UiT The Arctic University of Norway

Faculty of Health Science

Department of Community Medicine

The obesity epidemic; population levels of visceral adipose tissue and trends in body composition

Insights from The Tromsø Study

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Photo: Marie Wasmuth Lundblad

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Abbreviations

AUC	Area under the curve
BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
g	Grams
HDL	High density lipoprotein
kg	Kilograms
LDL	Low density lipoprotein
MetS	Metabolic syndrome
mmHg	Millimetre of mercury
mmol/L	Millimole per litre
MRI	Magnetic resonance imaging
NCEP ATP	National Cholesterol Education Program Adult Treatment Panel
ROC	Receiver Operating Characteristics
ROI	Region of interest
SES	Socioeconomic status
VAT	Visceral adipose tissue
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

List of papers

Paper I

Lundblad, M. W., Jacobsen, B. K., Johansson, J., De Lucia Rolfe, E., Grimsgaard, S., & Hopstock, L. A. **Reference values for DXA-derived visceral adipose tissue in adults 40 years and older from a European population: The Tromsø Study 2015–2016**. Journal of Obesity, 2021. 10.1155/2021/6634536.

Paper II

Lundblad, M. W., Jacobsen, B. K., Johansson, J., Grimsgaard, S., Andersen, L. F., & Hopstock, L. A. **Anthropometric measures are satisfactory substitutes for the DXA-derived visceral adipose tissue in the association with cardiometabolic risk. The Tromsø Study 2015–2016**. Obesity Science & Practice, 2021. 10.1002/osp4.517.

Paper III

Lundblad M. W., Johansson J., Jacobsen B. K., Grimsgaard S., Andersen L. F., Wilsgaard T., Hopstock L. A. **Secular and longitudinal trends in body composition: The Tromsø Study 2001-2016**. Obesity, [Accepted]. 10.1002/oby.23267.

Summary

Background: During the last four decades obesity has grown to be a global epidemic. Simultaneously with the growing obesity prevalence, mean population levels of cardiometabolic risk factors like total cholesterol and blood pressure have decreased in high-income countries. Thus, there has been a paradoxical trend of increase in obesity and decrease in other cardiometabolic risk factors. Body mass index (BMI) and waist circumference are the most frequently used measures to define general and abdominal obesity. However, these anthropometric measures cannot distinguish between different compositions of the body and are prone to measurement error. While anthropometry are proxy measures, more precise measures of excess fat accumulation can be studied with dual-energy X-ray absorptiometry (DXA) scans, including total body fat and visceral adipose tissue (VAT). VAT is recognized as the most metabolically active and harmful fat tissue with the highest association with cardiometabolic risk. As such, it is possible that BMI and waist circumference fail to represent the actual obesity status and the health risks associated with obesity in the population. The paradox between the decrease in cardiometabolic risk and the increase in obesity prevalence may reflect that populations attain more fat mass or muscle mass, while not increasing the more harmful VAT mass.

Aim: The aim of this thesis was to use a population-based study sample to a) establish reference values and suggest threshold values for DXA-derived VAT in a general population of adult women and men, b) to compare VAT with anthropometric measures and their association with cardiometabolic risk factors and the metabolic syndrome (MetS), and c) to study time trends in body composition including total body fat-, lean- and VAT mass during the last two decades.

Methods: All analyses were based on data from participants attending the Norwegian population-based Tromsø Study. In paper I we included 3675 women and men aged 40-84 years from the seventh survey of the Tromsø Study (2015-2016) with valid measurements of VAT and cardiometabolic risk factor measures. We used Receiver Operating Characteristics (ROC) analyses and c-statistics to investigate different units of VAT (grams, index [VAT grams/ body height^2], and percent (%) [VAT grams/ total fat in abdominal area * 100]) in association with MetS and single MetS components (hypertension, diabetes, elevated triglycerides, and low high-density lipoprotein [HDL] cholesterol). Youden's index was used

paper I, in addition to anthropometric measures (BMI, waist circumference, waist-to-hip ratio and waist-to-height ratio). We used ROC analyses and c-statistics to compare the association between VAT and MetS with the corresponding relationship between anthropometrics and MetS. In Paper III we included 1662, 901 and 3670 participants from the fifth (2001), sixth (2007-2008) and seventh (2015-2016) survey of the Tromsø Study, respectively, to study secular and longitudinal population trends in fat mass, VAT mass and lean mass using descriptive statistics and generalized estimation equation models.

Results: We presented reference values for women and men in 10-year age-groups, and for three measurement units of VAT (grams, index and %). The thresholds presented based on cardiometabolic risk were ≥1134 grams, index ≥0.44, and ≥40%, in women. In men, the thresholds were ≥1859 grams, index ≥0.55 and ≥61%. We found that VAT was strongly correlated with the anthropometric measures, but VAT was also statistically significantly stronger than the anthropometric measures in the prediction of MetS and single MetS components. However, the observed difference in Area Under the Curves (AUCs) were minor to non-existing. Further, we found that both VAT and fat mass increased in the population from 2001 to 2015-2016, with a larger increase in the most recent period (between 2007-2008 and 2015-2016), as well as for the youngest birth-cohort (40-49 years in 2001, particularly in women). Total lean mass remained stable over the three surveys.

Conclusion: The presented reference- and threshold values are valuable for future studies, clinical populations, and patient groups using DXA-derived VAT measured with the same system, protocols and in similar populations as ours. Secondly, although VAT was statistically stronger associated in predicting MetS than anthropometric measures, the clinical differences were minor, and the more commonly used anthropometric measures can be regarded as satisfactory substitutes for VAT. Finally, the observed trends of DXA-derived VAT and total body fat from 2001 to 2015-2016 are in accordance with the increasing trends in overweight and obesity presented by previous research using anthropometric measures. The increasing trends in VAT and total body fat were highest in the younger birth-cohorts. We conclude that the increase in obesity and the paradoxical concurrent decrease in other cardiometabolic risk factors cannot be explained by an increase in muscle mass, but rather a true increase in body fat. Thus, obesity remains a global health challenge.

Sammendrag

Introduksjon: Fedme har vokst til å bli en global epidemi. Det er et paradoks at mens forekomsten av overvekt og fedme øker i verdens befolkning de siste ti-årene, har det samtidig vært en nedgang i andre kardiometabolske risikofaktorer som totalkolesterol og blodtrykk. Antropometriske mål som kroppsmasseindeks (KMI) og midjemål er de vanligste målene for å kartlegge vekt og følge trender i overvekt og fedme over tid. Verken KMI eller midjemål skiller mellom ulike kroppssammensetninger, og begge er disponert for målefeil. Dual-energy x-ray (DXA) skanning gir en mer nøyaktig måling av kroppssammensetning, og dermed et mer nøyaktig mål av både totalt fettvev og visceralt fett (VAT). VAT er det mest metabolsk aktive fettvevet og er sterkt knyttet til kardiometabolsk risiko. Det er derfor mulig at KMI og andre vanlige antropometriske mål ikke representerer reell overvekt og fedme, samt risiko for fedmerelaterte helseutfordringer i befolkningen. Paradokset mellom nedgang i kardiometabolske risikofaktorer og økende forekomst av fedme kan muligens forklares av at populasjoner blir fetere eller mer muskuløse, men ikke nødvendigvis øker i det mer helsefarlige viscerale fettet.

Mål: Målet med denne avhandlingen var å bruke en populasjonsbasert studie for å a) etablere referanseverdier og terskelverdier for VAT målt med DXA i en generell populasjon bestående av voksne kvinner og menn, b) sammenligne VAT med de hyppigst brukte antropometriske målemetodene og deres assosiasjon til metabolsk syndrom (MetS), og c) undersøke endringer i kroppssammensetning i befolkningen over tid, inkludert totalt kroppsfett, VAT og fettfri masse gjennom de to siste ti-årene.

Metode: Alle analyser baserte seg på data fra deltakere i den befolkningsbaserte Tromsøundersøkelsen. I artikkel I inkluderte vi 3675 kvinner og menn (40-84 år) fra den syvende Tromsøundersøkelsen (2015-2016) som hadde mål på VAT og kardiometabolske risikofaktorer. Vi brukte ROC-analyser og c-statistikk for å undersøke ulike enheter av VAT (gram, indeks [VAT gram/ høyde^2], og prosent [VAT gram/ totalt abdominal fett * 100]) og assosiasjoner til MetS og enkeltstående MetS-komponenter (hypertensjon, diabetes, forhøyede triglyseridnivåer og lavt HDL-kolesterol). Youden's indeks ble brukt for å lage terskelverdier for VAT. I artikkel II ble samme utvalg som i artikkel I inkludert. I tillegg til variablene beskrevet for artikkel I inkluderte vi antropometriske målinger (KMI, midjeomkrets, midje-hofte-ratio og midje-høyde-ratio). Vi brukte ROC-analyser og c-

3670 deltakere fra Tromsø 5 (2001), Tromsø 6 (2007-2008) og Tromsø 7 (2015-2016) for å undersøke sekulære og longitudinelle tidstrender i kroppssammensetning ved bruk av beskrivende statistikk og «generalized estimation equation».

Resultater: Vi presenterte referanseverdier for både kvinner og menn i 10-års aldersgrupper, og for tre måleenheter av VAT (gram, indeks og %). Terskelverdiene presentert for VAT gram, indeks og % var henholdsvis ≥1134, ≥0,44 og ≥40 hos kvinner og ≥1859, ≥0,55 og ≥61 hos menn. Vi fant at VAT var sterkt korrelert med de antropometriske målene, men i prediksjon av MetS og enkeltstående komponenter av MetS var VAT statistisk sterkere enn de antropometriske målene. De observerte forskjellene mellom AUC-estimatene var dog små. Videre fant vi at både VAT og totalt kroppsfett økte i befolkningen fra 2001 til 2015-2016, med en større økning fra i siste periode (fra 2007-2008 til 2015-2016) samt i den yngste fødselskohorten (40-49 år, aldersforskjellen var kun signifikant hos kvinner). Total muskelmasse var stabil i de tre undersøkelsene.

Konklusjon: Referanse- og terskelverdiene av VAT er verdifull for fremtidige studier, kliniske populasjoner eller andre pasientgrupper som bruker VAT målt med samme DXA-utstyr, og på lignende populasjon som i denne studien. Vi fant ut at selv om VAT var statistisk sterkere assosiert med MetS, var de kliniske forskjellene mellom VAT og antropometriske mål minimale og de hyppig brukte antropometriske målene er tilfredsstillende erstatninger for VAT i populasjonsstudier. Til slutt viste vi at tidstrendene i VAT og kroppsfett i befolkningen fra 2001 til 2015-2016 sammenfaller med tidligere observerte trender i KMI og midjemål, også i henhold til aldersavhengige trender. Basert på våre resultater konkluderer vi med at paradokset mellom økende forekomst av overvekt og fedme, samtidig med nedgang i andre kardiometabolske risikofaktorer ikke kan forklares ved en økning i muskelmasse, men at det er en reell økning i kroppsfett. Fedme består som en av vår tids store utfordringer for folkehelsen.

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1 Introduction

The main topic of this thesis is body composition, abdominal obesity, and cardiometabolic health. Overweight and obesity are long-standing challenges to health. The continuous increase in the prevalence of overweight and obesity in both developed and developing countries, together with the close links to non-communicable diseases like cardiovascular disease, diabetes, cancer, and mental health underline the need for effective preventive measures (1-4). Most studies of overweight and obesity have used body mass index (BMI) or waist circumference to address associations with health outcomes and to assess trends. These commonly used anthropometric measures does not distinguish between fat mass and fat free mass, thus does not directly address the definition of overweight and obesity, aiming on identifying body fatness. Therefore, it is unclear whether increased BMI actually represents an unhealthy increase in total body fat, or if it reflects an increase in muscle mass in the population. Concurrent with the continuing increase in overweight and obesity in the last decades, risk factors associated with non-communicable diseases, like blood pressure (5), total cholesterol (6, 7), and overall cardiovascular risk (8-10) have decreased in developed countries. This implicates a paradoxical trend towards better overall population health despite a concurrent increase in obesity prevalence. This contradiction raises the question as to whether the anthropometric measures currently used to reflect overweight and obesity are accurate enough, or if more accurate measures are needed. Further, we questioned whether the paradoxical observation might be caused by an increase in fat mass, but not necessarily an increase in visceral fat mass. These theorizations form the background for this thesis, where we have investigated visceral adipose tissue (VAT) in association with the commonly used anthropometric measures, associations with cardiometabolic risk, and body composition trends in a large, adult population-based sample.

1.1 Overweight and obesity

1.1.1 Definition

Overweight and obesity are defined as "*abnormal or excessive fat accumulation that may impair health*" (11), and is most commonly classified by BMI. BMI is a clinically available and easy method to use and is calculated as weight (kg) divided by height (m) squared. BMI is further classified into different categories (Table 1).

Table 1: Categories of body mass index as defined by the World Health Organization

<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight/pre-obesity
30.0-34.9	Obesity class I
35.0-39.9	Obesity class II
≥40	Obesity class III

(12, 13)

Another commonly used measurement tool to classify obesity, and more specifically abdominal obesity, is waist circumference. Waist circumference is measured by a stretch-resistant measuring tape around the abdominal area. The exact placement of the tape differs according to different protocols (14). Waist circumference is classified into categories based on level of risk for disease (Table 2).

Table 2: Categories of waist circumference as defined by the World Health Organization

	Disease risk	
	Increased risk	Substantially increased risk
Women	> 80 cm	> 88 cm
Men	> 94 cm	> 102 cm

(14)

BMI and waist circumference are currently the most frequently used measures to quantify overweight and obesity, but regarding their clinical feasibility, they have both been criticized for their limited potential to address the actual definition of overweight and obesity and for being prone to measurement error (15-17). BMI represents overall body weight in relation to height but does not consider the actual proportions of body fat or muscle mass (15, 16). Thus, both excess fat mass and large muscle mass will give higher BMI, although increased muscle mass is not considered as overweight/obesity, nor associated with increased risk for disease. This limitation of BMI might lead to categorization of individuals with a large muscle mass and average height as overweight or obese. Likewise, individuals with low muscle mass and excess adiposity might be considered as normal weight. Waist circumference may also be affected by overall body size in that a large muscular person might have a larger waist area compared to a less muscular person, although they do not differ in risk for disease. Waist circumference is also highly prone to measurement error (17). The accuracy depends on the individual taking the measure, type of measurement tape and adherence to or use of a standard operation procedure. Other commonly used anthropometric measures are waist-to-hip ratio (WHR) (waist [cm]/hip [cm]) and waist-to-height ratio (WHtR) (waist [cm]/height $[m]^2$) (14, 18, 19). These measures are suggested as better at reflecting the core problem of overweight and obesity – namely body composition and distribution of fat, but no anthropometric measure is uniformly accepted as superior in disease prediction than other anthropometric measures. Thus, new measures to quantify body composition and association with morbidity are continuously created. Examples of such new measures are A Body Shape Index (ABSI) (waist/$[BMI^{2/3}*height^{1/2}]$) (20, 21) and WHT.5R (waist/$height^{0.5}$) (22), which are suggested as more accurate in prediction of obesity related disease than the more traditionally used measures.

1.1.2 Prevalence of overweight and obesity

The global obesity prevalence has tripled in the last four decades, and each year more than 2.8 million deaths can be attributed to overweight and obesity (23, 24). Among adults older than 18 years, almost 2 billion people were overweight in 2016. Of these, more than 250 million people suffered from obesity. The NCD Risk Factor collaboration presented that BMI continously increased in adults from 1975 to 2016 (25).

The prevalence of overweight and obesity in Norway has increased continuously the last decades and in 2017 the majority of the population had overweight or obesity according to the

classification of BMI (12). In both Norway and other countries, a steady increase in overweight and obesity measured as both BMI and waist circumference has been observed, with a larger increase in the younger part of the population (26-33). The Health status report in Norway in 2018 presented that, although several positive trends in major risk factors are observed in the Norwegian population, the goal to halt the increase in proportion of people with obesity and diabetes is not being achieved (34).

1.2 Health consequences of overweight and obesity

Several health consequences can be attributed to overweight and obesity. From childhood to adulthood there are complex, multidisciplinary, and interchangeable factors leading to overweight and obesity. These are further associated with numerous health issues with individual physical- and psychological consequences, and an economic burden for the society and health care services. Obesity can either serve as a direct cause for disease, or as an indirect cause, meaning that obesity leads to an increase in other risk factors for disease, such as increase in blood pressure, which in turn increase the risk of cardiovascular disease. Overall, excessive weight and high BMI alone (with absence of metabolic disturbances) might affect health through conditions such as musculoskeletal disorders and mental health problems. Further, obesity and especially abdominal obesity, is strongly associated with cardiometabolic disease and metabolic disturbances. Fat distribution and the effect of different phenotypes of obesity on health are highly important, and in particular high VAT mass is strongly associated with cardiometabolic disease (35). Both visceral obesity and severe general obesity should be identified and targeted to reduce the risk for obesity-related diseases.

1.2.1 Risk factors for disease – overweight as indirect cause

Overweight and obesity are linked to several cardiometabolic risk factors. Through mechanisms such as excess release of fatty acids, ectopic lipid accumulation (storing of fat in liver and organs), low-grade systemic inflammations, increased level of pro-inflammatory adipocytokines, and endothelial dysfunction, abdominal obesity can cause insulin resistance, type 2 diabetes, dyslipidemia, have an effect on the hemodynamic system including cardiac structure and function, and lead to neurohormonal disturbances and metabolic dysregulation (35). In 2019, high systolic blood pressure, smoking, and high fasting plasma glucose were

the leading risk factors for death and disability globally, and high systolic blood pressure accounted for 10.8 million deaths worldwide (36).

1.2.2 Diseases and mortality

In 2019, BMI was ranked as one of the leading risk factors for death and disability globally, and further one of the risk factors that had increased most since 1990 (36). In 2015, more than 4 million deaths worldwide could be attributed to high BMI, and more than two thirds of these deaths were due to cardiovascular disease (1). After cardiovascular disease, the leading causes of deaths attributable to BMI was diabetes, followed by chronic kidney disease and certain cancers (1). A substantial part of the association between obesity and disease is mediated through the cardiometabolic risk factors presented above.

Cardiometabolic disease

The term cardiometabolic disease includes both cardiovascular and metabolic disturbances. Both single risk factors, like hypertension and dyslipidemia, as well as established disease such as diabetes and atherosclerotic cardiovascular disease (coronary heart disease and ischemic stroke) are included in this definition. Metabolic syndrome (MetS) is a commonly used definition for metabolic abnormalities. Several different definitions of MetS exist (37), but one frequently used definition is the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III, which defines MetS as presence of three or more of the risk factors presented in Figure 1.

Obesity is related to both an increase in cardiovascular risk factors, and to increased risk of adverse cardiovascular outcomes like myocardial infarction, heart failure, atrial fibrillation, and ischemic stroke (35). Further, obesity is strongly associated to the development of diabetes type 2, and about 80% of people with diabetes have overweight or obesity (3). The mechanisms linking obesity to increased cardiometabolic risk are a complex interplay shortly addressed below (35).

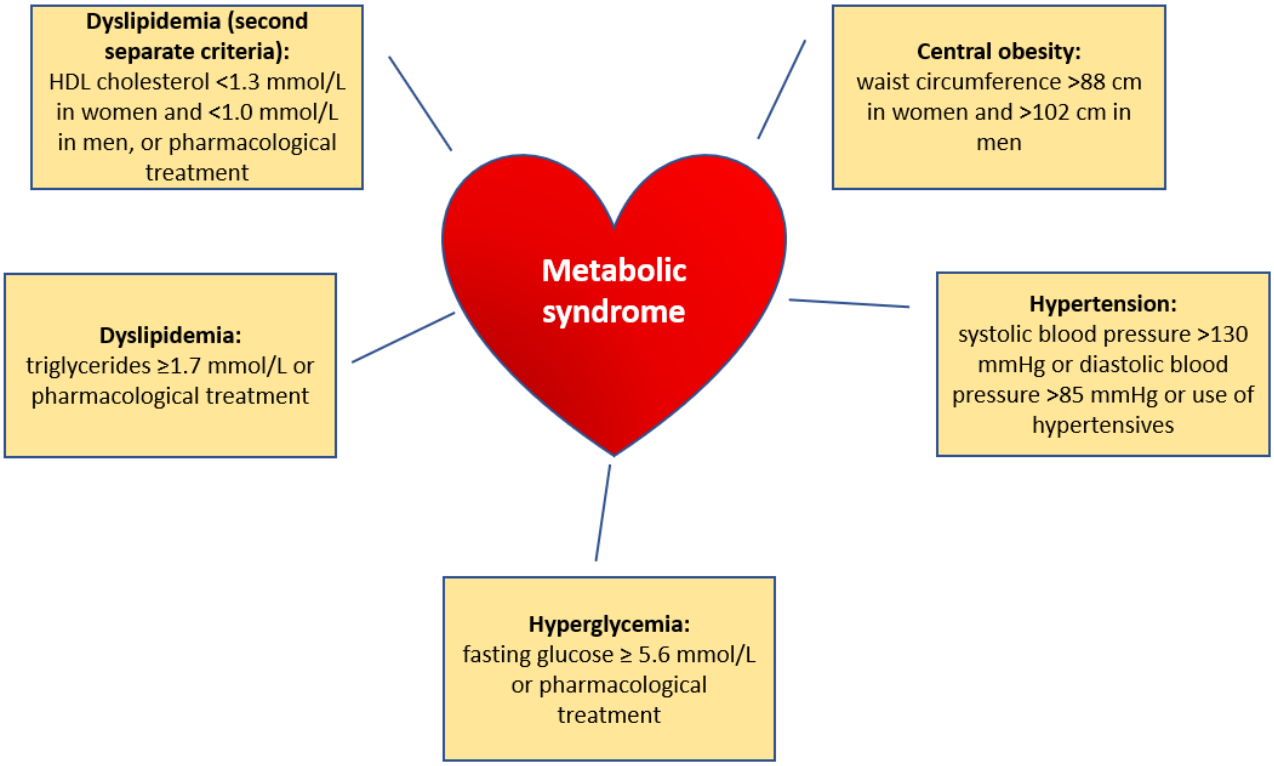

Figure 1: Metabolic syndrome and the single components of the metabolic syndrome criteria defined by the NCEP ATP III criteria (37)

Other diseases and conditions

After smoking, overweight and obesity are the most common preventable risk factors for cancer (38), and more than 10% of cancers are attributable to obesity (39). Obesity is associated with cancers in for example the esophagus, colon and rectum, liver, gallbladder and biliary tract, pancreas, breast, uterus, ovary and thyroid, as well as leukemia (1). The mechanisms linking obesity to cancer is thoroughly explained elsewhere (39). With the continuous increase in obesity together with the decline in smoking it is reasonable to assume that overweight and obesity will soon be the leading preventable risk factors for cancer.

Further, excess body weight may lead to functional disabilities, pain and musculoskeletal disorders such as osteoarthritis, low back pain, and fibromyalgia (40). In 2015, about 5% of disability adjusted life years related to high BMI were due to musculoskeletal disorders (1). In Norway, musculoskeletal conditions are the main reason for sick-leave (from work), non-fatal loss of health, and for the total disease burden in the adult working population (34). However,

overweight has also been shown to serve as a protective factor for osteoporosis in the elderly (41).

Psychological, mental, and cognitive health can be influenced by overweight and obesity. Although the causality between overweight/obesity and these conditions are difficult to establish, there is inevitably challenges linked to self-confidence and social stigma. Further, overweight and obesity has been linked to low self-esteem, mood disorders, eating disorders, impaired body image, and quality of life (2). Psychological health challenges and overweight/obesity, might be associated in a vicious circle further leading to humiliation, rejection, and social bias (2).

All-cause mortality

The association between overweight and all-cause mortality has not always been clear. In 2013 a large review (42) presented that people with overweight had a lower mortality risk compared to people with normal weight. On the other hand, people with obesity (above class I) had a higher mortality. Class I of obesity (BMI 30-35 kg/m^2) was not significantly associated with higher mortality, suggesting that the higher risk from overall obesity is actually attributable to BMI levels of 35 kg/m^2 or higher (obesity class II or III) (42). This corresponds to findings from the Global Burden of Disease project where, of the 4 million deaths globally attributable to high BMI, more than 60% was due to BMI levels of 30 kg/m^2 or more (1). More recently it has been questioned whether reverse causation of BMI might affect the observations between obesity and mortality, and whether this could explain why overweight seems protective compared to normal weight. Current weight status might be influenced by disease incidence, although incident disease or mortality could also be influenced by weight status earlier in life. Further, those who are normal weight at the time of examination could have been overweight or obese before. In 2018 Xu et al. (43) investigated the maximum BMI in cohort studies prior to follow-up and found that the mortality increased linearly with increasing maximum BMI. This implies that increasing levels of overweight increase the risk for disease, and that the results showing lower risk in overweight compared to normal weight might be caused by other factors. Risk of mortality attributed to body weight is not only related to overweight and obesity, but also to underweight. This finding is more frequent in the older adult population where weight loss due to loss of muscle mass and function, known as sarcopenia (44), is more common. In a Norwegian study the association

between both BMI and waist circumference with mortality were U-shaped in adults 65 years and older (45). However, a large review and meta-analysis from 2016 (46) showed that the U-shaped association between BMI and mortality was, to some extent, driven by confounding factors such as smoking, disease or short follow-up. Nonetheless, overweight and obesity during the life-course are associated with higher all-cause mortality, cardiovascular mortality, cancer mortality, death from diabetes or accidental death even after adjusting for smoking and disease status (3).

Economic burden and association with socio-economic status

In addition to the individual consequences of having obesity, the economic burden for the health care service including the increased need of care, hospitalization and medication use brings negative consequences for the whole society. Given the consistent increase in overweight/obesity, and the strong association with most non-communicable diseases, increased health care costs and burden are inevitable. Prevalence of obesity is associated with more frequent use of health care services, higher prevalence of surgery and more frequent need of prescriptive medications compared to normal weight status (4). In addition, people with obesity are prone to have lower wages, more sick leave, and more unemployment (4). In Norway the total societal costs attributed to obesity were estimated to 70 billion Norwegian kroner per year. Further, the costs of obesity-related diseases were estimated to 40 billion kroner per year (47). Loss of income and costs for sick-leave and disability attributed to obesity were 17 billion kroner/year, and health care expenses attributable to obesity were 12 billion kroner/year. Combined, these costs make obesity the most costly public health challenge in Norway (47).

Further, the association between socioeconomic status (SES) and obesity is negative in high-income countries, meaning that people with lower SES more often have a larger body size (48). This is potentially explained by a more unfavorable energy balance among people with lower SES originating from the higher costs of low energy dense and healthy foods, as compared to lower costs of high energy dense food (48). Thus, healthy foods become less accessible for those with lower SES and the risk for obesity increases. Also, people with obesity are observed to have lower levels of physical activity, suggested to partly be explained by lack of recreational facilities mediated through SES (48). The negative association between obesity and SES is also shown in children, where children and

adolescents with obesity has lower performance at school and are more likely to miss school days (4). This might further lead to lower SES in adulthood causing a vicious circle between SES and obesity.

1.3 Body composition

The body consists of several tissue types, divided into different components based on measurement method. DXA uses a three-compartment model, dividing the body into three main components; fat mass, lean mass and bone mineral content, from where the two first constitute the main part of the composition of the total body.

When studying sarcopenia and muscle loss in the elderly, muscle mass, and more specifically appendicular muscle mass (muscle mass in arms and legs) is often assessed (49). When studying overweight and obesity, fat mass is most relevant. Individuals with similar BMI may have significantly different amount and distribution of body fat. Further, different areas of fat distribution have different health impact, therefore examining the area of fat accumulation is essential. Also, establishing the distribution of subcutaneous fat relative to VAT is important and has been advocated in previous research (50, 51). VAT is fat located intraabdominally, behind the abdominal muscles and around organs, and is more harmful than subcutaneous fat, partly because of its close location to organs such as the liver (50) (Figure 2). VAT serves as protective padding to the organs and is involved in fat metabolism. With increasing size of VAT the metabolic activity and effect on other organs is enhanced (52).

The effects of VAT are comprehensive, and the physiological effects and implications are only slightly addressed in the current thesis to highlight the health challenges related to increased amount of VAT.

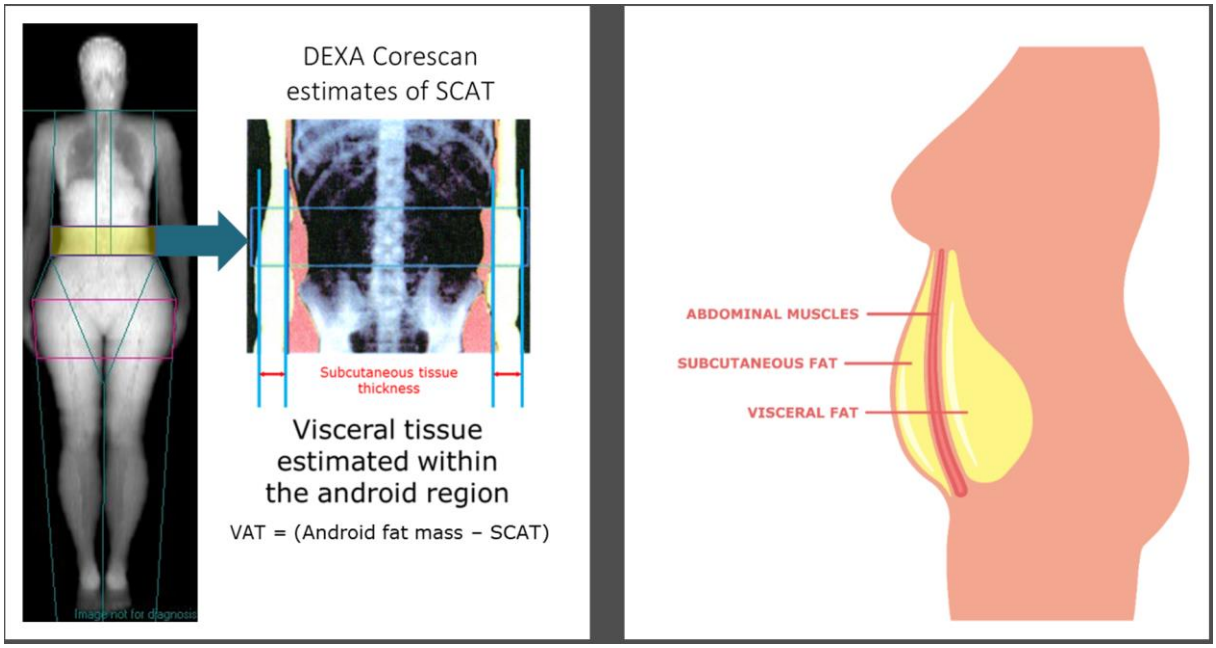

Figure 2: Abdominal subcutaneous and visceral adipose tissue. Left photo: NIHR BRC Anthropometry Platform, MRC Epidemiology Unit, University of Cambridge. Right photo: colourbox.com

Fat tissue is mainly constituted by fat cells called adipocytes. When the intake of energy exceeds the energy expenditure, the adipocytes have two ways to increase their storage - expand in numbers (limited possibilities) or expand in size. Thus, VAT as other fat tissues containing adipocytes, serve both as storage of fat and as protective padding for organs. However, VAT also serves as an endocrine organ in itself, releasing substances such as fat free acids and pro-inflammatory proteins (adipokines) affecting other organs and the metabolism (53, 54). With excess energy intake the adipocytes will increase in size leading to excess release of free fatty acids, hormones, and pro-inflammatory proteins, but also structural and cellular changes may occur in the fat tissue as it expands. First, the access to blood vessels decrease with the expansion of fat tissue, merely because the distance from adipocyte to blood vessels becomes larger (53). This reduced access to blood and oxygen leads to hypoxia and further death to the adipocytes. The cell-death further increases the releasing of substances from the adipocytes. In addition, as the fat tissue increases it gets infiltrated by macrophages, i.e., white blood cells that have the ability to remove dead tissue, cells or bacteria. The adipocytes, macrophages and other structures communicate together and might even further increase the level of pro-inflammatory proteins. This infiltration of macrophages and increased releasing of pro-inflammatory proteins is recognized as one of the

drivers behind insulin resistance and inflammation. Further, the congestion of macrophages is more frequently observed in VAT than in subcutaneous fat (53). The low-grade inflammation in the VAT causes damage to other tissues through releasing pro-inflammatory substances into the hepatic portal vein (blood vessel transporting blood from the intestines and to the liver) which further distributes it to other tissues and organs.

The high levels of free fatty acids in the bloodstream also affects the lipid metabolism and individuals with high amount of VAT often has a distinct lipid profile with, among others, high levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol (55). The higher turnover of triglycerides together with an unhealthy lipid profile again leads to potential complications in the blood vessels, increasing the risk for atherosclerosis and heart disease. The high levels of free fatty acids in the blood stream and the proximity between VAT and organs leads to an increased risk for ectopic fat accumulation. Ectopic fat accumulation is storage of fat in the liver, muscles or pancreas and might affect the normal function of these organs (55).

Due to these mechanisms, VAT is associated with hypertension, inflammation, insulin resistance, metabolic syndrome, cardiovascular disease and several types of cancer (51). VAT is shown to be independently associated with these conditions, even when no associations are observed with BMI or waist circumference (50). Several factors can influence amount of VAT, and as with other obesity indicators it varies according to sex, age, ethnicity, genetics, and hormone levels. Further, lifestyle habits such as diet, physical activity, smoking and medication use can influence VAT levels (50, 51). To quantify amount of VAT, one needs accurate body composition measure techniques, and no generally accepted reference values or thresholds for establishing risk for disease exists.

1.4 Measurement methods

There are several methods to assess body composition. Lohman and Milliken (56) have ranged the existing methods by their accuracy to determine percentage of fat mass (Figure 3). The accuracy of each level is presented as percent: 1% - 2%, 2% - 3%, 3% - 4% and 5% - 6%, for level 1, 2, 3 and 4, respectively. The most common and easily available anthropometric methods are ranked as the measures with least accuracy in their ability to establish fat mass.

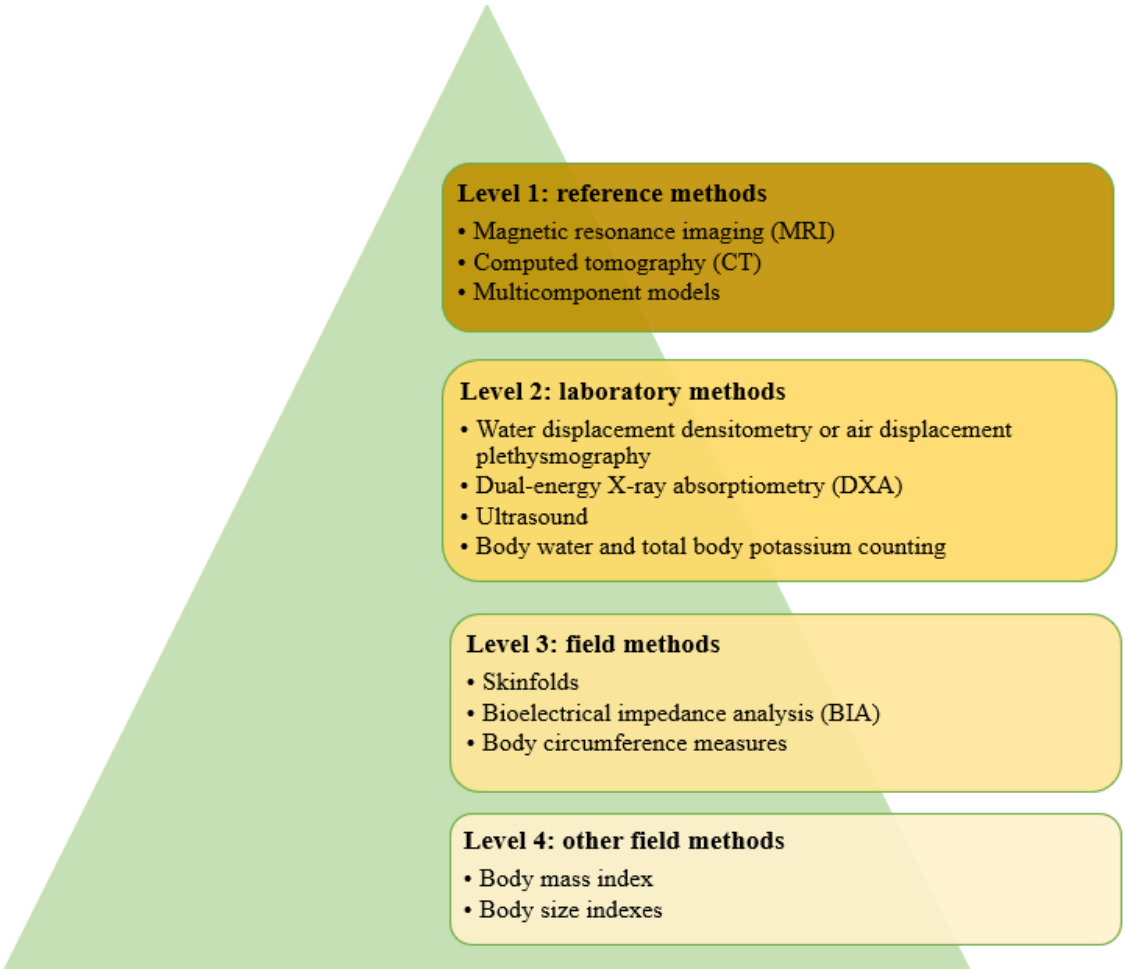

Figure 3: Level of accuracy of body composition measurements.

Several previous studies have discussed different measures to establish overweight, obesity and body composition (57-60). The level of accuracy of the different measures is well established, however, certain factors might be important to consider when determining what measure to use. One example is the biological changes in body composition with increasing age, where muscle mass typically decreases, while fat mass, and in particular VAT mass, increases. This concurrent increase in fat mass and decrease in muscle mass, might result in stable weight, and might mask potential sarcopenia in the elderly, if the shifting happens rapidly (61). Such changes would be difficult to detect with conventional anthropometric measures and their accuracy would therefore be poor. Thus, the need for more attention to body composition measures, especially in the elderly population, has been advocated (62, 63).

Because of its low radiation and high precision, DXA has become a popular tool for measuring body composition. DXA is a three compartment model, historically used to measure bone mineral content and is currently regarded as the gold standard method for this purpose (64). Further, DXA measures the amount of fat mass and lean tissue mass (i.e., muscle and other, bone and fat excluded) in addition to presenting tissue composition in different areas of the body (i.e., subcutaneous fat and VAT) (Figure 2 and Figure 4) (65). DXA-derived VAT is validated to VAT measures from both magnetic resonance imaging (MRI) and computed tomography (CT) (66, 67), and is considered an accurate measure of VAT. However, the DXA system is expensive and requires location site for storing the scanner and performing the measures, trained personnel, and radiation security measures, and is therefore not frequently used in everyday clinics. Because it produces significantly less radiation-exposure than for example CT it is increasingly included for measuring body composition in population studies and other facilities depending on body composition measures to ensure effective treatment, such as clinics for osteoporosis and eating disorders. While the radiation from CT equals the same amount of natural background radiation exposure during several years, the radiation from DXA scans equals natural background radiation for less than one day (65). Thus, DXA is far more feasible for frequent or large-scale use.

Figure 4: Illustration of DXA-scanner to the left (Photo: The Tromsø Study/Stina Grønbech) and DXA-scan images to the right (Photo: NIHR BRC Anthropometry Platform, MRC Epidemiology Unit, University of Cambridge)

1.5 Rationale for the thesis

The rationale for this PhD thesis was the observed paradox in high-income countries where cardiometabolic risk factors have decreased while prevalence of overweight and obesity continue to increase. This inverse association is unexpected because of the well-established association between obesity and cardiometabolic health described above. Because obesity is most frequently measured by BMI and waist circumference, which does not distinguish between fat mass and muscle mass, we questioned whether BMI and waist circumference actually represents what the definition of obesity is meant to capture. **We hypothesized that VAT would be a more accurate measure than BMI or waist circumference to address risk of cardiometabolic disease, and that the time trends for total fat and VAT might not correspond to those observed by anthropometric measures.**

Because most risk factors, diseases and mortalities attributed to obesity are of cardiometabolic character, and because MetS includes several risk factors for cardiometabolic disease, we used MetS and single components of MetS to establish risk for cardiometabolic disease in the current thesis and to examine whether prevalence and risk of MetS differs according to different obesity measures. Lastly, because it is well established that VAT is more metabolically harmful and more strongly related to disease than other fat tissue, it was considered important to determine whether measures of VAT is necessary for accurately representation of overweight and obesity in future population studies, or in clinical settings.

2 Aims of the thesis

The overall aims of this thesis were to obtain knowledge and insights about population body composition and to explore reference values of DXA-derived VAT, its correlation with cardiometabolic health and traditional overweight measures and time trends. We used the comprehensive population-based Tromsø Study which contains repeated surveys with detailed information about both body composition and cardiometabolic health.

Thus, the specific aims were to:

1. Establish reference and threshold values for VAT (absolute and relative units) in adults and elderly and investigate whether different measurement units of VAT differed in their association with cardiometabolic risk factors and MetS.

2. Investigate correlations between VAT and commonly used anthropometric measures (BMI, waist circumference, WHR, and WHtR), and further investigate and compare their association with cardiometabolic risk and MetS.

3. Investigate secular and longitudinal trends in body composition (fat, lean and VAT mass) in a Norwegian adult population over the last two decades.

3 Material and methods

3.1 The Tromsø Study

Tromsø municipality is located in the north of Norway above the Arctic Circle, with a current population of 77 000 inhabitants. Tromsø has both urban and rural settlements and is similar to the general population in Norway according to sex and age (68). In the 1970ies the prevalence of cardiovascular disease in the North of Norway was higher than in the rest of the country, and especially high in men. To understand the causes behind the higher prevalence of cardiovascular disease, the Tromsø Study was initiated, with the first data collection in 1974. Since then, a total of seven surveys have been conducted to date (Tromsø 1 1974, Tromsø 2 1979-1980, Tromsø 3 1986-1987, Tromsø 4 1994-1995, Tromsø 5 2001, Tromsø 6 2007-2008, and Tromsø 7 2015-2016), inviting whole birth cohorts and random samples of women and men in various age-groups, and continuously increasing in amount of data and information collected. The history and description of the Tromsø Study (survey 1-6) is thoroughly described elsewhere (69-71) and the seventh survey, together with questionnaires, are presented at the Tromsø Study webpage (72). Data collection has included questionnaires and interviews, biological sampling, and clinical examinations. From Tromsø 4 and onwards, more extensive clinical examinations were added, and each survey included two separate visits:

- The first visit consists of a basic examination for the total study sample. Data collections include questionnaires with (among others) questions about health, lifestyle, family health history and social relationships, examinations including (among others) measurements of anthropometry and blood pressure, and biological samples collected for analysis of (among others) blood lipids and glycated hemoglobin (HbA1c).
- The second visit consists of extended examinations for a subsample. The subsample is a pre-defined sub-sample of the total invited sample. Data collections include (among others) additional biological sampling, electrocardiography, echocardiography, carotid artery ultrasound, eye examinations, lung function tests, physical function tests, cognitive function tests, accelerometry, and body composition measurements (DXA). The information collected during the second visit has continuously been expanded

over time, thus not all the listed examinations has been included since Tromsø 4 but were included in later surveys.

3.1.1 The study sample

In Tromsø 5 (2001) 10 324 women and men aged 30 years and older living in Tromsø municipality were invited to participate. The invited sample consisted of two groups: 1) participants attending extended examinations in Tromsø 4 (n= 6961) and 2) participants attending the Norwegian Institute of Public Health's (NIPH) National health survey (n= 3363) (73). A total of 8130 women (57%) and men aged 30-89 years participated (89% from the first group, and 57% from the second [NIPH] group). The participants attending the basic examinations that also attended the extended examinations in Tromsø 4 were all invited to extended examinations in Tromsø 5. A total of 5952 attended the extended examinations, of which 1713 had valid total-body DXA scans.

In Tromsø 6 (2007-2008) 19 762 women and men living in Tromsø municipality were invited to participate. The invited sample consisted of four different groups: 1) all inhabitants aged 40-42 years or 60-87 years in the Tromsø municipality (n= 12 578), 2) a 10% random sample of inhabitants aged 30-39 years (n= 1056), 3) a 40% random sample of inhabitants aged 43-59 years (n= 5787) and/or 4) participants attending the extended examinations in Tromsø 4 (1994-1995) (n= 341) (74). A total of 12 984 women (53%) and men aged 30-87 years participated (66% of the originally invited sample). Of the 12 984 participants attending the basic examinations, the following was invited to extended examinations: all participants also attending extended examinations in Tromsø 4, all participants aged 50-62 years or 75-84 years, and a 20% random sample of participants aged 63-74 years. A total of 7307 attended the extended examinations, of which 906 had valid total-body DXA scans.

In Tromsø 7 (2015-2016), all inhabitants 40 years and older living in Tromsø municipality were invited to participate (n= 32 591) (75). A total of 21 083 women (53%) and men aged 40-99 years participated (65% of the originally invited sample). Of the 21 083 participants attending the basic examinations, a pre-defined sample (marked before attending basic examinations) of 13 028 participants from two groups were invited to extended examinations: 1) a random sample of the invited participants to Tromsø 7 (n= 9925), and 2) participants attending DXA, echocardiogram and eye examinations in Tromsø 6 (n=3103). A total of 8346 attended the extended examinations, of which 3675 had valid total-body DXA scans.

DXA measurements

In each survey DXA scans were performed with a GE Lunar Prodigy Advance (GE Healthcare Medical Systems, Madison, Wisconsin) as a part of the extended examinations. DXA-derived body composition measurements have been collected in the Tromsø Study since Tromsø 5 (2001). A predefined subsample of those pre-marked for the extended examinations were examined by DXA. Thus, not all invited to extended examinations were pre-defined for DXA-examination. Information to the extended examinations included instruction to wear light clothing. Before the DXA scan, the participants were asked to remove all metal objects (jewelry etc.). Special clothes were available for use during the scan if necessary (to avoid metal in clothes). No instructions were given regarding food- or water intake, or regarding physical activity before attending the scanning. The DXA scans were performed by trained technicians, who had received standard operating procedures about performing DXA scans according to the manufacturer's guidelines. Each morning the DXA system was calibrated with a standard phantom as recommended by the manufacturer. Post-scanning inspection of images and region of interest (ROI) adjustment was performed according to the manufacturer's guidelines. To standardize VAT analyses, the upper horizontal ROI separating the torso and the head was positioned below the lower boundary of the chin bone. The variables included from DXA scans measurements in the three papers are described below.

3.1.2 Paper I and Paper II study sample and variables

Sample

In paper I and paper II we included the 3675 participants with valid total-body measures from DXA scans in Tromsø 7 (Figure 5). The included sample consisted of 2152 women and 1523 men with a mean age 66.2 and 65.9 years, respectively.

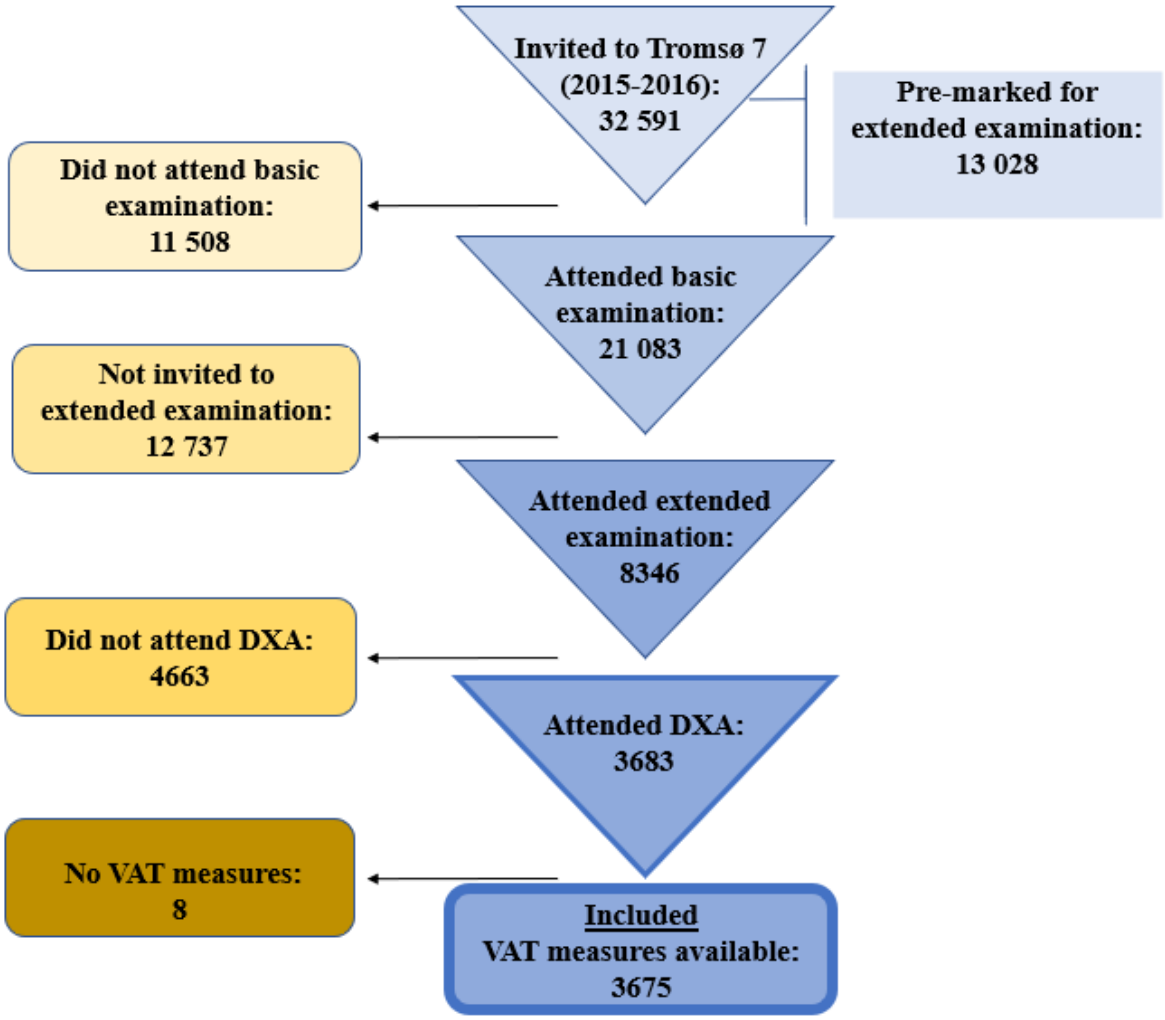

Figure 5: Inclusion of participants in paper I and paper II

Variables

In paper I and paper II we included information about age, sex, weight, and height, cardiometabolic risk factors and DXA-derived VAT (absolute and relative units). Self-reported information about diabetes (*Do you have, or have you had diabetes? "No", "Yes, now", "Yes, previously"*) and medication-use ("*Do you use, or have you used blood pressure lowering drugs?", "Do you use, or have you used cholesterol lowering drugs?", "Do you use, or have you used insulin?",* and *"Do you use, or have you used tablets for diabetes?",* all with answer alternatives *"Currently", "Previously, not now"* and *"Never used"*) was included. Blood pressure (systolic and diastolic blood pressure [mmHg]) was measured three times with two-minute intervals measured with a Dinamap ProCare 300 monitor (GE Healthcare,

Norway) and the mean reading from the two last readings was used. Further, we included information about triglycerides (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), HbA1c (%) and C-reactive protein (mg/L). Because only non-fasting blood samples were available, we could not create a MetS variable identical to the NCEPT ATP III (37) criteria, but we created a modified version of MetS based on the NCEPT ATP III: hypertension (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg and/or current use of antihypertensives), high non-fasting triglycerides (triglycerides ≥1.7 mmol/L and/or current use of lipid-lowering drugs), low HDL cholesterol (HDL cholesterol <1.3 [women] or <1.0 [men] mmol/L and/or current use of lipid-lowering drugs) and diabetes (self-reported current diabetes and/or HbA1c ≥6.5% and/or current use of antidiabetics). MetS (presence of three or more of the MetS components) based on the NCEP ATP III criteria was included in both papers. Among the 3675 participants with valid VAT measures information about prevalence of hypertension, high triglycerides, low HDL cholesterol and diabetes had percentage missing data ranging between 1-3%, and 4% missing for prevalence of MetS.

From the DXA scans information about total body fat (grams and percentage) and VAT mass (grams and volume) were included. Further, information about total body fat mass in the android region was included to enable for calculation of percent VAT in the android region (100*VAT mass/android fat). Index of VAT mass was calculated as VAT mass/height m^2. Relative measures of VAT were considered to be important because it is expected that larger persons (in regard to muscles or height) will have a larger amount of VAT mass, compared to a smaller person although the smaller person can have a more unhealthier VAT mass relative to body size.

In paper II, information about anthropometric measures (BMI [n= 3682], waist circumference [n= 3666], WHR [n= 3666] and WHtR [n= 3664]) were also included for the purpose of comparing VAT mass (grams) to anthropometric measures.

3.1.3 Paper III study sample and variables

Sample

In paper III, we aimed to present both longitudinal and secular trends in DXA-derived body fat, VAT mass and lean mass from Tromsø 5 in 2001 to Tromsø 7 in 2015-2016. Therefore, participants with valid total-body DXA scans from Tromsø 5, Tromsø 6 and/or Tromsø 7 were included (Figure 6). Participants younger than 40 years in Tromsø 5 and Tromsø 6 were

excluded (because they were few, n=51 and n=5, respectively). Initially, in Tromsø 5 a total of 1726 had total-body DXA scan measures, but 13 participants did not give consent and were not included in the data. Therefore, a total of 1662 (62% women), 901 (63% women) and 3670 (59% women) participants from Tromsø 5, 6 and 7, respectively, had measures for body fat mass and lean mass. We did not have complete repeated measures for all included participants. A total of 940 participants attended two or more of the three surveys, of which 382 attended all three. Both fat mass and lean mass were derived with Basic Mode analysis to harmonize between all three surveys. The EnCore software (version 17.0, GE Healthcare, Madison, Wisconsin) was used for extracting data at the three surveys. In 2010, a new application (CoreScan) to the software enabled for calculation of VAT mass. Thus, the stored images were re-analyzed in 2019 and VAT mass measures were extracted from all three surveys. Amount of VAT mass is not directly measured during DXA scanning but estimated by subtracting subcutaneous fat mass from total android fat mass. Not all stored raw images from Tromsø 5 were available for re-analyzation (images not found). Thus, in Tromsø 5, VAT measures were only available from 284 (65.2% women) participants. Further, information about android fat mass was not available from Tromsø 5, thus we were unable to estimate proportion of VAT mass from Tromsø 5. From Tromsø 6, all participants with total body fat and lean mass measures, also had valid VAT measures (n=901). From Tromsø 7, VAT images from an additional 5 participants (in addition to the 3670 participants with valid measures of total body fat mass and lean mass) were available.

Therefore, from Tromsø 7, there were 3670 total body fat and lean mass measures, and 3675 available VAT mass measures. Further, 2 participants from Tromsø 7 with VAT percent above 100% were excluded from all analysis of VAT, leaving 3673 participants from Tromsø 7 available for analysis.

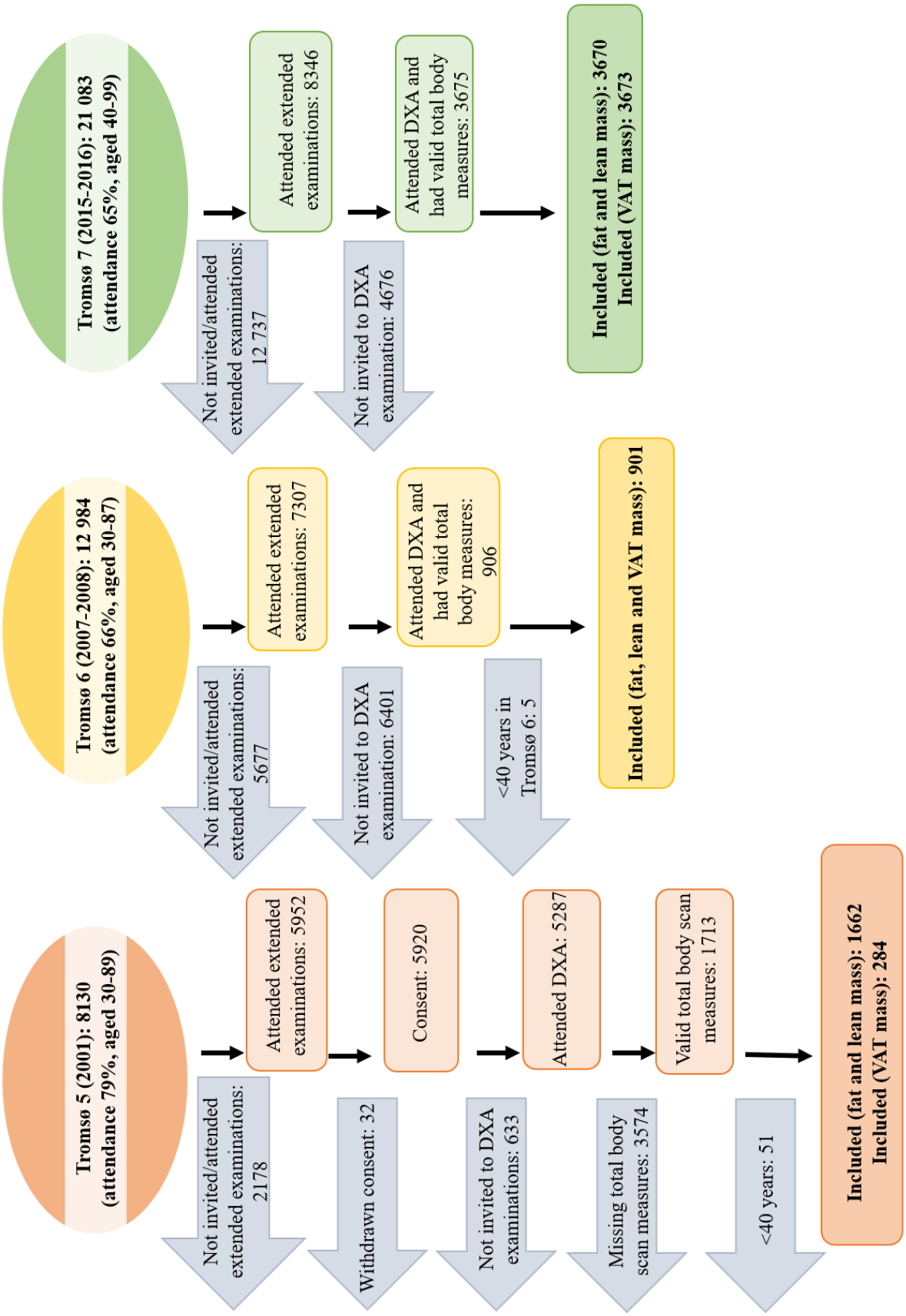

Figure 6: Inclusion of participants in paper III

3.2 Ethics

The Tromsø Study is performed in accordance with the 1964 Helsinki declaration and its later amendments. All participants gave written informed consent. Data from participants that had withdrawn their consent was excluded prior to data delivery from the Tromsø Study. This PhD project was approved by the Regional Committee for Medical Research Ethics (REC North ref. 2017/1967).

3.3 Statistical analyses

Paper I

In paper I we used descriptive analyses to examine the distribution of VAT presented as different units (grams, index, and %) and further created reference values for the different measurement units of VAT mass in 10-year age groups for women and men, separately. VAT volume (cm^3), which is also available from the DXA scans, were analyzed, but all results were close to identical to that of VAT grams and were therefore excluded from the paper. Descriptive analyses were used to present quantiles (5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th}) of VAT (grams, index, and %) in 10-year age-groups. Receiver operating characteristics (ROC) curve analysis were used to examine if VAT in different units (grams, index, and %) differed in association with MetS and the single MetS components, separately. To examine whether different units of VAT (grams, index, and %) showed different associations with MetS and single MetS components, we transformed the VAT measures by square root and subsequently created z-score units for all three units. It was necessary to standardize the different units to enable for comparison between them in regression analysis. Thereafter, we used logistic regression to present the association between z-scores of VAT and MetS and single MetS components in groups of BMI (normal weight, overweight, and obese). ROC analysis was also used to derive sensitivity and specificity for VATs prediction for MetS. We then used highest value of Youden's index ([sensitivity + specificity]-1) to create thresholds for VAT (grams, index, and %) (76, 77). Lastly, we used logistic regression to present the odds for MetS if VAT (grams, index, and %) was above the created threshold.

Paper II

In the second paper descriptive analysis was used to present demographics of the study population. We calculated Pearson's correlation coefficient between VAT mass (grams) and more commonly used anthropometric measures (BMI, waist circumference, WHR, and WHtR) in 10-year age-groups. ROC curves and c-statistics were used to present and compare the predictive abilities of VAT mass, BMI, waist circumference, WHR, and WHtR for MetS and single MetS components (hypertension, diabetes, high triglycerides, and low HDL cholesterol).

Paper III

In paper III we analyzed both the secular trends and the longitudinal trends in fat mass, VAT mass, and lean mass from Tromsø 5 (2001) to Tromsø 6 (2007-2008) and further to Tromsø 7 (2015-2016). Both absolute values and proportions of fat mass, lean mass, and VAT mass (proportion of VAT mass was only available from Tromsø 6 and Tromsø 7) were examined. Descriptive analysis was used to present study characteristics of participants attending only one of the surveys and for those attending two or more surveys. Descriptive analyses were also used to present mean values of fat mass, VAT mass, and lean mass in 10-year age-groups in women and men in the three surveys (Tromsø 5, Tromsø 6, and Tromsø 7). Kernel density plots were used to examine the distributions of fat mass, VAT mass, and lean mass in the three surveys. To examine the longitudinal trends, we used age adjusted/birth year adjusted generalized estimation equation. To investigate potential age-group differences in longitudinal trends we included interaction terms as two-way cross-product terms between indicator variables of 10-year age-groups (40-49, 50-59, 60-69 and 70-79) and an ordinal variable of time (Tromsø 5, Tromsø 6, and Tromsø 7). The age-groups were used to represent birth cohorts and will be addressed as birth cohorts in the rest of the thesis. Because we did not have repeated measures for all participants, we performed separate analyses for both those who attended two or more surveys (n=940) as well as for those who attended all three surveys (n=382).

All analyses were stratified by sex and conducted using STATA 14 (STATA Corp LP Texas, USA).

4 Results – summary of papers

4.1 Paper I: Reference values for DXA-derived visceral adipose tissue in adults 40 years and older from a European population

A total of 3675 women and men with DXA-derived VAT measures (grams, index, and %) were included. Mean age was 66.2 years in women and 65.9 years in men. When comparing participants attending DXA scans with participants not invited or not attending DXA scans we found that the DXA attenders had lower weight and height, and men attending DXA had slightly lower BMI (27.9 and 27.6 kg/m^2, respectively) while no differences were observed in waist circumference. VAT (grams, index, and %) was higher in men than women and was positively associated with age up to 70 years. All findings for VAT as grams or index were highly similar. VAT% increased steadily in women (all ages), while it flattened after age 70 in men. This continued increase in VAT% after age 70 in women is explained by the relationship between the slightly decreasing absolute VAT mass relative to the steeply decreasing subcutaneous fat mass in this age-group. VAT (all measurement units) was positively associated with cardiometabolic risk factors. VAT in grams and in index were stronger predictors of MetS and single MetS components than percentage of VAT. Logistic regression analysis of z-score units of VAT showed, overall, that increasing VAT increased the odds for all single MetS components and MetS. In analysis in categories of BMI there was no linear association, meaning that z-scores of VAT (all measurement units) in association to MetS components were not continuously stronger in higher categories of BMI. The thresholds according to the Youden's index presented were ≥1134 and ≥1859 grams, ≥0.44 and ≥0.55 index, and ≥40.3 and ≥61.2 %, in women and men, respectively, and are suitable for comparison with futures studies including similar populations and using the same DXA system.

4.2 Paper II: Anthropometric measures are satisfactory substitutes for the DXA-derived visceral adipose tissue in the association with cardiometabolic risk

In paper II, a total of 3675 participants were included. Mean age was 66.2 and 65.9 years in women and men, respectively. Men had higher mean VAT values and higher mean values of the anthropometric measures compared to women. The sample mean BMI value was similar to what is considered as being in the overweight category, while mean waist circumference levels were similar to having very high risk, or high risk for cardiometabolic disease in women and men, respectively. VAT was moderately to strongly associated with all anthropometric measures, although the correlations were slightly lower in women than men and in the older age groups. The correlation was strongest between VAT and waist circumference (r: 0.69-0.84 and 0.79-0.88 in women and men, respectively) and weakest between VAT and WHR (r: 0.43-0.64 and r: 0.63-0.72 in women and men, respectively). AUC's showed that both VAT and the anthropometric measures were strong predictors for MetS and single MetS components, and although c-statistics revealed that VAT was statistically a stronger predictor than the anthropometric measures, the AUCs were close to identical (e.g., AUC's for MetS in women were 0.728 for VAT versus 0.693 for BMI). In women, VAT was statistically stronger than BMI and waist circumference for prediction of diabetes, high triglycerides, low HDL and MetS. Compared to WHR, VAT was statistically stronger in prediction of high triglycerides, and statistically stronger than WHtR in prediction of high triglycerides, low HDL cholesterol and MetS. In men, VAT was statistically stronger than BMI and waist circumference in prediction of all MetS components and MetS, and statistically stronger than WHR and WHtR in prediction of MetS and all MetS components with the exception of diabetes. However, because all AUC's were high, and very similar between the anthropometrics and VAT, we concluded that the anthropometric measures were satisfactory substitutes for VAT.

When using ROC analysis to examine which of the anthropometric measures that was the best predictor for VAT, the strongest AUC's was observed for waist circumference (AUC: 0.90), while the weakest AUC's was observed for WHR (0.82 and 0.84, in women and men, respectively).

4.3 Paper III: Secular and longitudinal trends in body composition

In paper III a total of 1662 participants (62% women) from Tromsø 5, 901 participants (63% women) from Tromsø 6 and 3670 participants (59% women) from Tromsø 7 with fat mass and lean mass measures are included. Information about VAT mass was available for 284, 901, and 3673 participants from Tromsø 5, Tromsø 6 and Tromsø 7, respectively. The mean age was slightly higher in Tromsø 6 (68.5 and 69.9 years in women and men, respectively) than in Tromsø 5 (65.2 and 66.5 years in women and men, respectively) and Tromsø 7 (66.7, and 66.2 years in women and men, respectively). When examining potential differences in cardiometabolic risk factors between those attending one of the surveys and those that attended two or more surveys, we found only small, clinically minor differences.

Body fat and VAT mass increased from 2001 to 2015-2016, with a more pronounced increase from 2007-2008 to 2015-2016, than from 2001 to 2007-2008. Women had higher fat mass than men in all three surveys, and men had higher VAT mass across all three surveys than women had. Further, VAT mass increased at a higher rate across the three surveys in men than women. Longitudinal trends showed that the increase over time in fat mass and VAT mass across the surveys was most pronounced in the younger birth cohorts (40-49 years in 2001, particularly in women). This differences in fat and VAT mass changes between birth cohorts was, however, only significant in women.

Total lean mass was higher in men than women in all three surveys and remained unchanged from 2001 to 2015-2016. Lean mass in percent (relative to total fat and bone mass) did, however, decrease across surveys, with a larger decrease between 2007-2008 and 2015-2016 than between 2001 and 2007-2008. This reflects the larger increase in absolute fat mass compared to the smaller changes in absolute lean mass.

Sensitivity analysis including those attending two or more surveys, or those attending all three surveys, showed similar results to that observed in the main analysis (including all participants attending one of the surveys).

5 Discussion

The main aims of this thesis were to examine VAT in a general population, both regarding associations with cardiometabolic risk factors and associations with more commonly used anthropometric measures. Further, the aim was to examine the trends in body composition over time in a general population. Given that there is no consensus regarding reference, threshold, or preferred unit of DXA-derived VAT in population studies, our first objective was to thoroughly examine both absolute and relative measures of VAT in a general population to determine whether any of them showed stronger associations with MetS and/or single MetS components. Both absolute and relative measures showed similar associations with MetS, but VAT in grams and index were highly comparable and had slightly stronger coefficients than percentage of VAT. We further created threshold values for VAT (grams, index and percent) based on sensitivity and specificity in prediction of MetS and showed that VAT mass beyond these thresholds increased the odds for MetS by 3-4 times. In comparison with more traditionally used anthropometric measures such as BMI, waist circumference, waist-to-hip ratio and waist-to-height ratio, VAT was a statistically better predictor for MetS, although visual comparison of results indicated small clinical differences. Finally, both longitudinal and secular trends in VAT mass and body fat increased from 2001 to 2015-2016 with a larger increase between 2007-2008 and 2015-2016 and in the youngest birth-cohort (aged 40-49 in 2001, significant only in women). We believe our results are valuable contributions to the obesity and body composition research field, but that our study also has limitations and areas in need for caution when interpreting the results. Thus, methodological considerations will be addressed and discussed before a more general discussion of results, implications, and considerations for the future.

5.1 Methodological considerations

5.1.1 Internal validity

In the Dictionary of Epidemiology by Miquel Porta (78, p.287) validity is defined as *"the degree to which inferences drawn from a study are valid"*. Thus, it is a consideration of how trustworthy or reliable the results are, either in relation to what is measured in the study sample (internal validity, i.e., VAT in association with MetS) or whether the results and findings are applicable/generalizable to the general population beyond the study sample (external validity).

Internal validity is defined as *"the degree to which a study is free for bias or systematic error"* (78, p. 287). It refers to whether the design of the study, collection of data and analyses are satisfactory for answering the initial aims of the study. Thus, internal validity is a necessity for extrapolating the results from a study into external validity or generalizability (described below in section 5.1.6). Internal validity can be influenced by factors such as study design, bias/systematic error, confounding factors and statistical approaches (78). Because there is always a risk of bias and confounding factors in epidemiological studies, it is important to acknowledge and discuss the potential limitations. In the following sections, internal validity is considered an umbrella term, which covers important aspects and limitations addressed under the different headings considered most relevant for internal validity in the current thesis.

5.1.2 Study design

The Tromsø Study is an ongoing population-based cohort study inviting total birth cohorts or random samples from the general population and contains relevant information to address the aims presented in this thesis.

In paper I and II, we chose a cross-sectional design from where all information is collected at one point in time (2015-2016). For paper I, where we aimed to create reference and threshold values for VAT, we wanted the most recent data because the population characteristics are continuously changing. However, I acknowledge that a prospective cohort study is the best design to examine the association between VAT (absolute and relative units) and MetS, as a cross-sectional design make causal inferences impossible because one cannot show directions of associations. This consideration also applies to paper II where we chose a cross-sectional design to examine how well VAT correlated with the more commonly used anthropometrics. This was considered a valid approach both because we wanted to present recent data (as in paper I), but also because the anthropometric measures of overweight have increased over time, which could potentially affect the correlation between VAT and these measures. Again, if the aim had been to show which of the measures that caused MetS, we would need a prospective design. I acknowledge that the use of the word "predicted" in paper II when addressing the association between different overweight measures and VAT might cause confusion because to predict an outcome based on an exposure would require a study design where causal effects could be shown. However, the word "predict" was used based on the statistical method applied (ROC curve analyses), which estimated predicted probabilities (79).

Although the prospective cohort design is superior to a cross-sectional design in establishing causal relationships, the cross-sectional design was considered satisfactory to answer the aims in paper I and II, which were not to examine causal pathways, but to create reference- and threshold values for VAT based on the most recent measures, and to examine correlations between VAT and anthropometric measures at a given point in time. The findings are valuable to generate hypotheses for future studies investigating potential causal pathways between VAT and MetS.

In paper III, we chose a longitudinal design, together with analyses of secular trends in body composition. The definitions of both longitudinal and secular trends, together with challenges associated to these designs are more thoroughly described below in section 5.1.7 (Longitudinal studies: effect of cohorts and time). The longitudinal design allows us to describe time-trends in whole populations and population sub-groups, such as cohorts or age-groups. This design, together with the statistical methods (GEE) described below, was considered an appropriate approach to both examine the secular- and longitudinal trends in fat-, lean- and VAT mass in the Tromsø Study.

5.1.3 Selection bias

There are three subcategories to selection bias; population bias, response bias and Berkson's bias, from where the most relevant subcategories for this study are the two first (80). Population bias refers to sampling and choice of study population and response bias refers to the response of invited participants (80).

In the Tromsø Study, historically, the invited participants were selected for the purpose of investigating specific risk factors for a given disease. For example, in the first survey in 1974, only young and middle-aged men were invited and there was a focus on cardiovascular disease because the mortality of these diseases in men then was particularly high in northern Norway. However, in the fourth survey in 1994-1995, all inhabitants aged 25 years or older were invited, and since then there has been a more general invitation of participants within a wider age range (72). The Tromsø Study aims to re-invite previous participants to enable for follow-up, but also to invite new participants in order to, among other things, reduce the risk of selection bias. In paper I and paper II, participants from the extended examinations in the seventh survey of the Tromsø Study were included. In Tromsø 7 all women and men 40 years and older living in Tromsø municipality were invited to participate. Both a randomized pre-

marked sample of the originally invited participants, together with participants that attended extended examinations in Tromsø 6, were invited to visit 2 (extended examinations, including DXA scans). Thus, although bias attributed to differences between attenders and non-attenders might still exist, the risk of selection bias due to a particulate population being invited is limited. Potential bias caused by differences between non-attenders and attenders is difficult to avoid, because participation is voluntarily. Participants attending population surveys are often different from the non-attenders in regard to more favorable health status (81-84), higher socioeconomic status (82, 83, 85) and overall lower mortality (70, 81-83, 86-88). Statistical analyses can be used to compare attenders and non-attenders according to certain characteristics, like age and sex, but the lack of additional information makes it complicated to assume generalizability without discussing these limitations thoroughly.

In paper I, we observed a decrease in VAT after the age of 70. This was surprising because usually, the abdominal fat increases with increasing age. These age-dependent findings after age 70 might be affected by selection bias or survival bias. The attenders aged 70 years and older might be the healthiest representatives for this age-group as those with less favorable health might be unable to attend due to health complications. If this is the case, the result is a highly selected group of participants from the elderly, comprising the healthiest in this population. This might explain the observed decrease in VAT in those 70 years and older.

In paper I the results are sensitive to selection bias, because the reference- and threshold values presented reflect the amount of VAT in the included participants and their prevalence of MetS. Thus, if the participants are in better health or have lower VAT than non-attenders, the presented reference- and threshold values are only applicable to populations similar to the participants in regard to amount of VAT and prevalence of MetS. In paper II we compared VAT with the anthropometric measures. With this purpose the potential effects of selection bias are less worrisome unless the correlation between body composition and the anthropometric measures differs between attenders and non-attenders. There is, however, little reason to believe that there are large differences in these relationships between attenders and non-attenders.

In paper III, we included all participants that attended DXA during the second visit (extended examinations) in Tromsø 5, Tromsø 6, or Tromsø 7. In Tromsø 5, the invited sample to the second visit (extended examinations) consisted of 6185 participants attending the first visit in

Tromsø 5 (who had also attended the second visit in Tromsø 4). In Tromsø 6 the invited sample to the second visit (extended examinations) consisted of 1) all participants from the first visit in Tromsø 6 also attending extended examinations in Tromsø 4, 2) all participants from the first visit in Tromsø 6 aged 50-62 years or 75-84 years, and 3) a 20% random sample of participants from the first visit in Tromsø 6 aged 63-74 years (72). The re-invitation of previous participants might lead to selection bias because of the health profile differences between non-attenders and attenders described above (70, 81-88). If the participants included in our papers are in better health than the rest of the population, it is likely to assume that they have both lower VAT and lower prevalence of MetS, which would result in lower external validity of our results. One of the basic ideas behind epidemiological research is to monitor and understand risk factors and outcomes in populations (89), in addition to observing potential changes in these factors. Therefore, disregarding potential selection bias, it is important to also invite previous attendants to enable for longitudinal studies.

The results from paper III are also potentially subject to selection bias. The GEE analysis estimates values for the missing participants at each time point, but these estimates are created based on existing data and trends in the sample. Therefore, if non-attenders have higher VAT than attenders, the presented trends may only apply to the populations similar to the attenders, thus limit generalizability. Essentially, the prospective population-based cohort design of the Tromsø Study is exposed to potential differences in attenders and non-attenders. Therefore, potential differences should always be discussed in the light of external validity, even though the Tromsø Study has a relatively high attendance (65%-79% in the relevant time, compared to for example the Norwegian HUNT Study where the response was 54% in HUNT 3, 2006-2008 (90)).

5.1.4 Information bias and self-reported measures

Porta et al., (78, p. 149) defines information bias as *"A flaw in measuring exposure, covariate, or outcome variables that results in different quality (accuracy) of information between comparison groups"*. Epidemiological research is depending on measures. In the Tromsø Study, measures are collected repeatedly over time, and all these measures are potentially influenced by error. This error in measurements might result in information bias. Thus, information bias is an important concept to consider in population studies that often contains a large number of variables collected through different measures. Frequently used tools for collecting information are questionnaires (self-reported by the participants, with or

without the use of validated instruments), measures conducted by trained technicians (for example weight and height measured with standard protocols and calibrated devices) and biomarkers (for example analysis from blood samples performed with standard methods at accredited laboratories). Thus, information bias might influence internal validity.

Measurement error and misclassification

Before going deeper into the potential measurement errors occurring in this thesis, some clarifications of definitions are needed. When discussing error and bias there are several terms that address the same challenges, which might lead to confusion. Bias is defined by Porta et al, (78, p. 21) as "*systematic deviation of results or inferences from the truth*". The term systematic error refers to skewness of estimates or results in the same direction whereas random error is non-systematic errors (going in both directions) in estimates or results (91). Further from this, differential error is when the occurrence of measurement error differs in different groups (e.g., women and men).

Both systematic and random measurement error can occur at many stages during the study; during designing of the questionnaire for self-reported data, personal beliefs, and characteristics of the study participants, it can be influenced by the study technicians (i.e., the technicians performing the DXA scans or measuring waist circumference), or limitations of the actual tools used to collect information (the DXA scanner or the measurement tape).

Further, measurement error can be present at different levels, on a single variable or in association between variables leading to different effects on the outcome. On a single variable level, a systematic error will have consequences for the mean value of that variable, but also for prevalence, if that variable is used to classify the participants. An example of systematic error at variable level could be blood pressure measurement where the measurement tool is not accurate, leading the blood pressure to be consistently wrongfully measured in one direction (i.e., 10 mmHg higher than the actual blood pressure). This would lead the mean level of blood pressure in the participants to be higher than in reality, and the prevalence of participants with hypertension will be overestimated. If there is random error in the blood pressure measures, occurring from e.g., some participants having higher blood pressure measures than in reality (due to e.g., sneezing) while others having lower blood pressure measures (due to e.g., sleeping), the mean blood pressure in the participants might not be

affected, nor the prevalence of hypertension. In the current thesis, measurement error on a single variable level might have affected the prevalence of participants classified as having MetS.

Measurement error occurring when examining the association between variables might affect the observed association, depending on whether the measurement error in one variable is dependent on the other variable at interest. If the measurement error in one variable is not depending on another variable the error is non-differential and the association between the two will usually be weakened. An example could be that technicians accidentally measuring waist circumference inaccurate in both participants with and without obesity (some measures lower and some measures higher than actual waist circumference). Because this error can go in either direction in both participants with and without obesity, it is non-differential, but increases the uncertainty of the results and might hide potential associations between the variables (i.e., waist circumference and obesity) (91, p. 105).

On the other hand, if measurement error in one variable depends or differs depending on another variable it is called differential error (misclassification) and can lead to false associations (positive or negative) between these two variables (89). Differential error distorts the results in a given direction. A typical example is how mothers of children born with disease are more likely to remember and report their behaviours during pregnancy than women with healthy born babies. Thus, having a diseased child will seem to be associated with more reported risk factors, but in reality, it is just because these women report their behaviour more thoroughly. Examples of differential misclassification from the current thesis could be if the study technicians consistently measured waist circumference in a different area in participants with obesity than in participants with normal weight, leading to an over- or underestimating of waist circumference with a consistent error (for example 4 cm larger) in the participants with obesity. Another example, relevant for classification of the MetS criteria, is blood pressure measurements. If the study technicians failed to follow the study protocol and measured participants blood pressure just after they had climbed the stairs to the research site, the increase in blood pressure because of this protocol deviation might be higher in participants with obesity compared to participants with normal weight (although they would all have higher measures than their actual blood pressure at rest). In this case, more participants would be classified as being hypertensive among those with obesity, and further as having MetS.

In paper I and II the participants were classified as having MetS if three or more of the single components (hypertension, diabetes, high triglycerides or low HDL cholesterol) were present. Please note that we have created a modified version of the NCEP ATP III MetS criteria from Figure 1, where waist circumference was excluded as we aimed to compare associations with VAT and waist circumference as well as anthropometric measures that are all highly correlated with waist circumference. The MetS criteria included self-reported information (like diabetes and medication use) and objective measures (biological samples such as triglycerides). Misclassification of MetS might occur due to systematic or random measurement error in either of the included variables in the MetS criteria. This could alter our results in either direction depending on whether more cases were classified as having MetS among participants with higher or lower amount of VAT. If the MetS variable included a large number randomly misclassified cases the associations with VAT and anthropometric measures will most likely be weakened (80). However, random error is often more subtle and difficult to discover than systematic error, partly because mean values might remain the same in continuous variables, but also because the misclassification will go in both directions (equal distribution of wrongfully misclassified participants as having and not having MetS).

To minimize the risk of measurement error, all surveys of the Tromsø Study have included standard operating procedures for all measures performed (e.g., weight, height, waist circumference, blood pressure and DXA scans). All technicians are trained in accordance with the same protocol. Thus, measures have been taken to limit the risk for both random and systematic measurement error. However, there is always a possibility that errors might still occur.

Measurement error of the DXA-system

Two main DXA-systems manufacturers exists today; Hologic and GE Healthcare. GE Healthcare produce the Lunar Prodigy and the Lunar iDXA. The Lunar Prodigy scanner is used for addressing body composition and VAT in the current thesis. Findings and results across different scanners and systems are not directly comparable. Nor are results between different populations because the results are expected to differ due to differences in data extrapolation and software between different manufacturers. However, continuous software improvements enable future comparison between DXA scanners from the same manufacturer and the possibility of extrapolating more advanced data. The Lunar prodigy scanner was

supported by Enhanced Analysis mode, a method for extrapolating data that enables for comparison with the newer Lunar iDXA scanner, which initially provides higher resolution images. Further, updated software applications such as the CoreScan software EnCore version 17.0 enables for extrapolation of data such as VAT measures. While newer systems and software have improved the imaging and body composition estimation from DXA (67), measurement errors can occur before, during or after the scans.

Firstly, measurements can be affected by factors occurring pre-scan. The DXA system requires trained technicians in addition to standard guidelines or protocols. The manufacturer (GE Healthcare) has created standard guidelines including information such as cautions and safety instructions, standard operating procedures, and general information. In accordance with the manufacturer's guidelines, the DXA system were calibrated with a standard phantom each morning and the technicians were trained in accordance with standard operating procedures. Apart from this, errors might occur due to the behaviour of the participant prior to attending DXA. The DXA imaging can be influenced by hydration status (65). In the Tromsø Study, no preparations (such as fasting, emptying of bladder, or refraining from physical activity) were advised before the DXA scan. Hydration and intestinal content mainly affect the total body lean mass or lean mass in trunk and abdominal area, in that increased fluid- and food content in the stomach slightly increases the measures of lean mass. Further, high-intensity training increase the blood-volume in the working muscle, leading to a slightly larger muscle mass in the imaging (65). Thus, non-fasting imaging affects mainly lean mass, and further total body mass and indexes such as body fat percentage (higher total lean mass leads to lower percent body fat). Future studies aiming at examining total body- or trunk lean mass should take these factors into consideration, even though hydration within normal range in fat-free tissues (67%-85%) will not affect the results (65).

Secondly, measurement error during scanning might occur due to misplacement/wrongly positioning of the participant. This means that the participant is wrongfully placed in the DXA, causing scans to fail to include the whole body in the image, resulting in missing areas of the body. With missing areas of the body (e.g., left arm missing) the DXA application (CoreScan software, Encore 17.0) enables estimation of values for the missing part of the body by mirroring the other side of the body (e.g., the right arm). This is a useful solution when participants exceed the width of the DXA scanner. As such, the software reduces the potential errors arriving from this problem (65). The mirroring method has been enabled for

the image processing in the Tromsø Study, but during post-scan inspection of images the technicians discovered that some participants had exceeded the width of the DXA scanner on both sides with their arms. In those cases, mirroring is not possible to perform. This might affect the individual total-body measures, but abdominal area is fully imaged and therefore not influenced by this. Also, these errors accounted for only a small fraction of the participants.

Thirdly, measurement errors can occur related to the precision of the DXA system. The DXA does not directly measure amounts of VAT, but rather estimates VAT from subtracting subcutaneous fat from total fat in the abdominal area (67). Although, VAT is not directly measured by DXA, it is highly correlated with VAT derived from the gold-standard methods for body composition analysis; CT and MRI (66, 67). However, Meredith-Jones et al. (92) showed that the precision of DXA-derived VAT measurements varied depending on sex (lower precision in men) and body size (lower precision in those with obesity). Thus, the precision of DXA-derived VAT estimations decreases with increasing level of overweight. A potential explanation for the lower precision in men and participants with obesity might be that the imaging from DXA is influenced by the size of the participants, thus, more tissue and thickness means that there is more density, which might influence the attenuation of the X-rays (92). According to Meredith-Jones et al., the differences, or changes, in VAT values should exceed 130 grams for it to be considered as actual changes, and not due to measurement error. In paper III the changes in VAT from Tromsø 5 to Tromsø 6 was 48 g in women and 103 g in men, while the change from Tromsø 5 to Tromsø 7 was 200 g in women and 365 g in men. This is, however, mean changes of VAT.

Finally, potential limitations can occur during post-scan management of the images. Measurement error from DXA-scan measures, might occur if a technician misplaces the ROIs in the post-handling of DXA images. Ten ROIs are usually applied to DXA-scan images, both during and after scanning, to assess body composition, separating the body into head, trunk, upper- and lower limbs, and into android and gynoid region (Figure 4) (65). Misplacement of these lines can interfere with the measures from the different regions and further produce wrong measures of body composition. Measures to reduce such limitations can be recruiting trained personnel and use thoroughly developed protocols. Potential limitations arriving from post-scan management errors are both difficult to discover and difficult to solve and requires

arduous quality control protocols that might be difficult to operate in large-scale data collection settings.

5.1.5 Confounding and interaction

In addition to bias resulting from design, selection and collection of information, other factors can affect and disturb the association between variables. Such factors are known as confounding factors, mediators, covariates, and moderators and can all influence the observed effect between exposure and outcome.

A confounder is a variable that influences the association between an exposure and an outcome because the confounding variable is, in itself, associated with both the exposure and the outcome (80, 93). This can cause us to observe a false association because the association is driven by the confounder. A confounding variable is often recognized as a variable that alters the association between two variables with 15% (93). In paper I and II potential confounders are factors that alters the association between VAT, anthropometric measures and cardiometabolic risk factors. Such confounders might be dietary intake, physical activity, SES and hormones. We have not adjusted for these potentially confounding factors in the papers because the aim was merely to describe the association between VAT, anthropometrics and cardiometabolic risk, not explain or establish a causal association. However, studies aiming at describing a causal pathway between an exposure and an outcome are constantly being challenged by potential confounding factors (89, p. 33). Also, in paper III we described the changes in body composition over time, without trying to explain the mechanisms behind the changes. However, we adjusted for birth year because it is well known that body composition changes with increasing age.

Interaction is defined as *"Differences in the effect measure for one factor at different levels of another factor"* (78, p. 152). The term interaction is often described together with risk modification, because a factor that modify the effect of an exposure to an outcome is what leads to interaction between the exposure and outcome (80, p. 99). The concept of risk modification and interaction is different from confounding in that the modifying risk factor works interchangeably together with the exposure. Therefore, through a combined effect, increase or decrease the risk for the outcome. An example could be if the combined effect of higher VAT and e.g., hypertension increases the risk of cardiometabolic disease more than the expected effect of VAT and hypertension separately. Although it is accepted to use statistical

models to adjust for confounding effects (to remove the effect attributable to the confounding variable), merely adjusting for interaction is more complicated because removing the effect of a risk modifier might hide important results. In paper III, we assumed that the effect of time on changes in body composition might be different in different birth cohorts, and thus tested for interaction. This assumption was based on previous studies showing different trends in different birth cohorts regarding trends in overweight and obesity (27-29, 31). We found a significant interaction between time and birth cohorts in women, i.e., there were differences between different birth cohorts in changes in body composition over time. In men, the estimated changes were different in different birth cohorts, but the interaction term between birth cohorts and time was not statistically significant.

5.1.6 Longitudinal studies: effect of cohorts and time

In paper III, we presented both secular and longitudinal changes from Tromsø 5 (2001) to Tromsø 7 (2015-2016). Because both secular and longitudinal trends apply to trends over time, the definitions need to be clarified. Porta et al, (78, p. 257) defined secular trend as *"Changes over a long period of time, generally years or decades"*. According to the dictionary of epidemiology, longitudinal studies are synonymous with cohort studies and Porta et al, (78, p. 50) define longitudinal trends as *"The analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed or exposed in different degrees, to a factor or factors hypothesized to influence the occurrence of a given disease or other outcome."*. Although both definitions regard trends across time, secular trends are time trends without requiring the same participants, while longitudinal trends are repeated measures of the same individuals over time. In analyses of trend, the findings can be influenced by three factors: the time of the study, the age of the participants and the birth cohort of the participants. The aim of paper III was to examine if there was an effect of time on changes in body composition, in addition we knew that the effect across time might be influenced by both age and birth cohorts.

Longitudinal studies enable for examining potential differences in trends in sub-groups of the study population such as sex and cohorts. Thus, we had the opportunity to investigate if the trends over time differed in different sub-groups. Birth cohorts are defined as "*participants born at a particular time*" (89, p. 56). In paper III we presented trends in 10-year age groups (in 2001) to represent birth cohorts. The different age groups and their corresponding birth cohorts are clarified in Figure 7. In paper III we addressed these differences as age groups (in

2001) but have used the term birth cohorts in this thesis to avoid confusing the differences with age-effects.

The estimated overall time-trend might mask important findings, such as the findings from paper III where the increase in body fat and VAT mass were higher in the younger birth cohorts compared with older birth cohorts. This is important to explore when investigating changes across time because a stable time trend in mean level of a factor can be masked by positive time trends in one group and negative time trends in another.

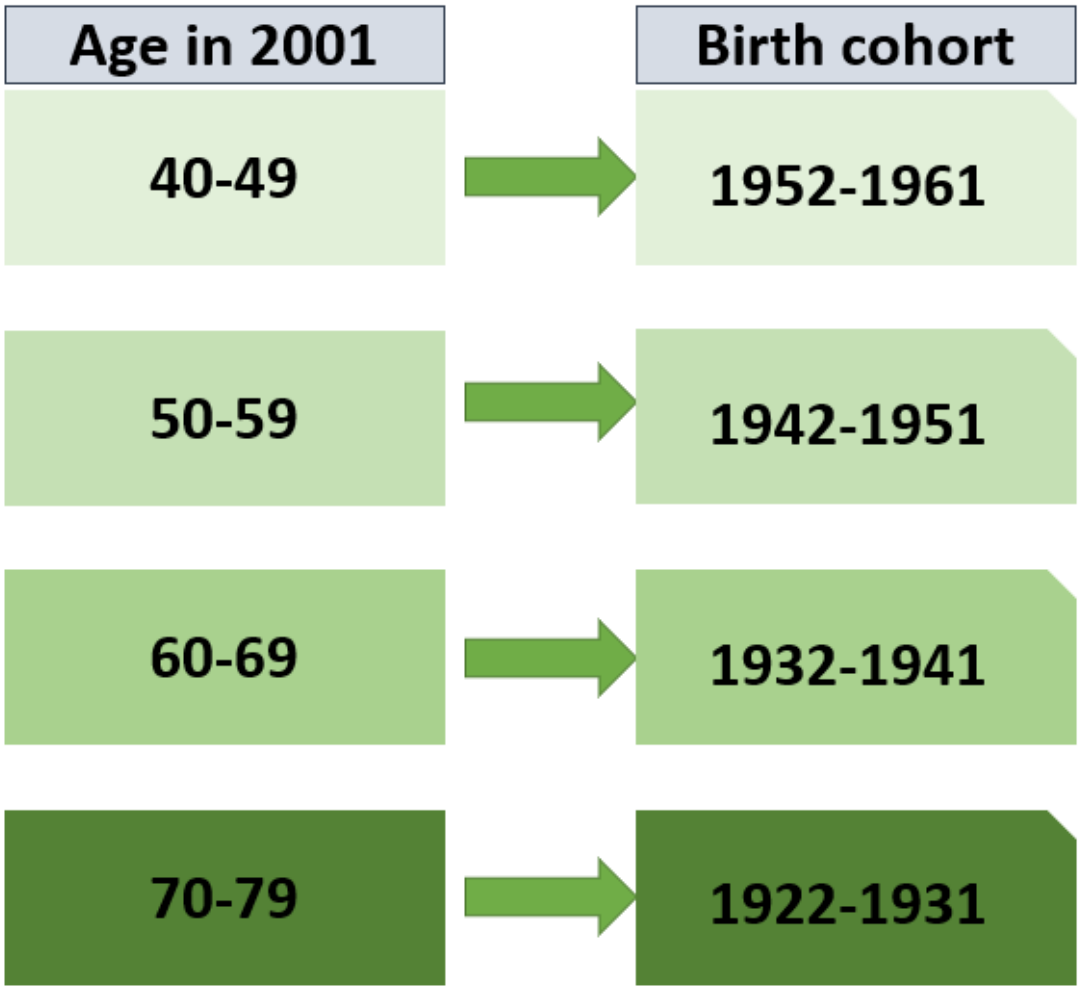

Figure 7: Age-groups in 2001 and their corresponding birth cohorts.

Time trend analysis was only performed in paper III, but it would be valuable to also investigate the association between VAT and cardiometabolic risk across time. Further, trend analyses would be important to establish whether VAT is a stronger causal factor for

cardiometabolic risk over time, compared to the anthropometric measures. However, the number of participants with valid VAT measures in Tromsø 5 and Tromsø 6 who had MetS in Tromsø 7 were limited, 26 women and 22 men in Tromsø 5 and 128 women and 86 men in Tromsø 6. Thus, showing a causal association between VAT mass and MetS (at a later time period) would have been challenging.

5.1.7 External validity

Porta et al, (78, p. 288) defines external validity as *"the degree to which results of a study may apply, be generalized, or be transported to populations or groups that did not participate in the study"*, i.e., that the study results are transferable and of interest to populations beyond those included in the study. In paper I, we created reference- and threshold values for comparison with other populations and time periods. However, there are several subjects for caution that needs to be addressed. Firstly, the reference- and threshold values are only comparable to other studies or settings using the Lunar Prodigy DXA. As stated above, the extrapolated data are specific for the manufacturer's scanner and software. Secondly, the reference- and threshold values are only applicable to similar populations, with similar ages and living conditions. Further, because the thresholds for VAT are created based on the sensitivity and specificity for MetS, all the potential causes for misclassification mentioned above might alter the classification, and further affect the thresholds presented. Therefore, caution is warranted when applying these thresholds outside this study sample. Further studies, using the MetS and the same statistical approach, is needed for comparison with the thresholds created in paper I. However, acknowledging the potential limitations arriving from the concepts discussed from section 5.1.2 through 5.1.6, overall, the findings in both paper II and III are concluded to be generalizable for the general adult population, given that the living conditions are similar, and that body composition is measured with the same DXA-system as in the Tromsø Study sample.

5.1.8 Statistical considerations

VAT was not normally distributed but rather positively skewed. However, VAT was transformed for one analytical purpose only, to enable for comparison between strength of association of different units of VAT (grams, index, and %) through regression analysis in paper I. We chose to not transform VAT for other purposes based on the following reflections. Firstly, the sample size included in the papers are quite large. The central limit theorem states that samples consisting of more than 30 participants are reasonable large, and

that in such samples the mean is often normal, even if skewness occurs (91, p. 125). This rationale is strengthened as sample size increases. The mean was similar to the median (a differences of 105 g in women and 83 g in men in Tromsø 7). Secondly, we mainly aimed to describe associations rather than examining the effect of VAT on MetS. The statistical methods applied did not rely on normal distribution. ROC curves with AUCs are merely graphical descriptive statistics and nonparametric ROC curves in combination with postestimation ROC curves from logistic regression was used. None of which includes an assumption of normality. In paper III we used GEE analysis, which is well suited for handling non-normally distributed variables (94).

In all three studies we started with, what Bhopal called *"the first key analysis in all epidemiological studies"* (80, p. 96), namely descriptive analysis of our study population. Paper I and II will be discussed together because the same study sample was included and because similar methods were used.

Paper I & II

We decided that the most important aspect of considering body composition is to relate it to risk of disease. We used ROC analysis to examine the different units of VAT (grams, index, and %) (paper I) and VAT mass (grams) plus the different anthropometric measures' (paper II) ability to predict MetS. ROC analysis is usually used for determining the predictive abilities of a medical test to confirm positive disease that is present, or to compare the diagnostic decision from two different factors (i.e., tests or doctors) (95, 96). It is a useful and increasingly used tool in epidemiological research to compare predictive effects of a variable against a measure considered better/more correct (VAT), and further to create threshold values. Youden's index is a commonly used post-estimation tool from ROC curves to create threshold values or cutoffs based on the sensitivity and specificity of a test (95). We used MetS to classify the threshold of VAT that had the best ability to discriminate between participants with and without MetS. It should be noted that this does not mean that slightly lower levels of VAT are not of concern, but rather that values above those reported in paper I are highly associated with having MetS. It should also be emphasized that the thresholds presented are depending on the prevalence of MetS in our population and is as such only applicable to populations similar to ours in regard to MetS. Finally, our definition of MetS is based on the commonly used NCEP ATP III criteria, but some modifications are made, such as removing waist circumference as a criterion and using our own definition of diabetes.

Paper III

We wanted to examine whether differences in sample characteristics between participants attending only one survey compared to those re-attending several surveys potentially could affect the observed trends in body composition. To present sample characteristics we compared mean levels of HDL cholesterol, triglycerides, waist circumference and proportion of smoking, hypertension, sedate physical activity level, and higher education in those with one compared to more than one Tromsø Study attendance. We first compared the characteristics between the sample in Tromsø 5 that attended only Tromsø 5 with those also attending Tromsø 6 or Tromsø 7. Further, we compared the sample in Tromsø 7 that attended only Tromsø 7 with those also attending Tromsø 5 or Tromsø 6. All participants attending DXA measurements in Tromsø 6 also attended DXA scans in either Tromsø 5 or Tromsø 7. The differences between the samples attending only one survey and those attending more than one of the included surveys were minor with respect to clinical significance. To examine secular trends, we presented mean values of VAT and body fat in 10-year age groups in the three surveys, compared kernel density plots and used GEE analysis to present overall trends in women and men. Because the GEE analysis estimates values for those that are missing in each survey, it could be considered an analysis of longitudinal trend (because we present it as trends in the same participants). Because we, in this specific analysis, only presented overall trends and did not examine sub-groups in the population, besides separating women and men, we present it as secular trends.

The number of participants attending DXA scans in the three surveys differed. GEE analysis is well suited for longitudinal analyses because it accounts for correlations within individuals with repeated measures, and also because it estimates changes and trends for the missing values at each time point (94). A total of 940 participants attended DXA scans at two or more of the surveys, and 382 participants attended DXA scans in all three surveys (Tromsø 5, Tromsø 6, and Tromsø 7). The highest number of participants attended DXA scans in Tromsø 7 and among these 3675 participants, 87% did not attend previous DXA scans. Thus, GEE estimates values for these participants in Tromsø 5 and Tromsø 6. To examine whether these estimated trends for missing variables were different from those with complete follow-up, we performed two rounds of sensitivity analysis: one including participants attending 2 surveys or more, and one including only those attending all three surveys. The results from these sensitivity analyses were similar to that observed in the main analysis (including all

participants attending one of the surveys). GEE analysis assumes that the missing values are missing at random. There is no reason to believe that the participants missing from survey to survey is due to systematic differences. Thus, together with the highly similar results from the sensitivity analysis presented above, we do not believe that wrongfully estimated results due to missing not at random has influenced our results.

Finally, the most important consideration when choosing a statistical method is that it should be suitable for answering the aims. We consider our statistical approaches to be suitable for the aims presented in the three papers.

5.2 Discussion of main results

The results have been discussed in detail in the three included papers. In this section I aim to review the findings with a wider perspective and reflect on how these results can have implications on further research, clinical practice and future interventions aiming at halting the obesity epidemic.

Overweight and obesity are increasing in all parts of the world (11). BMI is the most frequently used measure to quantify overweight and obesity. The increase in obesity is paradoxical to the improvement in cardiometabolic risk. We originally questioned whether the observed changes in BMI actually reflect an unhealthy increase in total body fat, or if the population is becoming generally larger, not merely fatter. Because BMI reflects weight divided by height squared, it does not address whether this increase in weight consists of fat mass or muscle mass. Thus, potentially increasing trends in muscle mass would be masked as overweight by using BMI alone. In the Tromsø Study, the adult population have over time increased their grip strength and their levels of leisure time physical activity (97, 98). Both these trends might indicate a better health status in the adult population and a higher muscle mass. VAT is identified as the most harmful fat depot in the body, closely associated to cardiometabolic disease. It was therefore of importance to use DXA to investigate whether the observed paradox could be explained by a low correlation between VAT and other overweight measures, and further if the trends in VAT differs from the observed trends in BMI.

5.2.1 VAT: reference values and thresholds

Although VAT for a long time has been recognized as a metabolically active component of body fat tissue (35, 51), the EnCore version 17.0 software enabling VAT estimations from DXA through the Corescan application was first evaluated in 2010-2011 (67). Previous studies creating reference values for DXA-derived VAT is rather limited, probably because the DXA system is quite expensive and requires extensive mobilizations of site, technicians, and protocols. Current reference values for VAT is based on younger populations (99, 100), based on the more recently released iDXA scanner (101, 102) or based on the DXA scanner from Hologic Inc. (Bedford, MA, USA) (103). Ofenheimer et al. (104) used the Austrian LEAD cohort to present reference values for European populations, however, they did not propose thresholds or compare VAT with cardiometabolic risk. Corresponding to Ofenheimer et al. (104) we observed that men had higher VAT mass than women. While they observed a continuous increase in VAT mass with increasing age, we observed a decrease in VAT mass after the age of 70. The mean VAT mass in different age groups presented by Ofenheimer et al. (104) were similar to that observed in paper I in women, while men in paper I had consistently slightly lower mean VAT mass in the different age groups than the Austrian men (104). Ofenheimer et al. emphasized the need for similar studies in different population to examine potential geographical differences (104). Recently, reference values and threshold values for VAT were presented from a New Zealand population by Meredith-Jones et al. (105). In this study, the proposed cutoff values were markedly lower than our findings; 800 grams versus 1100 grams in women, and 1200 grams versus 1860 grams in men. These large differences might be explained by the age differences in the samples. Meredith-Jones et al. (105) included participants 18-66 years, but presented reference values separately for women and men <40 years and 40 years and older. Thus, in our paper I, we compared our results with their presented reference values for women and men 40 years and older. Still, the mean age of our sample is older than that included by Meredith-Jones et al. (105) because the oldest participants in our sample were 84 years old while the oldest in their sample were 66 years. The mean age of participants 40 years and older included by Meredith-Jones et al. were about 45 years in both women and men, while the mean age in our sample were about 66 years in both women and men. Because the amount of VAT increases with increasing age, it is plausible that this age-differences explain the discrepancy between our findings. Other examples of potential explanatory factors might be study sample differences in diet and physical activity level, but possibly also because of different methods and criteria used when

creating cutoffs. Meredith-Jones et al. (105) used single metabolic components, and later combined these results, while we used the MetS definition. Further, they used a method presented as the Liu method, which is described as an alternative to the Youden's index method, which was used in our paper I. However, the differences in thresholds are still notably large (300 grams in women and 860 grams in men) (105).

Comparisons across studies provides new valuable insights about population health, enabling us to compare population differences and predict future risk for disease. Further, and importantly, we can motivate for public intervention targets. However, comparison would be more feasible if different studies used similar methods and outcomes when creating threshold values.

5.2.2 Overweight measures and cardiometabolic risk

Overweight, and particularly obesity, increases the risk of cardiometabolic disease, and previous results corresponds to ours regarding the high correlation between VAT and anthropometric measures (100, 106, 107), and the strong association between VAT and cardiometabolic risk (35, 100, 105, 106, 108). There was a statistically stronger association between VAT and MetS, but the predictive effects of VAT compared to anthropometric measures, represented by the AUC, was highly similar. Thus, anthropometric measures are concluded to be satisfactory substitutes for DXA-derived VAT in population surveys, and waist circumference more so than BMI, WHR and WHtR. This might be a controversial conclusion because imaging methods are more accurate than anthropometric measures.

The conclusion should be interpreted with caution and with the understanding that it is not necessarily generalizable to all settings or individuals. Firstly, it is possible that DXA-derived VAT is more strongly associated with disease occurrence over time. That is reasonable to assume since VAT is more strongly associated with reduced insulin-sensitivity, pro-inflammatory responses, and free fatty acids, than obesity in general (55). Further, individual differences in body compositions might be masked by anthropometric measures such as BMI. BMI has limited potential to capture whether excess weight consist of muscle mass. However, it is unlikely that BMI levels above e.g., 30 kg/m^2 is due to excess muscle mass alone. This would only occur in individuals with an extreme muscle mass, such as athletes in particular sports including body builders, and is not considered a fallacy of BMI in existing populations. Further, two individuals with similar BMI (e.g., obesity) might have different risk for

cardiometabolic disease depending on the amount of VAT (55). Also, there are several challenges to measuring and defining overweight and obesity in the elderly population. Not only have the more commonly used anthropometric measures shown to be inadequate in detecting obesity because of the biological changes in body composition with increasing age (61), but potentially also because of the suggested u-shaped association between BMI (and waist circumference) and disease in the older population as described in the introduction (45). Thus, if low weight/underweight serve as a risk factor in the elderly population, having overweight might seem protective compared to having underweight (62). However, a large review from 2016 (46) showed that there was a u-shaped association between BMI and mortality, but that this association most likely were influenced by potential confounding of factors such as smoking and presence of disease. The association between BMI and mortality in never-smokers was J-shaped and the BMI on 23-24 presented the lowest mortality (46).

Thus, although the findings from this thesis can be important for clinicians, the need for discretion and use of "common sense" is important because of the limitations of the anthropometric measures. In epidemiological studies it is not possible to draw inferences to individuals, mainly because we do not study individuals but populations. Epidemiology is *"the study of occurrence and distribution of health-related events, states, and processes in specified populations."* (78, p. 95). Therefore, these considerations about potential individual differences are presented as an area in need for caution when deciding which measures that are most appropriate.

Finally, we examined the associations between VAT, anthropometric measures and cardiometabolic risk factors, focusing on the MetS components hypertension, high triglycerides, low HDL cholesterol and finally diabetes prevalence. Thus, our conclusions and considerations only regard association to cardiometabolic risk and MetS, and we cannot conclude on either of these different measures in their association to other morbidities like e.g., cancer, or overall mortality.

5.2.3 Changes in body composition

In paper III, both VAT and body fat increased between 2001 and 2015-2016. The increase was higher during the two latest surveys (2007-2008 and 2015-2016) and in the youngest birth cohort compared to the older birth cohorts (with significant differences in women only).

We did not find any previous studies examining the secular trend in DXA-derived body composition. Therefore, the results were compared to other studies examining longitudinal trends in body composition (61, 109-112). The results from previous studies corresponded to the findings from paper III, but the previous studies had a small number of participants (N: 78-161) (61, 110, 112), and included older adults (60+ years), aiming at investigating change in body composition and sarcopenia. Further, all studies had short follow-up (2-5 years) (61, 109-112). It should be noted that one of these studies (109) used the Hologic DXA system, making direct comparison of results challenging. Nor did we find any studies presenting trends in DXA-derived VAT and paper III thus contributes with novel findings to the field.

Paper II showed high correlation and strong association between VAT and waist circumference. Previous findings from the Tromsø Study showed that trends in waist circumference corresponded to the trends in VAT observed in our paper. This related both to the increase over time, but also to the cohort effect where the younger birth cohorts have a higher increase in prevalence of obesity compared to the older birth cohorts (29, 31, 113). While we observed a more rapid change between the two latest surveys in our study, Jacobsen et al. (28) found a higher increase in BMI between the earlier time periods 1994-1995 to 2001-2002 than between 2001-2002 to 2007-2008. However, Jacobsen et al. followed the participants between Tromsø 4 (1994-1995) to Tromsø 6 (2007-2008), thus not fully overlapping the three surveys included in our paper (Tromsø 5 to Tromsø 7). Løvsletten et al. (31) showed that both body weight and waist circumference increased between Tromsø 6 and Tromsø 7, supporting the increasing trends observed in paper III. The more rapid increase in obesity among the younger generations observed in paper III is of special concern because overweight usually follows the person into adulthood and older age (114, 115). Thus, higher increase in younger generations might lead to a further increase in the prevalence of overweight and obesity, which again might hamper the positive development of cardiometabolic disease observed in developed countries.

Contrasting to the results from the Tromsø Study, the HUNT study showed in their public health report from 2019, that the increasing trend in overweight had flattened between 2006-2008 to 2017-2019 (116). The results from HUNT were presented for the participants overall and potential differences between different cohorts or age groups might have been camouflaged.

5.2.4 General considerations

This thesis's conclusion reflects that DXA-derived VAT is not necessarily essential to establish associations with cardiometabolic risk at a population level, and that the trends observed in VAT and body fat are similar to that observed using BMI, which is more accessible.

DXA is important when investigating changes in body composition across time, age, and cohorts. Firstly, DXA is valuable in intervention studies when measuring the effect of, for example, physical activity and dietary interventions over time. During such studies the participant's body composition might change by increasing muscle mass and reducing fat mass, while their weight might remain stable. In that case, conventional anthropometric measures, such as BMI, might not capture the positive changes in body composition and further the positive impact of the intervention. Secondly, the biological changes in body composition with increasing age is characterized by a decrease in muscle mass and increase in fat mass, and especially abdominal fat mass (44, 63). The loss of muscle mass and reduced function in the elderly population is defined as sarcopenia (49). Studies have shown that these transitions in body composition might not be detected by standard measures, because simultaneously with a reduction in muscle mass, fat mass increases, leading to a relatively stable body weight (61, 112). These changes occur more rapidly in some elderly leading to premature aging. To capture changes in body composition, imaging methods are undoubtable of high importance.

The results and conclusions from this thesis are based on a population approach and mean values. This means that the results are considered generalizable to the general population but may not be generalizable to those who differ from the general or average. Thus, for the average population, anthropometric measures and especially waist circumference is a satisfactory measure for determining risk for disease. However, for an individual that differ significantly from the average, e.g., regarding muscle mass or body size, anthropometric measures might prove less useful. Epidemiological studies aim at studying populations, therefore, applying the results to individuals should be done with caution, if done at all. Currently, individuals with particularly high muscle mass make up a small part of the general population and is not believed to have altered the conclusions from this thesis. With parts of the population being more physical active and stronger than previously, using anthropometric measures such as BMI might impose a challenge in the future.

Because DXA is a rather resource demanding tool, other body composition measuring tools such as bio-electrical impedance (bioimpedance) analysis is more frequently used in hospitals and in gyms. Bioimpedance is ranked as the third level of accuracy according to Lohman et al., (56), together with circumference measures (such as waist circumference). In comparison with MRI, bioimpedance is a good measure for abdominal fat overall, but not as good for estimating VAT (117). It is not clear if bioimpedance is better than waist circumference at estimating VAT, and also, the possibility of error is large with higher level of VAT (58). Further, the accuracy of bioimpedance is highly depending on the participants hydration status and correct placement of electrodes (56, p. 78). Overall, DXA scans are considered superior to bioimpedance according to level of accuracy in measuring body composition, and especially VAT. However, in some cases DXA is not possible to perform. The DXA-scanner cannot scan participants with a body weight over 200 kg (65). In such cases bioimpedance can be considered a potential substitute.

Due to the cross-sectional design of paper I and paper II, it cannot be concluded whether there is a causal relationship between VAT and MetS, nor can it be concluded that the anthropometric measures are equally good as VAT in future prediction of MetS, or other cardiometabolic conditions. Thus, the study design is a potential limitation that needs to be considered when deciding the usability of DXA in obesity research.

6 Conclusion

In this thesis we hypothesized that DXA-derived VAT would be a more accurate measure of obesity and that it would have stronger association to cardiometabolic risk. Further, we questioned whether the observed trends in obesity measured by BMI would reflect a similar trend in body fat and VAT.

The presented reference values and threshold values for DXA-derived VAT are of potential value to future studies or clinics using similar techniques and including similar populations as used here. In comparison with the commonly used and easily accessible anthropometric measures, BMI, waist circumference, WHR and WHtR, VAT was statistically, but not clinically, significantly stronger associated with MetS and the single MetS components (hypertension, diabetes, high triglycerides and low HDL cholesterol). Both VAT and body fat increased from 2001-2016 with a larger increase between 2007-2008 and 2015-2016, and in the youngest birth cohorts (40-49 years). The difference in estimated increase of VAT and body fat across time between different age-groups were statistically significant in women only.

In conclusion, the results imply that on a general basis and in large population studies, DXA-derived VAT seems to mirror the observations of anthropometric measures, and the anthropometric measures can therefore be regarded as satisfactory substitutes in studies and sites where DXA measures are challenging. Caution should be used when investigating longitudinal trends in intervention studies aiming on weight reduction or in the older part of the population. Further, the observed trend in body composition mirrored that observed by BMI, thus reflecting an actual increase in body fat across time.

The findings in this thesis suggests that the difference between DXA and anthropometric measures were minor, both according to their association to MetS and according to time trends. It is, however, important to highlight that the participants with obesity, regardless of measurement method, are at higher risk for cardiometabolic disease, and potentially also at higher risk for other diseases not addressed in this thesis. Our hypothesis that the paradox between improvements in cardiometabolic risk and a continuous increase in overweight and obesity could be explained by the population getting larger, not merely fatter, is not supported by the findings in this thesis.

7 Implications and future perspectives

There are several implications arriving from this thesis. The reference values and thresholds created for VAT is potentially valuable for future studies to enable for comparison, or to support decision-making in clinical settings. We have shown that VAT values over a given threshold implies a three to four times increased risk for MetS. It would be useful for future purposes to have generally accepted threshold values for VAT– across populations and diseases. Thus, more studies are needed to establish reference- and threshold values, preferably with similar methods and in prediction of cardiometabolic diseases. Further, showing that anthropometric measures are satisfactory substitutes for more advanced methods are of high value for both population studies and clinics that does not find it feasible to include advanced measures of body composition. However, caution should be made as the measures included should match the aim of the measurements. The secular and longitudinal trends in body fat and VAT mass confirms what has previously been observed in the obesity epidemic where overweight and obesity consistently increase, with the largest increase in the younger population. The higher increase of VAT and body fat in the younger generations is of considerable concern and should be a strong motivator for large public health measures aiming at halting the current and future increase in overweight and obesity.

From a cost-effectiveness perspective, given the high economic consequences of obesity, reducing both individual and societal costs arriving from obesity, is most likely highly cost-effective. The continuing challenge in the battle against obesity is not that we do not have the means, but that reducing weight and staying normal weight requires massive efforts and motivation from individuals. Overweight and obesity are caused by a complex interplay between genetic factors and lifestyle. However, although people with genetic predisposition for obesity has increased most in BMI, people not genetically predisposed have also increased in BMI, indicating that environmental factors are strong drivers behind the continuous increase (118). Therefore, preventive targets should be interdisciplinary, placing less focus on individuals, and more heavily emphasized on public and organizational measures. Such measures could include reducing the costs and increasing the availability of healthy foods, increasing the costs and reducing the availability of unhealthy foods, aiming at discovering and facilitate for early intervention of overweight and obesity, and enabling for physical

activity for all parts of the population. The solution to the obesity epidemic is complex, costly, and challenging, but the future health implications from not reacting is far worse.

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Paper I

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Research Article

Reference Values for DXA-Derived Visceral Adipose Tissue in Adults 40 Years and Older from a European Population: The Tromsø Study 2015–2016

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Background. Reference values for visceral adipose tissue (VAT) are needed and it has been advocated that body composition measures depend on both the technique and methods applied, as well as the population of interest. We aimed to develop reference values for VAT in absolute grams (VATg), percent (VAT%), and as a kilogram-per-meters-squared index (VATindex) for women and men, and investigate potential differences between these measures and their associations with cardiometabolic risk factors (including metabolic syndrome (MetS)). *Methods*. In the seventh survey of the population-based Tromsø Study, 3675 participants (aged 40–84, 59% women) attended whole-body DXA scans (Lunar Prodigy GE) from where VAT was derived. We used descriptive analysis, correlations, receiver operating characteristics (ROC), and logistic regression to propose reference values for VAT and investigated VAT's association with cardiometabolic risk factors, MetS and single MetS components. Further, Youden's index was used to suggest threshold values for VAT. *Results*. VATg and VATindex increased until age 70 and then decreased, while VAT% increased with age across all age groups. VAT (all measurement units) was moderate to highly correlated and significantly associated with all cardiometabolic risk factors, except for total cholesterol. Associations between MetS, single MetS components, and VATg and VATindex were similar, and VAT% did not contribute any further to this association. *Conclusion*. These VAT reference values and thresholds, developed in a sample of adults of Norwegian origin, could be applied to other studies with similar populations using the same DXA device and protocols. The associations between VAT and cardiometabolic risk factors were similar across different measurement units of VAT.

1. Introduction

The definition of overweight and obesity is "abnormal or excessive fat accumulation that may impair health" [1]. The most frequently used definitions of overweight and obesity are based on anthropometric measures such as body mass index (BMI) and waist circumference, which do not distinguish between fat mass and fat free mass, but rather represent overall body size. On the contrary, available body composition measures directly address the definition of overweight and obesity. There are several tools to determine body composition. Dual energy X-ray absorptiometry (DXA) determines body composition from scanning the body with X-ray beams that pass through the body and establish amount of fat mass, bone mass, and soft tissue lean mass based on composition of the tissues [2–4]. Visceral adipose tissue (VAT) located intra-abdominally (behind the abdominal muscles and around organs) is more metabolically active than subcutaneous adipose tissue and has been associated with insulin resistance, the metabolic syndrome (MetS), cardiovascular disease, and several types of cancer [5]. DXA provides area-specific body composition, and VAT

is estimated from fat mass located in the abdominal area when subcutaneous fat has been removed [3]. DXA-derived VAT has been validated against both MRI and CT [3, 6].

There are no generally accepted reference values for VAT. Previous studies have presented normative data, and there is a need for age-, sex-, and ethnicity-specific reference values [7–9]. In addition, different types of DXA systems and models as well as the type of unit used challenge VAT comparisons across studies. The most commonly parameters reported from the DXA systems are VAT mass expressed in grams (VATg) and VAT volume expressed in cubic centimeters ($VATcm^3$). There is a strong positive correlation between height and weight, and likely also between height and VAT, and between body fat and VAT. To increase comparability between individuals, it is of interest to adjust for potential confounding effects of height and central adiposity, warranting relative VAT values like VATindex ($VAT/height^2$) and percent visceral fat in the abdominal area (VAT%). Previous studies developing VAT reference values have highlighted the importance of technique and population-specific reference values [7]. Most other studies have used iDXA models [8, 10] or only included young adults [9, 11]. In addition, few studies have investigated the association between VAT and cardiometabolic risk factors [7, 9, 11, 12].

We aimed to develop reference values for DXA-derived VAT expressed in absolute and relative terms in an adult population, predominantly of European origin from the Tromsø Study, Norway. Additionally, we have investigated the associations of distinct VAT parameters with cardiometabolic risk factors, MetS and single MetS components. Further, we present suggested threshold values of VAT based on ability to predict MetS.

2. Materials and Methods

2.1. Study Population. The Tromsø Study is an ongoing population-based study [13] consisting of seven surveys (Tromsø 1–7) conducted from 1974 to 2016, inviting large representative samples of the population in the Tromsø municipality in Northern Norway. We included participants from Tromsø 7 (2015–2016) where all inhabitants aged 40 years and older ($N = 32591$) were invited to a basic examination including questionnaires, clinical measurements, and biological sampling (Figure 1). A subsample ($N = 13028$) was premarked for invitation to extended examinations approximately two weeks later. This subsample consisted of a randomized sample ($N = 9925$) as well as previous participants attending DXA, echocardiogram, and eye examinations in Tromsø 6 (2007–2008) ($N = 3103$). A total of 21083 women and men aged 40–99 years attended the basic examination (65%), and 8346 attended the extended examinations (of the premarked sample; 64% of the originally premarked and 90% of those attending the basic examination). Of these, 3683 participated in DXA scans from whom 3675 had VAT measures available (Figure 1).

This project was approved by the Regional Committee for Medical Research Ethics (REC North ref. 2017/1967), and all participants gave written informed consent.

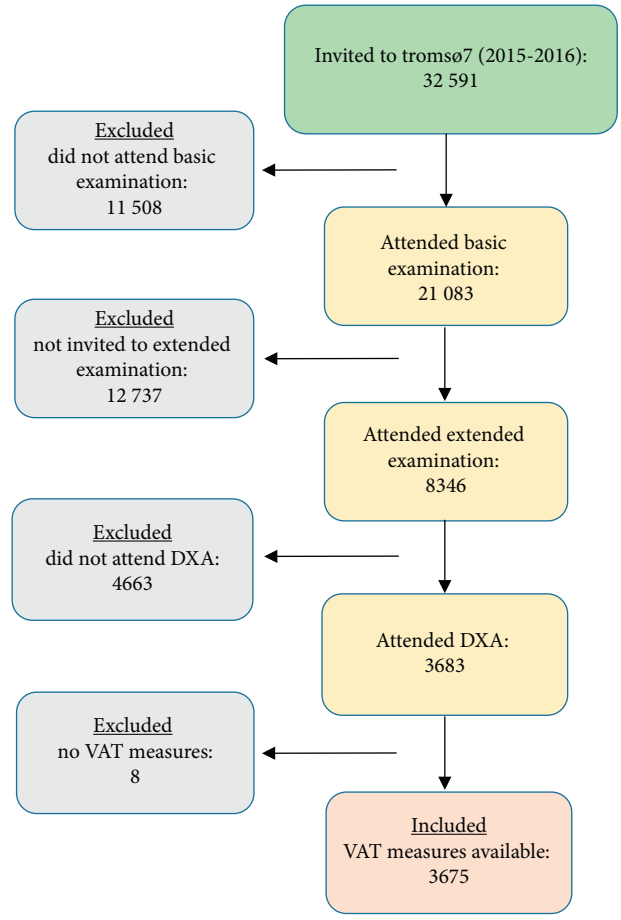

Figure 1: Inclusion of participants.

2.2. Study Measures. All measurements were performed by trained staff using standard protocols.

2.2.1. Cardiometabolic Risk Factors. We included information on diabetes and use of medications from self-administered questionnaires. Nonfasting blood samples were analyzed for total cholesterol (mmol/L), high-density lipoprotein (HDL) cholesterol (mmol/L), triglycerides (mmol/L), and glycated hemoglobin (HbA1c) (%), at the Department of Laboratory Medicine at the University Hospital of North Norway (ISO certification NS-EN ISO 15189 : 2012). Blood pressure was measured three times with two-minute intervals with a Dinamap ProCare 300 monitor (GE Healthcare, Norway) and the mean of the two last readings was used in the analysis. We used MetS components based on the NCEP ATP III diagnostic criteria for the MetS (2005 revision): hypertension (mean systolic blood pressure >130 mmHg and/or mean diastolic blood pressure >85 mmHg and/or use of antihypertensives), high nonfasting blood lipids (triglycerides ≥1.7 mmol/L and/or use of lipid-lowering drugs), low HDL cholesterol (HDL cholesterol <1.3 (women) or <1.0 (men) mmol/L and/or use of lipid-lowering drugs), and diabetes (self-reported diabetes and/or HbA1c ≥ 6.5% and/or use of insulin and/or other diabetes medication) [14]. As investigation of VAT was our main objective, we excluded elevated waist circumference as a criterion.

MetS was defined as presence of three or more of the MetS components presented above, as defined by NCEP ATP III (*n*: 493 (24%) women and 406 (28%) men).

2.2.2. Adiposity Measures. Weight and height were measured with light clothing and no shoes to the nearest 0.1 kilograms (kg) and 0.1 centimeters (cm) using the Jenix DS-102 height and weight scale (Dong Sahn Jenix, Seoul, Korea). Waist and hip circumference were measured to the nearest 0.1 cm with a Seca measurement tape at the level of the umbilicus and the greater trochanters, respectively. BMI (weight in kg divided by height in meters (m) squared) was defined as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). The 31 women and 2 men with underweight (BMI <18.5 kg/m^2) were merged with the normal weight category.

Whole-body DXA scans (Lunar GE Prodigy Advance, GE Medical Systems) were performed according to the manufacturer guidelines, by trained technicians who inspected the postscan images and made relevant quality corrections to the regions of interest according to a standardized protocol. The DXA device was calibrated each morning with a phantom ahead of measurements. Total body fat in grams and percentage and android fat mass in grams were measured directly by DXA, and VATg and VATcm^3 were subsequently computed by the validated CoreScan software (EnCore version 17.0). VAT% was calculated as 100 * VATg divided by android fat mass (g), and subcutaneous fat mass was calculated as android fat mass (g) − VATg. VATindex was calculated as VAT kg/height (m)^2.

2.3. Statistical Analysis. We used STATA 16 (STATA Corp LP, College Station, Texas, USA) to perform all analyses. *P* values were considered significant at a 0.05 level. VATg and VATcm^3 were highly similar in all analyses; thus, we present only VATg to represent absolute value.

A total of 3675 participants (58.6% women) aged 40–84 years were included (Figure 1). We used descriptive statistics to present characteristics of the study population (Table 1). VAT measures with value of 0 ($n = 10$) were transformed into lowest value (2 g). To compare participants attending only basic examination with those additionally attending extended examinations, we used Student's *t*-test (Supplementary Table 1). We present sex specific means with standard deviations (SDs), confidence intervals (CIs), and percentiles (5th, 25th, 50th, 75th, and 95th) by 10-year age groups for VATg, VATindex, and VAT% (Supplementary Tables 2–4). To explore the association with VAT (g, index and %) and cardiometabolic risk factors, we used age-adjusted partial Pearson correlation coefficients (Table 2). To investigate the ability of VAT to predict MetS and single MetS components (hypertension, diabetes, elevated triglycerides, and low HDL cholesterol), we performed receiver operating characteristic (ROC) analyses with presentation of age-adjusted area-under-the-curves (AUCs) (Table 3). To further explore if any of the included units of VAT were better than the other in predicting MetS or single MetS components, we used both log likelihood test (Supplementary Table 5) and c-statistics (Supplementary Table 6). As VATg and VATindex were not normally distributed, they were transformed to square root, and z-scores were subsequently created for inclusion to the logistic regression models to study their associations with MetS or single MetS components. In addition, we stratified the analyses of the association between z-scores of VAT (all units) and the presence of MetS or single MetS components in categories of BMI (normal weight, overweight, and obese) (Table 4). Lastly, we used ROC analysis of VAT in prediction of MetS to derive sensitivity and specificity. Further, we applied Youden's index ((sensitivity + specificity)-1) [15] to present suggested threshold values of VAT based on estimated optimal cutoffs (all units) (Table 5) [16]. We used logistic regression analysis to present the odds for MetS for each of the presented threshold values of VAT (all units) (Table 5).

Normality distribution of VAT (g, index and %) was checked by visual inspection (Figure 2). VATg and VATindex were positively skewed. We explored how mean VAT (g, index and %) and mean subcutaneous fat change across age (Figure 3). To investigate percentiles (5th, 25th, 50th, 75th, and 95th) of VAT (g, index and %) over 10-year age groups, we performed line plots with separate lines for each percentile (Figure 4).

3. Results

The mean age was 66.2 (8.92) and 65.9 (9.13) years, and mean BMI was 26.8 (4.70) and 27.6 (3.72) kg/m^2, in women and men, respectively (Table 1). The mean age of the women and men attending only basic examinations was 55.1 (10.9) and 55.9 (11.1). Compared to the participants attending the basic examinations only (Supplementary Table 2), those attending the DXA scanning had lower body weight and height. There were no differences in BMI or waist circumference in women and a small difference in BMI in men (27.9 and 27.6 kg/m^2, $P = 0.007$).

3.1. VAT Reference Values. VAT (all measurement units) was higher in men than in women and increased up to age 70 in both genders (Supplementary Tables 2–4 and Figure 3). The exception was VAT%, which continued to increase after attained age of 70–79 in women, while the curve flattened at age 70–79 in men (Figure 3). Subcutaneous fat, however, decreased rapidly after age group 70–79 in women and decreased linearly with age in men, which explains why VAT % continued to increase after age group 70–79, while both VATg and VATindex decreased in women. The investigation of VAT (all measurement units) in percentiles (5th, 25th, 50th, 75th, and 95th) across age groups showed highly similar patterns for VATg and VATindex in both women and men (Figure 4). In women, the pattern of the 5th percentile (VATg and VATindex) was quite consistent across age, while the 25th, 50th, and 75th percentile increased until age group 70–79 before it then slightly decreased (Figure 4). The pattern for the 95th percentile (VATg and VATindex) was markedly higher and differed from the other percentiles. In

Table 1: Descriptive of study population attending dual energy X-ray absorptiometry: the Tromsø Study 2015–2016.

	Women ($n = 2152$)	Men ($n = 1523$)
Age (years (%) (n))	66.2 (8.92)	65.9 (9.13)
40–49	5.95 (128)	6.70 (102)
50–59	13.2 (284)	12.3 (187)
60–69	43.3 (932)	47.4 (722)
70–79	32.1 (691)	27.5 (418)
80+	5.44 (117)	6.17 (94)
Weight (kg)	71.3 (13.0)	86.0 (13.2)
Height (cm)	163.0 (6.25)	176.4 (6.70)
BMI (kg/m^2)	26.8 (4.70)	27.6 (3.72)
VAT (g), mean (SD)	936.7 (632.5)	1660.9 (876.6)
VAT (g), median (25p–75p)	832 (444–1302.5)	1578 (1004–2222)
VAT (index), mean (SD)	0.35 (0.24)	0.53 (0.28)
VAT (index), median (25p–75p)	0.32 (0.16–0.49)	0.51 (0.33–0.71)
VAT (%), mean (SD)	37.1 (13.6)	60.2 (14.2)
VAT (%), median (25p–75p)	37.8 (28.3–46.7)	61.2 (52.0–69.9)

Presented as proportion (n) or mean (SD). VAT (all measurement units) is also presented as median with 25–75th percentile. VAT index: VAT kg/height (m)^2.

Table 2: Age-adjusted correlation for the association of VATg, VATindex, and VAT% with cardiometabolic risk factors: the Tromsø Study 2015–2016.

Cardiometabolic factors	VATg	VATindex	VAT%
Women			
Systolic blood pressure (mmHg)	0.12*	0.13*	0.10*
Diastolic blood pressure (mmHg)	0.08*	0.08*	0.08*
Triglycerides (mmol/L)	0.44*	0.44*	0.38*
Total cholesterol (mmol/L)	−0.006	−0.006	0.01
HDL cholesterol (mmol/L)	−0.43*	−0.43*	−0.36*
HbA1c (%)	0.24*	0.24*	0.17*
CRP (mg/L)	0.14*	0.15*	0.09*
Hypertension	0.20*	0.20*	0.15*
Diabetes	0.23*	0.24*	0.16*
Elevated triglycerides	0.35*	0.35*	0.31*
Low HDL	0.28*	0.29*	0.24*
Metabolic syndrome	0.29*	0.30*	0.24*
Men			
Systolic blood pressure (mmHg)	0.11*	0.11*	0.10*
Diastolic blood pressure (mmHg)	0.13*	0.11*	0.12*
Triglycerides (mmol/L)	0.38*	0.37*	0.31*
Total cholesterol (mmol/L)	−0.02	−0.03	−0.02
HDL cholesterol (mmol/L)	−0.38*	−0.37*	−0.29*
HbA1c %	0.27*	0.29*	0.19*
CRP (mg/L)	0.08*	0.09*	0.03
Hypertension	0.25*	0.25*	0.21*
Diabetes	0.22*	0.24*	0.18*
Elevated triglycerides	0.34*	0.34*	0.28*
Low HDL	0.25*	0.26*	0.20*
Metabolic syndrome	0.30*	0.32*	0.23*

*$P < 0.001$.

addition, the 95th percentile (VATg and VATindex) in women increased rapidly from age group 40–49 to age group 50–59, remained unchanged until age group 70–79, and decreased thereafter (Figure 4). Percentiles of VAT% in women increased across all age groups, with a steeper increase from age group 40–49 to 50–59 (Figure 4).

In men, the pattern for VATg and VATindex 5th percentile was M-shaped across age groups (Figure 4). In the 25th and 50th percentiles, there was a small continuous increase by age up to age group 70–79, while in the 75th and 95th percentiles, VATg and VATindex decreased from age group 40–49 to 50–59, before it then increased up to age group 70–79 and decreased thereafter. All percentiles for VAT% increased over age groups in men, but the 75th and the 95th percentile decreased after age 70–79 (Figure 4).

3.2. VAT and Metabolic Factors. Age-adjusted partial correlation showed that VAT (all measurement units) was positively associated with all cardiometabolic risk factors,

Table 3: AUC from different age-adjusted models with VAT (g), VAT (%), or VAT (index) in prediction of metabolic syndrome and single metabolic components: the Tromsø Study 2015–2016.

Dependent variables	Women			Men		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Hypertension	0.77	0.77	0.77	0.73	0.72	0.73
Diabetes	0.72	0.70	0.72	0.75	0.73	0.76
Elevated triglycerides	0.73	0.71	0.73	0.71	0.67	0.71
Low HDL	0.69	0.67	0.69	0.70	0.68	0.70
Metabolic syndrome	0.73	0.71	0.73	0.75	0.73	0.76

Independent: Model 1: age and VATg, Model 2: age and VAT%, Model 3: age and VATindex. Numbers indicating AUC for the model.

Table 4: Age-adjusted OR for the association of metabolic syndrome and single metabolic components and standardized/z-scores of VAT mass in categories of body mass index (BMI): the Tromsø Study 2015–2016.

Metabolic factors	zVATg (sqrt)			zVATindex (kg/m^2(sqrt))			zVAT%		
	Normal weight	BMI overweight	Obese	Normal weight	BMI overweight	Obese	Normal weight	BMI overweight	Obese
Women									
Hypertension	1.38 (1.09–1.73)	1.70 (1.32–2.19)	1.30 (0.92–1.84)	1.42 (1.12–1.79)	1.75 (1.35–2.27)	1.34 (0.95–1.90)	1.17 (0.99–1.38)	1.45 (1.19–1.76)	1.23 (0.89–1.71)
Diabetes	1.54 (0.94–2.52)	2.24 (1.47–3.42)	3.68 (2.37–5.70)	1.73 (1.05–2.87)	2.42 (1.56–3.76)	3.60 (2.32–5.60)	1.60 (1.11–2.30)	1.98 (1.42–2.78)	2.10 (1.45–3.02)
Elevated triglycerides	2.37 (1.83–3.06)	2.89 (2.25–3.71)	2.37 (1.75–3.20)	2.50 (1.93–3.24)	3.02 (2.33–3.90)	2.46 (1.80–3.35)	1.64 (1.37–1.97)	2.18 (1.80–2.64)	2.12 (1.60–2.81)
Low HDL	1.94 (1.49–2.52)	2.10 (1.64–2.69)	2.18 (1.62–2.92)	2.05 (1.57–2.67)	2.22 (1.73–2.87)	2.19 (1.63–2.94)	1.55 (1.29–1.87)	1.80 (1.48–2.17)	1.82 (1.40–2.37)
Metabolic syndrome	1.91 (1.40–2.60)	2.30 (1.76–3.02)	2.86 (2.04–4.00)	2.06 (1.50–2.82)	2.46 (1.85–3.25)	2.91 (2.07–4.10)	1.55 (1.24–1.93)	1.91 (1.55–2.36)	2.22 (1.65–2.98)
Men									
Hypertension	1.65 (1.22–2.23)	1.97 (1.51–2.56)	1.34 (0.87–2.07)	1.69 (1.25–2.29)	2.09 (1.60–2.74)	1.29 (0.82–2.01)	1.26 (1.03–1.55)	1.64 (1.33–2.01)	1.33 (0.88–2.01)
Diabetes	1.87 (1.02–3.43)	2.99 (1.95–4.59)	2.48 (1.51–4.06)	1.88 (1.03–3.44)	3.51 (2.23–5.51)	2.97 (1.79–4.95)	1.60 (1.03–2.49)	2.50 (1.76–3.55)	1.73 (1.12–2.66)
Elevated triglycerides	1.93 (1.41–2.65)	2.66 (2.09–3.38)	1.73 (1.19–2.52)	1.99 (1.44–2.73)	2.88 (2.25–3.70)	1.71 (1.17–2.50)	1.50 (0.20–1.87)	1.90 (1.58–2.28)	1.25 (0.90–1.74)
Low HDL	1.60 (1.14–2.26)	2.19 (1.71–2.81)	1.47 (1.03–2.09)	1.62 (1.15–2.29)	2.35 (1.81–3.04)	1.59 (1.11–2.28)	1.41 (1.10–1.80)	1.63 (1.34–1.98)	1.30 (0.94–1.78)
Metabolic syndrome	2.13 (1.42–3.20)	2.78 (2.10–3.68)	2.06 (1.40–3.03)	2.18 (1.45–3.27)	3.10 (2.31–4.16)	2.18 (1.47–3.25)	1.63 (1.22–2.18)	1.92 (1.54–2.39)	1.39 (0.99–1.94)

Women: VATg SD: 632.5; VATindex SD: 0.24; VAT% SD: 13.6. Men: VATg SD: 876.6; VATindex SD: 0.28; VAT% SD: 14.2.

Table 5: Suggested threshold values of VAT derived from Youden's index and odds for metabolic syndrome: the Tromsø Study 2015–2016.

	Women			Men		
	Threshold	OR (95% CI)	Youden's index	Threshold	OR (95% CI)	Youden's index
VAT (g)	≥1134	3.63 (2.94–4.49)	0.297	≥1859	4.03 (3.17–5.13)	0.331
VAT (index)	≥0.44	4.04 (3.26–4.99)	0.321	≥0.55	4.02 (3.15–5.13)	0.336
VAT (%)	≥40.3	3.36 (2.72–4.15)	0.298	≥61.2	3.12 (2.44–3.97)	0.276

OR: odds ratio; CI: confidence interval.

except for HDL that was negatively associated with VAT, and total cholesterol that was not significantly associated (Table 2).

When comparing the ability of VATg, VATindex, and VAT% to predict MetS and single MetS components, all AUCs were high (≥0.67). AUCs of VATg and VATindex were consistently higher than AUCs of VAT% (Table 3). When comparing log likelihood/fit of age-adjusted regression models by adding different VAT measurement units to the model with MetS and single MetS components, VATg and VATindex were the most important predictors (Supplementary Table 5). C-statistics revealed no significant differences between predictions of single MetS components from the different VAT measurement units (Supplementary Table 6). In prediction of MetS, there were significant differences by adding both VAT% and VATindex to the model

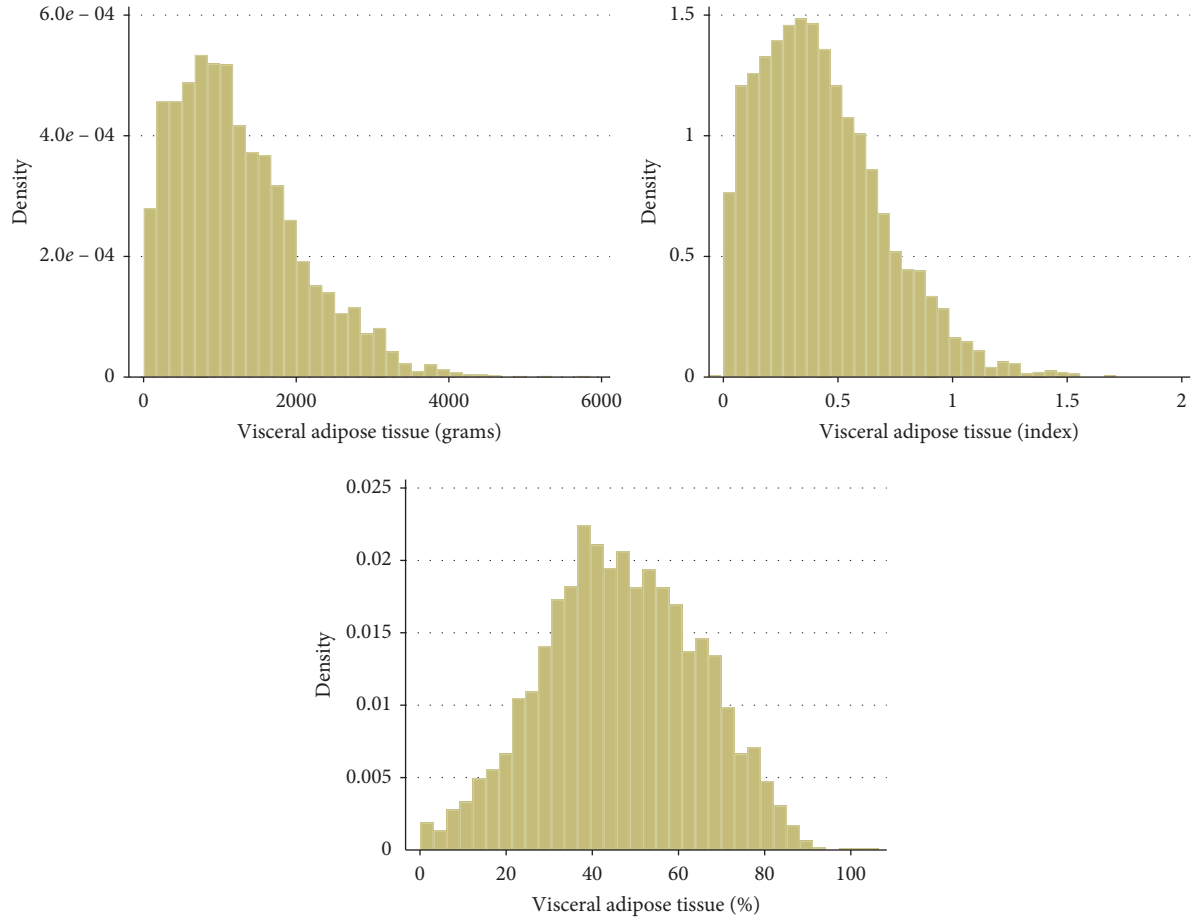

Figure 2: Normality curves of VAT (g), VAT (index), and VAT (%).

with VATg ($P \leq 0.04$ for both), but the AUCs were identical in women and only slightly different in men (Supplementary Table 6).

When investigating associations between z-score of VAT (all measurement units) and MetS and single MetS components in categories of BMI, the majority of associations showed significantly higher odds with increasing VAT. The pattern showed highest odds for elevated triglycerides with increasing VAT, in most categories of BMI in women, while the odds for diabetes were highest in most categories of BMI in men (Table 4). With regard to BMI differences, in women the highest odds for hypertension and elevated triglycerides in all z-score units of VAT were observed in the overweight category and the highest odds for diabetes, low HDL cholesterol, and MetS were observed in the obese category. The only exception was z-scores of VATindex in association with low HDL cholesterol which was highest in the overweight category (Table 4). In men, the highest odds for MetS and all MetS components were observed in the overweight category according to all z-score units of VAT (Table 4). The different z-score units of VAT and associations with MetS and MetS components were similar, although higher odds were observed in z-scores of VATg and VATindex compared to VAT%.

Based on Youden's index and the abilities to predict MetS, suggested thresholds of VATg, VATindex, and VAT% in women are ≥1134, ≥0.44, and ≥ 40.3, respectively, with corresponding odds for MetS of 3.63, 4.04, and 3.36, respectively. In men, suggested thresholds and odds for MetS were ≥1859 (OR: 4.03), ≥0.55 (OR: 4.02), and ≥61.2 (OR: 3.12), for VATg, VATindex, and VAT%, respectively (Table 5).

4. Discussion

Measures of VAT (expressed in absolute and derived variables) were positively associated with age, MetS, and single MetS components. VATg and VATindex consistently showed slightly stronger associations with MetS and single MetS components than VAT%, but overall, the associations were similar.

Because the distribution of fat, and especially VAT accumulation in abdominal area, rather than overall fat mass has been highlighted as the most robust predictor for cardiometabolic disease, it is valuable to determine reference values for VAT [17]. Relative measures (e.g., waist-to-height ratio) may be stronger predictors for disease than absolute measures (e.g., waist circumference) [18, 19], and it is therefore also relevant to assess whether relative measures of VAT are more strongly correlated with MetS and single MetS components than absolute measures.

We observed higher VATg in percentiles for both women and men as compared to other studies [9, 10]. Miazgowski et al. [9] included young adults only (30–40

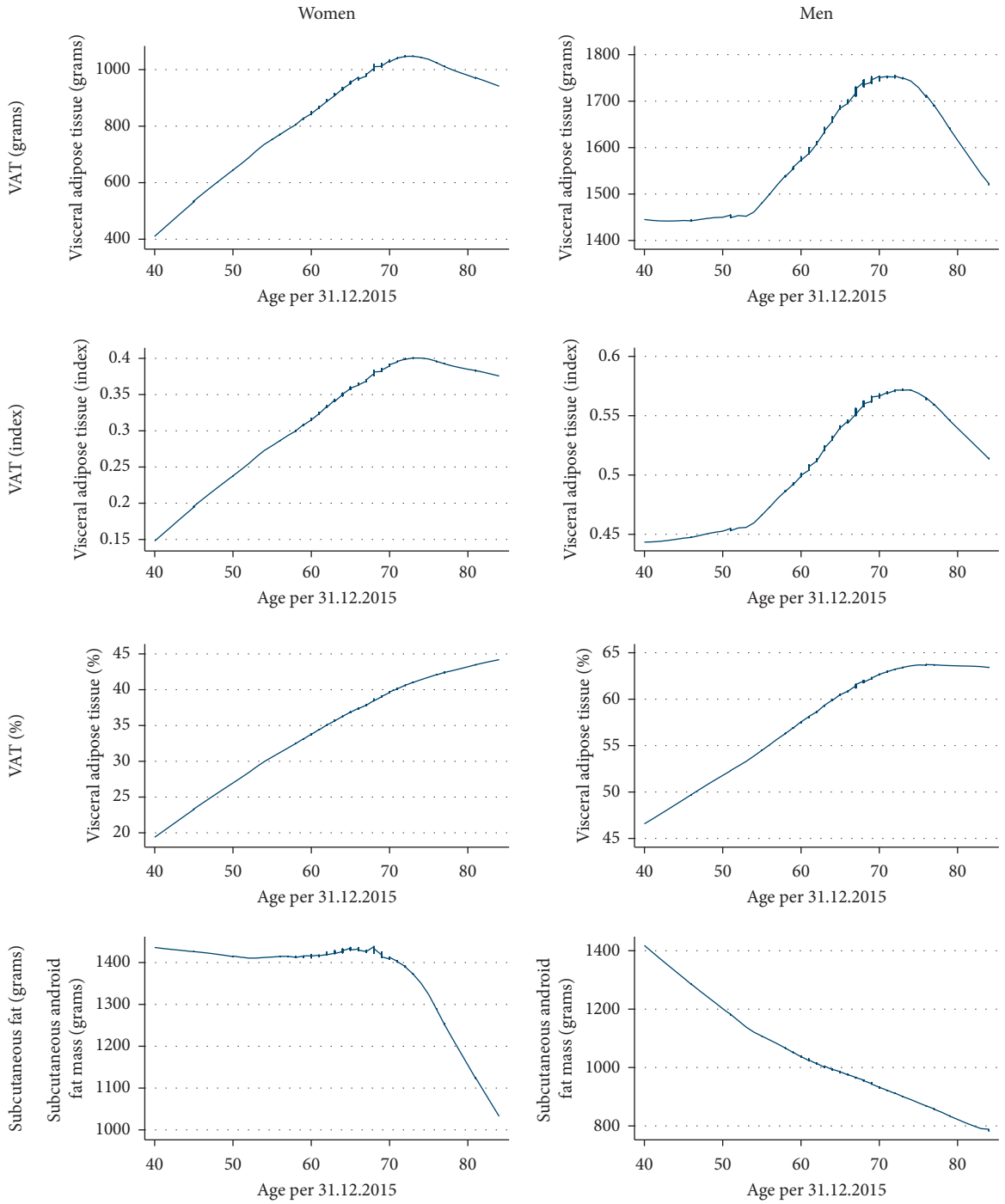

Figure 3: VAT (g, index, and %) and subcutaneous fat (g) in android region over age: the Tromsø Study 2015–2016.

years) and Hirsch et al. [10] used the next-generation DXA (iDXA), in addition to presenting different age groups than us (25–49 years and 50+ years), thus limiting direct comparison of results.

Our age-adjusted partial correlations were similar to those found by Rothney et al. [12], who used the iDXA system to study associations between VATg and cardiometabolic risk factors. Miazgowski et al. [9] found stronger correlations between VATg and cardiometabolic risk factors, than in our analysis, but the AUCs observed in the present study are higher. Miazgowski et al. [9] did, however, not adjust for age and presented cardiometabolic risk factors in different units than the present study; thus direct comparison is difficult.

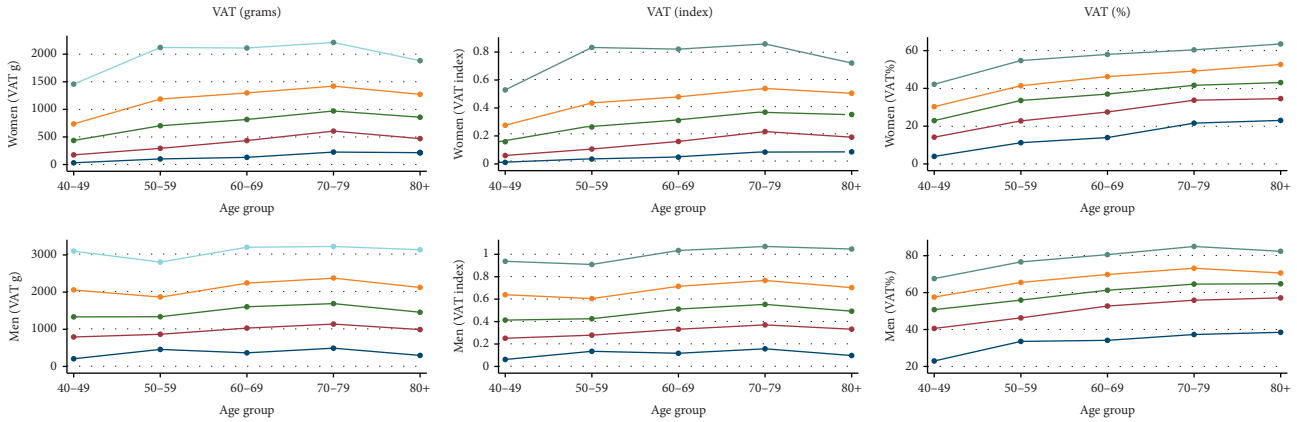

Figure 4: Quantities of VAT (g), VAT (index), and VAT (%) in 10-year age groups in women and men: the Tromsø Study 2015–2016.

VATg and VATindex decreased rapidly after the age of 70 years. A similar decrease in VAT after age 70 years was found in a study from the United States (using iDXA) [8], which suggested that this decrease could be explained by the small number of participants in the oldest population. This decreasing pattern after age 70 was, however, not confirmed by a larger population-based study ($n = 10\ 984$) from Ofenheimer et al. [7], conducted in Austria using the system Lunar Prodigy system. Among our participants, 1320 (61% women) were 70 years and older, and together with a high attendance among the older population in the Tromsø Study [20], we conclude that the decrease presented in this study cannot be explained by low participation. Although we did not have the opportunity to investigate potential anthropometric differences in nonattenders, we did compare the population only attending basic examinations, with those also attending extended examinations (DXA) and found no clinically or statistically significant differences in BMI or waist circumference. Previous studies investigating longitudinal change in BMI and waist circumference in the Tromsø Study population showed that adiposity increases with age, with a larger increase in the younger compared to the older birth cohorts [21–23]. One might hypothesize that central adiposity is less prevalent in the older than younger age groups in the present population. Body composition changes with age as total lean mass decreases, fat mass increases, and a greater proportion of fat accumulates within the abdomen as visceral fat [24]. This was reflected in the present study as VAT% (particularly in women) increased continuously, while VATg decreased after age 70. This observation is due to VATg decreasing relatively less than subcutaneous fat. A somewhat surprising finding was the steep decline in subcutaneous fat in women older than 70 years, compared to the linear decrease observed in men.

All cardiometabolic risk factors except total cholesterol showed statistically significant associations with VAT. Similar findings were observed in previous studies investigating the associations between DXA-derived VAT and cardiometabolic risk factors [9, 12, 25]. We could, however, find no other studies comparing how the different measurement units of VAT performed in their associations with MetS and single MetS components. Further, the threshold values were higher for men than women. Although one might expect absolute threshold values to be higher for men, it is quite interesting that the relative measures are also higher, indicating that men might tolerate a higher amount of VAT relative to body size before it becomes a risk for MetS.

To the best of our knowledge, this is the first study presenting reference values for VATindex and VAT% in addition to suggested threshold values for VAT (all units) in association with MetS. Therefore, the results presented are of importance to future studies utilizing DXA-derived VAT and may support clinicians, who use DXA in their daily routine, to make decisions on whether to initialize interventions for patients with abdominal obesity. Although previous studies have presented reference values for VAT in grams, it is highly important to complement previous proposed reference values and also to present reference values for measures that address VAT in relation to overall body size (VATindex and VAT%). It has long been known that VAT is of particular concern to cardiometabolic health, and tracking VAT as a representative for overweight and obesity is a more accurate indicator of the health status than traditional anthropometric measures such as BMI or waist circumference. The current study enables comparison with future studies aiming at presenting reference values and threshold values of VAT. We emphasize that the reference values and thresholds presented are applicable only to similar populations and measures from similar equipment as in the present study. Future studies are needed to confirm the thresholds suggested in our population.

4.1. Strengths and Limitations. A major strength of this study is the wide age range of participants, providing proposed VAT reference values in adults aged 40 and older. Further, we could investigate VAT's association with both MetS and single MetS components and propose threshold values for VAT (all units) based on sensitivity and specificity in prediction of MetS. Because of the population-based design, where fasting blood samples are unusual, we did not include fasting glucose as an indicator for diabetes, but rather self-reported diabetes, medication use, or HbA1c $\geq$ 6.5% which we believe incorporated both diagnosed and undiagnosed

diabetes. We did not have the opportunity to examine whether the study participants differed from nonattenders. We did however compare those attending only the basic examination of the survey to those included in this analysis and found no differences according to waist circumference or BMI, and together with the high attendance we conclude that our study is representative of the general population. It should be emphasized that the references derived here (from Lunar Prodigy in age group 40–84 in a Norwegian population) may not be directly comparable to reference values derived from other manufacturers, DXA equipment, age groups, or populations/ethnicities, but to similar populations and methods used in the current study.

5. Conclusions

DXA-derived VATg and VATindex increased with age up to 70 years, while VAT% increased continuously with age. The percentiles presented (5^{th}, 12^{th}, 50^{th}, 75^{th}, and 95^{th}) and suggested thresholds of VATg, VATindex, and VAT% can be used for comparison with studies of similar populations using the same technology. All VAT measurement units except total cholesterol showed statistically significant associations with cardiometabolic risk factors. Results did not substantially differ between measurements units of VAT; thus, any measurement unit seems acceptable to use.

Data Availability

No data are publicly available but may be obtained from a third party. The dataset supporting the article findings is available through application directed to the Tromsø Study by following the steps presented on their online page: https://en.uit.no/forskning/forskningsgrupper/sub?p_document_id=453582&sub_id=71247.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary Table 1: comparison of women and men attending basic examinations and extended examinations in Tromsø 7 (2015–2016). Supplementary Table 2: sex-specific percentiles of VATg by 10-year age groups. Supplementary Table 3: sex-specific percentiles of VATindex by 10-year age groups. Supplementary Table 4: sex-specific percentiles of VAT % by 10-year age groups. Supplementary Table 5: comparison of fit of models (log-likelihood test) by adding VAT % and VATindex to the model with VAT g: the Tromsø Study 2015–2016. Cont. Supplementary Table 5: comparison of fit of models (log-likelihood test) when adding VATg and VATindex to the model with VAT%: the Tromsø Study 2015–2016. Cont. Supplementary Table 5: comparison of fit of models (log-likelihood test) when adding VATg and VAT % to the model with VATindex: the Tromsø Study 2015–2016. Supplementary Table 6: comparison of age-adjusted c-statistics in different models in women: the Tromsø Study 2015–2016. Cont. Supplementary Table 6: comparison of age-adjusted c-statistics in different models in men: the Tromsø Study 2015–2016. (*Supplementary Materials*)

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Supplementary table 1: Comparison of women and men attending basic examinations and extended examinations in Tromsø 7: 2015-2016

	Women			**Men**		
	Basic	**Extended**	**P-value**	**Basic**	**Extended**	**P-value**
N	8922	2152		8486	1523	
Age (yr (SD))	55.1 (10.9)	66.2 (8.92)	<0.001	55.9 (11.1)	65.9 (9.13)	<0.001
Weight (kg)	72.9 (14.1)	71.3 (13.0)	<0.001	88.4 (14.3)	86.0 (13.2)	<0.001
Height (cm)	164.6 (6.55)	163.0 (6.25)	<0.001	178.0 (6.76)	176.4 (6.70)	<0.001
BMI (kg/m^2)	26.9 (5.00)	26.8 (4.70)	0.49	27.9 (4.05)	27.6 (3.71)	0.007
Waist (cm)	90.7 (13.0)	91.2 (12.4)	0.12	100.2 (12.4)	100.5 (10.5)	0.32

*BMI; Body mass index

Supplementary table 2: Sex specific percentiles of VAT (g) by 10-year age groups

	Mean (SD)	**95% CI's**	**5^{th}**	**25^{th}**	**50^{th}**	**75^{th}**	**95^{th}**
Women	937 (633)	910 – 963	129	444	832	1303	2094
40-49	515 (435)	439 – 591	36	182	437	735	1455
50-59	832 (651)	756 – 908	102	294	703	1184	2044
60-69	935 (636)	894 – 976	131	435	817	1297	2104
70-79	1063 (625)	1016 -1110	227	606	971	1421	2212
80+	920 (542)	820 – 1019	220	477	858	1267	1876
Men	1661 (877)	1617 – 1705	396	1004	1578	2222	3158
40-49	1471 (919)	1291 – 1652	215	794	1335	2060	3085
50-59	1448 (744)	1341 - 1556	464	866	1338	1871	2752
60-69	1687 (891)	1622 – 1753	370	1033	1607	2246	3207
70-79	1777 (886)	1692 – 1862	492	1141	1692	2380	3226
80+	1568 (823)	1400 - 1737	302	995	1459	2128	3118

Supplementary table 3: Sex specific percentiles of VAT index by 10-year age groups

	Mean (SD)	95% CI's	5th	25th	50th	75th	95th
Women	0.35 (0.24)	0.34 – 0.36	0.05	0.16	0.32	0.49	0.80
40-49	0.19 (0.16)	0.16 – 0.21	0.01	0.06	0.16	0.27	0.49
50-59	0.31 (0.24)	0.28 – 0.34	0.03	0.11	0.26	0.43	0.80
60-69	0.35 (0.24)	0.34 – 0.37	0.05	0.16	0.31	0.48	0.82
70-79	0.41 (0.24)	0.39 – 0.42	0.09	0.23	0.37	0.54	0.85
80+	0.36 (0.21)	0.33 – 0.40	0.09	0.19	0.35	0.51	0.72
Men	0.53 (0.28)	0.52 – 0.55	0.12	0.33	0.51	0.71	1.02
40-49	0.45 (0.28)	0.40 – 0.51	0.07	0.25	0.41	0.64	0.93
50-59	0.46 (0.24)	0.43 – 0.49	0.14	0.28	0.43	0.61	0.88
60-69	0.54 (0.28)	0.52 – 0.56	0.12	0.33	0.51	0.71	1.02
70-79	0.58 (0.29)	0.55 – 0.61	0.16	0.37	0.55	0.77	1.07
80+	0.52 (0.27)	0.47 – 0.58	0.10	0.34	0.49	0.70	1.05

Supplementary table 4: Sex specific percentiles of VAT % by 10-year age groups

	Mean (SD)	95% CI's	5th	25th	50th	75th	95th
Women	37.1 (13.6)	36.5 - 37.7	13.0	28.3	37.8	46.7	58.8
40-49	22.7 (11.1)	20.8 - 24.7	4.35	14.2	22.9	30.2	41.6
50-59	32.7 (13.2)	31.1 - 34.2	11.4	22.9	33.6	41.4	54.6
60-69	36.5 (13.5)	35.6 - 37.4	14.0	27.5	37.0	46.2	57.9
70-79	41.3 (11.8)	40.5 - 42.2	21.6	33.7	41.6	49.2	60.4
80+	43.1 (12.8)	40.7 - 45.4	23.2	34.6	43.1	52.7	63.5
Men	60.2 (14.2)	59.4 - 60.9	34.3	52.0	61.2	69.9	80.9
40-49	48.7 (14.3)	45.9 - 51.5	24.2	40.6	50.8	57.5	67.6
50-59	55.5 (13.0)	53.6 - 57.4	33.6	46.3	55.9	65.5	76.0
60-69	60.5 (13.7)	59.5 - 61.4	34.4	52.7	61.3	69.8	80.3
70-79	63.9 (14.0)	62.5 - 65.2	37.3	55.9	64.6	73.2	85.0
80+	63.0 (13.2)	60.3 - 65.7	39.3	57.4	64.8	70.6	82.4

Supplementary table 5: Comparison of fit of models (log likelihood test) by adding VAT % and VATindex to the model with VATg: the Tromsø Study 2015-2016

Dependent variables	Women		Men	
	P-value (M1 vs. M2)	P-value (M2 vs. M3)	P-value (M1 vs. M2)	P-value (M2 vs. M3)
Hypertension	0.90	0.03	0.22	0.20
Diabetes	0.37	0.14	0.009	0.001
Elevated triglycerides	<0.001	0.04	0.08	0.06
Low HDL	0.006	0.07	0.12	0.01
Metabolic syndrome	0.006	0.02	0.11	0.008

Independent: Model 1: age and VATg, Model 2: age, VATg and VAT%, Model 3: age, VATg, VAT% and VATindex
*p-value indicating whether adding variables significantly improve the fit of the model.

Cont. Supplementary table 5: Comparison of fit of models (log likelihood test) when adding VATg and VATindex to the model with VAT%: the Tromsø Study 2015-2016

Dependent variables	Women		Men	
	P-value (M1 vs. M2)	P-value (M2 vs. M3)	P-value (M1 vs. M2)	P-value (M2 vs. M3)
Hypertension	<0.001	0.03	<0.001	0.20
Diabetes	<0.001	0.14	<0.001	0.001
Elevated triglycerides	<0.001	0.04	<0.001	0.06
Low HDL	<0.001	0.71	<0.001	0.01
Metabolic syndrome	<0.001	0.02	<0.001	0.008

Independent: Model 1: age and VAT%, Model 2: age, VAT% and VATg, Model 3: age, VAT%, VATg and VATindex
*p-value indicating whether adding variables significantly improve the fit of the model.

Cont. Supplementary table 5: Comparison of fit of models (log likelihood test) when adding VATg and VAT% to the model with VATindex: the Tromsø Study 2015-2016

Dependent variables	Women		Men	
	P-value (M1 vs. M2)	P-value (M2 vs. M3)	P-value (M1 vs. M2)	P-value (M2 vs. M3)
Hypertension	0.30	0.69	0.98	0.35
Diabetes	0.99	0.42	0.04	0.05
Elevated triglycerides	0.81	0.002	0.97	0.19
Low HDL	0.76	0.01	0.26	0.30
Metabolic syndrome	0.46	0.01	0.41	0.31

Independent: Model 1: age and VATindex, Model 2: age, VATindex and VATg, Model 3: age, VATindex, VATg and VAT%
*p-value indicating whether adding variables significantly improve the fit of the model.

Supplementary table 6: Comparison of age adjusted c-statistics in different models in women: The Tromsø Study 2015-2016

Dependent variables	Women					
	AUC (M1)	AUC (M2)	AUC (M3)	P-value (M1 vs. M2)	P-value (M1 vs. M3)	P-value (M2 vs. M3)
Hypertension	0.77	0.77	0.78	0.80	0.12	0.12
Diabetes	0.72	0.72	0.73	0.11	0.06	0.20
Elevated triglycerides	0.73	0.73	0.73	0.68	0.22	0.08
Low HDL	0.69	0.69	0.70	0.49	0.13	0.07
Metabolic syndrome	0.73	0.73	0.73	0.25	0.02	0.02

Independent: Model 1: age and VATg, Model 2: age, VATg and VAT%, Model 3: age, VATg, VAT% and VATindex
*Numbers indicating AUC for the model, p value presents whether there is a significant AUC difference between the models

Cont. supplementary table 6: Comparison of age adjusted c-statistics in different models in men: The Tromsø Study 2015-2016

Dependent variables	Men					
	AUC (M1)	AUC (M2)	AUC (M3)	P-value (M1 vs. M2)	P-value (M1 vs. M3)	P-value (M2 vs. M3)
Hypertension	0.73	0.73	0.73	0.50	0.17	0.23
Diabetes	0.75	0.76	0.77	0.37	0.10	0.18
Elevated triglycerides	0.71	0.71	0.71	0.86	0.23	0.07
Low HDL	0.70	0.70	0.71	0.32	0.02	0.03
Metabolic syndrome	0.75	0.75	0.76	0.31	0.02	0.04

Independent: Model 1: age and VATg, Model 2: age, VATg and VAT%, Model 3: age, VATg, VAT% and VATindex
*Numbers indicating AUC for the model, p value presents whether there is a significant AUC difference between the models

Paper II

Lundblad, M. W., Jacobsen, B. K., Johansson, J., Grimsgaard, S., Andersen, L. F., & Hopstock, L. A.

Anthropometric measures are satisfactory substitutes for the DXA-derived visceral adipose tissue in the association with cardiometabolic risk. The Tromsø Study 2015–2016.

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ORIGINAL ARTICLE

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Anthropometric measures are satisfactory substitutes for the DXA-derived visceral adipose tissue in the association with cardiometabolic risk—The Tromsø Study 2015–2016

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Abstract

Background: Body mass index (BMI) increases while cardiometabolic risk factors decrease in individuals in high-income countries. This paradoxical observation raises the question of whether current measures of overweight and obesity properly identify cardiometabolic risk.

Methods: A total of 3675 participants (59% women) aged 40–84 years with whole-body dual-energy x-ray absorptiometry scans from the seventh survey of the Tromsø Study were included to examine the association between visceral adipose tissue (VAT) in grams and BMI, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). Further, their association with single cardiometabolic risk factors (blood pressure, triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, glycated hemoglobin, high-sensitivity C-reactive protein), modified single components from the ATP III criteria for metabolic syndrome (hypertension, diabetes, high triglycerides, and low HDL cholesterol), and metabolic syndrome were examined.

Results: VAT mass was strongly correlated with BMI ($r \geq 0.77$), WC ($r \geq 0.80$), WHR ($r \geq 0.58$), and WHtR ($r \geq 0.78$). WC was the strongest predictor for VAT (area under the curve: 0.90). Compared to anthropometric measures, the associations between VAT and metabolic syndrome as well as single components of metabolic syndrome were statistically significantly stronger, but the clinical differences were likely minor.

Conclusion: Although VAT mass showed statistically stronger associations with cardiometabolic risk compared to traditional anthropometrics, the clinical importance was likely small. Simple, clinically available tools seem to satisfactory substitute for VAT to identify cardiometabolic risk.

KEYWORDS
cardiometabolic health, dual energy x-ray absorptiometry, obesity, overweight, population studies, visceral adipose tissue

1 | INTRODUCTION

The global obesity prevalence has tripled in the last 4 decades, and more than 2.8 million deaths per year can be attributed to overweight and obesity.[1] Simultaneously, in high-income countries, there has been a decline in other cardiometabolic risk factors including total cholesterol[2] and blood pressure,[3] and in the overall burden of cardiovascular disease.[4–6] This paradox questions whether the current definition of overweight and obesity properly identifies cardiometabolic risk.

Traditionally, overweight and obesity are categorized by simple clinically available anthropometric measures including body mass index (BMI) or waist circumference (WC). The relevance of BMI has been questioned,[7,8] and WC has its limitations related to measurement error, that is, correct placement of measurement tape. Other measures, hypothesized to be more accurate in defining obesity compared to BMI and WC, are waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR).[9,10] However, none of these measures distinguish fat mass from fat-free mass, thus do not directly address the definition of overweight and obesity as "abnormal or excessive fat accumulation that may impair health."[1]

Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the most accurate assessment tools of body composition; however, they are resource demanding.[11] Visceral adipose tissue (VAT) from dual-energy x-ray absorptiometry (DXA) is highly correlated with the corresponding measures from MRI and CT.[12,13] VAT, located intra-abdominally and around the organs, is more metabolically active than subcutaneous fat and is linked to insulin resistance, metabolic syndrome, cardiovascular disease, and several types of cancer.[14] Therefore, the current study hypothesized that DXA-derived VAT might be a clinically more important marker than anthropometric measures when investigating the association between body composition and cardiometabolic disease risk. How DXA-derived VAT performs against anthropometric measures in the association with cardiometabolic risk factors is currently unknown, as the most previous studies investigating such differences used other measurement methods to derive VAT.[15–20]

The aim of this study was to investigate whether DXA-derived VAT is more strongly associated with cardiometabolic risk than traditional anthropometric measures, using a large population-based sample of middle-aged and older adults.

2 | MATERIAL AND METHODS

2.1 | Sample

The Tromsø Study[21] is an ongoing population-based study consisting of seven surveys (Tromsø 1–7) conducted from 1974 to 2016, inviting large representative samples of the population in the Tromsø municipality in Norway. In the seventh survey (2015–2016), all inhabitants, 40 years and older, were invited (n = 32,591). A selected sub-sample (n = 13,028) was invited to extended examinations about 2 weeks after attending the basic examination. This sub-sample included a randomized sample (n = 9925) in addition to participants previously attending DXA, echocardiogram, and eye examinations in Tromsø 6 (2007–2008) (n = 3103). A total of 21,083 (65%) participants aged 40–99 years attended the basic examination, and 8346 attended the extended examinations (of those attending extended examinations, this equaled 64% of the initially selected sub-sample). Among those attending basic examinations, 5232 participants were invited to DXA scans and 3683 (70%) attended whole-body DXA scans. Eight participants were excluded because of incorrect placement in the DXA machine, resulting in the CoreScan application being unable to calculate VAT in the abdominal area. Therefore, 3675 participants with VAT measures were included in the analysis (Figure 1).

This project was approved by the Regional Committee for Medical Research Ethics (REC North ref. 2017/1967), and all participants gave written informed consent.

2.2 | Cardiometabolic risk factors and metabolic syndrome components

Information about self-reported diabetes, use of antidiabetics (insulin or tablets), lipid-lowering drugs, and antihypertensives from self-administered questionnaires was included. Trained technicians performed all examinations using standard protocols. Non-fasting blood samples were analyzed at the Department of Laboratory Medicine at the University Hospital of North Norway (ISO certification NS-EN ISO 15189:2012) for total cholesterol (mmol/L), high-density lipoprotein (HDL) cholesterol (mmol/L), triglycerides (mmol/L), high-sensitivity C-reactive protein (hs-CRP, mg/L), and glycated hemoglobin (HbA1c, %). Systolic and diastolic blood pressures were measured three times with 2-min intervals with a Dinamap ProCare 300 monitor (GE Healthcare), and the mean of the two last readings was used in the analyses. Single cardiometabolic risk factors (WC and fasting glucose excluded) were defined based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diagnostic components for the metabolic syndrome (2005 revision)[22]: hypertension (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg and/or use of antihypertensives) (n: 2498 [57% women]), high non-fasting triglycerides (triglycerides ≥1.7 mmol/L and/or use of lipid-lowering drugs) (n: 1659 [52% women]), low HDL cholesterol (HDL cholesterol <1.3 [women] or <1.0 [men] mmol/L and/or use of lipid-lowering drugs) (n: 1164 [57% women]), and diabetes (self-reported diabetes and/or HbA1c ≥ 6.5% and/or use of antidiabetics) (n: 311 [54% women]). Metabolic syndrome (MetS) was defined as the presence of three or more of the metabolic syndrome components presented above, as defined by NCEP ATP III (n: 493 [24%] women and 406 [28%] men). Waist circumference was excluded from the definition of MetS because it was included in the study for comparison to VAT.

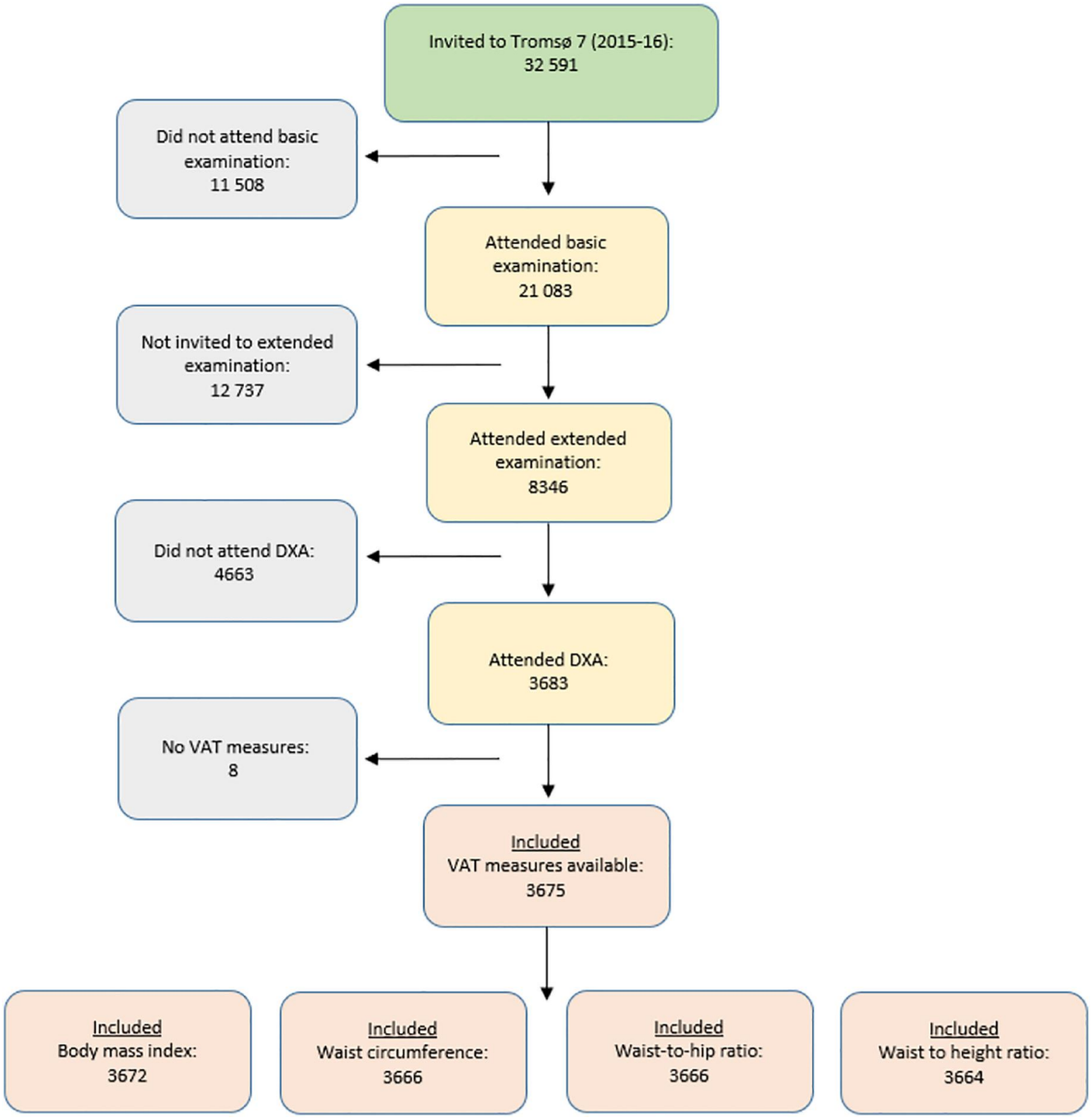

FIGURE 1 Inclusion of study participants: The Tromsø Study 2015–2016. DXA, dual-energy x-ray absorptiometry; VAT, visceral adipose tissue

2.3 | Measures of adiposity

Body weight and height were measured with light clothing and no shoes to the nearest 0.1 kg and nearest 0.1 cm, respectively, using a Jenix DS-102 height and weight scale (DongSahn Jenix). BMI was calculated as weight divided by height squared (kg/m^2). WC and hip circumference were measured to the nearest 0.1 cm with a Seca measurement tape at the level of the umbilicus and the greater trochanters, respectively. BMI, WC, WHR (WC divided by hip circumference, cm/cm), and WHtR (WC divided by height, cm/cm) were included as continuous variables for association with VAT.

Whole-body DXA scans were performed with a Lunar Prodigy Advance (GE Healthcare) according to guidelines from the manufacturer, and trained technicians inspected the post-scan images. The DXA device was calibrated each morning with a phantom before starting measurements. The CoreScan application (EnCore version 17.0) was used to compute VAT from DXA scans, and VAT in grams (g) and volume (cm^3) were included. Both VAT volume and VATindex (VAT [g] divided by height squared [g/m^2]) were highly correlated (*r*: 1.00 and 0.99, respectively) with VAT mass (g). Therefore, only VAT mass was included for further analyses in the present study.

2.4 | Statistical analyses

The software of the DXA machine is not sensitive enough to detect extremely low VAT values. Thus, we chose to transform VAT mass

with values of 0 (n = 10) into the lowest value (2 g) measured in the overall sample. Descriptive analyses, Student's t-test for comparison of means, and Wilcoxon rank-sum test for comparison of median were used to present the study population characteristics (Table 1). To display the correlation between VAT and anthropometric measures, Pearson's correlation coefficients (r) in 10-year age groups were presented (Table 2). Age-adjusted partial correlations were used to investigate correlations between VAT, anthropometric measures, and cardiometabolic risk factors (Table 3). Although the cross-sectional design of this study makes it difficult to establish causal pathways, receiver operating characteristics (ROC) analyses were performed to investigate the ability of VAT and anthropometric measures to predict MetS and single metabolic syndrome components (Figure 2). Area under the curves (AUCs) with confidence intervals (CIs) are presented. In addition, c-statistics was applied to compare the age-adjusted AUCs between VAT mass and the anthropometric variables in predicting MetS and single metabolic syndrome components (Table 4). Finally, to investigate which of the anthropometric measures that best predict VAT, VAT was dichotomized in two groups (at median), and the results from ROC analysis of VAT in relation to BMI, WC, WHR, and WHtR are presented (Figure 3). All analyses were performed separately in women and men. STATA 14 (STATA Corp LP) was used for all analyses.

3 | RESULTS

Of the 3675 participants with whole-body DXA scans, 3672, 3666, and 3664 also had valid BMI, WC/WHR, and WHtR measures, respectively (Figure 1). Mean age was similar in women and men (66.2 and 65.9 years, respectively). Men had higher mean values of VAT and anthropometric measures than women (Table 1). Mean values of BMI were in the overweight bracket for both women and men, and according to mean values of WC, women were at very high risk and men at high risk for cardiometabolic disease (Table 1). In women. 66% had hypertension, 8% diabetes, 41% high triglycerides,

TABLE 1 Descriptive of study population attending part 2: The Tromsø Study 2015–2016

	Women (n = 2152)	Men (n = 1523)	p-value
Age (years)	66.2 (8.92)	65.9 (9.13)	0.35
40–49	5.95 (128)	6.70 (102)	0.54
50–59	13.2 (284)	12.3 (187)	0.55
60–69	43.3 (932)	47.4 (722)	0.46
70–79	32.1 (691)	27.5 (418)	0.21
80+	5.44 (117)	6.17 (94)	0.36
Weight (kg)	71.3 (13.0)	86.0 (13.2)	<0.001
Height (cm)	163.0 (6.25)	176.4 (6.70)	<0.001
BMI (kg/m^2)	26.8 (4.70)	27.6 (3.72)	<0.001
Waist (cm)	91.2 (12.4)	100.5 (10.5)	<0.001
WHR (cm/cm)	0.88 (0.08)	0.97 (0.07)	<0.001
WHtR (cm/cm)	0.56 (0.08)	0.57 (0.06)	<0.001
VAT (g)—mean (SD)	936.7 (632.5)	1660.9 (876.6)	<0.001
VAT (g)—median (25p–75p)	832 (444–1302.5)	1578 (1004–2222)	<0.001
Hypertension (%[N])	66.2 (1415)	71.7 (1083)	<0.001
Diabetes (%[N])	8.05 (168)	9.67 (143)	0.09
High triglycerides (%[N])	41.1 (864)	53.1 (795)	<0.001
Low HDL cholesterol (%[N])	31.7 (666)	33.5 (498)	0.97
Metabolic syndrome (%[N])	24.0 (493)	27.8 (406)	0.01

Notes: Presented as proportion (n) or mean (SD). VAT mass is also presented as median with 25-75% percentile. Student's t-test was used to compare means and Wilcoxon rank-sum was used to compare medians. Chi-square test was used to compare proportions.

Among participants categorized as having low HDL (666 women and 498 men), 395 (59%) women and 351 (71%) was due to use of lipid-lowering medication, not low HDL levels <1.3 (women) or <1.0 (men).

There are minor differences in number of participants according to different variables included.

Abbreviations: BMI, body mass index; VAT, visceral adipose tissue; SD, standard deviation; p, percentile; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

32% low HDL cholesterol, and 24% had MetS. In men, 72% had hypertension, 10% diabetes, 53% high triglycerides, 34% low HDL cholesterol, and 28% had MetS (Table 1).

TABLE 2 Pearson's correlation coefficients of VAT with anthropometrics in 10-year age groups: The Tromsø Study 2015-2016

	BMI (kg/m^2)	WC (cm)	WHR (cm/cm)	WHtR (cm/cm)
Women	0.77	0.80	0.58	0.78
40–49	0.75	0.80	0.61	0.77
50–59	0.83	0.84	0.64	0.83
60–69	0.76	0.80	0.58	0.78
70–79	0.77	0.79	0.53	0.76
80+	0.70	0.69	0.43	0.60
Men	0.78	0.82	0.69	0.79
40–49	0.87	0.88	0.64	0.85
50–59	0.74	0.79	0.70	0.77
60–69	0.81	0.84	0.72	0.79
70–79	0.78	0.79	0.64	0.76
80+	0.73	0.81	0.63	0.76

Note: All associations were significant with p-value <0.001.

Abbreviations: BMI, body mass index; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

3.1 | Correlations between VAT mass and anthropometric variables

Table 2 shows that the age-specific correlations between VAT and the anthropometrics were all relatively high, although somewhat lower in women than in men, and lower in older adults. The strongest age-specific correlations in both women and men were observed between VAT and WC (r: 0.69–0.84 and 0.79–0.88 in women and men, respectively) and the weakest correlation between VAT and WHR (r: 0.43–0.64 and r: 0.63–0.72 in women and men, respectively) (Table 2).

3.2 | Associations with cardiometabolic risk, single metabolic syndrome components, and MetS

VAT and anthropometrics were consistently associated with all cardiometabolic risk factors (Table 3), except for total cholesterol. However, the correlations were low ($r < 0.3$) for most associations except for HDL cholesterol and triglycerides that were moderately correlated (both r: ≥0.3) to VAT and the anthropometric measures.

Based on the ROC analyses (Figure 2), VAT was not superior to the anthropometric variables in predicting hypertension or diabetes in women nor men, nor low HDL cholesterol in men. VAT was a stronger predictor for high triglycerides than BMI (AUC 95% CI: 0.72 [0.70–0.75] vs. 0.65 [0.63–0.67] in women, and 0.71 [0.68–0.73] vs. 0.65 [0.63–0.68]) in men). Also, VAT was a stronger predictor than BMI for low HDL cholesterol in women (AUC 95% CI: 0.68

TABLE 3 Partial* correlations between VAT, BMI, WC, WHR, WHtR, and cardiometabolic risk factors. The Tromsø Study 2015–2016

Women	VAT (g)	BMI (kg/m^2)	WC (cm)	WHR (cm/cm)	WHtR (cm/cm)
Systolic blood pressure (mmHg)	0.12	0.15	0.15	0.12	0.16
Diastolic blood pressure (mmHg)	0.08	0.07	0.09	0.08	0.08
Triglycerides (mmol/L)	0.44	0.33	0.37	0.33	0.29
Total cholesterol (mmol/L)	−0.006	−0.01	−0.02	0.006	−0.02
HDL cholesterol (mmol/L)	−0.43	−0.36	−0.37	−0.29	−0.39
HbA1c (%)	0.24	0.16	0.19	0.17	0.20
hs-CRP (mg/L)	0.14	0.16	0.14	0.09	0.16
Men	**VAT (g)**	**BMI (kg/m^2)**	**WC (cm)**	**WHR (cm/cm)**	**WHtR (cm/cm)**
Systolic blood pressure (mmHg)	0.11	0.09	0.10	0.08	0.10
Diastolic blood pressure (mmHg)	0.13	0.10	0.12	0.10	0.09
Triglycerides (mmol/L)	0.38	0.30	0.31	0.31	0.27
Total cholesterol (mmol/L)	−0.02	−0.009	−0.009	−0.02	−0.004
HDL cholesterol (mmol/L)	−0.38	−0.34	−0.36	−0.31	−0.34
HbA1c (%)	0.27	0.23	0.23	0.24	0.26
hs-CRP (mg/L)	0.08	0.08	0.10	0.12	0.10

Note: All correlations, were significant <0.001, except for total cholesterol (p-value: 0.41–0.80 and 0.33–0.88 in women and men, respectively).

Abbreviations: BMI, body mass index (kg/m^2); HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; mmol, millimole; mmHg, millimeters of mercury; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

*Age-adjusted.

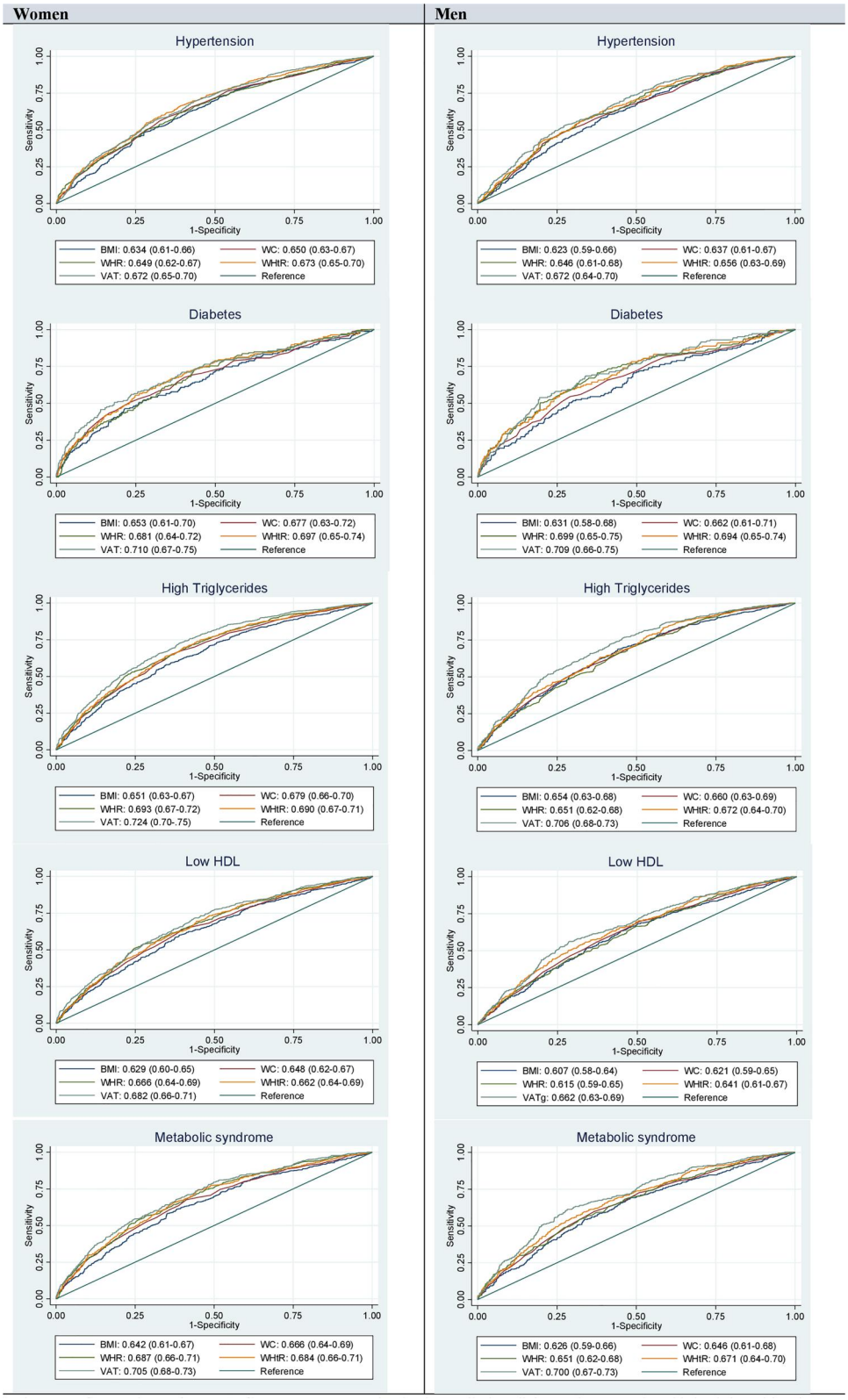

FIGURE 2 Comparison of BMI, WC, WHR, WHtR, and VAT in predicting diabetes, hypertension, high triglycerides, and low HDL cholesterol: The Tromsø Study 2015–2016. BMI, body mass index; HDL, high-density lipoprotein; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

TABLE 4 AUC in women and men in different age adjusted models and c-statistics comparison between models with VAT and models with anthropometric measures. The Tromsø Study 2015–2016

	Model 1 VAT (g)	Model 2 BMI (kg/m^2)	P	Model 3 WC (cm)	P	Model 4 WHR (cm/cm)	P	Model 5 WHtR (cm/cm)	P
Women									
Hypertension	0.774 (0.75–0.79)	0.775 (0.75–0.80)	0.72	0.778 (0.76–0.80)	0.29	0.777 (0.75–0.79)	0.57	0.782 (0.76–0.80)	0.07
Diabetes	0.722 (0.68–0.76)	0.681 (0.64–0.72)	0.001	0.700 (0.66–0.74)	0.04	0.703 (0.66–0.74)	0.20	0.711 (0.68–0.76)	0.37
High triglycerides	0.729 (0.71–0.75)	0.673 (0.65–0.70)	<0.001	0.695 (0.67–0.72)	<0.001	0.706 (0.68–0.73)	0.006	0.700 (0.68–0.72)	<0.001
Low HDL	0.691 (0.67–0.71)	0.655 (0.63–0.68)	<0.001	0.667 (0.64–0.69)	<0.001	0.679 (0.65–0.70)	0.17	0.674 (0.65–0.70)	0.02
Metabolic syndrome	0.728 (0.70–0.75)	0.693 (0.67–0.72)	<0.001	0.706 (0.68–0.73)	<0.001	0.721 (0.70–0.75)	0.37	0.715 (0.69–0.74)	0.05
Men									
Hypertension	0.732 (0.70–0.76)	0.718 (0.69–0.75)	0.04	0.714 (0.68–0.74)	0.005	0.713 (0.68–0.74)	0.01	0.719 (0.69–0.75)	0.05
Diabetes	0.752 (0.71–0.79)	0.717 (0.67–0.76)	0.002	0.726 (0.68–0.77)	0.01	0.750 (0.71–0.79)	0.90	0.741 (0.70–0.78)	0.32
High triglycerides	0.707 (0.68–0.73)	0.663 (0.64–0.69)	<0.001	0.663 (0.64–0.69)	<0.001	0.653 (0.63–0.68)	<0.001	0.673 (0.65–0.70)	<0.001
Low HDL	0.699 (0.67–0.73)	0.681 (0.65–0.71)	0.01	0.675 (0.65–0.70)	<0.001	0.676 (0.65–0.70)	0.006	0.683 (0.65–0.71)	0.03
Metabolic syndrome	0.753 (0.73–0.78)	0.725 (0.70–0.75)	0.001	0.723 (0.69–0.75)	<0.001	0.727 (0.70–0.76)	0.002	0.731 (0.70–0.76)	0.003

Notes: Model 1: age and grams of visceral adipose tissue, Model 2: age and body mass index, Model 3: age and waist circumference, Model 4: age and waist-to-hip ratio, Model 5: age and waist-to-height ratio. Numbers indicating AUC for the model.

P: *p*-Value from C-statistics by comparing to the model with VAT and age (Model 1).

CI for VAT changed slightly between comparisons of different anthropometrics due to small variations in N.

Abbreviations: BMI, body mass index (kg/m^2); HDL, high-density lipoprotein; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

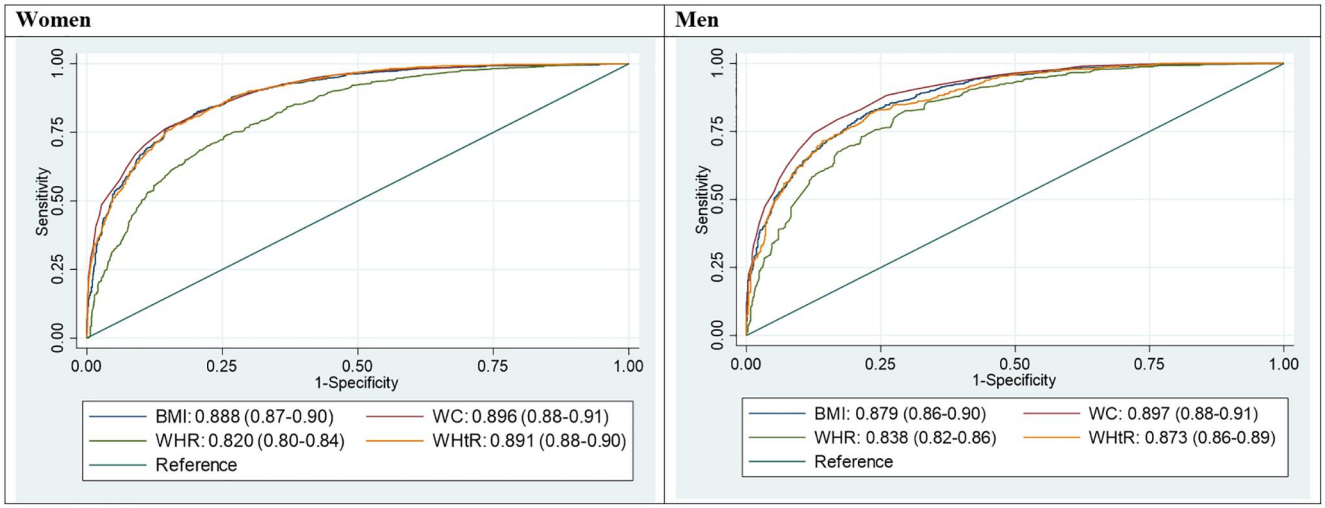

FIGURE 3 Comparison of VAT with anthropometric variables: The Tromsø Study 2015–2016. *VAT mas cut at median: women ≤832 or >832, men ≤1578 or >1578. BMI, body mass index; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

[0.66–0.71] vs. 0.63 [0.60–0.65]). For prediction of MetS, VAT was stronger than BMI in both women and men (AUC 95% CI: 0.71 [0.68–0.73] vs. 0.64 [0.61–0.67] in women, and 0.70 [0.67–0.73] vs. 0.63 [0.59–-0.66]) in men).

Comparison of AUCs between age-adjusted models with VAT and age-adjusted models with anthropometrics showed that VAT was a stronger predictor than all anthropometric measures (although only borderline significantly better than WHtR) to predict hypertension in men (Table 4). To predict diabetes, VAT was significantly stronger than BMI and WC in both men and women. VAT was significantly stronger than all anthropometrics to predict high triglycerides in both women and men (Table 4). In the prediction of low HDL cholesterol, VAT was stronger than BMI, WC, and WHtR in women and stronger than all anthropometrics in men. Finally, to predict MetS, VAT was in women stronger than BMI and WC, and borderline significantly stronger than WHtR. In men, VAT was stronger than all anthropometrics in the prediction of MetS (Table 4).

3.3 | Associations between the different anthropometric parameters with VAT mass

The ROC curves in Figure 3 show that all anthropometrics were strong predictors of VAT (AUC > 0.80). WC was the strongest predictor (AUC: 0.90), while the AUCs for WHR were the weakest (0.82 and 0.84, in women and men, respectively).

4 | DISCUSSION

In this analysis of 3675 middle-aged and older adults, we found that VAT was moderately to strongly correlated with all included anthropometric measures. The correlation between DXA-derived VAT measures and anthropometric measures is well established,[23–25] but previous studies include narrower age ranges (29–55 years)[20,23,25] or smaller samples (81–939 participants).[12,20,23,24] Thus, together with the additional ROC analysis and comparison with MetS and single metabolic syndrome components, the current study is an important contribution for establishing if DXA-derived VAT has clinical importance over and above traditional anthropometric risk factors to predict cardiometabolic risk. The association between anthropometric measures and VAT derived from CT or MRI,[16,19,26,27] ultrasound,[15] and bioelectrical impedance[17,18] has previously been investigated. Although CT and MRI are considered the most accurate techniques to quantify body composition, neither are suitable for population studies,[11] and because DXA-derived VAT is highly correlated with VAT measured by CT and MRI, it is considered a preferable substitute for the more resource-demanding measures.[12,13]

The presented ROC curves showed that among the anthropometric measures, WC had the strongest association with VAT; however, no other studies confirming this result were found. A previous study using DXA found that WHtR was the best anthropometric predictor for VAT, although closely followed by WC.[20] However, this study was based on a small sample ($n = 81$) with younger participants (mean age = 38.4) than the present study, which makes comparison challenging.[20] The high correlation between VAT and WC is considered as reasonable, as they are both measures from approximately the same area in the abdominal region. However, all anthropometric measures were considered strong predictors of VAT with high AUCs (≥0.82), and it is reasonable to assume that they all serve as satisfactory substitutes for VAT.

Although the correlations between VAT and all anthropometrics were overall moderate to strong, they were weakest in the oldest age group. This might be explained by changes in body composition with increasing age, where VAT mass increases relative to the

abdominal subcutaneous fat mass.[28,29] It has been observed that subcutaneous fat decreases rapidly after the age of 70 years, while VAT does not have the same steep decline.[30] Additionally, WC has been reported to be a satisfactory surrogate for VAT in adults, but not in older adults.[19] The age difference in body composition could potentially be explained by the change in sex hormones and in physical activity levels among the elderly.[19] Thus, conventional anthropometric measurements might not properly capture the changes in body composition that occurs with increasing age. This emphasizes the need for more accurate adiposity measurements in the older age groups.

VAT mass and anthropometric measures had similar associations and correlations to the cardiometabolic risk factors. The correlations were higher for triglycerides and HDL cholesterol compared to the other cardiometabolic risk factors. Although VAT was statistically significantly better than anthropometrics in the prediction of single metabolic risk factor components and MetS, the clinical differences were likely minor given the similar AUCs. Thus, the anthropometric measures are considered as satisfactory substitutes for VAT.

VAT was more strongly associated with high triglycerides compared to the anthropometric measures, which corresponds to the findings from a previous study.[23] Although VAT AUCs were significantly higher for several of the single metabolic syndrome components and MetS (Table 4), the clinical differences are likely small given the proximity between AUCs for VAT and anthropometric variables (e.g., the lowest AUC for MetS was 0.642 for BMI compared to 0.705 for VAT in women). Although VAT is statistically more accurate, the more accessible and less resource-demanding clinical measurements show similar predictive abilities of cardiometabolic risk factors and metabolic syndrome components. Longitudinal study designs and intervention studies are needed to investigate the potential differences between VAT and anthropometric measures and their association with incidence of metabolic syndrome and cardiometabolic disease.

4.1 | Strength and limitations

There are several strengths of this study. First, a large population-based sample with a wide age range of adults and older women and men was included. Second, all examinations and all definitions in the current analysis are performed and created by standard criteria, thus enabling comparison with future studies. Further, when performing DXA scans, the technicians were given standardized training and used protocols according to the manufacturer's recommendation. Also, all scans were inspected post-measurement, and regions of interest were adjusted to ensure standardization between participants. However, measurement error in DXA scans is a potential limitation.[31] The accuracy of VAT measured by DXA decreases with increasing BMI.[31] As about 46% and 22% of our study sample were overweight and obese, respectively, a measurement error may occur and is difficult to detect. Another limitation is that the cross-sectional design limits our possibility to study whether anthropometric measures are equally good as VAT to predict future health.

5 | CONCLUSION

VAT mass showed moderate to high correlations with all included anthropometric measures. The strongest association was observed between VAT and WC. Although VAT was a statistically more accurate predictor of single metabolic syndrome components and MetS, the clinical difference compared to the anthropometric variables was small given the similar AUCs. The conclusion from this study is that anthropometric measures are satisfactory substitutes to VAT in identifying cardiometabolic risk.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Marie W. Lundblad analyzed the data. Marie W. Lundblad, Bjarne K. Jacobsen, Jonas Johansson, and Laila A. Hopstock interpreted the results. Bjarne K. Jacobsen, Jonas Johansson, Lene F. Andersen, and Laila A. Hopstock were responsible for supervision. Sameline Grimsgaard and Laila A. Hopstock were responsible for the conceptualization, funding acquisition, and resources. Laila A. Hopstock administered the project. All authors were involved in writing and reviewing the paper and had final approval of the submitted version.

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Paper III

Lundblad M.W., Johansson J., Jacobsen B.K., Grimsgaard S., Andersen L.F., Wilsgaard T., Hopstock L.A.

Secular and longitudinal trends in body composition: The Tromsø Study 2001-2016.

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Secular and longitudinal trends in body composition: The Tromsø Study 2001-2016

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Study importance questions:

- What is already known about this subject?

- Overall overweight and obesity, usually measured by BMI, are increasing all around the world, and no efforts has shown to be effective in halting this trend.
- BMI is a proxy measure of overweight and obesity, which does not address the actual definition of overweight and obesity which is “excessive fat accumulations that may impair health”. Knowledge about trends in body composition and especially trends in the most harmful fat (visceral fat) is lacking.

- What are the new findings in your manuscript?

- Our manuscript contributes with new knowledge about secular and longitudinal trends in body composition, and more specifically body fat, visceral fat and lean mass, in a general adult population with a follow-up of 15 years.
- No other studies have presented trends in DXA-derived visceral adipose tissue in a general population.

- How might your results change the direction of research or the focus of clinical practice?

- We believe that our results are of importance to both researchers, clinicians and public health workers, as a motivation to enhance the battle against the obesity epidemic and especially targeting the younger generations where the increase in body fat and visceral fat was higher than in the older participants.

Abstract:

Objective: Overweight, defined as excessive fat mass, is a long-standing worldwide public health challenge. Traditional anthropometric measures used to identify overweight and obesity do not assess body composition. Our aim was to study population trends in general and abdominal fat mass during the last two decades.

Methods: We included participants from one or more consecutive surveys of the population-based Tromsø Study; Tromsø 5 (conducted in 2001, n=1662, 40-84 years), Tromsø 6 (2007-2008, n=901, 40-88 years) and Tromsø 7 (2015-2016, n=3670, 40-87 years) with total body dual-energy x-ray absorptiometry (DXA) scans. Trends in total fat and visceral adipose tissue (VAT) were analyzed by generalized estimation equation models, in strata of sex and age-groups.

Results: Total fat and VAT mass increased during 2001-2016, with a larger increase during 2007-2016 than from 2001 to 2007, and among the youngest age-group (40-49 years), particularly in women. Women had higher total fat mass than men, while men had higher VAT mass than women.

Conclusions: General and abdominal DXA-derived fat mass increased during the last two decades in this general population. Of particularly concern is the more pronounced increase in the last decade, and in the younger age-groups.

Introduction

The obesity epidemic cause concern in all parts of the world, and almost 40% of the adult population worldwide had overweight in 2016 according to the World Health Organization (WHO) (1). Obesity and overweight are major risk factors for non-communicable diseases, including cardiovascular diseases, which is the leading cause of death globally (2).

The definition of overweight and obesity is "abnormal or excessive fat accumulation that may impair health" (1). Anthropometric measures such as body mass index (BMI) (weight in kilograms divided by body height in meters squared [$kg/m^{2)}$]) and waist circumference are currently the most frequently used measures of general and abdominal overweight and obesity, in lack of more precise but available methods. BMI and waist circumference do not distinguish between fat mass and fat free mass, thus is not directly addressing the definition of obesity. Increased BMI indicates either increased muscle mass and/or increased fat mass, which have different effects on health. Most previous studies have used BMI to present increasing prevalence of overweight and obesity, but it is unknown whether body composition has changed over time.

There are several tools to examine body composition. The more accurate such as magnetic resonance imaging (MRI) and computed tomography (CT) are expensive, resource-demanding or involve considerable radiation exposure (3). Dual-energy x-ray absorptiometry (DXA) is a clinically applicable imaging method with negligible radiation exposure that also provides accurate measures of body fat, bone and lean tissue (i.e., muscle and organs, bone and fat excluded) (3). In addition, the CoreScan application (EnCore version 17.0) enables computation of visceral adipose tissue (VAT) from DXA scans, which is highly correlated with VAT derived from MRI and CT (4, 5). VAT, located intra-abdominal and around organs, is regarded as the most metabolically active body fat component, and has been associated with cardiometabolic diseases and several types of cancers (6). Previous studies investigating DXA-measured changes in body composition mainly included older adults (≥ 65 years) and had short follow-up (≤ 5 years) (7-12). To our knowledge, no studies have examined both secular and longitudinal changes in body composition and VAT mass in a general adult population sample measured by DXA.

The aim of this study was to examine trends in body composition during the last two decades using a population-based sample.

Methods

Study Sample

The Tromsø Study is an ongoing population-based study (13) conducted in Tromsø municipality, a municipality with about 77 000 inhabitants in Northern Norway (14). The majority of the population is native Norwegian and similar to the general Norwegian population in regard to age and sex (14). The Tromsø Study consists of seven surveys; Tromsø 1 (conducted in 1974), Tromsø 2 (1979-1980), Tromsø 3 (1986-1987), Tromsø 4 (1994-1995), Tromsø 5 (2001), Tromsø 6 (2007-2008), Tromsø 7 (2015-2016), inviting complete birth cohorts and large representative samples of the population in Tromsø municipality in Norway. The present study includes participants from Tromsø 5-Tromsø 7 (2001-2016). The data collections comprised a basic examination (total sample) with questionnaires and interviews, biological sampling and clinical examinations, and an extended examination (subsamples) with additional clinical examinations, including DXA scanning. The subsamples invited to the extended examination varied between studies; in Tromsø 5 (total number of participants in the basic examination=8130, 30-89 years, total attendance 79%) all participants attending basic examination in Tromsø 5 *and* had previously attended the extended examinations in Tromsø 4 were invited; in Tromsø 6 (total n=12 984, 30-87 years, total attendance 66%) all participants who attended extended examinations in Tromsø 4, all participants aged 50-62 years and 75-84 years, plus a 20% random sample aged 63-74 years were invited to the extended examinations; and in Tromsø 7 (total n=21 083, 40-99 years, total attendance 65%) a random sample plus all participants attending DXA and eye examinations in Tromsø 6 were invited to extended examinations.

A total of 1713, 905 and 3670 participants underwent whole-body DXA scans in Tromsø 5, Tromsø 6 and Tromsø 7, respectively. All participants attending one or more survey(s) were included in the analyses. Further, only participants aged 40 years and above were included in the analysis, due to few participants with DXA scans below 40 years in Tromsø 5 (n=51) and Tromsø 6 (n=5). After exclusions, the final sample for analysis consisted of 1662 (62% women, 40-84 years) participants from Tromsø 5, 901 (63% women, 40-88 years) participants from Tromsø 6 and 3670 (59% women, 40-87 years) participants from Tromsø 7 (Figure 1).

This project was approved by the Regional Committee for Medical Research Ethics (REC North reference 2017/1967). All participants gave written informed consent.

Body composition measures

In all three surveys, total body DXA scans were performed with Lunar Prodigy Advance (GE Medical Systems, Madison, WI, USA) in accordance with protocols from the manufacturer. The DXA machine was calibrated each morning with a phantom. Post-scanned images were inspected by technicians and corrected if necessary. To ensure comparison between surveys, fat mass and lean mass were derived with Basic Mode Analysis, and VAT mass was derived with Enhanced Mode Analysis. Total body fat, lean and VAT mass were included directly from DXA from all three surveys. Total body fat and lean mass percentage was included directly from the DXA scans in Tromsø 6 and Tromsø 7, and calculated as total body fat or lean mass, respectively, divided by total body mass*100 in Tromsø 5. Percent VAT was calculated as VAT mass divided by total body fat mass in the android area *100. Total body fat mass in the android area was not available from Tromsø 5. Thus, VAT in percent was only available from Tromsø 6 and Tromsø 7, and therefore, analysis of trend in VAT was performed for VAT in grams only. It should also be noted that of the 1662 participants with total body DXA scans in Tromsø 5, VAT mass measures were available for 284 of them, all participants attending total body scans had valid VAT mass measures from Tromsø 6. In Tromsø 7, 3675 participants had valid VAT mass measures. Two participants with VAT percent values >100 in Tromsø 7 were excluded from analysis of VAT, thus 3673 participants with valid VAT measures were included in Tromsø 7. Participants with VAT mass equal to 0 had their values transformed into the lowest registered value of VAT mass in the sample, which was 2 gram in both Tromsø 6 (n=5) and Tromsø 7 (n=10). There were no 0-values of VAT in Tromsø 5.

Statistical analyses

We used STATA 16 (STATA Corp LP Texas, USA) to analyze both secular and longitudinal trends in body composition across surveys. Total body mass consists of fat mass and lean mass, thus we have presented results from lean mass analysis in supplementary tables. Mean values are presented with standard deviation (SD) or 95 % confidence intervals (CIs). To examine whether there were systematic differences in study population characteristics between those who re-participated in two or three of the surveys compared to those who participated in only one of the surveys, we present sex-adjusted mean values and proportions of cardiometabolic risk factors in 10-year age-groups (Table S1) (all participants in Tromsø 6 attended Tromsø 5 and/or Tromsø 7).

Secular trends

We used descriptive analysis to present mean total body fat, lean (kg and %), VAT mass (g and %), BMI (kg/m^2), body weight (kg) and waist circumference (cm) in strata of 10 year-age groups for all three surveys (Table 1, Table

S2). We used kernel density plots to present distributions of total body fat, lean and VAT mass at all three different surveys (Figure 2, Figure S1). To visualize secular trends in total body fat and lean mass we plotted mean values from birth year-adjusted generalized estimation equation (GEE) analysis of each body composition measure at each survey (Figure 3, Figure S2).

Longitudinal trends

Because we did not have complete repeated measures for all included participants, and to account for repeated measures in the 940 participants attending two or more of the three surveys (of which 382 attended all three) we used GEE analysis (which estimates values for all participants attending one of the surveys) to examine the longitudinal trends overall and in 10 year-age groups (attained age in Tromsø 5, 2001). Longitudinal change in total body fat, lean and VAT mass across surveys were presented by adjusting for birth year using GEE analysis (Table 2, Table S3). Further, we assessed whether longitudinal change in body composition differed between different age-groups by performing GEE analysis in strata of attained age-groups in 2001 (40-49, 50-59, 60-69 and 70-79 years). Only participants aged < 80 years were included in these analyses because few participants were 80 years and older (n=74). In separate models we included two-way interaction terms between indicator variables of attained 10-year age-groups in 2001 and an ordinal variable of time (Table 3 and Table S4). All analyses are presented for women and men separately. P-values < 0.05 were considered statistically significant.

Results

There was a higher proportion of women (58-63%) than men in all three surveys, and a higher mean age in Tromsø 6 (68.5 and 69.9 years in women and men, respectively) compared to Tromsø 5 (65.2 and 66.5 years in women and men, respectively) and Tromsø 7 (66.7 and 66.2 years in women and men, respectively). There were minor differences in cardiometabolic risk factors between those attending one compared to two or more DXA scans (Table S1).

Secular trends

Overall, mean total body fat and VAT mass increased across the three surveys (Table 1). Correspondingly, total body lean mass % was slightly lower in Tromsø 7 than Tromsø 5 and 6 (Table S2). Overall, BMI (kg/m^2) and waist circumference (cm) in women increased between 2001 to 2007-2008 but remained relatively stable between 2007-2008 to 2015-2016. In men, BMI and waist circumference increased across the three surveys. Overall body weight

(kg) increased between the three surveys in both women and men (Table 1). The kernel density plots indicate that, for each survey added, the distributions for fat and VAT shifted to the right in both women and men. Density plots for lean mass in kg were slightly shifted to the right in men only, while lean mass in percent were shifted to the left for each added survey (Figure 2 and Figure S1).

Figure 3 shows that both total body fat and VAT mass increased from Tromsø 5 to Tromsø 6, and a much steeper increase was observed from Tromsø 6 to Tromsø 7. Total body fat mass was higher in women compared to men, while VAT mass was higher in men compared to women across all surveys ($p<0.001$ for both). VAT mass increased more rapidly in men than women over time ($p<0.001$). Overall, absolute body lean mass was higher in men than women, and lean mass (kg) remained stable across surveys in both women and men (Figure S2). Percent lean mass, on the other hand, decreased across surveys, especially from Tromsø 6 to Tromsø 7, which aligns with the increased absolute values of fat mass and the stable trend in lean mass (Figure S2).

Longitudinal trends

Results from GEE analyses (Table 2) show that total body fat mass increased across all surveys. There was a small increase from Tromsø 5 to Tromsø 6 (0.2 kg and 0.1 body fat % increase in women, and 0.5 kg and 0.6 body fat % points increase in men), while the increase from Tromsø 5 to Tromsø 7 was more pronounced (1.8 kg and 2.3 body fat % increase in women, and 3.0 kg and 3.7 body fat % increase in men). Also VAT mass increased across the follow-up period from Tromsø 5 to Tromsø 7 (200 g and 365 g in women and men, respectively), while a smaller increase was observed between Tromsø 5 and Tromsø 6 (48 g and 103 g increase in women and men, respectively). From Tromsø 6 to Tromsø 7 VAT percent increased by 5% in both women and men.

Table 3 shows that mean total body fat and VAT mass were lowest in the youngest age group (40-49 years) in Tromsø 5. The largest estimated increase in fat and VAT mass between Tromsø 5 and Tromsø 7 was observed in the same age-group (40-49 years) with an increase of 3.9 kg (4.0%) fat mass and 293 g VAT mass in women and 4.5 kg (4.1%) fat mass and 806 g VAT mass in men. The difference in estimated increase between age groups was not significant in men for fat nor for VAT mass (Table 3). In sensitivity-analyses including only participants with repeated DXA scans from all three (N=382), or from two *or* three surveys (N=940), the results in longitudinal trend did not change (not presented).

Discussion

In these secular and longitudinal analyses using a population-based sample we found that both total body fat and VAT mass increased over the two last decades in both women and men. The increases in total body fat and VAT mass were more pronounced in the last decade, and in the youngest age-groups (but statistically significantly different in women only).

Secular trends

We observed an increase in mean body fat and VAT mass across time. Previous literature on the secular trend in DXA-derived fat and VAT mass in adults is scarce, thus we were unable to compare our results with other studies. Overall, body weight increased across time, and in men, there was an increasing trend in both BMI and waist circumference across time. In women, neither BMI nor waist circumference increased between 2007-2008 to 2015-2016. The differences in mean BMI and waist circumference were, however, clinically minor between the two latter surveys. In addition, we have previously shown that DXA-derived VAT strongly correlates to the more commonly available anthropometric measures and then concluded that these measures are satisfactory substitutes for the DXA-derived measures (15).

Longitudinal trends

The longitudinal trends showed that fat and VAT mass increased in both women and men, in all age-groups, except for body fat in women aged 70-79. Further, the trends in fat (kg and %), VAT mass and lean mass were more prominent in men than women. This corresponds with findings from a previous study of 2040 elderly (aged 70-79 years) with a follow-up of two years (11). Previous longitudinal studies have shown that body fat increases and lean mass decreases with increasing age (7, 8, 10-12). The trends in body composition were present also after adjusting for age, which implies that change in body composition may not only be an effect of age, but also an effect of time. The changes in body composition differed between age groups and the younger part of the population had a more unfavorable change in body composition over time, although age group differences in men were non-significant. These generational differences are also observed in studies with longer follow-up of participants in the Tromsø Study (16-19) and other studies (20-23) where the younger birth cohorts experienced larger increases in weight, BMI and

waist circumference than the older birth cohorts. The more pronounced increase in overweight in younger populations is a cause of concern for this generation's future health.

Body composition trends and the paradox with cardiometabolic risk

Contrasting the documented increase in overweight, other cardiometabolic risk factors, such as total cholesterol (24, 25), blood pressure (26, 27), and overall burden of cardiometabolic risk (28-31) have decreased, both in this study population as well as in other high-income countries. In this study population, leisure-time physical activity levels (32) and grip strength (improved physical function) (33) has increased over time. Thus, the population seems to be in overall better health, while the trend in body composition suggests a health hazard. It is a paradox that the population is becoming physically stronger, while simultaneously muscular mass decreases, and further, that the cardiometabolic risk profile health improves while simultaneously the most metabolically harmful fat, VAT mass, increases. We may speculate that recent improvements in cardiometabolic health can be obstructed by the increase in prevalence of obesity in the younger generations.

Strengths and limitations

To our knowledge, no other study has presented secular trends in DXA-derived body composition in a general adult population and although previous longitudinal studies have found similar results, these studies examined changes in body composition by DXA in mostly elderly participants (65 years and older) and with shorter follow-up (a maximum of 5 years) (8, 10-12). We have included participants aged 40-88 years with 14 years of follow-up (1662, 901 and 3670 participants in Tromsø 5, Tromsø 6 and Tromsø 7, respectively). Notably, we do not have repeated measures for all participants. A total of 940 participants attended two or more of the DXA scans (two or more repeated measures) and only 382 participants attended all three DXA scans (three repeated measures). We performed separate analyses for both those who attended two or more times, and for those who attended all three DXA scans, and found similar results. Further, we examined cardiometabolic risk factors in those attending only one survey and in those attending two or more surveys and found that the clinical differences were minor. Of the 1662 participants in Tromsø 5, only 284 participants had valid VAT measures. The CoreScan EnCore software application for VAT extraction was not available in Tromsø 5 (2001). The images were therefore reanalyzed in 2019, and at this point many total body images were unavailable for extraction of VAT-measures.

As for all population-based studies, selection bias may influence the results. Attenders in population studies tend to have a more favorable health profile than the non-attenders (34, 35). This implicate that mean values of fat mass and VAT mass in the three surveys may be lower in the present study than in the general population.

Another limitation is the potential measurement error of the DXA equipment. Although Lunar Prodigy DXA was used in all three surveys, the more advanced Lunar iDXA machine could potentially have provided higher precision. Because all measurements were performed using identical protocols and equipment, we do not believe that our results are distorted by measurement error. Further, the inconsistency in VAT measures increase with increasing obesity (36). However, the least significant change for VAT mass is reported to be ± 130 g, meaning than observed changes larger than 130 g, as mostly observed in our study, can be considered actual changes (36). The results from this study is generalizable to similar populations measured with the same equipment as used in the current study.

Conclusion

During 2001 to 2016, fat mass and VAT mass increased while lean mass remained stable, in both sexes and all age-groups in this Norwegian general population. The findings confirm the observed unhealthy increase in general and abdominal obesity measured by traditional anthropometric measures. Particularly worrying is the more pronounced increase in the last decade, and in the younger age-groups.

Acknowledgements

We are grateful to all study participants and the staff responsible for data collection. No data are publicly available but may be obtained from a third party. The dataset supporting the article findings is available through application directed to the Tromsø Study by following the steps presented on their online page: https://uit.no/research/tromsoundersokelsen.

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Figures:

Figure 1: Inclusion of participants from Tromsø 5 (2001), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016). The Tromsø Study 2001-2016.

Figure 2: Kernel density plots of the distribution of body fat (kilograms and %) in women and men >40 years in Tromsø 5, 2001 (blue line), Tromsø 6, 2007-2008 (red line) and Tromsø 7, 2015-2016 (green line). The Tromsø Study 2001-2016.

Cont. Figure 2: Kernel density plots of the distribution visceral adipose tissue (grams and %) in women and men >40 years in Tromsø 5, 2001 (blue line), Tromsø 6, 2007-2008 (red line) and Tromsø 7, 2015-2016 (green line). The Tromsø Study 2001-2016.

Figure 3: Trends in age adjusted mean body fat (kilograms and %) and visceral adipose tissue (grams and %) mass in women (red line) and men (blue line). The Tromsø Study 2001–2016.

kg; kilograms, %; percent

Each dot represents mean fat mass or mean visceral adipose tissue in Tromsø 5 (2001), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016).

VAT% was only available from Tromsø 6 and Tromsø 7.

Table 1: Mean total body fat (kilograms and %) in Tromsø 5, Tromsø 6 and Tromsø 7 in women and men, by 10-year age-groups. The Tromsø Study 2001-2016.

	Tromsø 5 2001, N= 1662					Tromsø 6 2007-2008, N= 901					Tromsø 7 2015-2016, N= 3670				
Years	**N**	**Body fat (kg)**	**Body fat (%)**	**BMI (kg/m^2)**	**Weight (kg)**	**N**	**Body fat (kg)**	**Body fat (%)**	**BMI (kg/m^2)**	**Weight (kg)**	**N**	**Body fat (kg)**	**Body fat (%)**	**BMI (kg/m^2)**	**Weight (kg)**
Women															
40-49	46	22.6 (8.5)	32.8 (7.8)	25.1 (4.23)	67.8 (11.7)	32	22.8 (10.7)	32.5 (8.7)	25.3 (5.28)	67.8 (14.6)	128	26.4 (9.7)	35.9 (7.6)	26.0 (4.46)	71.9 (13.3)
50-59	216	26.5 (9.8)	36.3 (7.6)	26.7 (4.95)	71.6 (13.8)	31	26.7 (9.6)	36.9 (7.3)	26.6 (4.94)	71.4 (14.6)	283	27.0 (9.7)	36.9 (7.5)	26.5 (4.87)	71.7 (13.3)
60-69	407	25.6 (8.0)	36.8 (7.0)	26.5 (4.21)	69.9 (11.0)	278	26.4 (9.2)	36.7 (7.5)	26.9 (4.81)	70.6 (13.1)	931	27.7 (9.4)	38.2 (7.2)	26.6 (4.59)	71.3 (12.8)
70-79	313	26.5 (9.3)	37.8 (7.9)	27.2 (4.67)	68.7 (12.1)	187	26.1 (8.0)	37.2 (7.2)	27.0 (4.01)	69.1 (11.0)	690	28.6 (9.6)	39.3 (7.2)	27.5 (4.89)	71.9 (13.2)
80+	39	25.7 (8.3)	37.4 (6.8)	27.2 (3.90)	68.0 (11.5)	39	25.8 (10.2)	36.5 (8.8)	27.3 (5.26)	68.9 (13.7)	117	25.3 (7.9)	37.9 (7.1)	26.3 (3.88)	66.2 (10.8)
Overall	1021	26.0 (8.9)	36.8 (7.5)	26.7 (4.52)	69.4 (12.1)	567	26.0 (9.0)	36.6 (7.6)	26.9 (4.63)	69.9 (12.6)	2149	27.7 (9.5)	38.2 (7.3)	26.8 (4.70)	71.3 (13.0)
Men															
40-49	20	19.6 (6.9)	23.3 (6.2)	26.0 (2.41)	83.3 (12.4)	18	17.0 (6.3)	20.4 (6.0)	25.9 (2.85)	81.4 (11.4)	101	26.6 (11.1)	27.8 (7.7)	28.8 (4.59)	93.1 (17.2)
50-59	100	21.9 (7.0)	25.0 (5.7)	27.8 (3.01)	86.4 (11.1)	32	19.9 (7.3)	23.7 (6.6)	26.7 (2.68)	82.5 (9.69)	188	23.5 (7.9)	26.5 (6.3)	27.5 (3.39)	87.1 (11.8)
60-69	273	20.7 (7.6)	24.8 (6.4)	26.8 (3.43)	82.0 (12.5)	111	22.0 (7.0)	25.8 (6.1)	27.5 (3.11)	84.6 (10.0)	721	24.0 (8.6)	27.3 (6.8)	27.6 (3.69)	86.4 (12.3)
70-79	219	19.8 (7.7)	24.8 (7.1)	26.2 (3.67)	78.3 (12.0)	142	20.2 (7.9)	24.7 (6.5)	26.6 (3.62)	80.3 (12.6)	417	24.2 (8.1)	28.4 (6.4)	27.5 (3.60)	84.4 (12.3)
80+	29	19.5 (8.4)	24.7 (7.2)	25.3 (4.23)	75.4 (13.5)	31	24.0 (7.1)	29.1 (5.8)	27.2 (3.34)	81.8 (12.2)	94	22.4 (8.1)	28.0 (7.0)	26.3 (3.42)	78.8 (11.7)
Overall	641	20.5 (7.6)	24.8 (6.6)	26.6 (3.51)	81.2 (12.5)	334	21.0 (7.5)	25.1 (6.5)	26.9 (3.31)	82.1 (11.5)	1521	24.1 (8.6)	27.6 (6.7)	27.6 (3.71)	85.9 (13.2)

kg; kilograms, %; percent, BMI; Body mass index

Numbers are presented as mean (standard deviation) in 10-year age groups and overall.

Table 1 cont.: Mean total visceral adipose tissue (grams) in Tromsø 5, Tromsø 6 and Tromsø 7 and percent visceral adipose tissue in Tromsø 6 and Tromsø 7 in women and men, by 10-year age-groups. The Tromsø Study 2001-2016.

	Tromsø 5 2001, N= 284				**Tromsø 6 2007-2008, N= 901**				**Tromsø 7 2015-2016, N= 3673**			
Years	**N**	**VAT (g)**	**VAT (%)**	**WC (cm)**	**N**	**VAT (g)**	**VAT (%)**	**WC (cm)**	**N**	**VAT (g)**	**VAT (%)**	**WC (cm)**
Women												
40-49	10	442 (221)	NA	78.6 (9.79)	32	470 (467)	20.2 (13.1)	88.3 (13.8)	128	515 (435)	22.7 (11.1)	86.6 (11.2)
50-59	35	826 (664)	NA	84.9 (13.0)	31	797 (770)	28.2 (16.5)	90.2 (13.0)	284	832 (651)	32.7 (13.2)	89.6 (12.8)
60-69	64	895 (548)	NA	85.1 (10.4)	278	917 (621)	33.7 (12.5)	91.9 (12.3)	932	935 (635)	36.5 (13.5)	90.8 (12.2)
70-79	43	951 (665)	NA	86.5 (12.9)	187	956 (569)	37.9 (13.6)	92.2 (10.6)	691	1064 (625)	42.3 (11.8)	93.5 (12.6)
80+	10	1085 (442)	NA	88.5 (8.41)	39	871 (507)	37.2 (12.3)	92.4 (11.8)	117	920 (542)	43.1 (12.8)	89.6 (10.5)
Overall	162	878 (597)	NA	85.3 (11.6)	567	895 (607)	34.7 (13.6)	91.7 (11.9)	2152	937 (632)	37.1 (13.6)	91.2 (12.4)
Men												
40-49	4	874 (789)	NA	88.5 (13.5)	18	851 (599)	42.5 (28.4)	91.7 (7.01)	102	1471 (919)	48.7 (14.3)	101.2 (12.5)
50-59	24	1561 (698)	NA	97.2 (6.06)	32	1283 (762)	50.4 (20.1)	94.8 (7.87)	187	1448 (744)	55.5 (13.0)	98.7 (9.63)
60-69	52	1354 (769)	NA	95.3 (9.36)	111	1560 (767)	56.3 (16.1)	100.8 (9.00)	722	1687 (891)	60.5 (13.7)	100.5 (10.7)
70-79	35	1434 (836)	NA	93.8 (10.8)	142	1462 (880)	57.6 (14.3)	99.2 (10.0)	417	1775 (886)	63.8 (13.9)	101.3 (9.92)
80+	7	1590 (1075)	NA	99.4 (11.5)	31	1828 (644)	64.1 (13.6)	104.7 (9.41)	93	1571 (827)	62.6 (12.5)	99.8 (10.1)
Overall	122	1415 (793)	NA	95.2 (9.57)	334	1479 (819)	56.9 (16.0)	99.4 (9.67)	1521	1660 (877)	60.1 (14.2)	100.5 (10.5)

g; grams, %; percent, VAT; visceral adipose tissue, WC; waist circumference, cm; centimeter

Numbers are presented as mean (standard deviation) in 10-year age groups and overall.

Table 2: Estimated mean body fat (kilograms and %) and visceral adipose tissue (grams and %) in Tromsø 5 (2001) and subsequent change to Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016) using generalized estimating equation models. The Tromsø Study 2001-2016.

	Body fat (kg)	**Body fat (%)**	**VAT (g)**	**VAT (%)**
Women				
Intercept (Tromsø 5, 2001)[1]	26.3 (25.8, 26.8)	37.2 (36.8, 37.6)	920 (863, 977)	NA
Tromsø 6	0.2 (-0.3, 0.7)	0.1 (-0.3, 0.5)	47.5 (-1.4, 96.3)	40.2 (39.2, 41.2)[1]
Tromsø 7	1.8 (1.3, 2.4)	2.3 (1.9, 2.7)	200 (148, 251)	4.9 (4.0, 5.7)
Men				
Intercept (Tromsø 5, 2001)[1]	20.4 (19.8, 21.0)	24.6 (24.2, 25.1)	1428 (1313, 1543)	NA
Tromsø 6	0.5 (-0.2, 1.3)	0.6 (0.1, 1.2)	103 (-11.1, 217)	61.9 (60.7, 63.1)[1]
Tromsø 7	3.0 (2.3, 3.8)	3.7 (3.1, 4.3)	365 (247, 483)	4.6 (3.9, 5.3)

kg; kilograms, g; grams, %; percent, VAT; visceral adipose tissue, CI; confidence interval
Estimates are presented with 95% CI and are adjusted for birth year.
1. Intercept represents means in Tromsø 5, but for the analyses of VAT%, the intercept is for Tromsø 6

Table 3: Estimated means of body fat (kilograms and %) and VAT (grams) in Tromsø 5 (2001) and estimated change to Tromsø 7 (2015-2016) using generalized estimating equation by gender and 10-year age groups: The Tromsø Study 2001-2016.

	Body fat (kg)		Body fat (%)		VAT (g)	
Age in 2001, (years)	Tromsø 5, 2001	Estimated change[1]	Tromsø 5, 2001	Estimated change[1]	Tromsø 5, 2001	Estimated change[1]
Women						
40-49	23.0	3.9 (1.9, 5.8)	33.3	4.0 (2.5, 5.5)	547	293 (150, 436)
50-59	26.7	2.3 (1.3, 3.2)	36.5	2.7 (2.0, 3.4)	785	271 (194, 347)
60-69	25.7	0.9 (0.06, 1.7)	36.7	1.5 (0.9, 2.2)	806	176 (111, 241)
70-79	26.5	-1.6 (-3.8, 0.6)	37.8	-1.5 (-3.1, 0.1)	973	13.0 (-181, 207)
P-value[2]		<0.001		<0.001		0.047
Men						
40-49	19.3	4.5 (1.4, 7.5)	22.8	4.1 (1.7, 6.6)	783	806 (388, 1224)
50-59	21.8	2.6 (1.2, 4.0)	24.8	2.9 (1.8, 4.0)	1364	394 (188, 599)
60-69	20.5	2.7 (1.6, 3.7)	24.5	3.7 (2.8, 4.5)	1382	300 (150, 449)
70-79	19.8	3.1 (0.3, 5.9)	24.7	3.7 (1.5, 5.9)	1385	370 (-62.0, 802)
P-value[2]		0.72		0.69		0.21

kg; kilograms, g; grams, CI; confidence interval, VAT; visceral adipose tissue

1. Estimated change between 2001 and 2015-2016 presented with 95 % CI

2. P-value for equality between age groups.

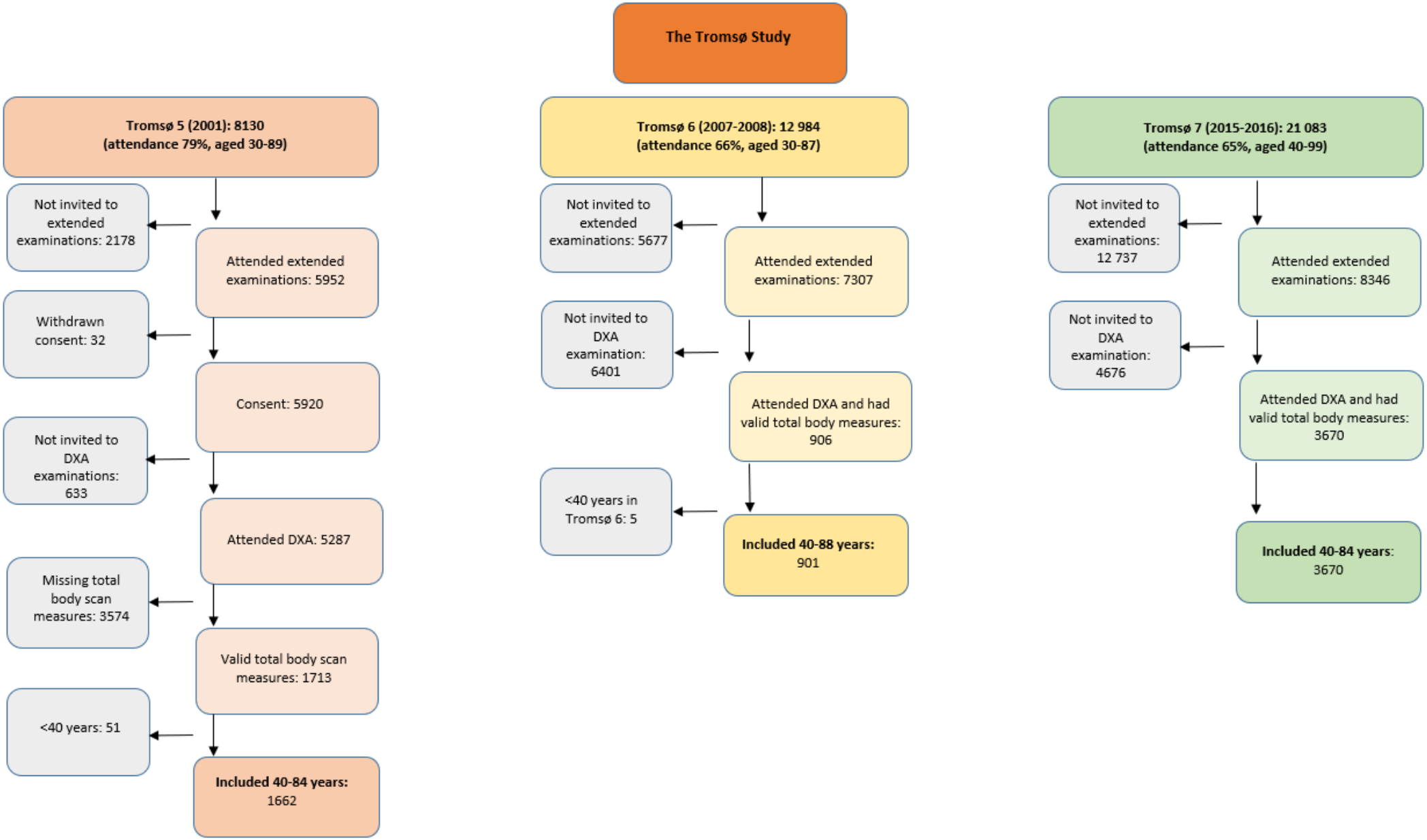

The Tromsø Study
Tromsø 5 (2001): 8130
(attendance 79%, aged 30-89)
Not invited to extended examinations: 2178
Attended extended examinations: 5952
Withdrawn consent: 32
Consent: 5920
Not invited to DXA examinations: 633
Attended DXA: 5287
Missing total body scan measures: 3574
Valid total body scan measures: 1713
<40 years: 51
Included 40-84 years: 1662
Tromsø 6 (2007-2008): 12 984
(attendance 66%, aged 30-87)
Not invited to extended examinations: 5677
Attended extended examinations: 7307
Not invited to DXA examination: 6401
Attended DXA and had valid total body measures: 906
<40 years in Tromsø 6: 5
Included 40-88 years: 901
Tromsø 7 (2015-2016): 21 083
(attendance 65%, aged 40-99)
Not invited to extended examinations: 12 737
Attended extended examinations: 8346
Not invited to DXA examination: 4676
Attended DXA and had valid total body measures: 3670
Included 40-84 years: 3670

Figure 1

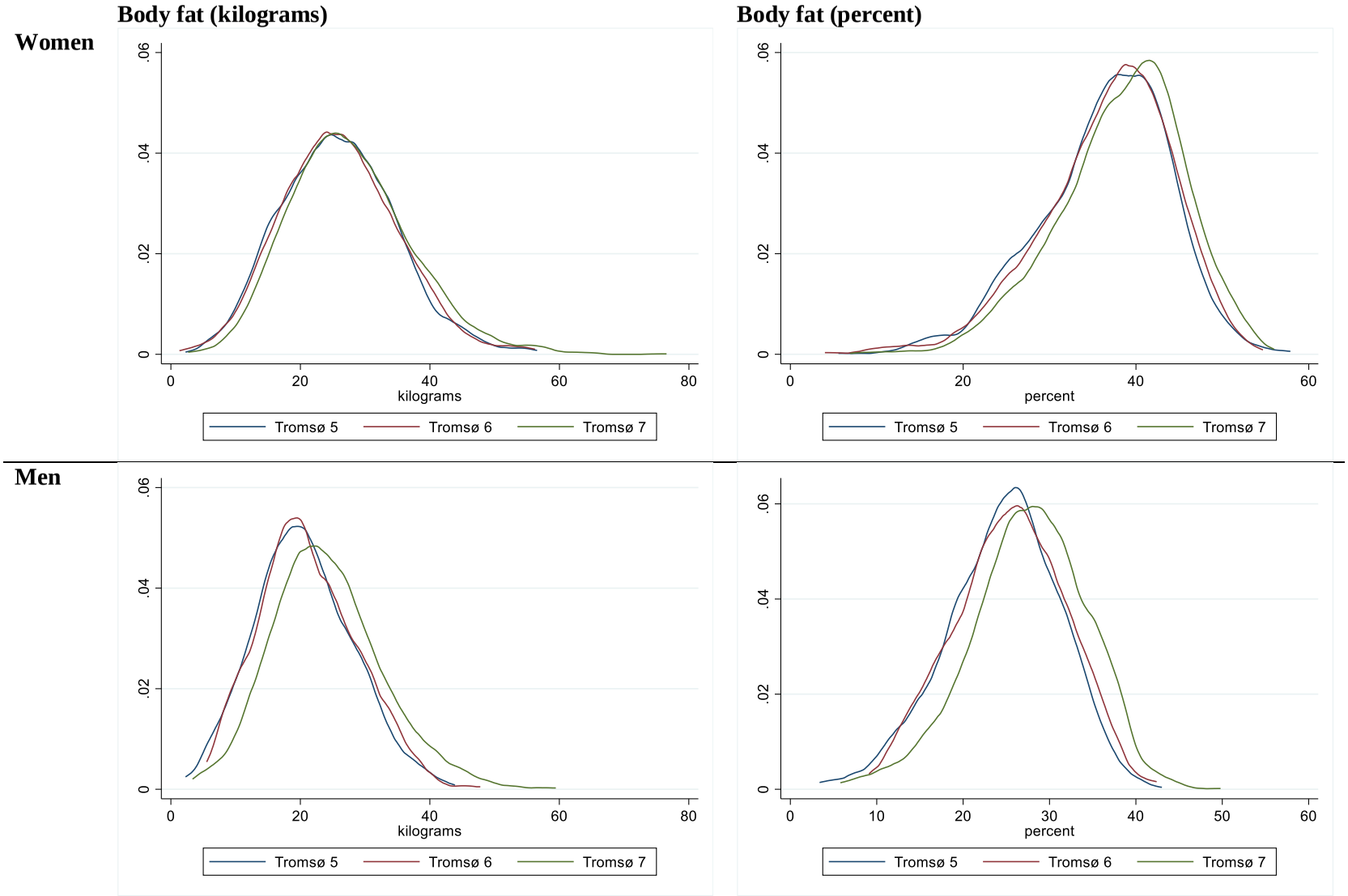
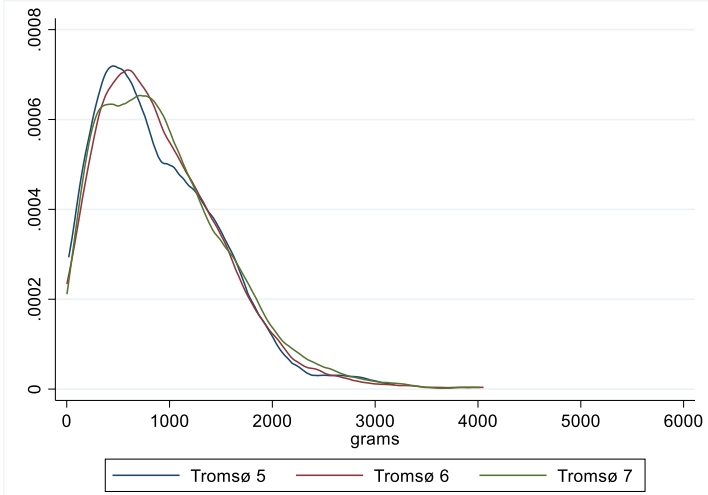
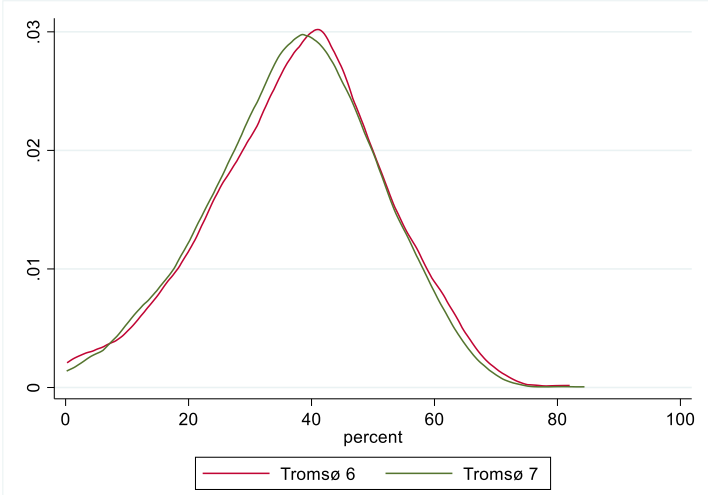
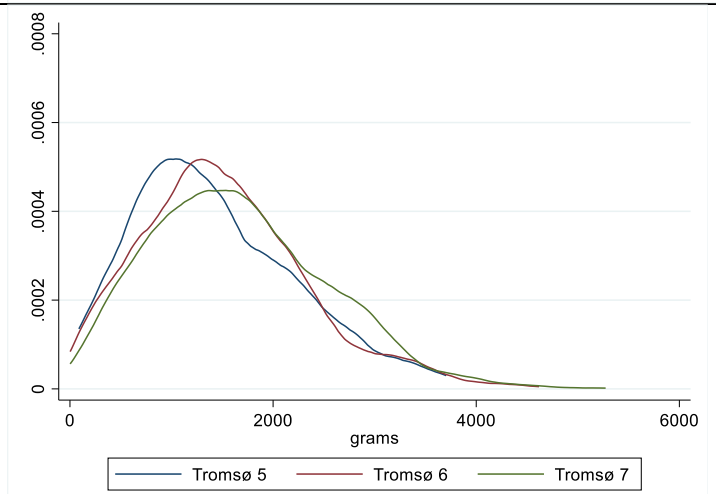
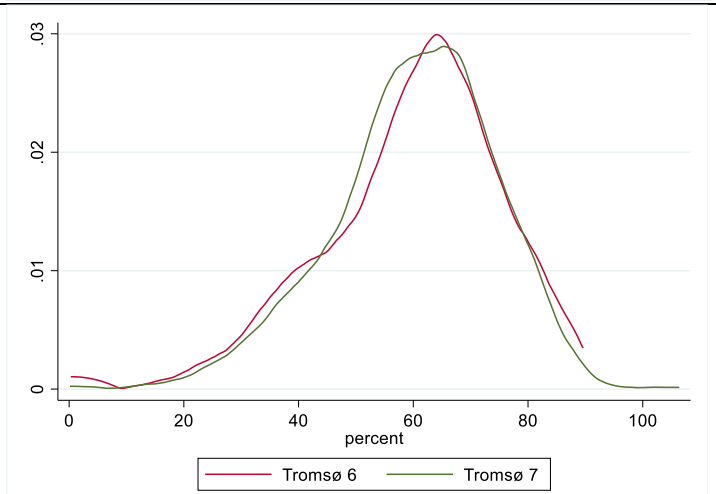

Body fat (kilograms)
Body fat (percent)
Women
Men
.06
.04
.02
0
0
20
40
60
80
kilograms
0
10
20
30
40
50
60
percent
Tromsø 5
Tromsø 6
Tromsø 7

Figure 2

	Visceral adipose tissue (g)	Visceral adipose tissue (%)
Women		
Men		

Cont. Figure 2

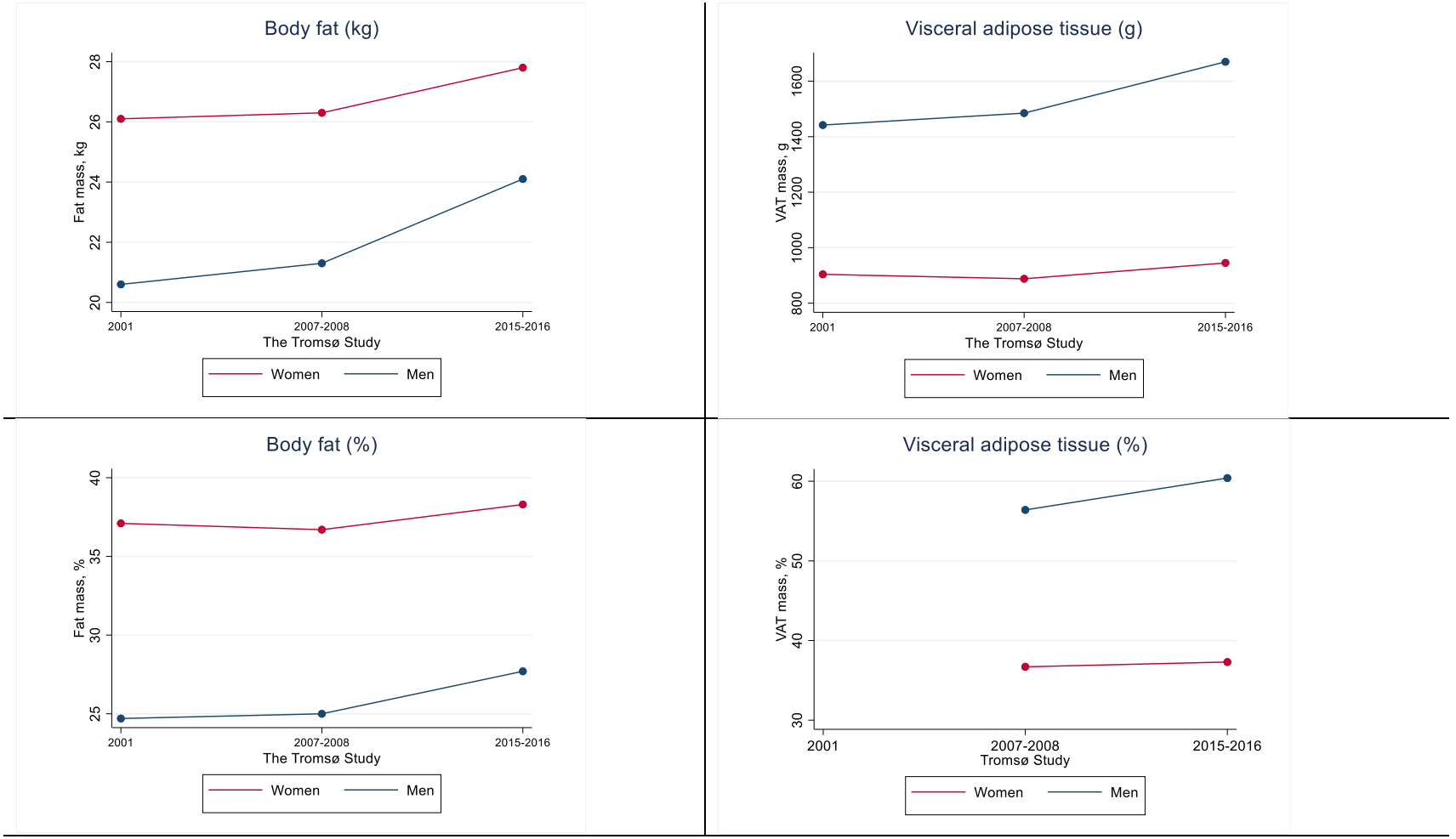

Body fat (kg)
Fat mass, kg
20
22
24
26
28
2001
2007-2008
2015-2016
The Tromsø Study
Women
Men
Visceral adipose tissue (g)
VAT mass, g
800
1000
1200
1400
1600
2001
2007-2008
2015-2016
The Tromsø Study
Women
Men
Body fat (%)
Fat mass, %
25
30
35
40
2001
2007-2008
2015-2016
The Tromsø Study
Women
Men
Visceral adipose tissue (%)
VAT mass, %
30
40
50
60
2001
2007-2008
2015-2016
Tromsø Study
Women
Men

Figure 3

Secular and longitudinal trends in body composition: The Tromsø Study 2001-2016

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Table S1: Characteristics of the study population attending only one survey (Tromsø 5 or Tromsø 7) and participants attending more than one survey. The Tromsø Study 2001-2016.

	Tromsø 5, 2001		**Tromsø 7, 2015-2016**	
	Attended also Tromsø 6 or Tromsø 7 N:893	**Attended only Tromsø 5 N: 769**	**Attended also Tromsø 5 or Tromsø 6 N: 457**	**Attended only Tromsø 7 N: 3213**
HDL cholesterol (mmol/L), mean (95 % CI)				
40-49	1.4 (1.3, 1.5)	1.4 (1.3, 1.6)	NA[1]	1.6 (1.5, 1.6)
50-59	1.4 (1.4, 1.5)	1.5 (1.4, 1.5)	1.5 (1.2, 1.8)	1.6 (1.5, 1.6)
60-69	1.5 (1.5, 1.5)	1.5 (1.5, 1.6)	1.7 (1.5, 1.8)	1.7 (1.6, 1.7)
70-79	1.5 (1.4, 1.6)	1.6 (1.5, 1.6)	1.6 (1.5, 1.7)	1.7 (1.6, 1.7)
80+	NA[1]	1.4 (1.3, 1.5)[3]	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)
Overall[2]	1.4 (1.3, 1.4)	1.4 (1.3, 1.5)	1.7 (1.5, 1.8)	1.6 (1.5, 1.6)
Triglycerides (mmol/L), mean (95 % CI)				
40-49	1.2 (1.0, 1.5)	1.4 (1.0, 1.8)	NA[1]	1.4 (1.3, 1.5)
50-59	1.6 (1.5, 1.7)	1.6 (1.5, 1.8)	1.5 (1.1, 1.8)	1.6 (1.5, 1.7)
60-69	1.5 (1.4, 1.6)	1.6 (1.5, 1.7)	1.4 (1.3, 1.6)	1.5 (1.4, 1.5)
70-79	1.6 (1.4, 1.7)	1.5 (1.4, 1.5)	1.4 (1.4, 1.5)	1.4 (1.4, 1.5)
80+	NA[1]	1.6 (1.4, 1.8)	1.3 (1.2, 1.4)	1.4 (1.3, 1.5)
Overall[2]	1.5 (1.3, 1.6)	1.5 (1.3, 1.7)	1.7 (1.6, 1.8)	1.7 (1.6, 1.8)
Waist circumference, mean (95 % CI)				
40-49	84.9 (82.1, 87.7)	88.4 (83.8, 93.0)	NA[1]	93.5 (91.9, 95.0)
50-59	89.6 (88.1, 91.1)	91.0 (88.5, 93.5)	92.4 (88.5, 96.2)	93.7 (92.6, 94.8)
60-69	89.2 (88.2, 90.2)	90.6 (89.3, 91.9)	95.6 (92.8, 98.4)	95.1 (94.5, 95.7)
70-79	91.2 (89.5, 92.9)	91.2 (90.0, 92.3)	96.8 (95.4, 98.2)	97.1 (96.3, 97.9)
80+	NA[1]	91.7 (89.3, 94.2)	93.5 (91.2, 95.8)	94.5 (92.8, 96.3)
Overall[2]	86.7 (84.6, 88.7)	87.7 (85.2, 90.1)	91.8 (89.5, 94.1)	92.1 (90.3, 93.8)
Hypertension, % (95 % CI)[4]				

40-49	32.1 (19.9, 47.3)	62.0 (36.2, 82.5)	NA[1]	28.1 (22.2, 34.5) [3]
50-59	67.0 (60.0, 73.4)	88.0 (77.0, 94.3)	47.0 (31.1, 63.5)	47.5 (42.8, 52.3)
60-69	83.9 (79.9, 87.2)	95.7 (91.9, 97.7)	65.5 (53.1, 76.1)	66.5 (64.2, 68.8)
70-79	94.7 (89.6, 97.4)	98.8 (96.7, 99.5)	85.9 (81.1, 89.6)	84.5 (81.8, 86.8)
80+	NA[1]	100 (93.0, 1.0) [3]	90.2 (81.3, 95.2)	91.1 (84.6, 95.0)
Overall[2]	82.0 (78.9, 84.7)	97.5 (96.1, 98.3)	82.6 (78.7, 85.9)	68.7 (66.9, 70.4)
Sedate leisure time physical activity, % (95 % CI)[5]				
40-49	27.4 (16.6, 41.7)	29.4 (12.7, 54.3)	NA[1]	11.3 (7.5, 16.2) [3]
50-59	20.7 (15.9, 26.6)	18.0 (10.7, 28.7)	5.6 (1.4, 19.9)	10.2 (7.7, 13.5)
60-69	17.1 (13.7, 21.0)	21.0 (16.1, 27.0)	12.0 (6.1, 22.2)	11.9 (10.4, 13.6)
70-79	NA[1]	NA[1]	13.0 (9.3, 17.7)	12.8 (10.6, 15.4)
80+	NA[1]	NA[1]	14.2 (7.8, 24.4)	18.5 (12.4, 26.8)
Overall[2]	17.9 (15.0, 21.2)	17.8 (13.2, 23.6)	12.3 (9.5, 15.9)	11.9 (10.8, 13.2)
Current smoking, % (95 % CI)				
40-49	29.7 (18.0, 44.8)	43.5 (21.1, 68.8)	NA[1]	14.1 (9.8, 19.4) [3]
50-59	24.8 (19.6, 30.9)	39.4 (28.8, 51.2)	22.4 (11.6, 39.0)	15.0 (11.9, 18.7)
60-69	22.0 (18.2, 26.2)	31.3 (25.4, 37.9)	6.1 (2.3, 15.2)	12.7 (11.2, 14.4)
70-79	11.7 (7.5, 17.9)	24.2 (19.8, 29.2)	7.7 (5.0, 11.5)	7.7 (6.0, 9.7)
80+	NA[1]	12.5 (5.2, 24.1) [3]	2.5 (0.6, 9.6)	6.1 (3.1, 11.9)
Overall[2]	20.8 (18.3, 23.8)	27.7 (24.2, 31.4)	7.8 (5.6, 10.6)	11.7 (10.5, 12.9)
Higher education level, % (95 % CI)[6]				
40-49	61.4 (46.8, 74.2)	63.6 (39.6, 82.3)	NA[1]	62.2 (55.4, 68.6) [3]
50-59	33.7 (27.9, 40.1)	24.9 (16.3, 36.1)	42.0 (27.0, 58.7)	47.4 (42.7, 52.1)
60-69	20.1 (16.5, 24.2)	13.7 (9.9, 18.8)	32.7 (22.6, 44.8)	40.4 (38.0, 42.8)
70-79	13.4 (8.9, 19.7)	8.3 (5.8, 11.9)	31.6 (26.1, 37.7)	28.3 (25.3, 31.6)
80+	NA[1]	5.1 (1.1, 14.1)[3]	20.2 (12.3, 31.3)	15.2 (9.6, 23.3)
Overall[2]	23.3 (20.5, 26.3)	11.2 (9.0, 13.8)	30.4 (26.1, 34.9)	38.3 (36.5, 40.1)

SD; Standard deviation, mmol; millimole, L; liter, mmHg; millimeter of mercury

Linear regression analysis was used for continuous variables and logistic regression was used for proportions. All numbers are adjusted for sex. In addition, numbers for overall are adjusted for age groups and sex.

All attendants (872) in Tromsø 6 had attended Tromsø 5 or Tromsø 7 and are therefore not included in the table.

1. <10 participants.
2. Age-group 80+ is removed when estimating overall mean values in Tromsø 5 and age-group 40-49 is removed when estimating overall mean values in Tromsø 7.
3. Results from crude proportions (not adjusted for sex).
4. Hypertension is defined as: mean systolic blood pressure >130 mmHg and/or mean diastolic blood pressure >85 mmHg and/or use of antihypertensives.
5. Leisure time physical activity in Tromsø 5 is reported only by those younger than 70 years.
6. Higher education level is defined as more than 12 years of schooling in Tromsø 5 and as tertiary education (short or long college/university education in Tromsø 7).

Table S2: Mean lean body mass (kilograms and %) in Tromsø 5, Tromsø 6 and Tromsø 7 in women and men, by 10-year age-groups. The Tromsø Study 2001-2016.

		Tromsø 5 2001, N= 1662		Tromsø 6 2007-2008, N= 901			Tromsø 7 2015-2016, N= 3670		
Years	**N**	**Lean (kg)**	**Lean (%)**	**N**	**Lean (kg)**	**Lean (%)**	**N**	**Lean (kg)**	**Lean (%)**
Women									
40-49	46	41.9 (5.0)	63.4 (7.5)	32	41.8 (4.5)	63.6 (8.4)	128	42.5 (5.4)	60.2 (7.3)
50-59	216	42.0 (5.1)	60.2 (7.3)	31	41.2 (6.1)	59.5 (7.0)	283	41.6 (5.1)	59.5 (7.2)
60-69	407	40.3 (4.4)	59.9 (6.8)	278	41.2 (5.2)	59.9 (7.3)	931	40.6 (4.6)	58.4 (7.0)
70-79	313	39.5 (4.2)	59.1 (7.7)	187	40.1 (4.2)	59.5 (7.1)	690	40.1 (4.7)	57.4 (6.9)
80+	39	39.4 (4.4)	59.5 (6.7)	39	40.1 (4.5)	60.3 (8.6)	117	37.8 (3.8)	58.8 (7.0)
Overall	1021	40.4 (4.6)	59.9 (7.2)	567	40.8 (4.9)	60.0 (7.4)	2149	40.5 (4.8)	58.4 (7.1)
Men									
40-49	20	59.8 (6.5)	72.7 (6.1)	18	60.9 (7.2)	75.4 (5.9)	101	62.2 (7.0)	68.3 (7.4)
50-59	100	60.6 (5.8)	71.1 (5.4)	32	59.2 (5.5)	72.3 (6.5)	188	59.8 (6.3)	69.5 (6.1)
60-69	273	57.4 (6.8)	71.3 (6.1)	111	58.7 (5.7)	70.2 (5.8)	721	58.4 (6.1)	68.8 (6.6)
70-79	219	54.8 (6.3)	71.3 (6.8)	142	56.2 (6.0)	71.3 (6.3)	417	56.1 (6.1)	67.7 (6.2)
80+	29	53.7 (5.6)	71.5 (7.0)	31	54.1 (5.9)	67.0 (5.7)	94	52.5 (5.1)	67.9 (6.8)
Overall	641	56.9 (6.8)	71.4 (6.3)	334	57.4 (6.1)	70.9 (6.3)	1521	57.9 (6.5)	68.5 (6.5)

kg; kilograms, %; percent

Numbers are presented as mean (standard deviation) in 10-year age groups and overall.

Table S3: Estimated mean lean mass (kilograms and %) in Tromsø 5 (2001) and subsequent change to Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016) using generalized estimating equation models. The Tromsø Study 2001-2016.

	Lean (kg)	**Lean (%)**
Women		
Intercept (Tromsø 5, 2001)[1]	40.4 (40.2, 40.7)	59.5 (59.1, 59.9)
Tromsø 6	-0.01 (-0.2, 0.2)	-0.06 (-0.4, 0.3)
Tromsø 7	-1.4 (-1.6, -1.2)	-2.2 (-2.6, -1.8)
Men		
Intercept (Tromsø 5, 2001)[1]	57.3 (56.9, 57.7)	71.6 (71.1, 72.0)
Tromsø 6	-0.6 (-0.9, -0.4)	-0.8 (-1.2, -0.4)
Tromsø 7	-3.3 (-3.6, -2.9)	-3.9 (-4.4, -3.5)

kg; kilograms, %; percent, CI; confidence interval

Estimates are presented with 95% CI and are adjusted for birth year.

1. Intercept represents means in Tromsø 5

Table S4: Estimated means of lean mass (kilograms and %) in Tromsø 5 (2001) and estimated change to Tromsø 7 (2015-2016) using generalized estimating equation by gender and 10-year age groups. The Tromsø Study 2001-2016.

	Lean mass (kg)		Lean mass (%)	
Age in 2001, (years)	Tromsø 5, 2001	Estimated change[1]	Tromsø 5, 2001	Estimated change[1]
Women				
40-49	42.1	-1.3 (-2.1, -0.4)	63.4	-4.2 (-5.6, -2.8)
50-59	42.1	-1.4 (-1.8, -1.0)	60.1	-2.6 (-3.3, -2.0)
60-69	40.5	-1.7 (-2.0, -1.3)	60.0	-1.6 (-2.1, -1.0)
70-79	39.6	-1.7 (-2.7, -0.8)	59.2	0.3 (-1.2, 1.9)
P-value[2]		0.11		<0.001
Men				
40-49	61.6	-2.7 (-4.4, -1.0)	74.2	-5.1 (-7.4, -2.9)
50-59	61.0	-2.8 (-3.6, -2.0)	71.6	-3.3 (-4.4, -2.2)
60-69	57.8	-3.7 (-4.3, -3.1)	71.7	-3.9 (-4.7, -3.1)
70-79	55.0	-4.0 (-5.5, -2.5)	71.5	-4.7 (-6.7, -2.6)
P-value[2]		0.016		0.49

kg; kilograms, g; grams, CI; confidence interval

1. Estimated change between 2001 and 2015-2016 presented with 95 % CI
2. P-value for equality between age groups

Table S5: Estimated means of VAT percent (%) in Tromsø 6 (2007-2008) and estimated change to Tromsø 7 (2015-2016) using generalized estimating equation by gender and 10-year age groups. The Tromsø Study 2007-2016.

	VAT (%)	
Age in 2001, years	Tromsø 6, 2007-2008	Estimated change[1]
Women		
40-49	23.1	7.3 (4.1, 10.5)
50-59	29.8	5.4 (2.2, 8.6)
60-69	36.2	4.3 (3.2, 5.5)
70-79	41.1	3.1 (1.3, 4.9)
P-value[2]		0.13
Men		
40-49	46.6	7.1 (4.3, 9.9)
50-59	53.1	6.0 (4.0, 8.0)
60-69	59.0	4.3 (3.1, 5.5)
70-79	61.1	3.2 (1.8, 4.6)
P-value[2]		0.03

%; percent, CI; confidence interval, VAT; visceral adipose tissue

1. Estimated change between 2007-2008 and 2015-2016 presented with 95 % CI

2. P-value for equality between age groups

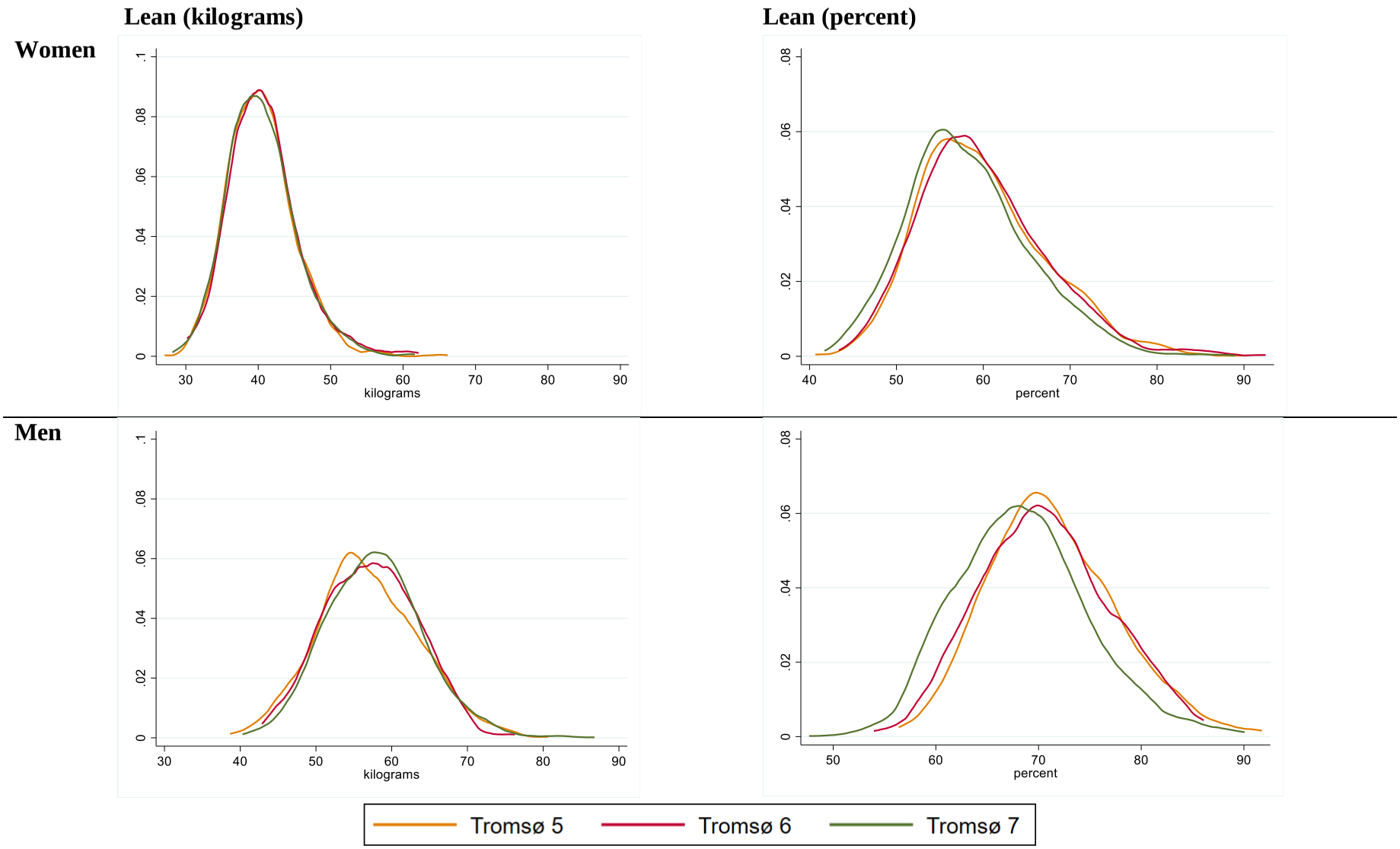


Figure S1: Kernel density plots of the distribution and lean mass (kilograms and %) in women and men ≥40 years in Tromsø 5, 2001 (orange line), Tromsø 6, 2007-2008 (red line) and Tromsø 7, 2015-2016 (green line). The Tromsø Study 2001-2016.

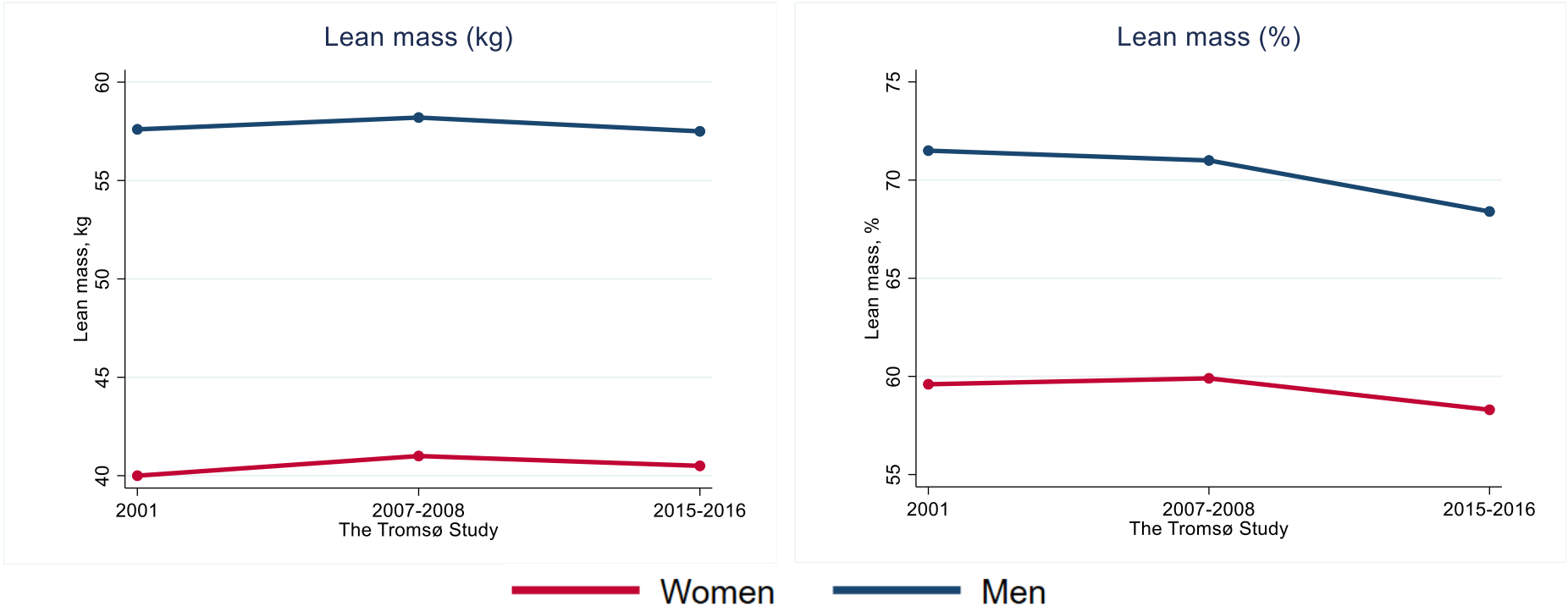


Figure S2: Trends in age adjusted mean lean mass (kilograms and %) in women (red line) and men (blue line). The Tromsø Study 2001–2016. kg; kilograms, %; percent

Each dot represents mean lean mass in Tromsø 5 (2001), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016).

Appendices

1. List of links to invitations, information brochures, consent forms and questionnaires in Tromsø 5 (2001), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016)
2. Invitation to extended examination Tromsø 5 (2001)
3. Invitation to extended examination Tromsø 6 (2007-2008)
4. Invitation to extended examination Tromsø 7 (2015-2016)
5. Approval for the study from the Regional Committees for Medical and Health Research Ethics (REK) North

Appendix 1

List of links to invitations, information brochures, consent forms and questionnaires in Tromsø 5 (2001), Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016)

Links to invitations, information brochures, consent forms and questionnaires

Tromsø 5-7

Tromsø 5 (2001) – basic examination

- Invitation: https://uit.no/Content/82032/innkalling_tr5.pdf
- Consent form: https://uit.no/Content/710358/cache=20203011130454/samtykkerklaering.tromso5.pdf

Tromsø 5 (2001) – extended examination

- Invitation: see appendix 2

Tromsø 6 (2007-2008) – basic examination

- Invitation: https://uit.no/Content/100340/Forespoersel_om_deltakelse_t6.pdf
- Consent form: https://uit.no/Content/111929/Samtykke%20Tr6.pdf

Tromsø 6 (2007-2008) – extended examination

- Invitation: see appendix 3

Tromsø 7 (2015-2016) – basic examination

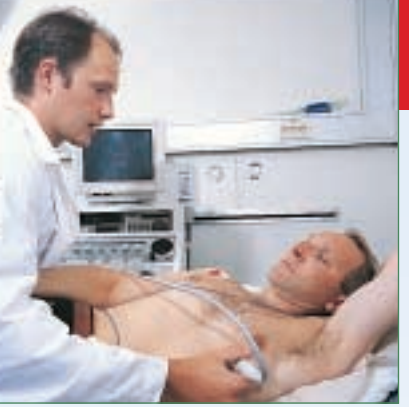
- Invitation: https://uit.no/Content/710341/cache=20203011123325/brosjyre.troms%C3%B87.pdf
- Questionnaire: https://uit.no/Content/710342/cache=20203011123337/Q1%2BTroms%C3%B8%2B7.pdf
- Consent form: https://uit.no/Content/575211/cache=20180805144729/Samtykke.den7.Tromsoundersokelsen.pdf

Tromsø 7 (2015-2016) – extended examination

- Invitation: see appendix 4

Appendix 2

Invitation to extended examination Tromsø 5 (2001)



DU ER INNBUDT TIL SPESIALUNDERSØKELSEN

Spesialundersøkelsen

Spesialundersøkelsen bruker apparater som lager bilder av blodårer og hjertet, og gir informasjon om kroppens beinvev og fettmengde. Det brukes ultralyd som reflekteres til et lite apparat som holdes mot huden (se bildet). Til benvevsmålingene brukes røntgenstråler, men dosene er svært lave. Disse undersøkelsene medfører ikke stikk eller smerter. Spesialundersøkelsen omfatter også blodprøve, urinprøve, pusteprøve, registrering av hjerteaktivitet (EKG). Dessuten gjøres enkle målinger av hukommelsen, evne til gjenkjenning av ord og grad av fingerbeveglighet.

Hvorfor spør vi deg?

Vi inviterer alle som møtte til spesialundersøkelsen i 1994-95 til en ny undersøkelse.

Hva er formålet?

Mange sykdommer utvikler seg over lang tid. Med avanserte metoder er det mulig å påvise forandringer på et tidlig stadium. I enkelte tilfeller kan forebygging eller behandling iverksettes før sykdommene utvikler seg. I andre tilfeller vet vi ikke sikkert hva forandringene betyr og videre forskning er nødvendig. Vi er nå spesielt interessert i å studere endringene siden undersøkelsen i 1994-95 og deres betydning for senere sykdom. På denne måten håper vi å få økt kunnskap om hvordan sykdommer oppstår og hvordan de kan forebygges og behandles.

SPESIALUNDERSØKELSEN OMFATTER

Ultralyd av blodårer og hjertet

▲ Alle får undersøkt halspulsårer og hovedpulsåren i magen. Vi ser da åreforkalkning og innsnevringer/utvidelser av årene. Halvparten får også undersøkt hjertets form og funksjon.

Måling av beintetthet og kroppens fettmengde

▲ Målingene brukes til å undersøke risiko for beinskjørhet og brudd, og om det er en sammenheng mellom kroppsfett og sykdom.

EKG og blodtrykk

▲ EKG er en registrering av hjerteaktivitet som også gir informasjon om hjertesykdom. Ved registrering festes ledninger til armer, ben og til brystet. Blodtrykket måles både på overarmen og ved ankelen.

Pusteprøve

▲ Ved å puste inn i et apparat, får en registrert hvordan lungene fungerer.

Blodprøve

▲ I blodprøven undersøkes fettstoffer og stoffer som forteller om nyrefunksjon, stoffskifte (kalk og sukker) og blodlevring. Det er også aktuelt å analysere arvestoff i blodprøven. Prøven blir frosset ned, slik at den senere kan brukes i utforsking av sykdom.

Videre oppfølging

- Dersom du trenger videre undersøkelse eller behandling, får du tilbud om det.
- Enkelte kan senere bli forespurt om å komme til ny undersøkelse som ledd i forskning.

PRAKTISKE OPPLYSNINGER

Sted og tid

Undersøkelsen foregår i 2.etasje av Elisabeth-senteret - den gamle kvinneklinikken (Mellomveien 50) - i etasjen under Tromsø-undersøkelsen. Undersøkelsen tar omlag 1,5 time og er gratis.

Vi håper du kan benytte den avtalte time. Dato og klokkeslett står i brosjyren. Dersom du må bytte time, ber vi om at du gir beskjed på telefon: ***77 64 48 16*** eller e-post: ***Tromsous@ism.uit.no***

Urinprøve

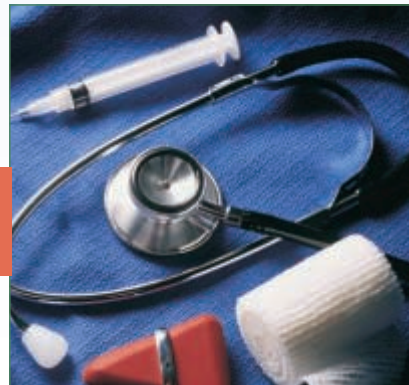
Du har fått utlevert tre uringlass merket 1, 2 og 3. Vi ønsker at du de siste tre dagene før spesialundersøkelsen lager en morgen-urinprøve i hvert glass. Du har fått ett glass for hver morgen.
Følg bruksanvisning som følger med glassene.

Fall

Du blir bedt om å registrere fall fram til spesialundersøkelsen.

Påkledning

Av hensyn til måling av blodtrykk og taking av EKG ber vi om at du tar på plagg som ikke strammer på armen og beinet. Ved undersøkelse av hjertet er det nødvendig å ta av seg på overkroppen. Ved undersøkelse av hovedpulsåren, må klær trekkes noe ned slik at huden i mageregionen blir bar. Ved undersøkelse av bentetthet, trenger du ikke kle av deg, men det er viktig ikke å ha metallgjenstander i klærne som f. eks. glidelås, knapper, hemper eller nagler av metall.



Appendix 3

Invitation to extended examination Tromsø 6 (2007-2008)

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Tromsø-
undersøkelsen

Vil du delta i Spesialundersøkelsen?

Rundt halvparten av de som deltar i **Hovedundersøkelsen** blir spurt om å delta i en oppfølgende **Spesialundersøkelse.** Denne undersøkelsen tar cirka to timer, avhengig av hvor mange deler du er invitert til. Det er frivillig å delta.
Vi minner samtidig om utfylling av kostholds skjemaet du fikk utlevert ved første oppmøte, dersom du ikke har gjort det allerede.

Tid og sted

Du har fått time

Vi håper den avtalte timen passer. Dersom du må bytte time, ber vi om at du gir beskjed tidligst mulig på telefon: **77 62 07 00** (telefontreffetid kl. 09.00 -15.00) eller per e-post: **tromso7@uit.no.**

Undersøkelser som utføres ved Spesialundersøkelsen.

Blodprøve

Det tas blodprøver av alle ved oppmøte.

Urinprøve

Vi ber om at du tar tre morgen-urinprøver. Du har fått ett uringlass for hver morgen, merket 1, 2, og 3. Første prøve tas to dager før undersøkelsesdagen, den siste tas samme morgen som undersøkelsen. Følg bruksanvisningen og lever prøvene når du møter til Spesialundersøkelsen.

Avføringsprøve

Vi minner om å sende inn avføringsprøven du fikk utstyr til ved første oppmøte, innen 24 timer etter at du tok prøven. Bruk konvolutten du fikk utdelt eller avlever prøven ved Spesialundersøkelsen (innen 24 timer).

Du inviteres videre til <u>én eller flere av følgende undersøkelser</u>:

EKG

Registrering av hjerterytmen utføres via elektroder som festes på brystet.

Kognitiv funksjon

Kognitiv funksjon undersøkes ved hjelp av enkle spørsmål knyttet til gjenkjenning av ord, kobling av symboler og tall samt grad av fingerbevegelighet.

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undersøkelsen

Fysisk funksjon
Fysisk funksjon undersøkes ved test av balanse, gange og gripestyrke.

Ultralyd av halspulsåre
Halspulsåren undersøkes for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.

Fotografering av øyebunnen
Det gis en øyedråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Synet kan forbigående bli noe uklart. Effekten avtar etter ca en time og går deretter gradvis over. Det anbefales å ta med solbriller da sterkt lys kan oppleves ubehagelig når pupillen er utvidet.
Det gjøres også en enkel synstest.

Lungefunksjonen
Lungefunksjonen testes ved at du puster så hardt du klarer gjennom et munnstykke. I tillegg vil det gjøres lydopptak av lungelyder og hjertelyder.

Måling av beintetthet.
Måling av beintetthet og kroppssammensetning gjøres ved hjelp av et eget apparat (DEXA).

Ultralyd av hjertet
Ultralyd av hjertet utføres for å undersøke hjertets form og funksjon.

Måling av fysisk aktivitet
Graden av fysisk aktivitet måles ved å ha en aktivitetsmåler festet til hoften i en uke. Noen deltakere får i tillegg en aktivitetsmåler festet til brystet, i ett døgn.

Påkledning
Av hensyn til undersøkelsene ber vi om at du har på lett påkledning. Ha gjerne på kortermet plagg og løse bukser, og unngå strømpebukser og høye hæler. Ved undersøkelse av hjertet må man ta av seg på overkroppen og ha tilgang til bar hud på ankelen. Ved undersøkelse av beintetthet kan det ikke være metallgjenstander i klærne og på kroppen, som glidelås, knapper eller hemper av metall, smykker, ringer mm. Fotografering av øyebunnen gjennomføres uten linser, det anbefales derfor å ha på briller. Ta gjerne med solbriller som beskytter mot skarpt lys etter øyeundersøkelsen.

Viktig hvis du kjører bil til undersøkelsen
Etter drypping med øyedråper (Tropikamid) anbefales det å vente til man føler at synet har normalisert seg nok til at man kan kjøre bil på en trygg måte. Effekten av dråpene avtar etter ca 1 time og går deretter gradvis over. Dersom lyset oppleves ubehagelig anbefales det å benytte solbriller.

Videre oppfølging
Dersom resultatet av prøvene viser at det er nødvendig med oppfølging av lege, blir du orientert om det. Noen deltakere vil i ettertid bli spurt om å delta i videre undersøkelser. Du vil da få en forespørsel i posten. Det er frivillig å delta i videre undersøkelser.

Vel møtt til undersøkelsen!

Appendix 4

Invitation to extended examination Tromsø 7 (2015-2016)

Vil du delta i Spesialundersøkelsen?

Spesialundersøkelsen er en utvidelse av Tromsøundersøkelsen.
Om lag halvparten av de som deltar i første del av undersøkelsen blir spurt om å delta. Det er frivillig å delta i Spesialundersøkelsen.

Tid og sted

Du har fått time

Undersøkelsen foregår i 2. etasje, samme sted som første del av Tromsøundersøkelsen.
Varigheten av spesialundersøkelsen tar en til to timer.

Vi håper du kan benytte den avtalte time. Dersom du må bytte time, ber vi om at du gir beskjed på telefon: **77 64 48 16** mellom **kl.09.00-11.00**, eller e-post: **tromsous@ism.uit.no**

Undersøkelser som utføres

Ultralyd av blodårer og hjerte

Alle som møter vil få undersøkt halspulsårer. Om lag halvparten vil også få undersøkt hjertets form og funksjon.

Måling av beintetthet og kroppens fettmengde

Alle vil få undersøkt beintetthet, men type undersøkelse vil variere.

Fotografering av øyebunn

Vi vil ta fotografi av øyebunnen av alle deltakere. Du vil få en øyedråpe i hvert øye en tid før fotografering. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten er borte etter en time. Alle får tilbud om en enkel synstest som du vil få svar på med en gang.

Tester av hukommelse

Tester av hukommelse gjøres ved hjelp av enkle spørsmål og omfatter også evne til gjenkjenning av ord og grad av fingerbevegelighet.

Det medisinske fakultet
Institutt for samfunnsmedisin
Tromsøundersøkelsen
Universitetet i Tromsø
N-9037 Tromsø, Norge

tromsous@ism.uit.no
www.tromso6.no
tlf.77 64 48 16
Undersøkelsessted:
Breivangvn.23, 9010 Tromsø

EKG og blodtrykk
Ved EKG-registrering festes ledninger til kroppen. Blodtrykket måles både på overarmen og ved ankelen.

Pusteprøve
Du skal puste så hardt du klarer inn i et apparat. Hvor mye luft som blåses ut per sekund, er et mål på hvordan lungene fungerer.

Bakterieprøve fra nese og hals
Bakterieprøven gjøres på samme måte som sist hos de som fikk utført denne prøven ved første frammøte.

Blodprøve
Det vil tas ny blodprøve av alle.

Intervju
Et utvalg vil bli spurt om bruk av antibiotika (penicillin og lignende legemidler) de siste 24 timer.

Urinprøve
Du har fått utlevert tre uringlass merket 1, 2, og 3. Vi ønsker at du de siste tre dagene før spesialundersøkelsen tar en morgenurinprøve. Du har fått ett glass for hver morgen. Følg bruksanvisningen.

Påkledning
Av hensyn til måling av blodtrykk, taking av EKG og ultralydundersøkelsen ber vi om at du tar på plagg som ikke strammer på armer og bein. Ved undersøkelse av hjertet er det nødvendig å ta av seg på overkroppen. Ved undersøkelse av beintetthet trenger du ikke kle av deg, men det er viktig ikke å ha metallgjenstander i klærne og på kroppen, for eksempel glidelås, knapper eller hemper av metall, smykker, ringer mm.

Videre oppfølging
Dersom resultatet av prøvene viser at det er nødvendig med oppfølging av lege, vil du bli orientert om det.

Noen deltakere vil i ettertid bli spurt om å delta i videre undersøkelser. Hvis dette gjelder deg, vil du få en forespørsel i posten. Det er frivillig å delta i videre undersøkelser.

Vel møtt til undersøkelsen!

Med vennlig hilsen

Tromsøundersøkelsen

Appendix 5

Approval for the study from the Regional Committees for Medical and Health Research Ethics (REK) North

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			10.10.2017	2017/1967/REK nord
			Deres dato:	Deres referanse:
			19.09.2017	

Vår referanse må oppgis ved alle henvendelser

Laila Hopstock
Institutt for helse og omsorgsfag

2017/1967 Kardiometabolsk helse: Kosthold, næringsinntak og trend i kroppssammensetning

Forskningsansvarlig institusjon: UiT - Norges arktiske universitet
Prosjektleder: Laila Hopstock

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden er behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) ved sekretariatsleder, på fullmakt gitt av komiteen med hjemmel i forskningsetikkforskriften § 10 annet ledd. Søknaden er vurdert med hjemmel i helseforskningsloven.

Prosjektleders prosjektomtale
1) I hvilken grad samsvarer næringsinntaket i befolkingen med de nasjonale kostrådene? 2) Hva er assosiasjonen mellom trender i kroppssammensetning og trend kroppsmasseindeks, hofte-midje-ratio og andre tradisjonelle overvektsmål? 3) Hvilke kostholdsmønster samsvarer best med god kardiometabolsk helse?

Vurdering
Formålet med prosjektet er å kartlegge kosthold og næringsinntak i befolkningen, studere sammenhengen mellom kosthold og kardiometabolsk risikoprofil i befolkningen og studere trender i kroppssammensetning og andre overvektsmål i en definert befolkning og tidsperiode.

Vurdering av om det avgitte samtykket er dekkende
Prosjektet vil kun benytte seg av allerede innsamlet materiale som ligger innenfor hovedformålet med Tromsøundersøkelsen. Skriftlig samtykke er innhentet, og deltakerne kan til enhver tid reservere seg mot at deres data blir brukt i analyser. Data fra deltakere som har reservert seg vil ikke bli brukt i analysene.

Etter fullmakt er det fattet slikt

vedtak
Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 31.07.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen

er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Kopi til:nina.emaus@uit.no