so I will not consider between-country differences, but only a comparison of obesity according to six indices in KYH and other Russian studies.

The prevalence of obesity varied according to the measurement method used. Both men and women had the highest age-standardised prevalence of obesity according to WHtR (75.8% and 65.0%) and the lowest according to FMI (17.2% and 23.6%). These results appear rather paradoxical, as all these indices measure the prevalence of obesity and the thresholds for all the indices used have been previously validated (8, 37, 111, 137, 146, 147). However, these indices measure different obesity types using anthropometric characteristics and fat volume in different ways.

The age-standardised prevalence of obesity according to BMI was 33.6% in KYH women and 25.8% in KYH men. BMI is widely used for obesity assessment (146), regardless of the, it limited ability to determine the difference between elevated body weight due to high levels of fat mass or lean mass (63, 113, 116, 227, 228).

For this reason, I assessed the differences in the obesity identification based on BMI compared to other indices. Among those who were not obese but classified as overweight (BMI = 25.0-29.9 kg/m^2), obesity was identified using other indices in 20.7-94.6% of men and in 45.4-87.0% of women. In both sexes, the highest proportions of obesity in participants with overweight, as defined according to BMI, were found obese using WHtR.

In addition, among those with a BMI < 25.0 kg/m^2, up to 16.2% of women were classified as obese according to WHtR and up to 40.0% of men according to WHR. According to the theory of normal weight obesity, it is highly important to detect high body fat accumulation. Normal weight obesity is associated with an increased risk of MetS and higher mortality rates (229). Therefore, using BMI alone may significantly underestimate abdominal fat accumulation. Moreover, since the end of the twentieth century, there has been a trend towards an increase in AO worldwide, and the growth rate of AO is higher than that of GO (230). Therefore, an AO index is recommended to be used in addition to BMI for the appropriate evaluation of general and abdominal fat accumulation (8).

All anthropometric indices of AO are based on WC measurements, although some of them also consider body size, adjusting for HC or height (115). Our findings of the higher prevalence of obesity according to anthropometric indices of AO compared to BMI and BIA indices are consistent with previous studies (10, 11, 230).

Sex differences in the prevalence of AO should be analysed with caution. The predominance of women or men in AO prevalence depended on the index used (10, 211, 230, 231). In KYH, women had a higher prevalence of AO compared to men when assessed by WC, but a lower prevalence when assessed by WHR and WHtR. Besides, men had a higher obesity prevalence based on WHtR and WHR compared with the prevalence estimates obtained using other indices. These differences reflect the contrasting types of adipose tissue accumulation between the sexes. Men tend to accumulate fat in the upper body, while women, on the contrary, are prone to fat accumulation in the lower body. The female type of fat accumulation, usually assessed by WHR, is considered safer for the risk of cardiometabolic disorders (63).

Obesity metrics received by BIA, allow to assess total body fat in more accurate way. Both BFP and FMI are the metrics of GO similar to BMI (232). In KYH, categorisation according to BFP gave approximately 1.5 times higher proportion of obesity and FMI about 30% less compared to BMI. A similar differential prevalence between BFP and BMI was reported previously (233). However, assessing body fat as a percentage of weight results in similar limitations as BMI. In both metrics, the contribution of lean mass to body weight is not taken into account. Besides, BFP tends to overestimate obesity compared to BMI (37, 232). FMI takes into account height, which significantly decreases the obesity prevalence compared to BFP. In KYH, FMI underestimated the prevalence of obesity compared to BMI when obesity presence according to five indices was compared by BMI categories and sex. Besides, BFP does not allow to differentiate between GO and AO (232).

The data received in KYH are consistent with previous studies based on the Russian population, which have reported a higher prevalence of obesity by BMI and WC in women compared to men (18, 29, 200, 202, 234, 235). Although the KYH prevalence of obesity by BMI and WC was within the range of earlier estimates for other Russian populations, direct comparisons are complicated due to the different ages of the participants and the thresholds used to determine obesity by WC.

The Russian multi-center Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of the Russian Federation study (ESSE-RF, 2014-2015, N = 20,190, 25-64 years) is the largest population-based study, assessing obesity in Russia (200, 234). In ESSE-RF, the prevalence of obesity by BMI and WC was 31.4% and 61.8% in women and 27.5% and 44.0% in men. However, ESSE-RF used lower thresholds (94 and 80 cm for men and women, respectively) to measure obesity by WC. A higher threshold for WC obesity was used (102 and 88 cm for men and women, respectively) in the analysis of the KYH population, because I applied the definition of WC-based AO in accordance with a high disease risk comparable to the risk of BMI ≥ 30 kg/m^2 (8). Different thresholds for obesity measured by the same index complicate the use of WC in practice and the comparisons with other studies.

To date, no population-based studies have been conducted in Russia to determine the prevalence of obesity based on WHR, WHtR or BIA indicators. Although WHtR is a promising index of AO that takes into account not only WC but also the height of individuals (121, 123, 236). However, its use is limited in Russia, which may be related to a lack of knowledge about its distribution in the population. For this reason, in Paper III age-adjusted

WHtR reference values were modeled for the total KYH population and for men and women. The conventional WHtR obesity threshold of 0.5 corresponded to the value of the 25th percentile for the combined male and female population, assuming that 75% of the KYH population had AO. This, on one hand, may suggest that the conventional obesity threshold of WHtR ≥ 0.5 maybe too low for the KYH population. On the other hand, using this threshold in Paper II has led to a conclusion that WHtR-based obesity was the strongest correlate of cardiometabolic disorders, particularly in women. Therefore, WHtR reference values presented in Paper III provide a comprehensive overview of the WHtR distribution in the Russian population, but the conventional threshold value of 0.5 should not be changed because of its high sensitivity with respect to detecting the cardiometabolic AO consequences.

Thus, based on the results of Paper II, the following suggestions can be made. For direct comparisons between studies and populations, several conditions must be met. Firstly, the populations should be comparable in terms of sex and age characteristics. Secondly, the same measures of obesity should be used. Thirdly, obesity index identical thresholds should be established and used each compared population. Fourthly, when less common or newly proposed indices are used, their reference values and obesity thresholds should be established using the empirical data obtained through population studies.

The choice of a specific obesity index depends on the purpose of its use. If one aims to compare the prevalence of obesity with other countries or studies, then the most common indices such as BMI for GO and WC for AO are appropriate (2, 8). Studying the relationships between different measures of obesity allows to identify the features of the total volume and distribution of fat mass in populations of interest, as well as in groups with specific ethnic or lifestyle characteristics (237). In order to find a better indicator for risk assessment in a specific population, direct comparisons of the predictive ability of indices for outcomes of interest can be particularly useful.

5.2.3 Different obesity indices and their associations with cardiometabolic disorders

The obesity index that is useful in practice should allow not only an adequate assessment of obesity but also the identification of cardiometabolic risk. Both GO and AO demonstrate associations with metabolic health effects (228, 230, 232, 238-240), but AO indices have a stronger association with cardiometabolic consequences compared to GO indicators (63, 113, 228, 241). When studying obesity and the associated cardiometabolic risk, particular attention should be paid to assessing the amount of adipose tissue and the type of its distribution (8, 61). Upper body obesity resulting from visceral fat accumulation associates with the development of metabolic health consequences (63).

I also attempted to compare BFP and FMI as metrics for estimating the amount of body fat with other indices. In KYH, the prevalence of obesity according to BFP was closest to WC obesity rates. Although WC is the AO index recommended by the WHO, BFP may have similar properties for identifying cardiometabolic health effects.

All studied cardiometabolic disorders were more prevalent in the KYH study compared to ESSE-RF (242, 243). These variations may be associated with the younger age of ESSE-RF participants and different definitions of disorders used in these studies. However, if there is indeed a higher prevalence of disorders in KYH, then this indicates a lower level of health in the studied population.

All obesity indices had a significant predictive ability in detecting the presence of all analysed metabolic disorders. Compared with all other obesity indices studied, WHtR was a better indicator of hypertension (AUC 0.784) and a combination of at least two disorders (AUC 0.779) in women. WHtR was better at predicting hypertension and a combination of disorders in KYH men compared to BMI and WC, and was not inferior to WHR, BFP and FMI.

The better performance of WHtR compared to other idices in predicting cardiometabolic disorders has been demonstrated in several studies. WHtR had stronger associations with hypertension (67, 121, 236), T2D (67, 123, 244) and hypercholesterolaemia (67, 123).

The close associations of all obesity indices with diabetes and hypertension compared to hypercholesterolaemia could be explained by pathophysiological mechanisms of insulin resistance progression and direct associations of AO with hypertriglyceridemia, but not with high cholesterol levels (50, 57, 58, 63, 64).

The coexistence of carbohydrate metabolism disorders, hypertension and dyslipidaemia in an individual with AO is associated with an extremely high risk of developing adverse CVD events. MetS should therefore be actively detected in people with AO to prevent adverse outcomes (44, 51). However, early CVD prevention aims to avoid the development of MetS and even its individual components in obese people (44, 65).

The optimal cutoff points for BMI in both sexes, and for FMI, WC and BFP in men (all except for diabetes) were below the standard ones. Thus, the risk of hypertension and hypercholesterolaemia may be underestimated if standard cutoff values for these indices are used in the KYH population. The estimated cutoff values of WHtR for hypercholesterolaemia with the highest combination of sensitivity and specificity were closest to the standard value of 0.5 in men (0.51) and women (0.53), whereas they were higher for other cardiometabolic conditions. Thus, a standard WHtR threshold of 0.5 is plausible for identifying obesity-related cardiometabolic disorders in the KYH population.

The revealed superiority of WHtR over other indices may be due to the fact that its formula takes into account the height. The proportion of abdominal fat determined by WC and WHtR may vary with height (120). WHtR assumes that a certain amount of abdominal fat is acceptable for a certain height (122). When comparing individuals across height tertiles, the prevalence of MetS was 30% higher in those in the lowest height tertile compared to those in the highest height tertile. Moreover, this difference was observed in both the high and the low WC groups. However, this effect was not observed when individuals were grouped into high or low WHtR (245). In addition, people with normal WC but elevated WHtR were more likely to have T2D, hypertension or CVD (120). Thus, WHtR is more sensitive in detecting cardiometabolic disorders, especially in people of short stature. This evidence may explain the greater sensitivity of WHtR in KYH women.

When the associations between WHtR and other CVD factors were assessed in Paper III, inflammation according to hs-CRP levels had the strongest association with WHtR compared to other factors in both women (standardised β-coefficient 0.435) and men (standardised β-coefficient 0.321), with women having stronger associations of WHtR with hs-CRP than men.

A previous study based on an Arkhangelsk subsample of the KYH demonstrated that AO according to WC (> 94/80 cm for men and women) had the strongest association with low-grade systemic inflammation in both men and women. This suggests that low-grade systemic inflammation is most often obesity-dependent (246).

Dysregulation of the inflammatory process is one of the main concepts in the theory of adiposopathy (43, 228). In obese individuals, adipose tissue is infiltrated by macrophages, and blood flow in adipose tissue decreases. Hypoxia promotes the synthesis and release of a cascade of cytokines, including the inflammatory types. Inflammation occurs earlier than cardiometabolic consequences of obesity (247-249). This pathophysiological cascade leads to a closer relationship between obesity and inflammation, but not with cardiometabolic disorders or CVD (54, 63, 247, 248).

Based on existing evidence, in 2022, National Institute for Health and Care Excellence (NICE) of the United Kingdom revised clinical guidelines for the identification, assessment and management of obesity (250). In adults with a BMI below 35 kg/m^2, the NICE recommends to use WHtR in addition to BMI for AO assessment. In individuals with a BMI over 35 kg/m^2, WHtR may not be a useful addition for predicting health risks, as they always likely to have a high WHtR (250).

Thus, despite giving the highest prevalence of obesity in KYH compared to other indices, WHtR with a threshold of 0.5 is an advantageous index in the clinic. It is easy to measure and interpret and may perform superior to other obesity measures in predicting cardiometabolic disorders and their joint manifestation, known as MetS, as shown on KYH women.

5.3 Implications for public health practice and research

In the KYH adult population, using BMI as the sole index for obesity screening was ineffective, as it underestimated the prevalence of obesity. One in three women and one in four men were obese according to BMI, which is the most commonly used anthropometric index of obesity in clinical practice. However, about 70% of both sexes had AO according to WHtR. Furthermore, the empirically defined optimal BMI cutoff points for hypertension and hypercholesterolaemia were lower than the standard ones in both sexes. In contrast, the estimated cutoffs of WHtR for detecting hypercholesterolaemia were the closest to the standard cutoff.

Thus, using BMI as the sole index underestimates the health risks associated with obesity. For Russian population, I recommend the combined use of BMI and WHtR, which allows both the commonly accepted measurement of GO and the earliest identification of AO, as well as the possibility of early initiation of preventive measures for obesity-related health consequences. For routine practice, WHtR is a valuable measure of obesity-related risk with a single threshold >0.5 for both sexes, all ages and ethnicities. It also provides an easy-to-remember health-promoting message: “Keep your waist circumference to less than half your height”.

It is alarming that the prevalence of hypertension, T2D and hypercholesterolaemia in adults of both sexes in KYH was higher than in other Russian epidemiological studies. These findings require further investigation. Besides, in KYH, the prevalence of other CVD risk factors and their associations with obesity and obesity-related disorders differ by sex. In women, obesity is most strongly associated with hypertension and a combination of at least two conditions (hypertension, T2D or hypercholesterolaemia). This should be taken into account during medical examinations. Socio-demographic factors and health behaviours, such as smoking and alcohol consumption, as well as psychological factors should also be addressed differently in men and women.

According to this thesis, perimenopausal women are a risk group for developing obesity in the urban population of Russia. Special programmes should be developed for them. This includes a set of measures to prevent obesity and effective measures to correct overweight and obesity before the development of obesity-related consequences. The fact that the age of increasing prevalence of obesity coincides with the retirement age for women in the northern regions of Russia highlights the need to develop a tailored approach to prevention. Many women are at home, caring for their families and relatives. There is a need to reach them through information, so information sharing is vital. This includes developing information programmes for radio, television and other advertisements in the urban environment.

Promotion of free health checks for early detection of obesity could also be effective and provide an opportunity for timely introduction of preventive measures. Development of effective weight correction programmes should focus primarily on promoting the concept of healthy eating. There should also be a focus on ways to increase physical activity both indoors and outdoors in the urban environment.

6 Conclusion

The main findings of this thesis were:

- The age-adjusted prevalence of GO and AO measured by BMI and WHR was higher in Russian compared to Norwegian women (36.7 vs. 22.0% and 44.2 vs. 18.4%, respectively), but not different in men (26.0 vs. 25.7% and 74.8 vs. 72.2%, respectively).
- Between-study differences in the associations of obesity with socio-demographic factors were: a stronger association of GO and AO with age in Russian compared to Norwegian women; a positive association of GO with living with a partner in Russian compared to Norwegian men; a negative association of frequent drinking with both types of obesity in Norwegian participants and the opposite association of AO in Russian men; a stronger association of drinking large amounts of alcohol per occasion with AO in Norwegian compared to Russian men.
- The age-standardised prevalence of obesity in KYH depended significantly on the anthropometric index used. The variation was 17.2-75.8% for men and 23.6-65.0% for women according to FMI and WHtR, respectively.
- The commonly used BMI measures only GO and underestimates abdominal fat distribution, especially in overweight people. AO should therefore be assessed in parallel with GO.
- The most useful tool for identifying AO in KYH was WHtR.
- Compared to other obesity indices, WHtR showed the strongest association with hypertension and a combination of at least two disorders (hypertension, T2D or hypercholesterolaemia) in women and non-inferiority in men.
- Three quarters of the men and women in KYH had WHtR values exceeding the conventional cutoff of 0.5 for obesity.
- WHtR exhibited stronger associations with age, higher education, blood pressure, hs-CRP and HDL-C levels in KYH women compared to men, while in men it was stronger associated with being married, LDL-C and HbA1c.
- WHtR is recommended for use in clinical practice as an easy-to-measure tool for AO screening and early prevention of cardiometabolic disorders.

7 Future perspectives

Obesity rates will continue to rise in high-, middle- and low-income countries in the coming years. Russia has the same negative outlook. The increasing incidence of obesity among children and adolescents is especially disturbing. Previous efforts by scientists have been aimed at studying individual obesity risk factors. To date, it is well known that obesity is a multifactorial disease based on an imbalance between energy intake and expenditure. However, it is now important to identify factors that are crucial in specific populations to provide targeted action for specific risk groups.

In addition to what has already been studied both in this thesis and in other research projects, data from KYH allows for the exploration of other avenues of research related to obesity. For example, quality of life and functional status are associated with the severity of fat accumulation. Obesity affects the function of all systems, especially the heart. Echocardiographic data could be used to assess cardiac function in detail. The effect of obesity on the degree of atherosclerosis and on renal and respiratory function can also be studied using KYH data.

It will also be possible to study the impact of obesity on outcomes, including all-cause mortality, cardiovascular mortality and the incidence of socially important diseases in KYH participants. Such an opportunity to study the prognosis arose from the organisation of the register of outcomes for study participants as a result of collaboration between the Northern State Medical University in Arkhangelsk and the Ministry of Health of the Arkhangelsk Region.

Finally, I recommend that the next waves of KYH be organised and carried out regularly in the Arkhangelsk region, as in the Tromsø study. This will make it possible to study the health of the population and identify changes in health indicators in time. These data can be used as a basis for the timely organisation of preventive programmes and medical care.

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Paper I

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Obesity Prevalence and Associated Socio-Demographic Characteristics and Health Behaviors in Russia and Norway

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Abstract: Associations between obesity and socio-demographic and behavioral characteristics vary between populations. Exploring such differences should throw light on factors related to obesity. We examined associations between general obesity (GO, defined by body mass index) and abdominal obesity (AO, defined by waist-to-hip ratio) and sex, age, socio-economic characteristics (education, financial situation, marital status), smoking and alcohol consumption in women and men aged 40–69 years from the Know Your Heart study (KYH, Russia, *N* = 4121, 2015–2018) and the seventh Tromsø Study (Tromsø7, Norway, *N* = 17,646, 2015–2016). Age-standardized prevalence of GO and AO was higher in KYH compared to Tromsø7 women (36.7 vs. 22.0% and 44.2 vs. 18.4%, respectively) and similar among men (26.0 vs. 25.7% and 74.8 vs. 72.2%, respectively). The positive association of age with GO and AO was stronger in KYH vs. Tromsø7 women and for AO it was stronger in men in Tromsø7 vs. KYH. Associations between GO and socio-economic characteristics were similar in KYH and Tromsø7, except for a stronger association with living with spouse/partner in KYH men. Smoking had a positive association with AO in men in Tromsø7 and in women in both studies. Frequent drinking was negatively associated with GO and AO in Tromsø7 participants and positively associated with GO in KYH men. We found similar obesity prevalence in Russian and Norwegian men but higher obesity prevalence in Russian compared to Norwegian women. Other results suggest that the stronger association of obesity with age in Russian women is the major driver of the higher obesity prevalence among them compared to women in Norway.

Keywords: obesity; waist-to-hip ratio; cross-sectional study; socio-demographic factors; smoking; alcohol; sex; Russia; Norway

1. Introduction

Between 1975 and 2014, the worldwide age-standardized prevalence of obesity has been estimated to have increased from 3.2% to 10.8% in men and from 6.4% to 14.9% in women [1]. In 2016, more than 13% of the population, or 650 million adults, were estimated to be obese [2]. In European countries, the prevalence of obesity has risen despite the overall improvements in population health indicators, such as life expectancy at birth and adult mortality rate [3]. The prevalence varies from 19.7% in Denmark to 27.8% in the United Kingdom [3].

Obesity is a risk factor for many diseases, including diabetes, hypertension, cardiovascular diseases, chronic kidney disease, cancer and general mortality [4–8]. Recent research also shows that obesity is a strong risk factor for unfavorable outcomes of coronavirus infection [9].

The substantial global rise in obesity prevalence is related to societal changes, and the imbalance between energy consumption from food and its expenditure through exercise [6,10–12]. In this way, obesity is largely preventable [6]. Although there are non-modifiable risk factors, such as genetic predisposition [10], identification and control of modifiable risk factors allows for effective prevention [6,10,12,13]. Despite existing knowledge about etiology, the growing worldwide prevalence of obesity and its variation across countries [1,3] indicate that obesity has socio-economic and behavioral determinants.

Socio-economic position (SEP) can be defined in different ways; for example, based on education, occupation or income. In high-income countries, there are ecological associations between lower income and education levels and higher obesity prevalence [14–16]. However, in low-income countries, obesity is associated with higher SEP [17]. The association of obesity with gender also varies across socio-economic levels and different cultural contexts [15,17].

According to the WHO, the prevalence of obesity has grown in Russia over the last thirty years, reaching 23.1% in 2016 [3]. These changes were observed against the background of socio-economic changes in the country [18,19]. The collapse of the Union of Soviet Socialist Republics in 1991 had dramatic economic, social and public health consequences, but the situation stabilized in the mid-2000s [18]. In parallel, the annual growth in obesity prevalence ranged between 0.1–0.2% in 1998–2004 and 0.2–0.3% in 2005–2016 [3].

Low SEP is associated with higher levels of smoking and alcohol consumption [18]. While smoking is associated with reduced levels of obesity [20–22], the role of alcohol consumption in weight gain is controversial and depends on the drinking pattern [23]. Therefore, these lifestyle factors can have diverse confounding effects on the associations between SEP and obesity [19].

Several epidemiologic studies have addressed obesity prevalence in Russia [18,24–29], but only a few have looked at the role of socio-demographic factors [27–29]. A large population-based study, "Epidemiology of cardiovascular diseases and risk factors in the regions of the Russian Federation" (ESSE-RF), described a positive association of obesity with high education and low income in men. In contrast, obesity levels were lowest in women with high education and low income [28].

One way to throw new light on the etiology of obesity is compare obesity levels and related factors in different populations. In this respect, Norway is suitable for comparison with Russia, as it is a neighboring country with similar geographic location and climate conditions but with substantially different socio-demographic characteristics. Interestingly, the prevalence of obesity among adults was the same in Norway and Russia in 2016 (23.1%) and rose in both countries in the preceding years, from 16.0% in Norway and from 19.0% in Russia in 2000 [3,30]. Income as an SEP indicator also increased in both countries during the same period. The inflation-adjusted gross domestic product (GDP) per capita increased between 2000–2019 from 14,600 to 27,000 USD in Russia and from 57,300 to 65,000 USD in Norway [31]. However, GDP in Norway was initially higher and has been more stable over time [31].

The aim of our study was to compare the prevalence of obesity and its possible associations with socio-demographic characteristics and health behaviors in Russia and Norway.

2. Materials and Methods

2.1. Study Design and Participants

This paper is based on data from two population-based studies, the Know Your Heart study in Russia and the seventh survey of the Tromsø Study in Norway.

2.1.1. Know Your Heart (KYH)

During 2015–2018, the KYH cross-sectional study was conducted with random population samples of men and women aged 35–69 years from Arkhangelsk in northwestern Russia and Novosibirsk in Siberia (N = 5089). Further details on the KYH study design have been published previously [32]. Briefly, the participants were recruited using address databases from regional health insurance funds. Trained interviewers visited randomly selected addresses to recruit persons of the required age and sex to participate in the study. Those who agreed were interviewed at home to collect data on demographic, socio-economic and lifestyle characteristics. At the end of the interview, participants were invited to a health check at a polyclinic. The health check included a medical interview, anthropometry and other laboratory and instrumental examinations. The health check attendance was 66% for Arkhangelsk and 34% for Novosibirsk, taking as the denominator all those who were initially approached and contacted in their homes. A total of 4121 participants aged 40–69 years underwent the health check (2129 from Arkhangelsk and 1992 from Novosibirsk) and were included in this study.

2.1.2. The Seventh Tromsø Study (Tromsø7)

The Tromsø Study was initiated in 1974, with repeated surveys in Tromsø municipality, Norway [33]. In 2015–2016, the seventh survey of the Tromsø Study was carried out [34]. All citizens of Tromsø aged 40 years and above (32,591) were invited by mail. Participants (21,083, 65% attendance) completed self-administered questionnaires with questions about lifestyle, socio-demographic parameters and medical anamnesis. They also underwent anthropometric, instrumental and functional measurements and provided biological samples. Further details on the study design have been published elsewhere [34]. In this study, we restricted analyses to participants aged 40–69 years (N = 17,646).

2.2. Measurements of Obesity

We defined obesity in two ways in this study: general obesity (GO) and abdominal obesity (AO).

We defined GO according to the classification from the World Health Organization (1997) as body mass index (BMI) $\geq$ 30.0 kg/m^2 [35]. BMI was calculated as weight in kilograms divided by squared height in meters. In the description of GO patterns in the two countries participants', BMI was divided into: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity class I (BMI 30.0–34.9 kg/m^2), obesity class II (BMI 35.0–39.9 kg/m^2) and obesity class III (BMI $\geq$ 40.0 kg/m^2) [35].

Abdominal or central obesity was defined as waist-to-hip ratio (WHR) > 0.9 for men and >0.85 for women [36]. WHR was calculated as the mean of two waist circumference (WC) measurements divided by the mean of two measurements of hip circumference (HC).

In both studies, weight and height were measured without shoes in light clothing by trained research technicians [32]. Weight was measured to the nearest 100 g using a TANITA BC 418 body composition analyzer (TANITA, Europe GmbH) in KYH and using an electronic digital scale (DS-B02, Dongsahn JENIX Co. Ltd., Seoul, Korea) in Tromsø7. Height was measured to the nearest millimeter using a Seca® 217 portable stadiometer (Seca limited) in KYH and an electronic stadiometer (DS-103, Dongsahn JENIX Co. Ltd.) in Tromsø7. WC was measured using centimeter tape: in KYH this was undertaken at the narrowest part of the trunk to the nearest millimeter; in Tromsø7, at the level of the umbilicus [37]. A conversion equation proposed by Mason and Katzmarzyk [38] for WC in Tromsø7 (for men: narrowest = $-1.19141 + 0.09503$ (age) + 0.94491 (umbilicus); for women:

narrowest = −1.02517 + 0.03207 (age) + 0.90184 (umbilicus)) was used to compare WC in the two studies [37]. HC was measured at the widest part of the hips in both studies.

2.3. Socio-Demographic Characteristics

In KYH, the following socio-demographic variables were collected: age (years); sex (male/female); marital status (living together with a spouse/partner in a registered marriage, living together with spouse/partner but not in a registered marriage, divorced or separated, widower, never married); education (incomplete secondary, complete secondary, professional no secondary, professional and secondary, specialized secondary (college, 3 years), incomplete higher, higher); and self-perceived financial situation of the household measured on a categorical scale with six options (not even enough money for food, it is difficult to make ends meet; enough money for food, but difficult to afford clothes and other items; enough money for food and clothes, but difficult to buy large domestic appliances; can afford to buy large domestic appliances, but difficult to buy a large new car; can afford to buy a large new car, but difficult to buy a flat or a house; no financial constraints, can afford to buy a flat or a house).

In Tromsø7, the corresponding socio-demographic variables were: age (years), sex (male/female), living with a spouse/partner (yes/no); education (primary/partly secondary education (up to 10 years of schooling); upper secondary education (a minimum of 3 years); tertiary education, short (college/university less than 4 years); tertiary education, long (college/university 4 years or more)); and annual total income of the household (less than 150,000 NOK, 150,000–250,000 NOK, 251,000–350,000 NOK, 351,000–450,000 NOK, 451,000–550,000 NOK, 551,000–750,000 NOK, 751,000–1,000,000 NOK, more than 1,000,000 NOK).

For the comparisons of KYH with Tromsø7, the socio-demographic variables were harmonized by recoding them into a unified format: age (5 year age groups); marital status: living with spouse/partner (yes/no); education: primary/secondary education (incomplete secondary, complete secondary, professional no secondary and professional and secondary in KYH; primary/partly secondary education and upper secondary education in Tromsø7) and college/university education (specialized secondary, incomplete higher, and higher in KYH; short and long tertiary education in Tromsø7); and financial situation of the household: level 1 (not enough/enough money for food but difficult to afford clothes in KYH; ≤350,000 NOK in Tromsø7), level 2 (enough money for food and clothes but difficult to buy large domestic appliances in KYH; 351,000–1,000,000 NOK in Tromsø7) and level 3 (enough money for large domestic appliances and higher categories in KYH; >1,000,000 NOK in Tromsø7).

2.4. Health Behaviours

In both studies, questions on health behaviors included daily tobacco/cigarette smoking (never, ex-smoker, current smoker). Both studies used the Alcohol Use Disorders Identification Test (AUDIT) [39], from which we took data on frequency of alcohol use, categorized as “2 or more times per week” or less often, and data on the number of standard alcohol units normally taken per drinking occasion, categorized as “5 or more” (binge drinking) or less.

2.5. Statistical Analysis

Data were expressed as mean values and standard deviations (SD) for continuous variables. Absolute numbers (Abs) and proportions (%) were reported for categorical variables. Age-standardized prevalence of GO and AO was calculated based on the European Standard Population 2013 with 5 year age intervals. Within-study assessments of the associations of GO and AO with socio-demographic and lifestyle characteristics were performed in the KYH and Tromsø7 datasets, separately. Logistic regressions with three-step entry of covariates were used. At step one (model 1), only adjustments for age were made. At the second step (model 2), we added SEP characteristics. At the third step (model 3), we entered all analyzed SEP and health behavior variables. In these and further analyses, we excluded all participants with missing values for any of the covariates, so the studied samples comprised 4024 participants from KYH and 15,892 from Tromsø7. Between-study comparisons of the strength of associations of GO and AO with covariates of interest were performed in Models 3 repeated with pooled KYH and Tromsø7 data and added “study” variable. These comparisons were made by assessing interactions of the “study” variable with all other entered covariates. Interactions were assessed by comparing models with and without interaction terms using likelihood ratio tests. We used similar regressions (models 1–3) for the KYH and Tromsø7 pooled dataset to assess the effects of the socio-demographic and health behavior characteristics on the between-study differences in GO and AO. Statistical analysis was performed using STATA V.16 (StataCorp, College Station, TX, USA).

3. Results

3.1. Socio-Demographic Characteristics and Health Behaviors

The average age of men and women in KYH (55.7 and 55.4 years) was slightly higher than that of men and women in Tromsø7 (53.8 and 53.6 years) (Table 1). There were more men and women in KYH with college or university education (70.0% and 78.3%) compared to Tromsø7 (50.5% and 55.7%), but higher proportions of KYH participants belonged to the low financial level category (17.8% vs. 6.5% for men and 22.7% vs. 10.8% for women). Men living with their spouse/partner was marginally more common in KYH compared to Tromsø7 (84.8% vs. 81.8%), but among women it was much more common in Tromsø7 compared to KYH (75.4% vs. 56.9%). The proportion of current smokers was higher among KYH men than Tromsø7 men (35.7% vs. 13.8%), but similar among women (15.0% vs. 15.3%). Drinking alcohol $\geq$ 2 times per week was more common in Tromsø7 compared to KYH for men (34.2% vs. 20.7%) and women (27.3% vs. 2.81%), while drinking $\geq$5 drinks per occasion was more common in KYH (35.7% vs. 14.8% among men and 8.2% vs. 4.2% among women).

Table 1. Socio-demographic characteristics and health behaviors of studied populations by study and sex.

	Men		**Women**	
	KYH † **(*N* = 1732)**	**Tromsø7 ‡** **(*N* = 8346)**	**KYH †** **(*N* = 2389)**	**Tromsø7 ‡** **(*N* = 9300)**
Age, years (Mean, SD)	55.7 (8.5)	53.8 (8.5)	55.4 (8.7)	53.6 (8.4)
	Abs (%)		Abs (%)	
Age groups, years				
- 40–44	226 (13.1)	1473 (17.7)	351 (14.7)	1678 (18.0)
- 45–49	254 (14.7)	1581 (18.9)	349 (14.6)	1700 (18.3)
- 50–54	279 (16.1)	1434 (17.2)	381 (16.0)	1705 (18.3)
- 55–59	290 (16.7)	1356 (16.3)	411 (17.2)	1540 (16.6)
- 60–64	347 (20.0)	1320 (15.8)	423 (17.7)	1420 (15.3)
- 65–69	336 (19.4)	1182 (14.2)	474 (19.8)	1257 (13.5)
Education				
- Primary/secondary	519 (30.0)	4090 (49.5)	519 (21.7)	4081 (44.3)
- College/university	1213 (70.0)	4173 (50.5)	1870 (78.3)	5128 (55.7)
Living with spouse/partner (yes)	1469 (84.8)	6609 (81.8)	1360 (56.9)	6532 (75.4)
Financial situation, level				
- Lower	301 (17.8)	537 (6.5)	535 (22.7)	968 (10.8)
- Middle	1284 (76.0)	4991 (60.8)	1709 (72.6)	5769 (64.4)
- Upper	104 (6.2)	2684 (32.7)	110 (4.7)	2226 (24.8)
Smoking status				
- Never	497 (28.7)	3705 (45.3)	1723 (72.1)	3897 (42.7)
- Ex-smoker	617 (35.6)	3349 (40.9)	307 (12.9)	3840 (42.0)
- Current smoker	618 (35.7)	1133 (13.8)	358 (15.0)	1402 (15.3)
Drinking alcohol 2+ times per week (yes)	357 (20.7)	2845 (34.2)	67 (2.81)	2524 (27.3)
Drinking 5+ alcohol drinks per occasion (yes)	615 (35.7)	1225 (14.8)	195 (8.19)	387 (4.21)

Abs—absolute number of participants with corresponding characteristic. † Missing data in KYH: financial situation—78 (1.9%), drinking alcohol 2+ times per week—13 (0.3%), drinking 5+ alcohol drinks per occasion—18 (0.4%). ‡ Missing data in Tromsø7: education—77 (1.0%), living with partner—896 (5.1%), financial situation—471 (2.7%), smoking status—320 (1.8%), drinking alcohol 2+ times per week—72 (0.4%), drinking 5+ alcohol drinks per occasion—197 (1.1%).

3.2. Prevalence of Obesity

The age-standardized prevalence of GO (BMI $\geq$ 30 kg/m^2) was higher among KYH women (36.7%) compared to women in Tromsø7 (22.0%), but it was very similar among men (26.0% and 25.7%, respectively). In KYH women, GO prevalence increased steeply with age. There was no evidence of equivalent increases with age in Tromsø7 women, nor in men in either study (Figure 1 and Table S1).

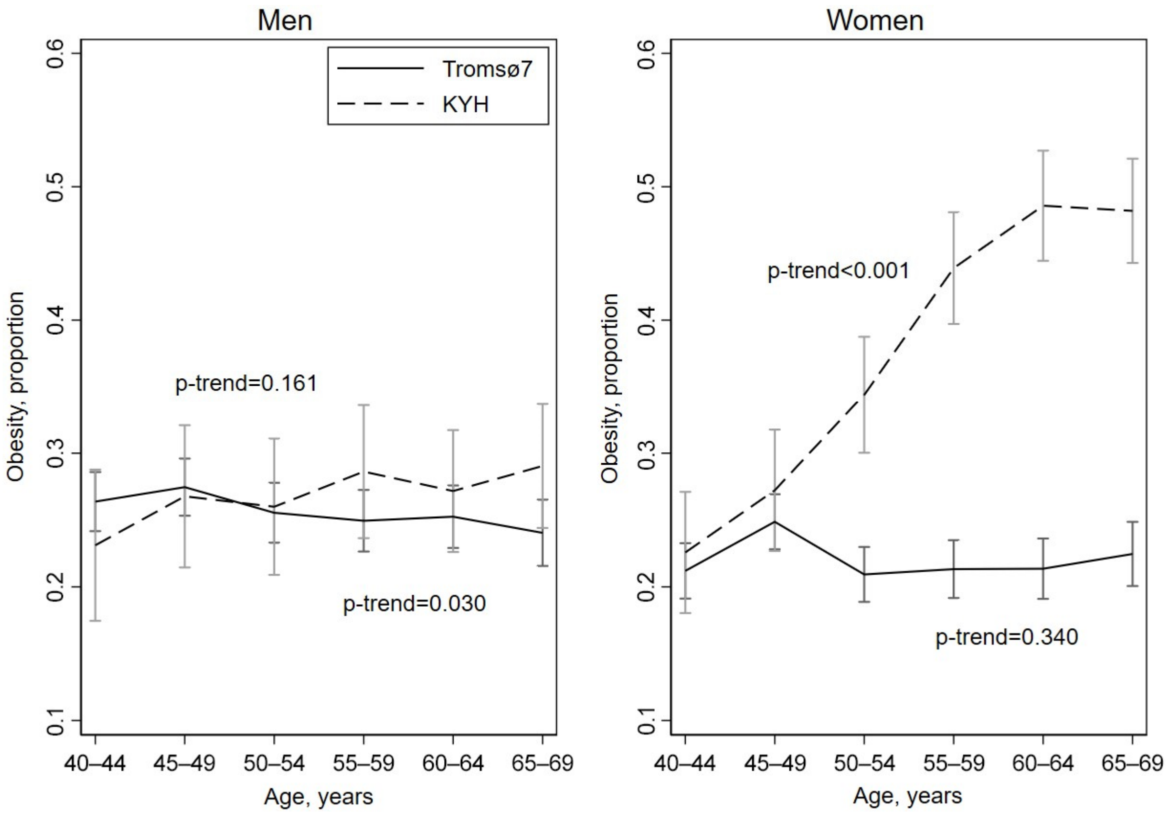
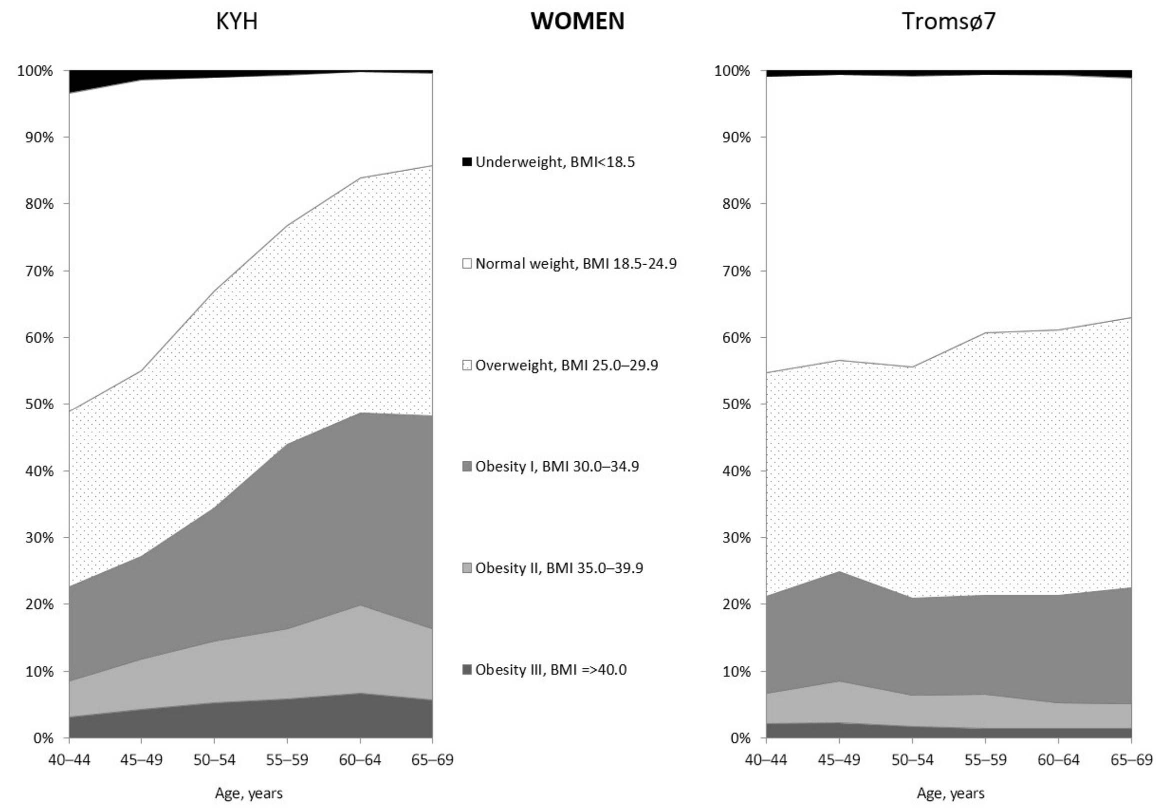


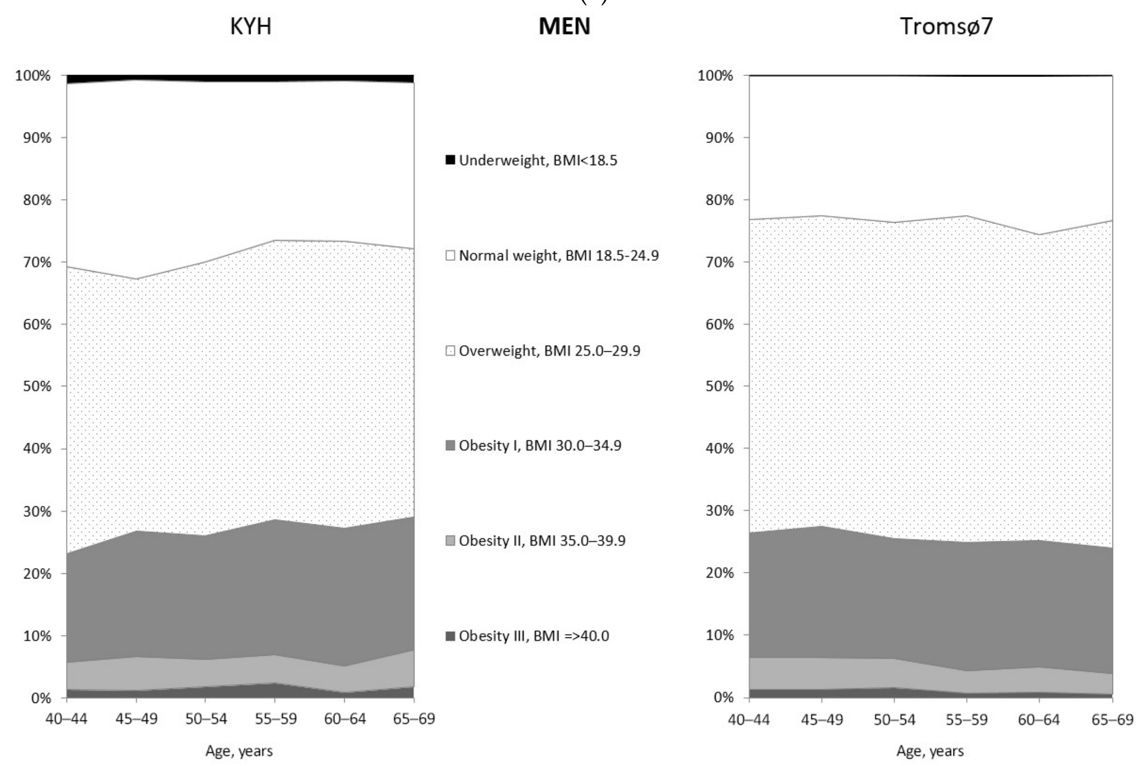
Figure 1. Prevalence of general obesity (BMI $\geq$ 30 kg/m^2) with 95% confidence intervals by study, sex and age.

The age-standardized prevalence of overweight was 44.2% in KYH and 50.9% in Tromsø7 men and 31.8% and 36.3% in KYH and Tromsø7 women. The age-standardized prevalence of normal weight was 28.1% and 23.3% in men and 30.3% and 40.8% in women in KYH and Tromsø7, respectively. The proportion of KYH women who were overweight was 26.3% at 40–44 years and 37.6% at 65–69 years (Figure 2a and Table S2), while in Tromsø7 women, the proportions were 33.5% and 40.5%, respectively. Normal weight was found in 44.4% of Tromsø7 women at 40–44 years and in 35.9% at 65–69 years, while in KYH women the corresponding proportions were 47.7% and 13.8%. In both studies, the proportions of men who were overweight and had normal weight were stable across age groups (Figure 2b and Table S3).

The age-standardized prevalence of AO (WHR > 0.9 for men and >0.85 for women) was higher in KYH compared to Tromsø7 women (44.2% vs. 18.4%) and similar (74.8% vs. 72.2%) in KYH and Tromsø7 men (Figure 3 and Table S4). Unlike for GO, the prevalence increased with age in both sexes and studies. Among participants without GO, 67.8% vs. 63.9% of men and 30.9% vs. 12.2% of women had AO in KYH vs. Tromsø7, respectively (Table S5). The majority of those with AO but without GO were overweight (76.5% men and 79.7% women in KYH, 81.2% men and 75.6% women in Tromsø7) (Table S6).



(**a**)



(**b**)

Figure 2. Distribution of women (**a**) and men (**b**) in the compared populations by study, age and BMI categories.

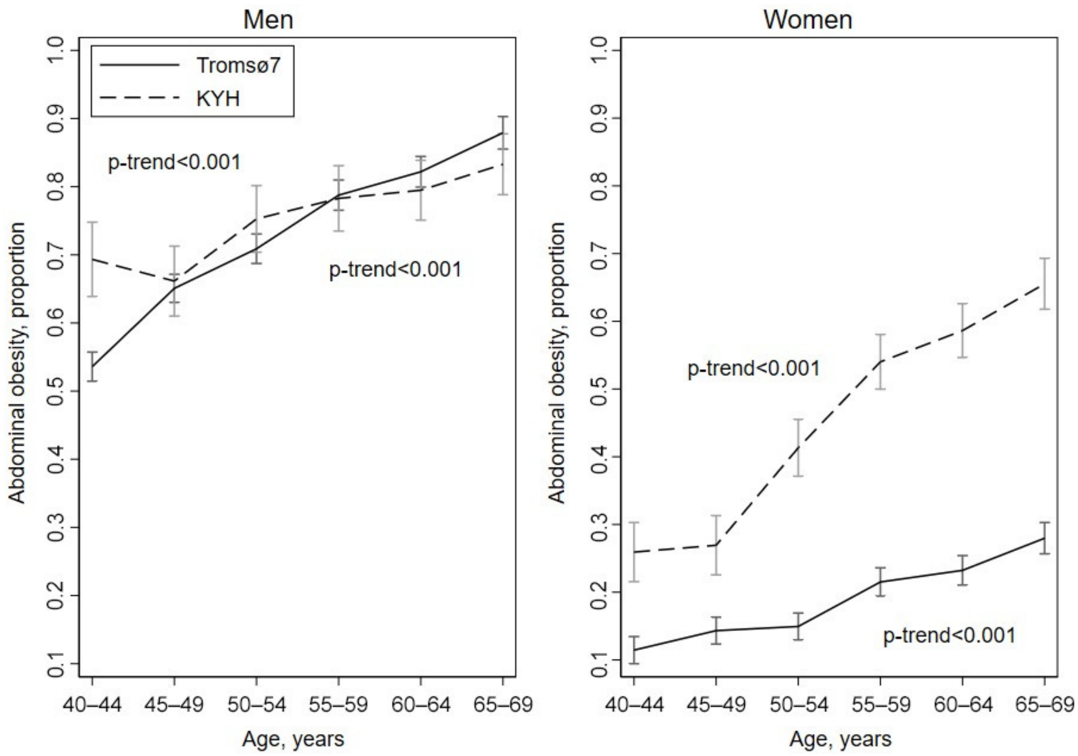


Figure 3. Prevalence of abdominal obesity (WHR > 0.9 for men and >0.85 for women) with 95% confidence intervals by study, sex and age.

3.3. Age of Participants

In Tromsø7 men, but not in KYH men, odds ratios (ORs) of GO decreased with age in the unadjusted model (model 1) and with adjustments for SEP covariates (model 2) and health behaviors (model 3, p-trend = 0.049) (Table 2a). However, there were no significant between-study differences in GO trends by age in the fully adjusted models (p = 0.42). Odds of AO were higher with older age for men in both studies before and after all adjustments (Table 3a), but the trend was steeper for Tromsø7 men (p interaction < 0.001). For KYH women (Table 2b), ORs of GO went up with age in unadjusted and adjusted models. For Tromsø7 women, a downward trend in ORs of GO with age was observed after adjustments for SEP and lifestyle covariates (p-trend = 0.026). Among women, the between-study differences in trends of GO with age were highly significant. Odds of AO were higher with higher age for women in both studies, irrespectively of adjustments (Table 3b). The trend was steeper among KYH women (p < 0.001).

Table 2. (a). Associations of socio-demographic and behavioral characteristics with general obesity (BMI $\geq$ 30 kg/m^2) by study among men. (b) Associations of socio-demographic and behavioral characteristics with general obesity (BMI $\geq$ 30 kg/m^2) by study among women.

(a)

		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	**Model 2 [b]**	**Model 3 [c]**	**Model 1 [a]**	**Model 2 [b]**	**Model 3 [c]**	
Age, years	- 40–44	1.00	1.00	1.00	1.00	1.00	1.00	-
	- 45–49	1.15 (0.75–1.76)	1.15 (0.75–1.77)	1.21 (0.79–1.87)	1.11 (0.94–1.31)	1.08 (0.91–1.28)	1.10 (0.93–1.30)	-
	- 50–54	1.14 (0.75–1.72)	1.14 (0.75–1.73)	1.22 (0.80–1.86)	0.97 (0.82–1.15)	0.92 (0.77–1.09)	0.97 (0.82–1.16)	-
	- 55–59	1.31 (0.88–1.97)	1.29 (0.86–1.95)	1.39 (0.92–2.10)	0.97 (0.81–1.15)	0.90 (0.76–1.08)	0.97 (0.81–1.16)	0.423
	- 60–64	1.19 (0.80–1.77)	1.14 (0.76–1.70)	1.19 (0.79–1.79)	0.93 (0.78–1.11)	0.87 (0.72–1.04)	0.95 (0.79–1.14)	-
	- 65–69	1.34 (0.90–1.99)	1.31 (0.88–1.96)	1.33 (0.89–2.00)	0.87 (0.73–1.05)	0.79 (0.66–0.96)	0.87 (0.71–1.05)	-
	p-value for trend	0.161	0.244	0.256	0.030	0.001	0.049	-
Education	- College/university	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Primary/secondary	1.05 (0.83–1.33)	1.08 (0.85–1.37)	1.18 (0.92–1.50)	1.57 (1.42–1.75)	1.51 (1.35–1.68)	1.36 (1.21–1.52)	0.296
Living with spouse/partner	- No	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Yes	1.63 (1.17–2.27)	1.64 (1.17–2.29)	1.58 (1.13–2.21)	0.86 (0.75–0.98)	0.90 (0.78–1.04)	0.93 (0.81–1.08)	0.005
Financial situation, level	- Upper	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Middle	1.05 (0.67–1.66)	1.02 (0.64–1.62)	1.02 (0.64–1.63)	1.37 (1.23–1.54)	1.18 (1.05–1.34)	1.12 (0.99–1.27)	-
	- Lower	0.98 (0.59–1.64)	0.99 (0.59–1.66)	1.09 (0.65–1.85)	1.39 (1.09–1.75)	1.04 (0.80–1.36)	1.00 (0.77–1.31)	0.625
Smoking status	- Never	1.00		1.00	1.00		1.00	-
	- Ex-smoker	1.17 (0.90–1.52)		1.09 (0.83–1.42)	1.46 (1.30–1.63)		1.32 (1.18–1.48)	-
	- Current smoker	0.61 (0.46–0.81)		0.56 (0.42–0.74)	1.04 (0.88–1.23)		0.80 (0.68–0.96)	0.100
Drinking alcohol 2+ times per week	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.48 (1.14–1.91)		1.48 (1.14–1.92)	0.61 (0.54–0.68)		0.66 (0.59–0.74)	<0.001
Drinking 5+ alcohol drinks per occasion	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.25 (0.99–1.56)		1.34 (1.06–1.69)	1.84 (1.61–2.10)		1.66 (1.44–1.91)	0.118

(b)

		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	**Model 2 [b]**	**Model 3 [c]**	**Model 1 [a]**	**Model 2 [b]**	**Model 3 [c]**	
Age, years	- 40–44	1.00	1.00	1.00	1.00	1.00	1.00	-
	- 45–49	1.24 (0.88–1.76)	1.28 (0.90–1.82)	1.30 (0.91–1.84)	1.21 (1.02–1.43)	1.17 (0.98–1.39)	1.21 (1.02–1.44)	-
	- 50–54	1.70 (1.22–2.37)	1.70 (1.22–2.38)	1.75 (1.25–2.45)	0.96 (0.80–1.14)	0.88 (0.74–1.06)	0.94 (0.79–1.13)	-
	- 55–59	2.66 (1.93–3.65)	2.54 (1.84–3.50)	2.60 (1.88–3.60)	0.94 (0.78–1.13)	0.83 (0.69–1.00)	0.91 (0.75–1.10)	<0.001
	- 60–64	3.17 (2.31–4.35)	2.96 (2.15–4.08)	3.08 (2.22–4.27)	0.99 (0.82–1.19)	0.84 (0.69–1.01)	0.93 (0.77–1.13)	-
	- 65–69	3.18 (2.33–4.34)	2.97 (2.17–4.06)	3.08 (2.23–4.25)	1.04 (0.86–1.26)	0.82 (0.67–1.00)	0.90 (0.74–1.11)	-
	p-value for trend	<0.001	<0.001	<0.001	0.340	<0.001	0.026	-
Education	- College/university	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Primary/secondary	1.57 (1.28–1.93)	1.53 (1.25–1.88)	1.54 (1.26–1.90)	1.59 (1.43–1.78)	1.44 (1.28–1.62)	1.37 (1.21–1.54)	0.317
Living with spouse/partner	- No	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Yes	0.94 (0.79–1.12)	1.00 (0.84–1.20)	1.00 (0.84–1.19)	0.89 (0.79–1.01)	0.99 (0.87–1.14)	1.00 (0.87–1.14)	0.996

Table 2. *Cont.*

(b)								
		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 1 [a]	Model 2 [b]	Model 3 [c]	
Financial situation, level	- Upper	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Middle	1.25 (0.81–1.93)	1.24 (0.80–1.91)	1.25 (0.81–1.94)	1.67 (1.46–1.91)	1.49 (1.29–1.72)	1.40 (1.21–1.62)	-
	- Lower	1.73 (1.10–2.74)	1.66 (1.04–2.64)	1.68 (1.06–2.68)	1.84 (1.50–2.26)	1.50 (1.18–1.91)	1.37 (1.07–1.75)	0.081
Smoking status	- Never	1.00		1.00	1.00		1.00	-
	- Ex-smoker	1.19 (0.91–1.54)		1.14 (0.87–1.48)	1.27 (1.13–1.43)		1.21 (1.08–1.37)	-
	- Current smoker	1.02 (0.79–1.31)		0.89 (0.68–1.15)	0.95 (0.81–1.13)		0.76 (0.64–0.91)	0.500
Drinking alcohol 2+ times per week	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.53 (0.92–2.54)		1.58 (0.95–2.63)	0.51 (0.45–0.58)		0.55 (0.48–0.63)	0.001
Drinking 5+ alcohol drinks per occasion	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.32 (0.97–1.81)		1.26 (0.91–1.75)	1.84 (1.45–2.33)		1.68 (1.31–2.14)	0.173

[a] Model 1—age-adjusted for all variables except age; [b] model 2—adjusted for age and socio-economic variables; [c] model 3—adjusted for age, socio-economic variables and health behaviors; [d] likelihood ratio test for interaction with "study" variable in model 3 repeated with pooled KYH and Tromsø7 data and the introduced "study" variable.

Table 3. (a) Associations of socio-demographic and behavioral characteristics with abdominal obesity (WHR > 0.9) by study among men. (b) Associations of socio-demographic and behavioral characteristics with abdominal obesity (WHR > 0.85) by study among women.

(a)								
		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 1 [a]	Model 2 [b]	Model 3 [c]	
Age, years	- 40–44	1.00	1.00	1.00	1.00	1.00	1.00	-
	- 45–49	0.82 (0.55–1.21)	0.82 (0.55–1.22)	0.82 (0.55–1.23)	1.60 (1.37–1.86)	1.56 (1.34–1.82)	1.58 (1.36–1.85)	-
	- 50–54	1.36 (0.91–2.04)	1.37 (0.92–2.05)	1.40 (0.93–2.10)	2.06 (1.75–2.41)	1.96 (1.67–2.30)	2.04 (1.74–2.41)	-
	- 55–59	1.54 (1.03–2.31)	1.54 (1.03–2.32)	1.60 (1.06–2.41)	3.22 (2.71–3.83)	3.04 (2.56–3.62)	3.22 (2.69–3.84)	<0.001
	- 60–64	1.66 (1.12–2.46)	1.64 (1.11–2.45)	1.66 (1.11–2.49)	3.97 (3.31–4.75)	3.74 (3.12–4.49)	3.90 (3.23–4.69)	-
	- 65–69	2.24 (1.48–3.39)	2.26 (1.49–3.43)	2.26 (1.48–3.46)	6.28 (5.08–7.77)	5.77 (4.65–7.16)	6.13 (4.92–7.63)	-
	p-value for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
Education	- College/university	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Primary/secondary	0.99 (0.77–1.27)	1.01 (0.78–1.30)	1.05 (0.81–1.37)	1.72 (1.55–1.91)	1.63 (1.46–1.82)	1.38 (1.23–1.55)	0.062
Living with spouse/partner	- No	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Yes	1.22 (0.90–1.66)	1.21 (0.89–1.65)	1.16 (0.85–1.59)	0.89 (0.78–1.03)	0.95 (0.81–1.10)	1.01 (0.87–1.18)	0.427
Financial situation, level	- Upper	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Middle	0.94 (0.58–1.52)	0.93 (0.57–1.50)	0.91 (0.56–1.48)	1.48 (1.33–1.65)	1.26 (1.12–1.42)	1.18 (1.04–1.33)	-
	- Lower	0.84 (0.49–1.44)	0.85 (0.49–1.45)	0.88 (0.51–1.53)	1.26 (0.99–1.61)	0.94 (0.72–1.24)	0.84 (0.63–1.11)	0.211
Smoking status	- Never	1.00		1.00	1.00		1.00	-
	- Ex-smoker	1.60 (1.19–2.16)		1.54 (1.14–2.07)	1.95 (1.74–2.18)		1.75 (1.56–1.97)	-
	- Current smoker	0.94 (0.72–1.24)		0.89 (0.67–1.18)	1.87 (1.58–2.21)		1.46 (1.22–1.74)	0.012

Table 3. *Cont.*

(a)

		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	**Model 2** [b]	**Model 3** [c]	**Model 1** [a]	**Model 2** [b]	**Model 3** [c]	
Drinking alcohol 2+ times per week	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.30 (0.97–1.74)		1.25 (0.93–1.68)	0.73 (0.66–0.82)		0.81 (0.73–0.91)	0.007
Drinking 5+ alcohol drinks per occasion	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.34 (1.05–1.71)		1.35 (1.06–1.73)	2.35 (2.00–2.78)		1.96 (1.66–2.33)	0.015

(b)

		KYH, OR (95% CI)			Tromsø7, OR (95% CI)			*p*-Value for Interaction [d]
		Model 1 [a]	**Model 2** [b]	**Model 3** [c]	**Model 1** [a]	**Model 2** [b]	**Model 3** [c]	
Age, years	- 40–44	1.00	1.00	1.00	1.00	1.00	1.00	-
	- 45–49	1.02 (0.73–1.43)	1.05 (0.75–1.48)	1.06 (0.75–1.49)	1.30 (1.04–1.61)	1.25 (1.00–1.55)	1.26 (1.01–1.56)	-
	- 50–54	1.90 (1.39–2.61)	1.91 (1.39–2.62)	1.98 (1.43–2.73)	1.36 (1.10–1.69)	1.25 (1.01–1.56)	1.26 (1.02–1.57)	-
	- 55–59	3.31 (2.43–4.51)	3.19 (2.33–4.35)	3.56 (2.59–4.90)	2.11 (1.71–2.59)	1.85 (1.50–2.29)	1.89 (1.53–2.34)	<0.001
	- 60–64	3.94 (2.89–5.36)	3.69 (2.71–5.04)	4.38 (3.17–6.04)	2.29 (1.86–2.83)	1.94 (1.56–2.40)	2.01 (1.61–2.49)	-
	- 65–69	5.38 (3.96–7.31)	5.08 (3.73–6.93)	6.10 (4.42–8.43)	3.09 (2.50–3.81)	2.36 (1.90–2.92)	2.49 (1.99–3.10)	-
	p-value for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
Education	- College/university	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Primary/secondary	1.48 (1.20–1.82)	1.43 (1.16–1.76)	1.34 (1.08–1.65)	1.66 (1.47–1.86)	1.45 (1.28–1.65)	1.33 (1.17–1.52)	0.981
Living with spouse/partner	- No	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Yes	0.95 (0.80–1.13)	1.02 (0.85–1.21)	1.06 (0.88–1.26)	0.87 (0.76–0.99)	1.01 (0.87–1.16)	1.03 (0.89–1.19)	0.804
Financial situation, level	- Upper	1.00	1.00	1.00	1.00	1.00	1.00	-
	- Middle	1.37 (0.89–2.10)	1.36 (0.89–2.09)	1.30 (0.85–2.01)	1.73 (1.48–2.01)	1.53 (1.30–1.81)	1.44 (1.22–1.70)	-
	- Lower	1.98 (1.26–3.11)	1.92 (1.21–3.03)	1.80 (1.13–2.86)	2.32 (1.87–2.88)	1.89 (1.46–2.43)	1.70 (1.32–2.20)	0.534
Smoking status	- Never	1.00		1.00	1.00		1.00	-
	- Ex-smoker	1.17 (0.90–1.53)		1.11 (0.85–1.46)	1.34 (1.18–1.53)		1.28 (1.12–1.46)	-
	- Current smoker	2.04 (1.59–2.63)		1.79 (1.38–2.33)	1.64 (1.39–1.94)		1.35 (1.13–1.61)	0.077
Drinking alcohol 2+ times per week	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.16 (0.69–1.94)		1.15 (0.68–1.94)	0.65 (0.56–0.74)		0.72 (0.63–0.83)	0.090
Drinking 5+ alcohol drinks per occasion	- No	1.00		1.00	1.00		1.00	-
	- Yes	1.80 (1.31–2.47)		1.48 (1.06–2.05)	1.62 (1.23–2.12)		1.28 (0.97–1.70)	0.521

[a] Model 1—age-adjusted for all variables except age; [b] model 2—adjusted for age and socio-economic variables; [c] model 3—adjusted for age, socio-economic variables and health behaviors; [d] likelihood ratio test for interaction with "study" variable in model 3 repeated with pooled KYH and Tromsø7 data and the introduced "study" variable.

3.4. Education

In Tromsø7, men with primary and secondary education had increased odds of GO compared to men with higher education in all models (Table 2a). Similarly, Tromsø7 men with lower education had higher odds of AO (Table 3a). Education did not show significant associations with odds of GO and AO in KYH men. However, there were no between-study differences in the strength of the association of education with GO and AO. In both KYH and Tromsø7, women with lower education had higher ORs of GO and AO after adjustments for age and other covariates (Tables 2b and 3b). Associations of education with GO and AO did not differ between studies, neither in men nor in women.

3.5. Marital Status

Men in KYH, but not in Tromsø7, had higher odds of GO if living with spouse/partner regardless of the adjustments (Table 2a). The association was the opposite in Tromsø7 men but only before controlling for other SEP covariates. Similarly, living with spouse/partner was negatively associated with AO in Tromsø7 women but only before adjustments for other SEP covariates (Table 3b). Living with spouse/partner had a stronger association with GO among KYH men compared to men in Tromsø7 (p = 0.005) but not among women and not with AO among both sexes.

3.6. Financial Situation

Among Tromsø7 men, but not KYH men (Table 2a), there were higher odds of GO at the middle and lower financial levels compared to the upper level in the age-adjusted model, which were gradually attenuated to non-significance by adjustments for other SEP covariates and health behaviors. Middle-income Tromsø7 men also had elevated odds of AO, which were attenuated by the same adjustments but sustained statistical significance. Women at the lower financial level had higher odds of GO and AO in both KYH and Tromsø7 compared to those at the upper financial level, irrespectively of adjustments (Tables 2b and 3b). Significantly elevated odds of GO and AO were also found in Tromsø7 women at the middle vs. higher financial level, and these persisted through all the adjustments. There were no between-study differences in the strength of the association of financial situation with GO and AO.

3.7. Smoking

In the fully adjusted models for men, both KYH and Tromsø7 current smokers had lower odds of GO compared to those who had never smoked (Table 2a). Smoking men in Tromsø7, but not in KYH, had elevated odds of AO (Table 3a), giving a difference in the association strength (p = 0.012). Among women, lower odds of GO for current smokers were observed in Tromsø7 only (Table 2b), while odds of AO were similarly elevated in smokers relative to those who had never smoked in both studies. Ex-smokers among men and women in Tromsø7 had higher odds of GO (Table 2a,b), while elevated odds of AO were observed in ex-smoking KYH men and Tromsø7 men and women (Table 3a,b). The strength of associations between smoking and AO did not differ between the studies.

3.8. Alcohol Consumption

Frequent male drinkers had increased odds of GO in KYH and reduced odds of GO in Tromsø7 (Table 2a), reflecting the opposite associations (p < 0.001). A similar situation with respect to GO was observed in KYH vs. Tromsø7 women (p = 0.001), as well as relative to AO in KYH vs. Tromsø7 men (p = 0.007) (Tables 2b and 3a). In both studies, binge drinkers, both male and female, had elevated odds of GO and AO, although the OR of GO in KYH women and the OR of AO in Tromsø7 women did not reach statistical significance (Tables 2a,b and 3a,b). The association of binge drinking with AO in Tromsø7 men was stronger compared to KYH men (p = 0.015).

3.9. Country Effect on Associations of Obesity with Socio-Demographic and Lifestyle Characteristics

Men in KYH and Tromsø7 showed no significant differences in odds of GO and AO in age-adjusted models, and this did not change after adjustments for SEP characteristics and health behaviors (Table 4). Women in KYH had substantially increased odds of GO (OR = 2.20) and AO (OR = 3.86) compared to Tromsø7 women in age-adjusted models. The ORs were insubstantially attenuated by adjustments for SEP and behavioral covariates.

Table 4. Odds ratios of general and abdominal obesity in Know Your Heart study versus the seventh Tromsø Study with stepwise adjustments for socio-demographic characteristics, lifestyle characteristics and their interactions with the study-defining variable.

	Model 1 [a]	Model 2 [b]	Model 3 [c]
General obesity			
Men	1.09 (0.97–1.23)	1.13 (1.00–1.29)	1.06 (0.92–1.21)
Women	2.20 (2.00–2.43)	2.23 (2.01–2.49)	2.02 (1.80–2.26)
Abdominal obesity			
Men	1.11 (0.98–1.26)	1.15 (1.00–1.32)	0.96 (0.83–1.11)
Women	3.86 (3.49–4.27)	3.88 (3.47–4.34)	3.76 (3.33–4.24)

[a] Model 1—adjusted for age; [b] model 2—adjusted for age and socio-economic covariates; [c] model 3—adjusted for age, socio-economic and health behaviors.

4. Discussion

Compared to Norwegian women, Russian women demonstrated a higher prevalence of GO and AO, while there was no difference for men. Older age was stronger associated with higher odds of GO and AO in Russian vs. Norwegian women and with higher odds of AO in Norwegian vs. Russian men. We observed a stronger association between GO and living with a spouse or partner in Russian vs. Norwegian men. Furthermore, Norwegian men showed a positive association of current smoking with AO vs. no association in Russian men. Drinking alcohol two or more times per week had a positive vs. negative association with GO and AO in Russian vs. Norwegian men and with GO in Russian vs. Norwegian women. Binge drinking was more strongly associated with AO in Norwegian vs. Russian men.

Higher obesity prevalence at an older age has been described previously [14,26,36,40–45]. It may be explained by metabolic changes at the age of 40–69 years in both sexes [46] and by menopause-related hormonal changes in women [36,47,48]. The higher GO prevalence we observed in Russian women between 40 and 69 years is consistent with findings from other Russian studies [25,26,28,49]. Possible explanations of the higher obesity prevalence in Russian versus Norwegian women may be grounded in a more pronounced traditional female gender role [50] and related daily life contexts of ageing women in Russia [47,51].

The lower levels of GO found with higher age in Norwegian men and women might indicate a higher obesity prevalence among younger age groups (<40 years of age) in this population [52–54]. A possible explanation could be a cohort effect [54–57], but it was not possible to assess this objectively in our study.

We saw a higher GO prevalence in Tromsø7 men compared to women, while KYH women had higher GO prevalence compared to men. Sex differences, such as that found in Tromsø7, were previously found in high-income European studies [40–42,58,59], while the higher GO prevalence in women compared to men was previously described in low- and middle-income countries [60,61] and in previous studies in Russia [26,28,49,62–64]. This supports our abovementioned presumption that socio-economic and cultural factors contribute to the higher obesity levels in Russian vs. Norwegian women, but they make no difference when comparing Russian men to Norwegians.

Obesity can be defined using BMI only. However, this approach does not consider the distribution of adipose tissue in the body and may not detect AO [48,65,66]. This is in line with our finding concerning the higher AO prevalence compared to GO prevalence among men in both studies and is consistent with prior research comparing different obesity measurements [40,53,65]. Our data have also shown that up to 60% of men and 30% of women without GO could be misclassified as non-obese if we did not consider AO. In addition, there is evidence that obesity-related disorders can be more prevalent in non-obese people with high visceral fat accumulation compared to those with GO [67]. This indicates the importance of assessing both obesity types.

Trying to apprehend and understand our findings concerning the higher AO compared to GO, we also discovered that the majority (80%) of the total participants in our study with AO but without GO were overweight according to the BMI-based classification [35]. This partly explains our other finding concerning the overall higher AO prevalence in men (73%) compared to women (24%), as we could see that a larger proportion of men were overweight (50%) relative to women (36%).

Another important observation made by prior researchers is that AO prevalence depends on how it is measured. It can be higher in women than in men if assessed using WC data [27,53,54], but it can be the opposite, as in our study, when the assessments are based on WHR or waist-to-height ratio (WHeR) [40,68].

Assessing AO is important because it is commonly combined with other components of metabolic syndrome [48,66] and is a stronger predictor of CVD and diabetes compared to GO [24,28,69]. WHR showed the strongest associations with overall and cardiovascular disease mortality compared to other AO indicators (WC or WHeR) [27,48,65,66]. Obesity-related complications are less common in patients with a predominant deposition of fat in the buttocks and thighs; thus, increased HC is protective in both genders when controlling for WC and should be included in obesity anthropometric measurements [24,27,65].

Previous studies have shown that, in high-income countries, women with higher income had lower levels of obesity [40,43,44]. Lower levels of education were associated with AO either in both sexes [40] or in men only [44]. These associations could be explained by better knowledge of healthy nutrition and obesity-related health risks among people with higher education and, commonly associated, higher income [40,44,62]. Higher income may be associated with higher availability for the components of a healthy diet and lower barriers to having a healthier diet [15,17,63], as well as being more physically active [15,70].

In our study, no university education, low income and middle income were associated with higher odds of GO and AO in men and women in Norway, but in Russia the association of increased odds of GO and AO with low income and education was only observed in women. However, the differences in the strength of the association between education and financial situation and obesity were not statistically confirmed for either of the sexes. This is generally in line with prior findings of SEP associations with obesity [40,44,62,63], but the results of our international comparisons may reflect the fact that the differences in obesity-related knowledge and behaviors are not as distinguished between Russian men with different SEPs compared to those of Norwegian men with different SEP levels. Interestingly, our comparisons of the association between obesity and education and income in the two countries could have been affected by the overall difference in income levels between Russia and Norway [31]. For example, being middle-income in Norway is associated with an objectively different standard of living compared to being middle-income in Russia. Furthermore, our comparisons of SEP–obesity associations could have been affected by the ways in which the compared categories of education and income were derived from the different original variables in the two studies.

It has previously been described that the association between SEP and obesity is different in low- and high-income countries and becomes inverted when countries transit into a higher income category [15,16,70,71]. In 2020, LM Jaacks et al. proposed the theory of obesity transition, comprising four stages based on a given country's socio-demographic characteristics and obesity patterns [16]. Based on this theory, Norway is at the third stage of the obesity transition, as there is no difference in GO prevalence between men and women and high SEP is associated with reduced GO levels in both men and women. Perhaps Norway is even approaching the end of the third stage, given that the increase in obesity prevalence is slowing down [3]. In contrast, Russia is at the second stage, as GO prevalence among women is higher compared to men and SEP shows little relationship with GO in men.

In our study, living with a spouse or partner was associated with GO only in Russian men. Several prior studies report that both sexes showed higher obesity prevalence when married or living with partner [40,72], while others did not find any association [43]. Some results were consistent with ours in showing that being married was associated with obesity in men only [41,62]. Possible explanations could be that Russian married men eat more regularly, have a larger number of meals and consume more sugar- or salt-rich homemade preparations (traditional dishes in Russia) [63,73]. Conversely, single men may eat less regularly and are more commonly smokers [73]. The observed between-country difference in the strength of the association between GO and marital status in men may be due to Russian–Norwegian differences in the gender roles of married men and women [74], but this hypothesis requires further investigation.

Some studies have suggested that current smokers have lower BMI compared to those who have never smoked and ex-smokers [20–22], whereas others have found no associations of this kind [75]. Conversely, current smoking has a positive association with AO [20,75]. The highest risk of AO has been found for former smokers and is explained by weight gain after smoking cessation [21]. There are also contradictory data on the association of GO with alcohol intake. This may be due to the varying types of beverages consumed and different alcohol-associated food intake patterns [23,76–79]. For example, drinking wine may have a protective effect on weight gain compared to consumption of spirits, which can lead to overweight and obesity [76]. Several studies show higher obesity levels with higher volumes of alcohol consumed [78–82], while others found that low but regular intake of alcohol protected against weight gain [76,77,83]. However, binge drinking has been described as positively associated with GO and AO [82], predominantly in men [80,81].

Being concerned about the possible mediating effect of health behaviors in the associations between socio-demographic characteristics and obesity, we included smoking and alcohol consumption characteristics in our analyses. Entering these variables in regression models resulted in only modest attenuations of the ORs of GO and AO for education and financial situation among men and women in Tromsø7 but not in KYH. This may have reflected between-country differences in the associations between SEP and health behaviors and partially confirms our earlier hypothesis that obesity-related health behaviors may not be as variable between Russian men with different SEPs compared to the variation in Norwegians with SEP differences.

The differences in associations of obesity with smoking and alcohol discovered reflect the varying lifestyle patterns of the two populations. For instance, we found smoking to be more prevalent among Russian men and, thus, it may be "less selective" in its health effects. Specifically, it may have weaker associations with other unhealthy behaviors compared to among Norwegian men. An earlier study comparing alcohol consumption in the KYH and Tromsø7 study populations showed that hazardous and problem drinking were more prevalent in KYH men compared to men in Tromsø7, but it was the opposite in women [84]. This may indicate more complex between-study differences in the alcohol–obesity associations compared to what we could detect with a relatively rough categorization of participants by alcohol-related quantity and frequency variables.

The low prevalence (2.81%) of drinking alcohol $\geq$2 times per week among KYH women could be connected with underreporting of drinking frequency. Although underreporting of alcohol consumption may be inherent for both samples, previous studies have shown that Russian women underreport alcohol consumption compared to their Norwegian and Finnish counterparts [85,86].

Strengths and Limitations

We examined the prevalence of both GO and AO in Russian and Norwegian adult populations and described socio-demographic and lifestyle correlates of both conditions comparatively, thus shedding new light on risk groups and preventive measures to be prioritized. One strength of the study is that we used data from two large population-based studies conducted during the same time period. Another strength is that anthropometric measurements were undertaken by trained personnel and not self-reported, which is prone to bias [87].

An important limitation is that we could only take into account a limited spectrum of health behaviors. Smoking and alcohol consumption were the only obesity-related lifestyle characteristics that were measured comparably in the two studies. For this reason, we did not study the effects of diet and physical activity, although the imbalance between high energy intake from food and low levels of physical activity is a major etiological factor for obesity development.

Another limitation is that harmonization of the variables used in KYH and Tromsø7 for between-study comparisons included some approximations and assumptions. For instance, WC was measured using different anatomical landmarks, so the comparisons might have been partially biased, although we used a previously proposed and validated conversion equation. The harmonized education variable was derived from categorical variables reflecting different education systems in the two countries. Questions about the financial well-being of families implied self-reported assessments and were also asked in different ways. In Norway, respondents indicated the annual household income, while in Russia participants were asked to assess their capacities to buy certain goods. Therefore, the studied associations of these variables with obesity could have been underestimated.

The KYH study was based on data from two cities in Russia (Arkhangelsk in the European north and Novosibirsk in the south of Western Siberia), while Tromsø7 was based on data from Tromsø municipality in the north of Norway. Tromsø municipality is demographically and economically similar to the rest of Norway [88,89]. The populations of Arkhangelsk and Novosibirsk were described as comparable in age and education distribution to the total Russian urban population [32]. Therefore, the sampled populations should not have major socio-demographic and lifestyle differences compared to the entire Russian and Norwegian populations.

Finally, the attendance was 65% in Tromsø7, 66% in the Arkhangelsk part of the KYH study and 34% in its Novosibirsk part. Therefore, our study populations might not have been fully representative of the underlying target populations due to potential non-response bias.

5. Conclusions

The prevalence of GO and AO was higher in Russian compared to Norwegian women but did not differ in men. Older age was more strongly associated with GO and AO in Russian compared to Norwegian women and with AO in Norwegian relative to Russian men. Low SEP increased the odds of both obesity types among men and women in Norway and among women in Russia, but not in Russian men. However, living with a spouse or partner was associated with GO in Russian but not Norwegian men. Current smoking was associated with reduced odds of GO in Russian men and increased odds of AO among men in Norway. Frequent alcohol drinking was associated with increased odds of GO in Russian men but reduced odds of GO in Norwegian men, and the same discrepancy in drinking frequency associations with GO was observed in Russian compared to Norwegian women. Conversely, drinking large volumes per occasion was more strongly associated with AO in Norwegian vs. Russian men. These differences shed new light on the socio-demographic and lifestyle predictors of obesity to be addressed in each of the two countries.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph19159428/s1, Table S1: Prevalence of general obesity (BMI $\geq$ 30 kg/m^2) by study, sex and age; Table S2: Distribution of BMI categories according to age and study in women; Table S3: Distribution of BMI categories according to age and study in men; Table S4: Prevalence of abdominal obesity (WHR > 0.9 for men and >0.85 for women) by study, sex and age; Table S5. Cross-tabulation of general obesity (BMI $\geq$ 30 kg/m^2) and abdominal obesity (WHR > 0.9 for men and >0.85 for women) for men and women in Tromsø7 and in KYH; Table S6. Proportions of participants who were overweight (BMI 25.0–29.9 kg/m^2) among men and women in Tromsø7 and in KYH with abdominal obesity (WHR > 0.9 for men and >0.85 for women) but without general obesity (BMI $\geq$ 30 kg/m^2).

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Institutional Review Board Statement: The KYH study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine (approval number 8808), Novosibirsk State Medical University (approval number 75; 21 May 2015), the Institute of Preventative Medicine, Novosibirsk (approval received 26 December 2014) and the Northern State Medical University, Arkhangelsk (approval number 01/01–15; 27 January 2015). Tromsø7 received ethical approval from the Regional Committee of Medical and Health Research Ethics (REC North, approval number 2014/940) and the Norwegian Data Protection Authority.

Informed Consent Statement: All participants in both studies signed an informed consent form. Both studies were conducted in accordance with the Helsinki Declaration.

Data Availability Statement: Researchers may apply for access to KYH and Tromsø7 data. See data access regulations and instructions at https://metadata.knowyourheart.science (accessed on 15 May 2022) and https://uit.no/research/tromsostudy (accessed on 15 May 2022), respectively. All data requests will be guided by the protection of personal information, the confidentiality agreement with the participants and participants' informed consent.

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Paper II

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Assessing the prevalence of obesity in a Russian adult population by six indices and their associations with hypertension, diabetes mellitus and hypercholesterolaemia

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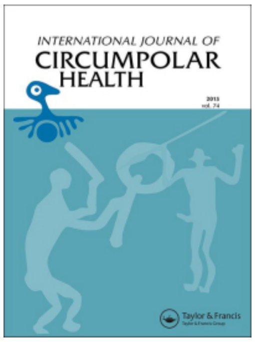

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ORIGINAL RESEARCH ARTICLE

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Assessing the prevalence of obesity in a Russian adult population by six indices and their associations with hypertension, diabetes mellitus and hypercholesterolaemia

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ABSTRACT

The anthropometric index that best predicts cardiometabolic risk remains inconclusive. This study therefore assessed the prevalence of obesity using six indices and compared their associations with obesity-related cardiometabolic disorders. We determined obesity prevalence according to body mass index, waist circumference, waist-to-hip ratio, waist-to-height ratio (WHtR), body fat percentage and fat mass index (FMI) using data from the Know Your Heart study ($n = 4495$, 35–69 years). The areas under the receiver operating characteristic curves (AUCs) provided predictive values of each index for detecting the presence of hypertension, hypercholesterolaemia and diabetes. Age-standardised obesity prevalence significantly varied according to anthropometric index: from 17.2% (FMI) to 75.8% (WHtR) among men and from 23.6% (FMI) to 65.0% (WHtR) among women. WHtR had the strongest association with hypertension (AUC = 0.784; $p < 0.001$) and with a combination of disorders (AUC = 0.779; $p < 0.001$) in women. In women, WHtR also had the largest AUCs for hypercholesterolaemia, in men – for hypertension, diabetes and a combination of disorders, although not all the differences from other obesity indices were significant. WHtR exhibited the closest association between hypertension and a combination of disorders in women and was non-inferior compared to other indices in men.

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Background

Globally, excessive fat mass accumulation in the general population is a growing health threat as it predisposes to non-communicable diseases, such as metabolic and cardiovascular diseases (CVD) [1–3]. The Russian Federation is a country with high incidence and mortality from CVD (30.5 per 1000 population and 640.3 per 100 000 population in 2021, respectively) [4]. It is therefore a troublesome development that body shape phenotypes have changed significantly in European populations over the last several decades, consistent with the emergence of the obesity epidemic [5,6]. Thus, reliable and easy-to-measure obesity indicators are needed in practice not only for detection of obesity but also for screening people with increased risks of obesity-related cardiometabolic disorders [7].

Anthropometric indices used in clinical practice today measure obesity in different ways. The body mass index (BMI), the function of weight and height, is the most common method to assess general obesity at the population level [8–10]. However, if obesity is defined based on BMI alone, one cannot distinguish between high levels of lean mass versus fat body mass [8,11–13]. Other measures of obesity rest on the assessment of fat accumulation in the abdominal region, reflecting abdominal or central obesity, i.e. visceral adiposity [14]. These measures include waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), body roundness index and a body shape index [11,15,16]. Other measurements of obesity could reflect body fatness in a more accurate way [8,10,13]. Imaging techniques, such as computed tomography and magnetic resonance imaging, are the most

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precise methods for quantifying muscle and fat mass and estimating visceral and total adipose tissue [17,18]. Body fat percentage (BFP) and fat mass index (FMI) are obtained from bioelectrical impedance analysis (BIA), the simplest and least expensive method for assessing body composition and measuring body fat [8]. However, these measurements are not included in the standard clinical examination protocols as they require special equipment and additional time.

The estimated obesity prevalence varies depending on the method used to determine the amount of adipose tissue. BMI is most commonly used to assess the prevalence of obesity in epidemiological studies. However, since the end of the twentieth century, there has been a shift towards accumulation of abdominal fat in European countries [5,19]. Prevalence of abdominal obesity measured by WC is higher compared to that of general obesity assessed by BMI both in Europe (47.2% vs 23%) and in the Russian Federation (55% vs 23.1%) [19–21]. The direct comparisons of abdominal obesity are complicated due to the different WC thresholds used in these studies. Data on obesity according to other metrics in Europe are limited [15,22]. Population-based assessments of obesity prevalence based on WHR, WHtR, BFP and FMI indices have not been reported for Russia to date.

Obesity is not only a CVD risk factor but is also associated with other major CVD risk factors (e.g. type 2 diabetes mellitus (diabetes), hypertension and dyslipidemia), which could be the consequence of obesity-related metabolic abnormalities [3,12,23–28]. Thus, early detection of obesity and its related complications is a key for the prevention of adverse cardiovascular outcomes.

Basically, general and abdominal obesity have different associations with metabolic CVD risk factors. Accumulation of adipose tissue in the abdominal region is closer related to the development of obesity-related disorders, CVD outcomes and even all-cause mortality compared to general obesity as defined using BMI [11,23,24,26]. Diabetes, hypertension and hypercholesterolaemia in combination with abdominal obesity constitute a cluster of criteria for the metabolic syndrome [3,29]. These conditions, also called cardiometabolic disorders, are highly prevalent in obese and overweight people and, when occurring simultaneously, accelerate the early onset of CVD [23,25].

To predict risks of developing non-communicable diseases, such as CVD, the World Health Organization (WHO) recommends using indicators of abdominal obesity in addition to BMI, as abdominal fat accumulation could be observed even in those with normal BMI [30]. However, to date, there is no consensus of the value of WC, WHR and WHtR indices of abdominal obesity for better prediction of cardiometabolic disorders [31]. WHtR is a promising index that allows the same cut-off across age and gender and therefore could be a superior tool to identify obesity-related cardiometabolic risks [15,31–33]. Since obesity itself could be prevented and contextualises the development of other diseases, comparing the relationship between different anthropometric indices and cardiometabolic disorders is essential for the prevention and early detection of obesity-related diseases [34]. To date, there are limited data on associations of the anthropometric indices of general obesity, abdominal obesity and obesity according to fat mass with cardiometabolic disorders [8,10,35,36]. The aim of this study was to assess the prevalence of obesity using six indices and compare their associations with hypertension, hypercholesterolaemia and diabetes in a Russian adult population.

Methods

Study design and participants

The Know Your Heart study (KYH) is a cross-sectional study that was conducted in the Russian Federation in 2015–2018. A random population-based sample of 5089 men and women aged 35–69 years was selected from the population of two Russian cities: Arkhangelsk and Novosibirsk, as described earlier [37]. The participants were interviewed in their homes about their health, as well as socio-demographic and lifestyle characteristics. The respondents were then invited to undergo a health check at a polyclinic. The health check included an interview, anthropometry and physical, laboratory and body impedance examinations. Our analysis was based on 2352 and 2143 participants, from Arkhangelsk and Novosibirsk, respectively.

Anthropometric measurements

Anthropometry was done by trained personnel according to a standard protocol. The participants were wearing light clothes and without shoes during all anthropometric measurements. Height was measured with a Seca® 217 portable stadiometer (Seca limited). Body weight, total fat mass and BFP were measured with a TANITA BC 418 body composition analyser (TANITA, Europe GmbH). WC was measured twice at the narrowest part of the trunk. Hip circumference (HC) was measured twice at the widest part of the hips [37].

BMI was calculated as weight in kilograms divided by the square of height in metres and was classified as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) [38]. We applied the definition of high disease risk (comparable to BMI ≥ 30 kg/m^2) for WC >102 cm for men and >88 cm for women [30]. WHR was calculated as the mean of two WC measurements divided by the mean of two HC measurements. According to WHR, obesity was defined as >0.9 for men and >0.85 for women [30]. We calculated WHtR as the mean of two WC measurements divided by height, both in centimetres (cm). Obesity was defined as WHtR >0.5 for both sexes [39].

A BFP ≥25% for men and ≥35% for women was considered obesity [9]. FMI was calculated as the total fat mass in kg divided by the height squared in metres. Obesity, according to FMI, was defined as FMI >9 kg/m^2 in men and >13 kg/m^2 in women [40,41].

Clinical parameters

Systolic and diastolic blood pressure was measured on the brachial artery using an OMRON 705 IT automatic blood pressure monitor (OMRON Healthcare). Three measurements were performed at two-minute intervals; the mean of the second and third measurements was used for the analysis.

As the health check was performed throughout the day, participants were asked to fast for at least 4 h prior to attending the polyclinic. Levels of total cholesterol (mmol/L) and low-density lipoprotein cholesterol (LDL, mmol/L) were assessed in serum using enzymatic colour tests (AU 680; Chemistry System Beckman Coulter). Levels of glycated haemoglobin (HbA1c, %) were measured using immuno-turbidimetric tests (AU 680; Chemistry System Beckman Coulter) [37].

Medication use

The commercial name, dosage, indication and frequency of use of up to seven medicines were recorded during the health check. The names of the medicines were coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system version 2016 as follows: antidiabetic medication (ATC class A10); antihypertensive medication (ATC classes C02, C03, C07, C08 or C09); lipid-lowering medication (ATC class C10) [42,43].

Cardiometabolic disorders

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at the health check and/or self-reported daily use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol ≥5.2 mmol/L and/or LDL cholesterol of >3.0 mmol/L and/or self-reported daily use of lipid-lowering medication. Diabetes was defined as HbA1C ≥6.5% and/or self-reported daily use of antidiabetics.

Statistical analysis

Continuous variables were presented as means (M) with standard deviations (SD); categorical variables as absolute numbers (Abs) and proportions (%). Proportions of participants with obesity according to different indices were sex- and age-stratified. Sex-specific obesity prevalence estimates were age-standardised to the European Standard Population 2013 (ESP2013) with 5-year bands and presented with 95% confidence intervals (CI) [44]. We performed comparisons of men and women on continuous variables with a two-sample t-test. Pearson's chi-squared test was used for between-group comparisons of categorical variables. We applied receiver operating characteristic (ROC) analysis and calculated the area under the ROC-curve (AUC) to evaluate and compare the predictive value of the studied obesity indices for the presence of cardiometabolic disorders (hypertension, diabetes, hypercholesterolaemia and a combination of at least two disorders) in men and women. A test was considered perfect if AUC was equal to 1.0, whereas an AUC equal to 0.5 indicated that the predictive value is no better than chance [45]. The AUCs were presented with 95% CIs, and the lower confidence limit above 0.5 was indicating a significant predictive value [45]. We compared the AUCs for six indices simultaneously by using the DeLong test with the level of significance $p < 0.05$ [46]. Subsequently, we conducted multiple pairwise comparisons with the Bonferroni correction and the level of significance $p < 0.003$. The Liu method for empirical estimation of the optimal cutpoint for a diagnostic test (maximising the product of sensitivity and specificity) was applied to identify optimal cut-off values in the adiposity indices to distinguish between participants with and those without cardiometabolic disorders [47,48]. Respective sensitivity and specificity values were reported. Finally, we examined associations of cardiometabolic disorders with the presence of obesity defined according to six indices by calculating age-adjusted prevalence ratios (PRs) with 95% CI. Statistical analysis was performed using the Stata version 17 (StataCorp, College Station, Texas, USA).

Results

Characteristics of the study subjects

All obesity indices were significantly different between sexes, except the WHtR (Table 1). Mean values of BMI, BFP and FMI were higher in women, while WC and WHR were higher in men. When comparing cardiometabolic disorders, the proportion of those with hypertension was larger in men (63.3% vs 53.4%), while diabetes was more prevalent in women (9.1% vs 7.4%). The majority of all participants (84.1%) had hypercholesterolaemia with no sex differences.

Obesity prevalence

The estimated proportions of participants with obesity varied depending on the index applied. In men, obesity ranged from 18.4% if defined by FMI to 77.9% when defined by WHtR (Table 1). There were higher proportions of women with obesity compared to men if obesity was defined by BMI, WC, BFP or FMI, in contrast to WHR or WHtR.

After standardisation to ESP2013, between-sex differences in obesity prevalence by each of the six parameters did not change (Figure 1). However, in both sexes, the proportions decreased by 1–3% compared to the respective non-standardised ones. The difference between the prevalence of abdominal obesity according to WHtR and WHR was 24% in women, in contrast to 2.5% in men.

Men had higher proportions of WHtR and WHR obesity in all age groups with a gap between these two indices and all other metrics of obesity (Figure 2). The proportions of participants with obesity according to WHtR and BFP were higher in women independently of age. The proportions of obese, according to all parameters, increased with age in both sexes except obesity according to BMI in males. In contrast to men, women exhibited a steep increase in all indices in the age group of 40–45 years and upwards.

Differences in diagnosing obesity based on BMI versus other indices

When the participants were classified by the conventional BMI categories (Figure 3), those without overweight or obesity according to BMI (<25.0 kg/m^2) had proportions categorised as obese according to other indices, except for FMI. These proportions ranged from 2.4% according to WC to 16.2% according WHtR in women and from 0.18% according to WC to 40.0% according to WHR in men. Of those who were classified as overweight based on BMI (25.0–29.9 kg/m^2), obesity was identified in 45.4–87.0% of women and in 20.7–94.6% of men according to the used indices of abdominal obesity and BFP. The highest proportions of obese among those who were classified as overweight according to BMI were found in both sexes if applying WHtR. The lowest proportions were registered for FMI (0.8% in women and 2.4% in men). Of those with obesity as defined by BMI (≥30.0 kg/m^2), the largest share of the surveyed women had obesity according to WHtR, BFP

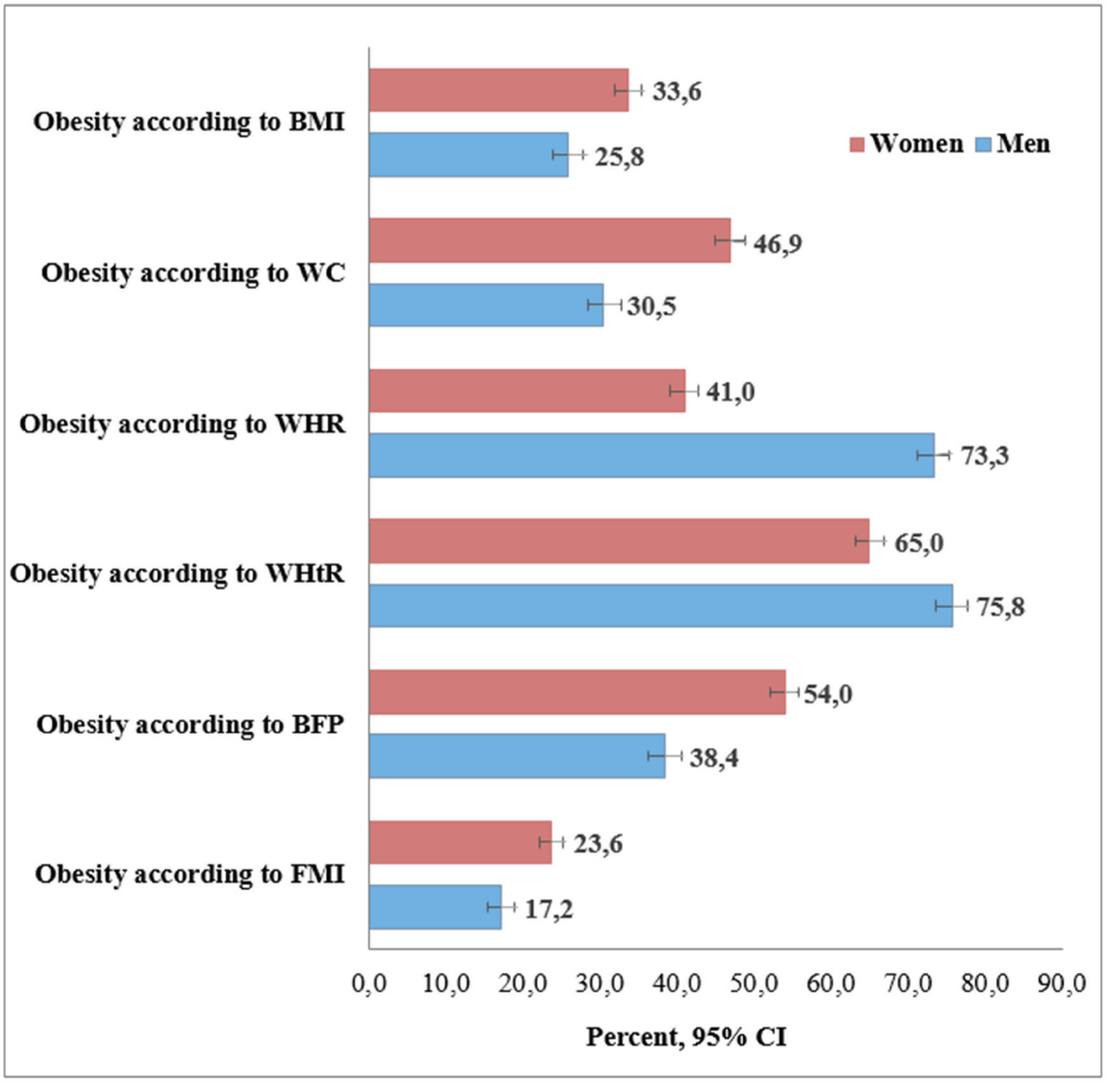
Table 1. Anthropometric and clinical characteristics of the studied population by sex.

Characteristic	Women *N* = 2611	Men *N* = 1884	p
Age, years (Mean, SD)	53.82 (9.72)	54.15 (9.58)	0.264
Anthropometric parameters	Mean (SD)		
BMI, kg/m^2	28.60 (6.17)	27.62 (4.78)	<0.001
WC, cm	89.85 (14.28)	96.88 (12.53)	<0.001
WHR, ratio	0.84 (0.075)	0.95 (0.068)	<0.001
WHtR, ratio	0.56 (0.092)	0.55 (0.072)	0.194
BFP, %	36.02 (7.58)	23.19 (6.94)	<0.001
FMI, kg/m^2	10.70 (4.36)	6.67 (2.99)	<0.001
Proportions of participants with obesity	Absolute (%)		
BMI ≥30.0 kg/m^2	953 (36.5)	499 (26.5)	<0.001
WC ≥102 cm for men and ≥ 88 for women	1333 (51.1)	606 (32.2)	<0.001
WHR >0.9 for men and > 0.85 for women	1172 (44.9)	1415 (75.1)	<0.001
WHtR ≥0.5	1815 (69.5)	1467 (77.9)	<0.001
BFP >25% for men and >35% for women	1493 (57.7)	771 (41.3)	<0.001
FMI >9 kg/m^2 for men and >13 kg/m^2 for women	670 (25.9)	344 (18.4)	<0.001
Cardiometabolic disorders	Absolute (%)		
Hypertension	1289 (53.4)	1100 (63.3)	<0.001
Hypercholesterolemia	2162 (84.1)	1560 (84.2)	0.931
Diabetes	231 (9.1)	135 (7.4)	0.041

BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index.

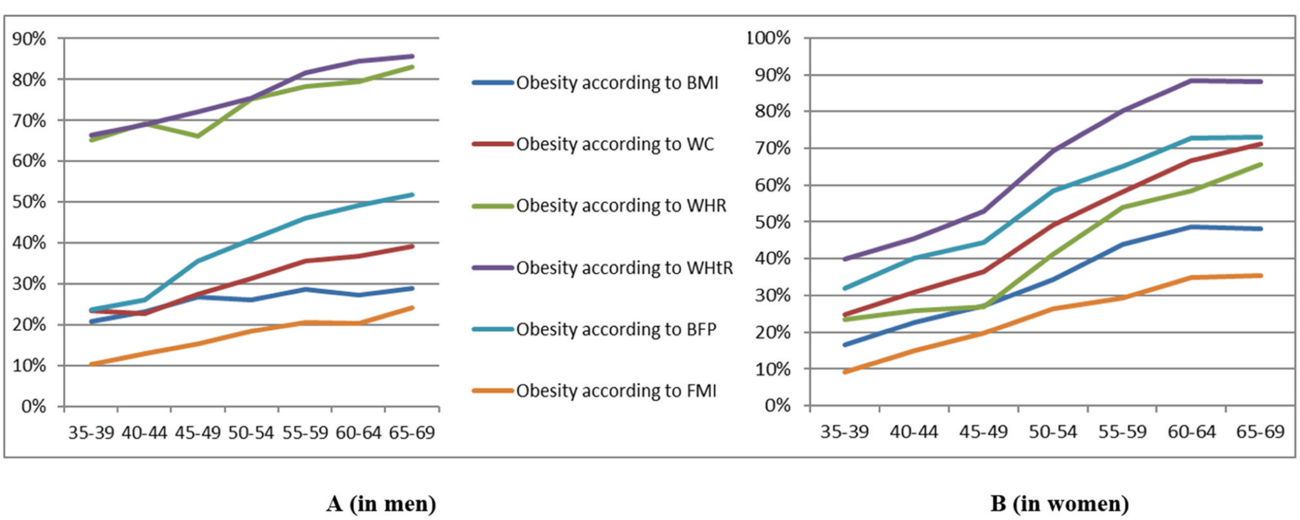
Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at the medical examination (average of the 2nd and 3rd measurements) and/or self-reported daily use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol ≥5.2 mmol/L and/or LDL cholesterol of >3.0 mmol/L and/or self-reported daily use of lipid-lowering medication. Diabetes was defined as HbA1C ≥ 6.5% and/or self-reported daily use of antidiabetics.

Missing data: anthropometric parameters – 594 (11.7%), body fat – 38 (0.8%).



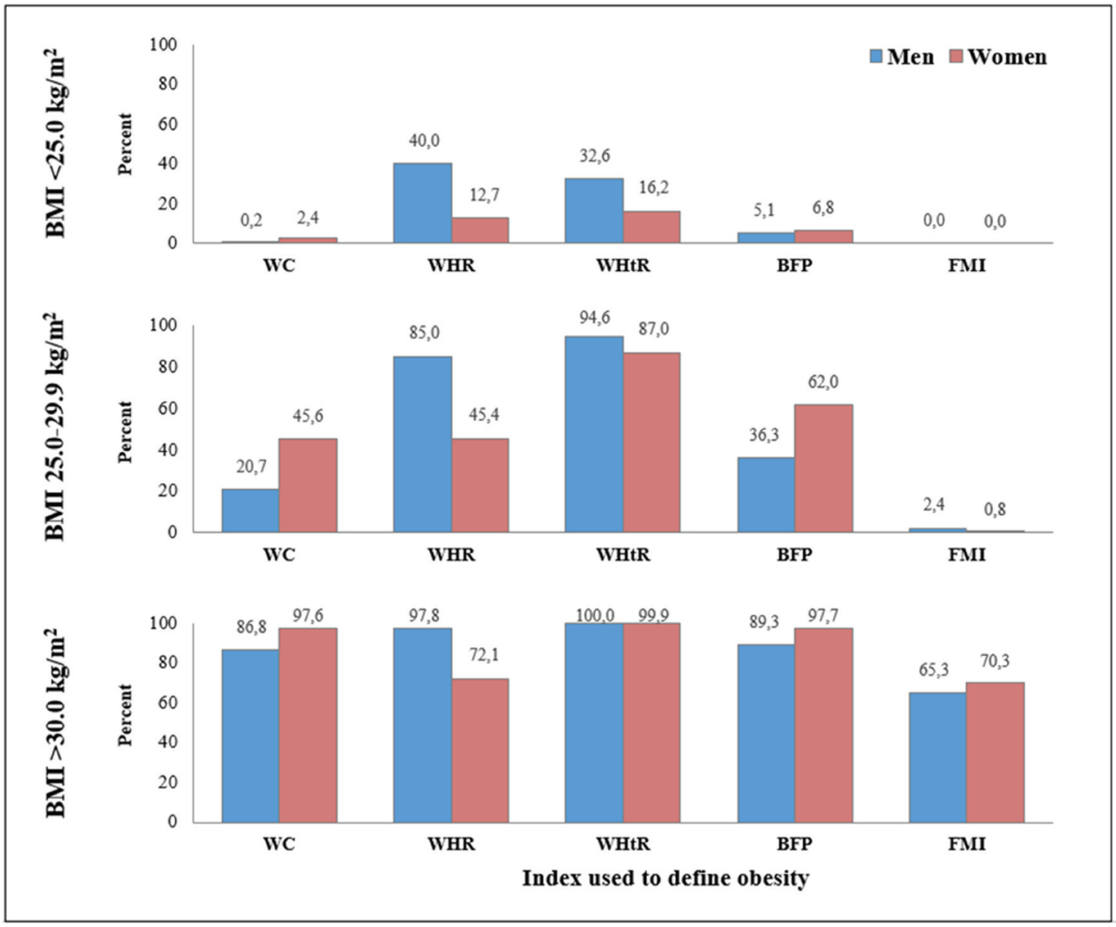
BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index.

Figure 1. Age-standardised prevalence of obesity according to BMI, WC, WHR, WHtR, BFP and FMI by sex.



BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index

Figure 2. Obesity proportions according to BMI, WC, WHR, WHtR, BFP and FMI by age and sex.



BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index.

Figure 3. Obesity presence according to WC, WHR, WHtR, BFP and FMI by BMI categories and sex.

and WC, and a major part of the surveyed men were obese according to WHtR and WHR. FMI demonstrated the lowest obesity proportion in both sexes (70.3% in women and 65.3% in men).

Associations of the six obesity indices with cardiometabolic disorders

The AUCs between each cardiometabolic disorder and obesity index are shown in Table 2. While all obesity metrics had a reasonable predictive capacity in detecting the presence of all analysed disorders, the AUCs between the six indices were significantly different for all risk factors both in women and in men. Among women, the discriminatory power of WHtR for hypertension (78.4%) and a combination of disorders (77.9%) after pairwise comparisons were significantly different from all other indices. WHtR for hypercholesterolaemia (65.2%) was significantly higher compared to BMI (62.5%) and WC (63.7%) in women. Among men, the discriminatory power of WHtR for hypertension (68.2%) was significantly higher compared to BMI (64.5%) and WC (65.6%). At the same time, the discriminatory power of WHtR for diabetes (78.3%) was higher compared to BMI (75.6%) and BFP (74.8%). Furthermore, the discriminatory power of WHtR for a combination of disorders (67.6%) was higher compared to BMI (64.4%) and WC (65.4%) in men.

The optimal empirically defined cut-off points of the six indices that best balanced sensitivity and specificity for cardiometabolic disorders, in women and men, are shown in Table 3. All these cut-off values were the lowest for hypercholesterolaemia and the highest for diabetes in both sexes. The calculated cut-offs for all cardiometabolic disorders were lower than conventionally used for BMI in both sexes (except for diabetes in women) and for FMI, WC and BFP (except for diabetes) in men.

Regardless of the index used, the prevalence of hypertension, hypercholesterolaemia and diabetes were higher in participants with obesity (Table 4). The only exception was obesity according to FMI,

Table 2. AUC for obesity indices relative to cardiometabolic disorders in women and men.

	Hypertension	Hypercholesterolemia	Diabetes	At least 2 of 3 disorders
Obesity index	$n = 2389$	$n = 3687$	$n = 366$	$n = 2106$
Women				
BMI	0.749 (0.729; 0.768)[b,d,e]	0.625 (0.594; 0.655)[d]	0.732 (0.701; 0.763)[b,c,d,e]	0.739 (0.719; 0.759)[b,d]
WC	0.766 (0.747; 0.785)[a,d,e,f]	0.637 (0.607; 0.667)[d]	0.775 (0.746; 0.804)[a,e,f]	0.762 (0.742; 0.781)[a,d,e,f]
WHR	0.748 (0.728; 0.767)[d]	0.633 (0.603; 0.662)	**0.791 (0.763; 0.820)**[a,e,f]	0.749 (0.729; 0.768)[d]
WHtR	**0.784 (0.766; 0.802)**[a,b,c,e,f]	**0.652 (0.622; 0.683)**[a,b,f]	0.786 (0.758; 0.814)[a,e,f]	**0.779 (0.761; 0.798)**[a,b,c,e,f]
BFP	0.730 (0.710; 0.750)[a,b,d,f]	0.633 (0.603; 0.663)	0.696 (0.664; 0.728)[a,b,c,d,f]	0.727 (0.706; 0.747)[b,d,f]
FMI	0.746 (0.726; 0.765)[b,d,e]	0.632 (0.601; 0.662)[d]	0.724 (0.693; 0.755)[b,c,d,e]	0.739 (0.719; 0.759)[b,d,e]
p-value*	<0.001	<0.001	<0.001	<0.001
Men				
BMI	0.645 (0.618; 0.672)[d,f]	0.611 (0.573; 0.648)	0.756 (0.711; 0.801)[d]	0.644 (0.617; 0.670)[d,f]
WC	0.656 (0.630; 0.682)[d]	0.606 (0.568; 0.644)	0.774 (0.731; 0.817)	0.654 (0.627; 0.680)[d]
WHR	0.666 (0.640; 0.692)	0.594 (0.557; 0.631)	0.758 (0.715; 0.800)	0.664 (0.638; 0.690)
WHtR	**0.682 (0.656; 0.708)**[a,b]	0.613 (0.575; 0.651)	**0.783 (0.741; 0.825)**[a,f]	**0.676 (0.650; 0.701)**[a,b]
BFP	0.669 (0.643; 0.696)	0.628 (0.590; 0.665)	0.748 (0.703; 0.793)[d]	0.668 (0.642; 0.694)
FMI	0.667 (0.640; 0.693)[a]	**0.624 (0.586; 0.662)**	0.758 (0.713; 0.803)	0.665 (0.639; 0.691)[a]
p-value*	<0.001	0.009	<0.001	<0.001

Data are shown as AUCs (95% confidence interval). The highest AUC value for a cardiometabolic disorder is shown in bold.
*DeLong test was used for simultaneous comparisons of the six indices. At the next step, multiple pairwise comparisons were made with the Bonferroni correction and the level of significance $p < 0.003$, and [a]In the table denotes significant difference between the corresponding index with BMI, [b]Difference with WC, [c]Difference with WHR, [d]Difference with WHtR, [e]Difference with BFP, [f]Difference with FMI.
AUC – area under curve, BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index.
Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at the medical examination (average of the 2nd and 3rd measurements) and/or self-reported daily use of antihypertensive medication. Hypercholesterolaemia was defined as total cholesterol ≥5.2 mmol/L and/or LDL cholesterol of >3.0 mmol/L and/or self-reported daily use of lipid-lowering medication. Diabetes was defined as HbA1C ≥ 6.5% and/or self-reported daily use of antidiabetics. A combination of at least two disorders was defined as simultaneous presence of at least any two of the three cardiometabolic disorders (hypertension, hypercholesterolaemia or diabetes).

where the association did not reach statistical significance for hypercholesterolaemia in either sex. Obesity exhibited closer associations with diabetes, as prevalence ratios of diabetes in obese people were higher compared to hypertension and hypercholesterolaemia for all indices and in both sexes. Being obese, according to WHTR, is associated with a 6.2-fold increase in the probability of having diabetes among women and 4.4-fold increase among men. Obesity, according to WHtR, had a significantly closer association with hypertension (PR 2.16) compared to other indices in women.

Obesity according to all six indices was associated with simultaneous presence of at least two cardiometabolic disorders (Table 4). However, among women, the prevalence ratio of at least two disorders was significantly higher for obesity according to WHtR (PR 2.24) compared to all other metrics. Among men, the difference in the prevalence of at least two disorders was not significant only between WHtR (PR 1.70) and WHR (PR 1.51).

Discussion

In our study, the prevalence of obesity varied substantially depending on the measure used. In men, it ranged from 17.2% according to FMI to 75.8% according to WHtR. In women, it ranged from 23.6% to 65.0% according to FMI and WHtR, respectively. Compared to FMI, the prevalence of obesity defined by WHtR was 4.4-fold higher in men and 2.8-fold higher in women. Out of the six indices studied, WHtR had the strongest associations with hypertension and a combination of at least two cardiometabolic disorders in women.

Prevalence of obesity according to different indices

Obesity prevalence depends on both the population and the measure used. In Europe, obesity prevalence varies from 19.7% in Denmark to 27.8% in the United Kingdom if assessed using BMI (≥30 kg/m^2) and from 25.9% in France to 73.9% in Romania if based on WC measurements (combined data of >94 or 102 cm for men and >80 or 88 cm for women) [1,19,49–51]. Women have higher prevalence of obesity according to both indices [20]. In our study, the prevalence of obesity according to BMI and WC (33.6% and 46.9% in women and 25.8% and 30.5% in men) were comparable to the Bulgarian, Czech, Hungarian and Portuguese populations, higher than in other European and Asian studies, especially in women, but lower compared to the U.S. data [1,7,52–57].

According to the Russian multi-centre Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of the Russian Federation (ESSE-RF) study

Table 3. Empirically defined optimal cut-off points for the six indices to predict cardiometabolic disorders.

		Predicted cardiometabolic disorder											
		Hypertension			Hypercholesterolaemia			Diabetes			At least 2 of 3 disorders		
		$n = 2389$			$n = 3687$			$n = 366$			$n = 2106$		
Index	Conventional cut-off	Optimal cut-off	Sensitivity, %	Specificity, %	Optimal cut-off	Sensitivity, %	Specificity, %	Optimal cut-off	Sensitivity, %	Specificity, %	Optimal cut-off	Sensitivity, %	Specificity, %
Women													
BMI, kg/m^2	30.0	27.25	71	68	26.11	64	57	30.12	69	68	27.25	72	66
WC, cm	88.0	88.28	69	72	84.83	63	58	94.68	74	69	88.28	69	70
WHR, ratio	0.85	0.82	77	62	0.82	61	59	0.87	74	72	0.84	70	68
WHtR, ratio	0.5	0.54	73	70	0.51	71	55	0.59	73	69	0.55	71	72
BFP, %	35.0	35.75	71	66	33.75	67	55	37.85	72	59	36.25	69	66
FMI, kg/m^2	13.0	9.53	73	66	8.78	67	56	11.29	74	63	9.53	74	64
Men													
BMI, kg/m^2	30.0	27.08	59	64	26.51	59	57	28.94	72	68	27.08	60	61
WC, cm	102.0	96.18	59	66	93.38	62	56	103.38	67	76	96.18	60	64
WHR, ratio	0.9	0.94	61	65	0.92	69	48	0.97	72	67	0.94	63	62
WHtR, ratio	0.5	0.55	62	66	0.53	67	53	0.58	74	70	0.55	63	62
BFP, %	25.0	22.75	64	62	21.55	64	57	27.15	63	75	23.15	62	62
FMI, kg/m^2	9.0	5.74	68	57	5.70	63	56	7.45	72	68	5.74	70	54

Data are Cut-off, Sensitivity (%), Specificity (%).

BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index.

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at the medical examination (average of the 2nd and the 3rd measurements) and/or self-reported daily use of antihypertensive medication. Hypercholesterolaemia was defined as total cholesterol ≥5.2 mmol/L and/or LDL cholesterol of >3.0 mmol/L and/or self-reported daily use of lipid-lowering medication. Diabetes was defined as HbA1C ≥6.5% and/or self-reported daily use of antidiabetics. A combination of at least two disorders was defined as simultaneous presence of any two of the three cardiometabolic disorders (hypertension, hypercholesterolaemia or diabetes).

Table 4. Age-adjusted prevalence ratios of cardiometabolic disorders in the presence of obesity measured with six indices.

	Hypertension	Hypercholesterolaemia	Diabetes	At least 2 of 3 disorders
	n = 2389	*n* = 3687	*n* = 366	*n* = 2106
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Women				
BMI ≥30.0 kg/m^2	1.52 (1.43; 1.62)	1.04 (1.01; 1.08)	2.83 (2.18; 3.67)	1.54 (1.44; 1.65)
WC ≥88 cm	1.70 (1.57; 1.83)	1.05 (1.02; 1.09)	3.99 (2.76; 5.76)	1.71 (1.57; 1.86)
WHR >0.85	1.48 (1.39; 1.59)	1.05 (1.01; 1.08)	4.10 (2.94; 5.71)	1.54 (1.43; 1.66)
WHtR ≥0.5	2.16 (1.90; 2.46)	1.11 (1.07; 1.16)	6.15 (3.09; 12.23)	2.24 (1.94; 2.57)
BFP >35%	1.64 (1.51; 1.79)	1.07 (1.03; 1.10)	2.18 (1.59; 2.99)	1.66 (1.51; 1.82)
FMI >13 kg/m^2	1.42 (1.34; 1.50)	1.02 (0.99; 1.05)	2.29 (1.80; 2.90)	1.42 (1.33; 1.52)
Men				
BMI ≥30.0 kg/m^2	1.27 (1.19; 1.35)	1.07 (1.02; 1.11)	4.05 (2.92; 5.61)	1.34 (1.24; 1.45)
WC ≥102 cm	1.31 (1.23; 1.39)	1.05 (1.01; 1.09)	4.29 (3.02; 6.08)	1.36 (1.26; 1.47)
WHR >0.9	1.35 (1.22; 1.49)	1.14 (1.08; 1.21)	4.61 (2.22; 9.60)	1.51 (1.33; 1.71)
WHtR ≥0.5	1.45 (1.29; 1.62)	1.22 (1.14; 1.30)	4.36 (1.99; 9.52)	1.70 (1.47; 1.97)
BFP >25%	1.27 (1.19; 1.36)	1.11 (1.06; 1.15)	3.24 (2.25; 4.68)	1.36 (1.25; 1.47)
FMI >9 kg/m^2	1.25 (1.17; 1.34)	1.05 (0.997; 1.10)	4.33 (3.17; 5.91)	1.32 (1.22; 1.44)

PR – prevalence ratio. BP – blood pressure. BMI – body mass index. WC – waist circumference. WHR – waist-to-hip ratio. WHtR – waist-to-height ratio. BFP – body fat percentage. FMI – fat mass index. CI – confidence interval.

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at the medical examination (average of the 2nd and the 3rd measurements) and/or self-reported daily use of antihypertensive medication. Hypercholesterolaemia was defined as total cholesterol ≥5.2 mmol/L and/or LDL cholesterol of >3.0 mmol/L and/or self-reported daily use of lipid-lowering medication. Diabetes was defined as HbA1C ≥ 6.5% and/or self-reported daily use of antidiabetics. A combination of at least two disorders was defined as simultaneous presence of any two of the three cardiometabolic disorders (hypertension, hypercholesterolaemia or diabetes).

(2014–2015), the prevalence of BMI-based and WC-based obesity in population of 25–64 years was 27.5% and 44.0% in men vs 31.4% and 61.8% in women, respectively [21,58]. Our study population was, on average, older and showed a higher prevalence of BMI-based obesity in women (33.6%), but lower WC-based obesity prevalence in both sexes (30.5% in men, 46.9% in women). However, the lower prevalence of abdominal obesity could not be concluded because of the higher threshold for WC-based obesity (102/88 cm for men/women) used in our study compared to ESSE-RF (94/80 cm for men/women) [21]. These findings are in line with an earlier Russian population study with participants aged 45–69 years. There, the prevalence of BMI-based obesity was 21% in men and 47% in women [59]. In the study based on Siberian population of Russia aged 45–64, the prevalence of abdominal obesity by WC (94/80 cm) according to the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) project was 46% in men and 79% in women [28]. An earlier study in the Siberian part of Russia demonstrated that WC-based obesity defined by 94 cm for men and 80 cm for women was 49% in men and 81% in women, respectively, while the corresponding estimates would be 24% and 58%, if 102 and 88 cm thresholds for men and women had been used [60]. Such difference in the cut-offs originates from changes in obesity-related health risk estimates, which are of practical importance but complicate the use of the WC index in routine practice and for comparisons between studies [30].

The direct relationship between obesity prevalence and age is well known [30,61,62]. We also found that the prevalence of obesity according to each of the studied indices was positively associated with age, except for BMI in males, reflecting potential deficiencies of this tool.

We observed sex differences in obesity prevalence regardless of the index used. These findings are in line with previous studies showing a higher obesity prevalence in women according to BMI, BFP and FMI [9,52,58,63]. However, the anteriority of men or women in the prevalence of abdominal obesity depends on the anthropometric index used. In our study, obesity prevalence was higher in women compared to men if assessed by WC, but lower when using WHR or WHtR. This is in agreement with several previous studies [19,49,63,64], but others came up with different conclusions [22,55]. De facto, taking into account hip circumference leads to a decrease in the prevalence of obesity in women. Women are more likely to accumulate adipose tissue in the lower body, which is considered safer in terms of metabolic disorders [11].

To our knowledge, there were no population-based studies reporting WHR, WHtR or BIA measures in Russia. The results of the Swedish Malmö Diet and Cancer (MDC) cohort study showed prevalence of obesity according to WHR ranging between 16.6% and 22.0% in men and 42.0% and 48.3% in women aged 45–73 years; whereas according to BFP, it was between 19.8% and 21.8% in men and 36.8–43.4% in women [22]. These prevalences were lower compared to our data, although different thresholds were used for both indices (>1.00 for men and >0.80 for women for WHR obesity and ≥25% for men and ≥33% for women for BFP obesity). Mean WHtRs in our study population (0.56 in women and 0.55 in men) were lower than in Portugal for both sexes [52], but higher than in Korean or Taiwanese adults [54,65]. The WHtR-based obesity prevalence in our study was lower compared to the US (75.8% vs 83.1% and 65.0% vs 72.9% in men and women, respectively), but higher compared to adults in the United Kingdom, Sweden or Nepal [7,15,66]. The mean FMI in our population (10.7 kg/m^2 in women and 6.67 kg/m^2 in men) was higher than in Korean adults [65]. The prevalence of FMI-defined obesity was lower compared to the US but higher compared to Swedish adults [9,22].

In men, there is a gap between the prevalence of obesity assessed using WHR or WHtR and the prevalence estimates based on other indices. This could be explained by the predisposition to the upper body but not the lower body, fat accumulation among men [11]. A rising global trend in abdominal obesity prevalence has been observed since the 1990s, and this trend has been more drastic in men and young adults [19]. Therefore, simultaneous accounting for waist and hip circumferences leads to a significant increase in the prevalence of obesity among men.

As obesity prevalence varies depending on the measure used, direct comparisons of studies using different anthropometric indices are problematic. It is preferable to obtain data based on the same obesity measurement tools in separate populations. In addition, studies of relationships between different obesity indices allow a better understanding of adiposity-related features of specific ethnic groups. For example, for the same BFP, Caucasians have a higher BMI compared to American Blacks and Polynesians [67]. Having presented assessments of obesity prevalence in a Russian population sample based on six indices, including age- and sex-stratified prevalence estimates, we believe our study provides a comprehensive material for domestic and international comparisons.

Abdominal obesity in those with BMI <30 kg/m^2

When using BMI, one relies on the assumption that the distribution of adipose tissue is homogenous [9]. However, obesity is a heterogeneous condition due to the variability in regional body fat deposition. Furthermore, the BMI value has limitations to correctly assess adiposity in those with increased body fat and normal BMI or with low lean mass and high body fat [8,11–13].

In our study, obesity prevalence, according to WHtR, was the highest in women and in men. Moreover, 87.0% of women and 94.6% of men who were overweight according to BMI had obesity according to WHtR. If assessing BMI-based obesity only, one would underestimate excess abdominal fat distribution, especially in overweight people [9]. Thus, WHtR could detect more obesity cases than other indices, reflecting its superiority compared to the other metrics. Early detection of obesity, especially in abdominal region, is critical for early strategies to prevent obesity-related consequences.

Our study may have several practical implications. First, BMI should not be the only method of screening for obesity, but additionally an index of abdominal obesity should be used for screening and early intervention [30]. Second, for routine practice, the WHtR index is an attractive anthropometric measure with a single threshold >0.5 for both sexes, in all ages and in all ethnicities [68,69]. On the other hand, WHO thresholds for WHtR (>0.5) may not be appropriate for every population [10], thus specific cut-offs should be found for different settings [68]. In our setting, the empirically estimated cut-offs of WHtR with highest sensitivity and specificity for detecting hypercholesterolaemia (0.51 vs 0.53 for women and men) are the closest to the standard cut-off, while the empirical cut-offs for other conditions were higher. Therefore, a standard cut-off value for WHtR (>0.5) is plausible for early detection and prevention of cardiometabolic disorders in the study population. This standard cut-off value for WHtR will reasonably work with an easy-to-understand public health message “keep your waist circumference to less than half your height” [69,70].

The empirically defined optimal cut-off points for BMI in men (26.51–28.94 kg/m^2) and in women (26.11–27.25 kg/m^2), except for diabetes, were lower than the standard ones (BMI ≥30 kg/m^2 for both sexes). Among men, the calculated cut-offs for FMI (5.45–5.74 kg/m^2) and for WC (93.38–96.18 cm) and for BFP (21.55–23.15%), both except for diabetes, were also lower than the standard ones (FMI ≥9 kg/m^2, WC ≥102 cm and BFP ≥25%). For this reason, relying on the standard definitions of obesity based on BMI, BFP and FMI, one underestimates the risk of cardiometabolic disorders in the studied population. Therefore, recommended cut-offs for these indices are not always appropriate and are not fully suitable in our setting.

Obesity and cardiometabolic disorders

The prevalence of cardiometabolic disorders in our study was higher compared with data from another

Russian study. In the ESSE-RF study, the prevalence of hypertension was 49.1% and 39.9%, the prevalence of hypercholesterolaemia (total cholesterol ≥5 mmol/l) was 58.1% and 57.9%, and the prevalence of diabetes was 3.8% and 5.4% in men and women, respectively [71,72]. This could be connected with the younger age of ESSE-RF participants (25–64 years) and differences in the definitions of these conditions [71,72].

Previous studies show that indices of obesity are associated with cardiometabolic disorders and can predict CVD [10,12,19,66,68,73]. Although numerous studies and meta-analyses demonstrate a strong link between visceral and ectopic fat and the development of obesity-related metabolic conditions [11–13,74], a consensus on the best anthropometric predictor of cardiometabolic abnormalities remains to be achieved [66,68]. We found that all indices were associated with hypertension, diabetes and hypercholesterolaemia, although the AUCs for the latter were the lowest compared to other conditions and the prevalence of hypercholesterolaemia did not differ significantly in both sexes regardless of the obesity status defined according to FMI.

In our study, WHtR was the strongest indicator of hypertension (AUC 0.784) and a combination of at least two disorders (AUC 0.779) in women compared to all other indices. In men, WHtR had a significantly higher predictive value for hypertension and for having two of the three studied cardiometabolic disorders compared to BMI and WC, but it was non-inferior compared to WHR, BFP and FMI. Indices based on BIA, a more sophisticated method to assess fat accumulation, had no advantage over anthropometric indices in relation to cardiometabolic disorders and thus in the ability to predict them. Although these indices accurately detect true fat mass, they do not differentiate between regional fat distribution and subcutaneous or visceral fat, thus having questionable advantages compared with simpler WC-based obesity measurements [75].

WHtR also showed a better performance compared to other indices in different studies. Among Taiwanese adults, WHtR had a stronger association with hypertension compared to BMI and was non-inferior compared to WC [54]. In a screening of Brazilian female population aged 20–49 years, WHtR had a higher discriminatory power to detect hypertension, compared to BMI, WC, WHR, BFP and C index (based on WC, weight and height) [76]. In the Korean adult population, the WHtR had the highest AUCs for components of metabolic syndrome, including elevated blood pressure, fasting glucose level, triglyceride level and reduced high-density lipoprotein cholesterol level compared to BMI, lean mass, fat mass, trunk fat mass and bone mineral content [65]. Using WHtR ≥0.5 helps to identify more people with metabolic syndrome components compared to obesity defined by BMI and WC simultaneously [15]. In several studies, WHtR was also found to be a better predictor of cardiometabolic disorders and CVD compared to other obesity indices [69,70,77], but not in the others [68,78–80]. These contradictions may be related to the different cut-offs for anthropometric indices to predict metabolic abnormalities in different populations.

In our study, using standard cut-off points, we identified a significantly higher prevalence of cardiometabolic conditions among participants with obesity defined according to each of the six studied indices, except for FMI. Participants with obesity defined as WHtR greater than 0.5 were 1.11–6.15 times more likely to have hypertension, hypercholesterolaemia or diabetes, compared with those with WHtR below 0.5. These PRs were higher than for other indices used, and the finding agrees with several other studies in different countries [66,68,81].

In addition to assessing the deposition of fat in the abdominal region, the possible explanation of the comparative superiority of WHtR can be the fact that, this index also takes into account the individual height. WC or WHR do not account for the variation in body height, although the proportion of abdominal fat assessed by these indices may differ according to different height [7]. WHtR is more useful than WC or WHR because it assumes that a certain amount of abdominal fat is acceptable for a certain height [33]. If height is not accounted for, one may face a finding that individuals with the lowest height tertile have 30% higher prevalence of metabolic syndrome than subjects with the highest height tertile despite the WC. This effect was observed in both the high WC group (WC >102 cm in males and >88 cm in females) and the low WC group but not if grouped by high or low WHtR [82]. It was also shown that people with normal WC but elevated WHtR were more likely to have hypertension, diabetes and CVD [7], reflecting a higher sensitivity of WHtR in terms of detecting cardiometabolic abnormalities. Finally, the threshold for abdominal obesity on the WHtR scale is placed rather low, which, on the one hand, results in increased prevalence estimates, but on the other, it denotes cardiometabolic risk among subjects who are not classified as obese using other anthropometric indices [54], which seems a valuable advantage to be relied upon in early prevention.

Strengths and limitations

This is the first population-based study that examines the prevalence of obesity in the Russian adult population using six indices. One strength of the study is that it has described the associations of six metrics with obesity-related cardiometabolic disorders, thus shedding new light on the pros and cons of using different indices in screening for metabolic abnormalities. Another strength of the study is that all anthropometric measurements were made by trained staff, without self-reported data, which could be prone to bias [83]. Two indices (BFP and FMI) were measured using special equipment (BIA), which is uncommon in large-scale epidemiological studies. The third strength is that the definitions of the studied cardiometabolic disorders (hypertension, hypercholesterolaemia and diabetes) were based on the combined data of self-report and clinical and laboratory examination, which makes them reasonably reliable.

The study also has some limitations. First, the data on medications were self-reported and thus could be biased due to the inaccurate reports and subsequent misclassification of the treatment received. However, participants were asked to show the prescribed medications and indicate their commercial names, doses and frequency of use, which must have reduced the reporting bias. In addition, the bias was unlikely substantial as the self-reported data on daily intake of medicines for hypertension, diabetes and hypercholesterolaemia were shown to be in good agreement with medical documentation [84]. Second, blood samples were collected without full fasting that could affect the studied measurements of blood lipids. Triglyceride levels are most affected by the recent food intake, while total cholesterol and LDL cholesterol are considerably reduced in 4-h period [85]. For this reason, we could not include hypertriglyceridaemia into our analysis although it is an important obesity-associated cardiometabolic disorder. Third, the findings of a cross-sectional study are not a conclusive evidence of a causal relation between obesity and cardiometabolic disorders, although it may be reasonably assumed that pathophysiological pathways most commonly go from gaining weight to hypertension, hypercholesterolaemia and diabetes, rather than vice versa. Finally, the study included a Caucasian population, residents of two Russian urban settings [37]. Generalisability of the findings may therefore be limited to populations with similar sociodemographic characteristics and/or ethnic composition.

Conclusion

In men, the prevalence of obesity ranged from 17.2% according to FMI to 75.8% according to WHtR. In women, it ranged from 23.6% to 65.0%, respectively. This reflects its strong dependence on the tool used. Using BMI only, we underestimate excess abdominal fat distribution, especially in those overweight. Therefore, indices of abdominal obesity should be used in parallel with BMI for early detection of abdominal obesity and prevention of its consequences. WHtR, an easily determined anthropometric index, was identified as the most useful tool for obesity screening and early prevention of hypertension and combinations of cardiometabolic disorders in women. It also demonstrated superiority compared to BMI and WC but non-inferiority compared to WHR, BFP and FMI in relation to the above-mentioned disorders in men.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authors' contributions

Conceptualisation, K.K., A.V.K., S.M.; Data curation, K.K., A.V.K. Methodology, K.K., A.V.K., A.K., S.M.; Project administration A.V.K.; Formal analysis, K.K., A.V.K.; Visualisation, K.K., A.V.K.; Interpretation of data, K.K., A.V.K., A.K.; Writing – original draft preparation, K.K.; Writing – review and editing, A.V.K., A.K., I.D., S.M.; Supervision, A.V.K., A.K., I.D. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Researchers may apply for access to KYH data. See data access regulations and instructions at https://metadata.knowyourheart.science. All data requests will be guided by the protection of personal information, the confidentiality agreement with the participants and participants' informed consent.

Ethical approval and informed consent

The authors declare that all procedures that contributed to this work comply with the ethical standards of the WMA Declaration of Helsinki. All participants signed an informed consent form. Ethical approval for the study was received from the ethics committees of the London School of Hygiene and Tropical Medicine (approval number 8808), Novosibirsk State Medical University (approval number 75; 21 May 2015), the Institute of Preventive Medicine, Novosibirsk (approval received 26 December 2014) and the Northern State Medical University, Arkhangelsk (approval number 01/01–15; 27 January 2015).

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Paper III

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Waist-to-height ratio – reference values and associations with cardiovascular risk factors in a Russian adult population

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