Journal of the American Heart Association

ORIGINAL RESEARCH

Independent Relevance of Different Measures of Adiposity for Carotid Intima-Media Thickness in 40 000 Adults in UK Biobank

Preyanka Pillay, MBChB, MSc; Jennifer Carter, PhD; Hannah Taylor, PhD; Sarah Lewington, DPhil; Robert Clarke, MD

BACKGROUND: Uncertainty persists about carotid intima–media thickness (CIMT) as a marker of subclinical atherosclerosis and the independent relevance of different measures of adiposity for CIMT. We assessed the independent relevance of general adiposity (body mass index), central adiposity (waist circumference), and body composition (fat mass index and fat-free mass index) with CIMT among adults in the United Kingdom.

METHODS AND RESULTS: Multivariable linear regression of cross-sectional analyses of UK Biobank assessed the mean percentage difference in CIMT associated with equivalent differences in adiposity measures. To assess independent associations, body mass index and waist circumference were mutually adjusted, as were fat mass index and fat-free mass index. Among 39 367 participants (mean [SD] age 64 [8] years, 52% female, 97% White), median (interquartile range) CIMT was 0.65 (0.14) mm in women and 0.69 (0.18) mm in men. All adiposity measures were linearly and positively associated with CIMT after adjusting for confounders. Fat-free mass index was most strongly associated with CIMT after adjustment for fat mass index (% difference in CIMT: 1.23 [95% CI 0.93–1.53] women; 3.44 [3.01–3.86] men), while associations of fat mass index were attenuated after adjustment for fat-free mass index (0.28 [−0.02, 0.58] women; −0.59 [−0.99, −0.18] men). After mutual adjustment, body mass index remained positively associated with CIMT, but waist circumference was completely attenuated.

CONCLUSIONS: Fat-free mass index was the adiposity measure most strongly associated with CIMT, suggesting that CIMT may reflect vascular compensatory remodeling rather than atherosclerosis. Hence, screening for subclinical atherosclerosis should evaluate carotid plaques in addition to CIMT.

Key Words: adiposity ■ carotid intima-media thickness atherosclerosis ■ fat mass ■ fat-free mass

Adiposity is an independent risk factor for atherosclerotic cardiovascular diseases (CVD),[1] including ischemic heart disease and stroke, which are the leading causes of morbidity and mortality worldwide.[2] The prevalence of obesity, defined as a body mass index (BMI) ≥30 kg/m^2,[3] has doubled over the last 4 decades in >70 countries.[4] Moreover, ≈65% of adults in the United Kingdom (UK) were overweight or obese in 2019.[5] Central adiposity is more strongly associated with atherosclerotic CVD than BMI, which is a measure of general adiposity.[6] Importantly, BMI does not distinguish fat mass from fat-free mass,[7] which have different associations with atherosclerotic CVD.[8] Moreover, lean mass is associated with compensatory structural and functional changes, including higher mean levels of left ventricular mass,[9,10] and higher risks of atrial fibrillation.[11]

Correspondence to: Robert Clarke, MD, Nuffield Department of Population Health, Big Data Institute, Headington, Oxford OX3 7LF.
Email: robert.clarke@ndph.ox.ac.uk and Sarah Lewington, DPhil, Nuffield Department of Population Health, Big Data Institute, Headington, Oxford OX3 7LF.
Email: sarah.lewington@ndph.ox.ac.uk

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026694

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is one of largest studies to assess the sex-specific independent relevance of measures of general adiposity (body mass index), central adiposity (waist circumference), and body composition (fat mass index and fat-free mass index) with carotid–intima media thickness (CIMT).
- Among adults in the United Kingdom, fat-free mass index was the single adiposity measure most strongly and positively associated with CIMT, independent of fat mass index.
- The positive associations of fat mass index and waist circumference with CIMT were completely attenuated after mutual adjustment for fat-free mass index and body mass index, respectively.

What Are the Clinical Implications?

- Because fat-free mass index was the adiposity measure most strongly associated with CIMT, CIMT may be influenced to a greater extent by compensatory remodeling of the arterial wall rather than subclinical atherosclerosis.
- The findings could explain why CIMT, specifically at lower levels, is less predictive of atherosclerotic cardiovascular disease risk than carotid plaques.

Nonstandard Abbreviations and Acronyms

CCA	common carotid artery
CIMT	carotid intima–media thickness
SBP	systolic blood pressure
UK	United Kingdom

Carotid intima–media thickness (CIMT) is a widely used marker of subclinical atherosclerosis.[12,13] However, the currently available ultrasound methods cannot distinguish the intima from the media layers of the carotid artery wall. The thickness of the media may be influenced by compensatory remodeling in response to changes in blood flow, blood vessel diameter, and blood pressure rather than atherosclerosis, which typically increases the thickness of the intima layer of the artery wall.[14,15] The inability of existing ultrasound methods to distinguish the thickness of the intima from the media layers of the carotid artery[16,17] may account for the uncertainty about the independent causal relevance of CIMT as a marker of subclinical atherosclerosis and its role for prediction of risk of atherosclerotic CVD.[18–20] Because carotid plaques chiefly represent subintimal atherosclerosis[21] and are stronger predictors of atherosclerotic CVD than CIMT,[20] some have suggested that CVD risk prediction should include carotid plaques in addition to CIMT rather than CIMT alone.[16]

Previous studies have demonstrated that central adiposity is more strongly and positively associated with CIMT than BMI.[22–24] However, little is known about the independent relevance of different adiposity measures for CIMT. Importantly, relatively few studies have evaluated the independent associations of body composition (including fat mass and fat-free mass) with CIMT.[24,25] Elucidation of the independent relevance of different adiposity measures for CIMT may be informative about the relevance of CIMT for prediction of risk of ischemic heart disease and stroke. Moreover, determining the independent associations of fat-free mass and fat mass with CIMT could provide an opportunity to assess whether CIMT chiefly reflects vascular compensatory remodeling or subclinical atherosclerosis.

The UK Biobank is one of the largest multimodal imaging studies worldwide[26] with data on high-quality measurements of CIMT, anthropometry, and body composition. The present cross-sectional analyses used data from the UK Biobank imaging survey to assess the sex-specific independent relevance of different measures of general adiposity (BMI), central adiposity (waist circumference), and body composition (fat mass index and fat-free mass index) with CIMT after adjustment for potential confounders and mutual adjustment for other adiposity measures.

METHODS

Procedures for requesting the data, methods used in the analyses, and materials used to conduct this study are provided on the Nuffield Department of Population Health website (https://www.ndph.ox.ac.uk/files/about/ndph-data-access-policy.pdf).[27]

Study Population and Methods

The study design and data collection methods used in the UK Biobank have been previously reported.[28,29] In brief, the UK Biobank is a prospective cohort study of ≈0.5 million adults who were recruited from the general population of the United Kingdom from 2006 to 2010. Sociodemographic, lifestyle, and health-related data were collected using self-completed touchscreen questionnaires and verbal interviews. Physical measurements, including anthropometry and blood pressure, were recorded in all participants, and a blood sample was collected for long-term storage. An imaging survey, aiming to recruit 100 000 participants from the baseline assessment, commenced in 2014 and is scheduled to be completed in 2023.[26] All surviving

UK Biobank participants will be invited for the imaging survey, except those who declined to provide consent and those living outside the United Kingdom. The imaging assessment centers were located in Stockport (Central), Newcastle-upon-Tyne (North), Reading (South-East), and Bristol (South-West).[26] At the imaging visit, participants underwent brain, cardiac, and abdominal magnetic resonance imaging, dual-energy x-ray absorptiometry, and carotid ultrasound, in addition to a baseline assessment.[26] The UK Biobank received ethical approval from the North West Multicentre Research Ethics Committee (REC reference: 11/NW/03820). All participants provided written informed consent.[28]

Standing height was measured to the nearest 0.1 cm using a Seca 240 cm height measure (Seca; Hamburg, Germany). Weight was measured to the nearest 0.1 kg using a Tanita BC418MA body composition analyzer (Tanita, Tokyo, Japan).[30] BMI was calculated by dividing the weight in kilograms by the height in meters squared. With participants standing and dressed in light clothing, waist circumference was measured on expiration using a 200-cm Seca tape (Seca) at the narrowest part of the trunk (ie, the natural indent) or the level of the umbilicus if the natural indent was not found.[30] Whole-body fat mass and fat-free mass were measured to the nearest 0.1 kg using a Tanita BC418MA body composition analyzer (Tanita; Tokyo, Japan). Fat mass index and fat-free mass index were obtained by dividing fat mass and fat-free mass by the height squared in meters, respectively.[30] CIMT was measured using a CardioHealth Station ultrasound system (Panasonic Healthcare Corporation of America; Newark, NJ).[31] Participants were placed in the supine position, with their head rotated at 45°. A 5 to 13 MHz linear array transducer imaged the CIMT of the right common carotid artery at an angle of 150° and 120°, and the left common carotid artery at 210° and 240°.[31] At each angle, the mean CIMT was measured 10 mm proximal to the flow divider at end-diastole using automated edge-detection software. Sonographers assessed CIMT scan quality against predefined UK Biobank criteria, and a senior radiographer reviewed all scans at regular intervals. Approximately 10% of randomly selected scans and borderline quality scans were externally validated at the Oxford Cardiovascular Clinical Research Facility.[31]

Statistical Analysis

Analyses were based on measurements recorded at the UK Biobank imaging survey, which began in 2014 and included assessments of 49 000 participants by March 1, 2020. Analyses excluded participants with a self-reported diagnosis of CVD (angina, myocardial infarction, or stroke) or cancer, missing data for all adiposity and CIMT measurements, and sex-specific outliers of each adiposity measure. Potential categorical confounders (ethnicity, Townsend deprivation, smoking status, alcohol status, and physical activity) with <1% missing data were imputed using the age- and sex-specific mode. Among the adiposity exposures, ≈2% were missing, and these continuous variables were imputed with regression imputation. Imputation was performed under the missing at random assumption after considering all known variables that could predict missing data.

CIMT was moderately positively skewed, and so values were $\log_e$-transformed. Adiposity measures included BMI (general adiposity) and waist circumference (central adiposity), fat mass index, and fat-free mass index (both body composition measures). Potential confounders included age (continuous), ethnicity or race (White, Mixed, Indian, Black, Chinese, Other), Townsend deprivation quintile (ordinal), which is an area-based score of social deprivation based on 4 variables (unemployment, non-car ownership, non-house ownership, and household crowding) and was obtained from the most recent national census before participant enrollment in the UK Biobank (with positive values indicating higher deprivation and negative values indicating less social deprivation).[32] Key covariates included smoking status (never, previous, current), alcohol intake (never, previous, monthly or less, 1–2 times/week, 3–4 times/week, daily or almost daily), self-reported physical activity measured as metabolic equivalent of task hours/wk based on the International Physical Activity Questionnaire guidelines[33] (ordinal: <10 [low], 10–50 [moderate], >50 [high] metabolic equivalent of task hours/wk), and family history of atherosclerotic CVD (no, yes). Because associations between adiposity measures and $\log_e$ CIMT were all linear, adiposity measures were included in the sex-specific multivariable linear regression models as continuous variables to estimate the mean (95% CI) difference in $\log_e$ CIMT per given increase in each adiposity measure (1.1 SD for women and 1.3 SD for men, chosen to correspond to 5 kg/m^2 BMI). To assess the independent associations of each adiposity measure with $\log_e$ CIMT, the change in the likelihood ratio statistic was calculated for multivariable models before and after mutual adjustment for other adiposity measures. BMI and waist circumference were adjusted for each other, as were fat mass index and fat-free mass index. Effect modification by age (45–59; 60–69; ≥70 years) was assessed by including an interaction term in the multivariable model and performing a likelihood ratio test. A semiquantitative estimate of mediation was evaluated using a likelihood ratio test, which assessed the change in the likelihood ratio χ^2 statistic for each adiposity measure following sequential adjustment for potential intermediate factors, including systolic blood

pressure (SBP), antihypertensive medication, and diabetes. A variance inflation factor <5 indicated multicollinearity between adiposity measures. There were no violations of linear regression assumptions. Sensitivity analyses also evaluated the potential impact of confounding and reverse causality by excluding current smokers, and participants with emphysema or diabetes. Multivariable logistic regression also assessed the odds of CIMT being above the sex-specific 75th percentile per given increase in each adiposity measure. Statistical analyses were performed using STATA version 16.

RESULTS

The present analyses were conducted in 39 367 participants after excluding individuals with previously diagnosed CVD (n=1909), cancer (n=4668), missing data for all adiposity and CIMT measurements (n=3008), and sex-specific outliers of each adiposity measure (n=46). The mean (SD) age of these 39 367 participants was 64 (8) years, 52% were women, and 97% reported White race. Mean (SD) levels of SBP were higher in men than in women (142 [17] versus 136 [19] mm Hg) (Table). In both sexes, those with higher CIMT tended to be older, have a higher mean SBP, and use antihypertensive medication and statins. However, deprivation levels were similar across CIMT levels, with participants having less social deprivation overall (Tables S1–S3). Men had a higher mean BMI, waist circumference, and fat-free mass index than women. However, women had a higher fat mass index than men. Median (interquartile range) CIMT was greater in men than in women (0.69 [0.18] versus 0.65 [0.14] mm) (Table).

All adiposity measures were linearly and positively associated with CIMT after adjustment for potential confounders, with stronger associations in men than in women (Figure 1). In both sexes, fat-free mass index was most strongly and positively associated with CIMT, and associations were largely unaltered by mutual adjustment for fat mass index. After adjusting for fat mass index, mean CIMT increased by 1.23% (95% CI, 0.93–1.53) for every 1.7 kg/m^2 higher fat-free mass index in women and by 3.44% (3.01–3.86) for every 2.3 kg/m^2 higher fat-free mass index in men. By contrast, after adjusting for fat-free mass index, associations of fat mass index with CIMT were attenuated in both women and men, from 1.15% (0.93–1.36) to 0.28% (–0.02, 0.58) for every 3.6 kg/m^2 higher fat mass index (with a 97% reduction of the χ^2 statistic) for women, and from 1.53% (1.20–1.86) to –0.59% (–0.99, –0.18) for every 3.1 kg/m^2 higher fat mass index (with a 91% reduction of the χ^2 statistic) in men (Figure 2). BMI remained independently related to CIMT after adjustment for waist circumference in both women and men. However, waist circumference was completely attenuated after adjustment for BMI, with a 98% reduction of the χ^2 statistic in women and a 97% reduction in men (Figure 2). The associations of all adiposity measures with CIMT were attenuated with increasing age (Figure 3). Following adjustment for SBP and antihypertensive medication, the positive associations of all adiposity measures with CIMT attenuated, but fat-free

Table. Characteristics of Participants in the UK Biobank Imaging Survey, by Sex

Characteristics	Women (n=20 571)	Men (n=18 796)
Sociodemographic factors		
Age, mean (SD), y	63 (8)	64 (8)
Ethnicity or race, n (%)		
White	19 938 (97)	18 180 (97)
Mixed	128 (0.6)	65 (0.4)
Indian	168 (0.8)	266 (1.4)
Black	136 (0.7)	128 (0.7)
Chinese	72 (0.4)	51 (0.3)
Other	129 (0.6)	106 (0.6)
Townsend deprivation, median (IQR)	–2.5 (3.4)	–2.7 (3.4)
Medical history, n (%)		
Hypertension*	10 607 (52)	11 757 (63)
Type 2 diabetes	701 (3)	1234 (7)
Self-reported medication use		
Anti-hypertensive	3536 (17)	5035 (27)
Statin	2909 (14)	5359 (29)
Family history of CVD	12 379 (60)	10 091 (54)
Lifestyle behaviors, n (%)		
Current smoker	613 (3)	779 (4)
Daily/almost daily alcohol intake	2734 (13)	3887 (21)
Moderate physical activity†	10 885 (53)	10 005 (53)
Clinical measures, mean (SD)		
Systolic blood pressure, mm Hg‡	136 (19)	142 (17)
LDL cholesterol, mmol/L§	3.6 (0.8)	3.6 (0.8)
Glycated hemoglobin, %§	5.3 (2.6)	5.4 (2.7)
Adiposity measures, mean (SD)		
Height, cm	163 (6.2)	176 (6.6)
Weight, kg	69 (13.0)	83 (13.2)
Body mass index, kg/m^2	26.0 (4.7)	26.9 (3.8)
Waist circumference, cm	82.7 (11.8)	94.0 (10.6)
Fat mass index, kg/m^2	9.6 (3.4)	7.0 (2.4)
Fat-free mass index, kg/m^2	16.4 (1.6)	19.9 (1.8)
Carotid measures, median (IQR)		
Carotid intima–media thickness, mm	0.65 (0.14)	0.69 (0.18)

CVD indicates cardiovascular disease; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic equivalent of task; and UK, United Kingdom.

*Defined as self-reported hypertension or measured systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

†Moderate physical activity classified as a 10–50 MET hours/wk.

‡Systolic blood pressure measured in 17 207 women and 15 974 men.

§Represents baseline values from 2006 to 2010.

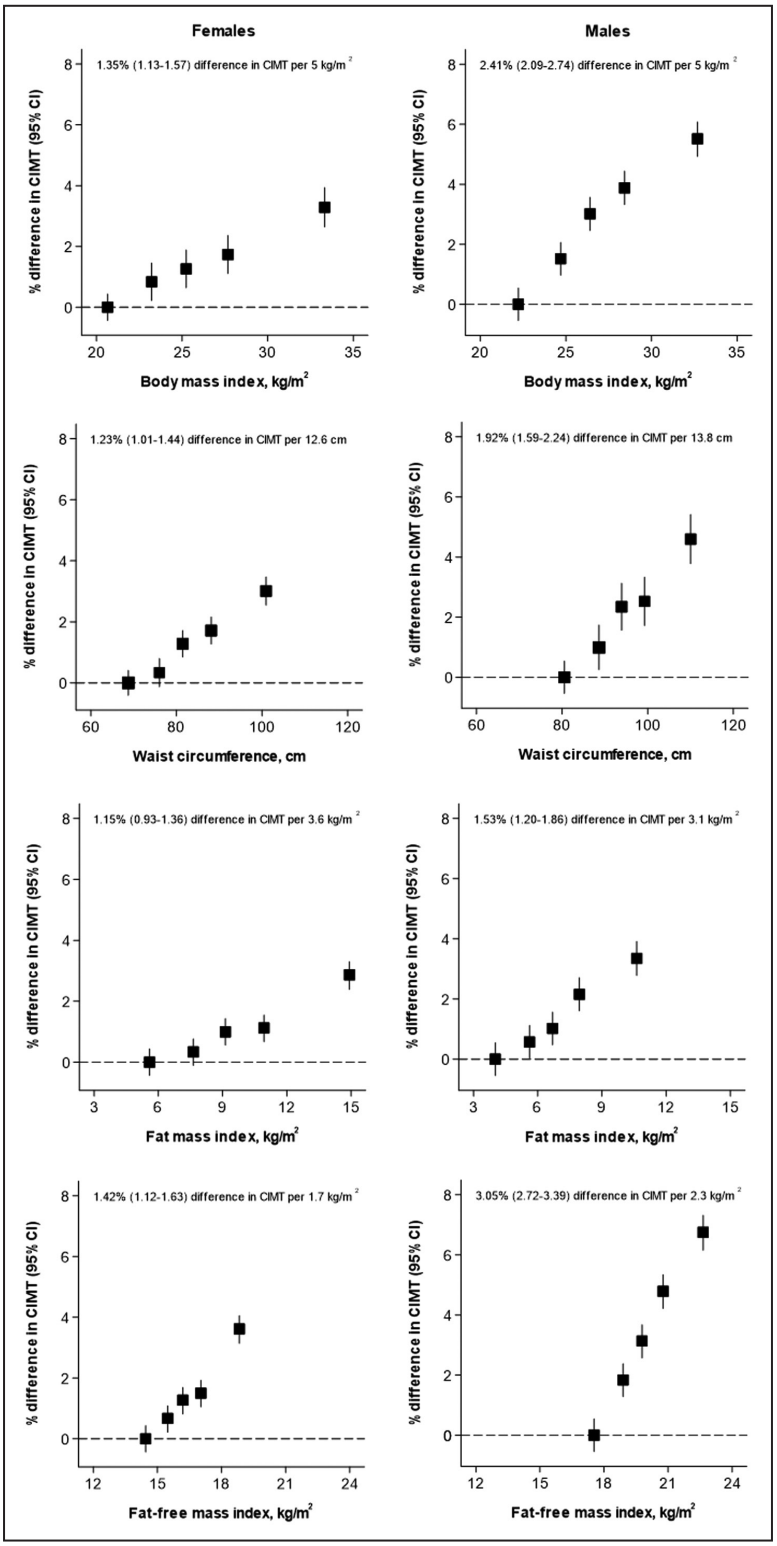


Figure 1. Mean percentage difference in CIMT per specified unit increase in adiposity measures, by sex.

All models adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease. Group-specific estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Vertical lines represent group-specific 95% CIs. CIMT indicates carotid–intima media thickness.

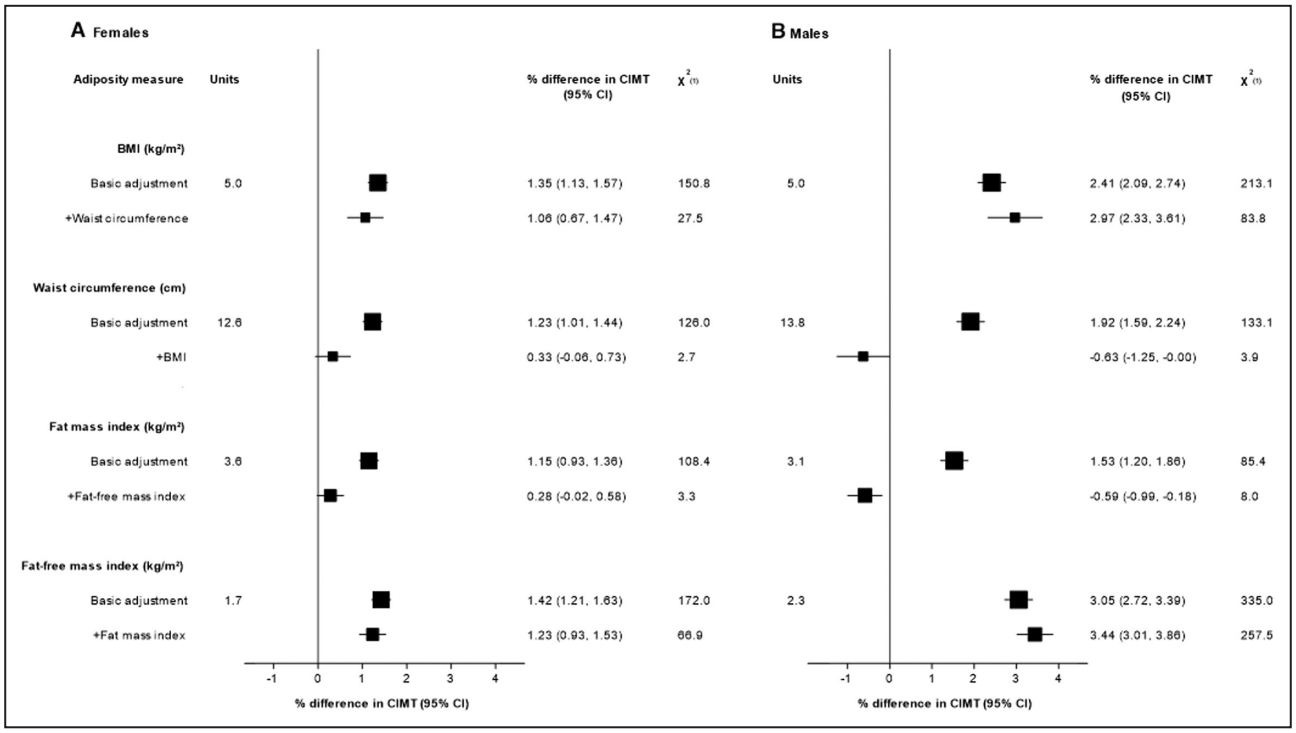


Figure 2. Mean percentage difference in CIMT per specified unit increase in adiposity measures after basic adjustment and mutual adjustment for adiposity measures, by sex.
Analyses adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease with further mutual adjustment for other adiposity measures. Point estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Horizontal lines represent 95% CIs. BMI indicates body mass index; and CIMT, carotid–intima media thickness.

mass index maintained the strongest positive association with CIMT in both sexes (Figure 4). In sensitivity analyses, the associations of all adiposity measures with CIMT were largely unaltered after excluding current smokers and individuals with chronic diseases (Figure S1–S3), or when restricted to complete case

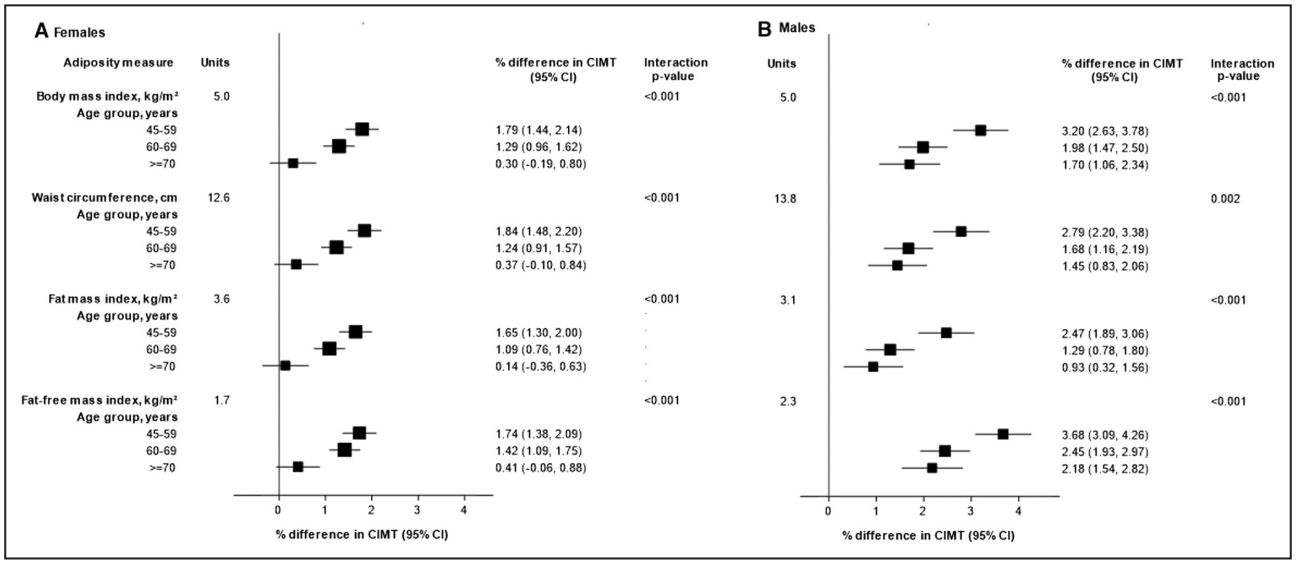


Figure 3. Mean percentage difference in CIMT per specified unit increase in adiposity measures, by age group and sex.
All models adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease. Point estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Horizontal lines represent 95% CIs. CIMT indicates carotid–intima media thickness.

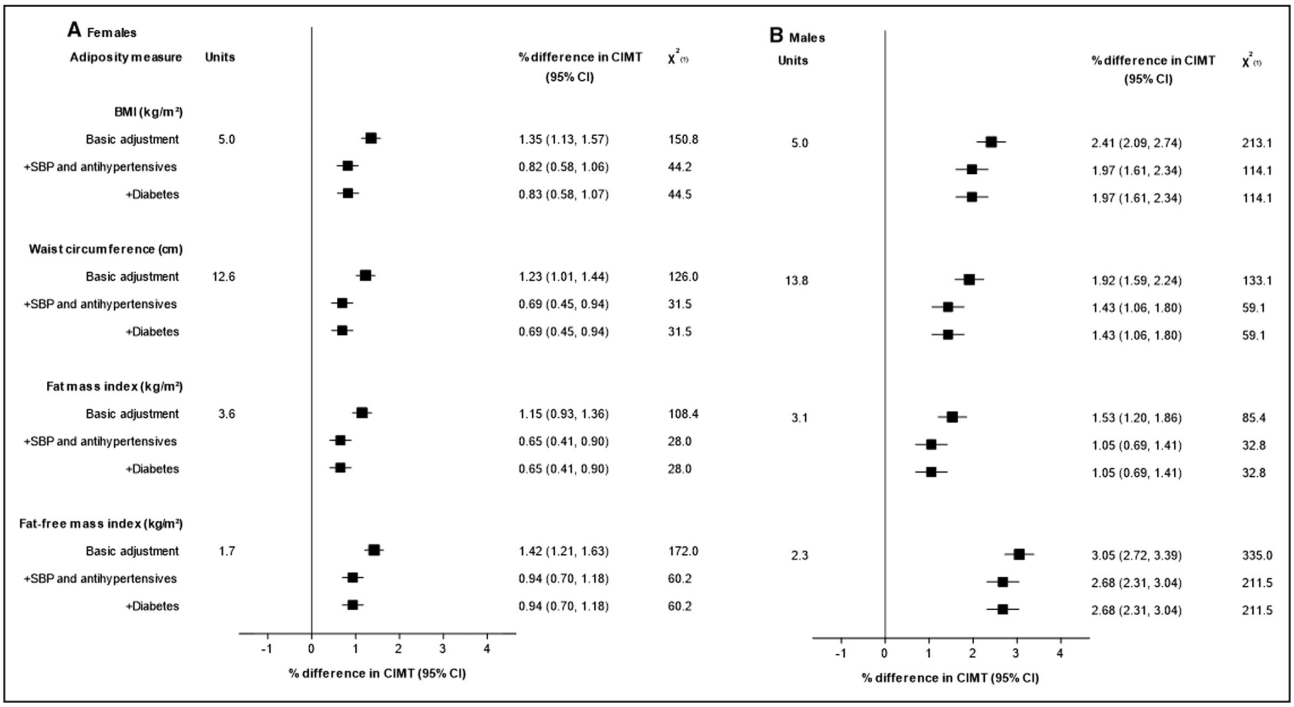


Figure 4. Mediation analyses showing the mean percentage difference in CIMT per specified unit increase in adiposity measures, by sex.

Basic adjustment was made for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease. Point estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Horizontal lines represent 95% CIs. BMI indicates body mass index; CIMT, carotid–intima media thickness; and SBP, systolic blood pressure.

analyses (Figure S2). Following mutual adjustment, the odds of CIMT being above the sex-specific 75th percentile was greatest for increasing fat-free mass index, while higher fat-mass index demonstrated no association with CIMT in both sexes (Table S3).

DISCUSSION

All measures of general and central adiposity and body composition were linearly and positively associated with CIMT after adjusting for potential confounders. The strengths of associations of each adiposity measure with CIMT were more extreme in men than in women and were attenuated with increasing age. In both sexes, fat-free mass index and BMI were independently associated with CIMT after adjustment for fat-mass index and waist circumference, respectively. However, fat-free mass index was the single adiposity measure most strongly and independently associated with CIMT in both sexes. In contrast, the strong positive associations of fat mass index and waist circumference with CIMT were completely attenuated after adjustment for fat-free mass index and BMI, respectively. Following adjustment for SBP and antihypertensive medication, associations of adiposity measures with CIMT attenuated, but fat-free mass index remained the most strongly and positively associated with CIMT in both men and women.

The findings of the present study demonstrated that fat-free mass index was the most important determinant of CIMT. The results showed that among the wide range of CIMT values studied, CIMT may be influenced to a greater extent by compensatory remodeling of the arterial wall rather than subclinical atherosclerosis, because fat-free mass index is associated with compensatory vascular remodeling.[34] Furthermore, higher levels of blood pressure attributable to higher fat-free mass was associated with increasing thickness of the media layers of the arterial wall to maintain the arterial circumferential wall stress.[34] Fat-free mass was also the single adiposity measure most strongly associated with left ventricular mass[10] and atrial fibrillation.[11,35] The mechanisms underlying these associations are not fully understood, but the present study suggests that fat-free mass may also influence vessel wall thickness.[36] Further research is needed to elucidate possible thresholds at which fat-free mass contributes to structural changes in the blood vessel wall and effects on CVD outcomes. Because fat-free mass index was most strongly associated with CIMT, this could explain why CIMT, specifically at lower levels, is less predictive of atherosclerotic CVD risk than carotid plaques, which chiefly involve subintimal atherosclerosis.[21,37–40] However, higher levels

of CIMT have demonstrated positive associations with atherosclerotic CVD and may refine risk prediction in individuals at intermediate CVD risk.[39,41–43] The American Society of Echocardiography has also defined CIMT as a diffuse plaque when CIMT is at least 1.5 mm because it is hypothesized that CIMT in such circumstances may reflect increased intimal thickness.[44]

Therefore, further research is required to assess the associations of adiposity measures at levels of CIMT, which are considered plaque equivalents. In contrast with the present report, previous studies that evaluated CIMT as a marker of subclinical atherosclerosis demonstrated that central adiposity was more strongly associated with CIMT than BMI.[22,23,45] However, these findings were limited by a smaller sample size, incomplete assessment of independent associations, adjustment for intermediate factors, and use of different methods to measure CIMT. Importantly, few studies assessed measures of body composition in addition to anthropometric adiposity measures.[24,25] Consistent with the findings of the present study, a cross-sectional study involving ≈6500 healthy young Chinese adults also reported that fat-free mass was the single adiposity measure that was most strongly associated with CIMT.[25] Furthermore, fat-free mass remained positively associated with CIMT after adjustment for fat mass, while fat mass attenuated after adjustment for fat-free mass.[25] Likewise, another cross-sectional study involving ≈3000 Chinese adults reported that percentage body fat was the single least strongly associated adiposity measure with CIMT,[24] albeit, fat-free mass was not evaluated and independent associations were not assessed.[24] The findings of the present study are consistent with the previous study of Chinese adults and suggest that despite differences in body composition between Chinese and Europeans,[46] fat-free mass was positively associated with CIMT in both populations. The inverse associations of fat mass with CIMT after adjusting for fat-free mass among men in the present study requires replication in independent populations. However, a study in adolescents and young adults also reported that fat mass was inversely associated with CIMT, and that higher levels of fat mass were associated with an increased arterial lumen diameter without a corresponding increase in CIMT resulting in increased circumferential wall stress.[34] Importantly, the present study adds to the reliability of the available evidence on those with CIMT associations by conducting analyses in ≈40 000 adults from the general UK population and assessing the independent relevance of different adiposity measures with CIMT. Furthermore, evaluating the relevance of body composition has enhanced our understanding of the possible mechanisms underlying associations of adiposity with CIMT by distinguishing fat mass from fat-free mass.[47]

The associations of fat-free mass index with CIMT were stronger in men than in women, which may reflect sex differences in hormonal regulation of body composition and higher fat-free mass in men.[48] An increased fat-free mass may increase cardiac output and blood pressure in response to the metabolic demands of skeletal muscle,[49] resulting in physiological compensatory thickening of the media and an increased CIMT.[50] In the present study, men had higher mean levels of SBP than women, which may also increase CIMT chiefly by thickening of the media layer.[51] However, after adjusting for SBP and antihypertensive medication, fat-free mass index remained positively associated with CIMT in both sexes, which suggests that fat-free mass was associated with CIMT independent of blood pressure. Although CIMT increases with advancing age,[52] the present study demonstrated that older individuals had smaller increases in CIMT per unit increase in each adiposity measure. The strength of the associations of each adiposity measure with CIMT attenuated above age 70 years in women and above age 60 years in men. The sex differences in age of onset may be explained by men developing CVD risk factors such as hypertension at an earlier age than women, and highlight the importance of initiating lifestyle modification and medication to reduce CIMT.[53,54]

The chief strengths of the present study included the large number of participants studied. Furthermore, it was the first large-scale study to be conducted in the United Kingdom that assessed the independent relevance of adiposity measures, including body composition, with CIMT. Analyses were sex-stratified to control for the different patterns of adiposity in women and men.[55] Importantly, the UK Biobank had a detailed ultrasound protocol for measurement of CIMT and rigorous quality control to ensure high levels of reliability and validity. The ability to determine independent associations of fat mass index and fat-free mass index with CIMT enhances our understanding of CIMT reflecting compensatory vascular remodeling. The study has potential clinical implications for assessing subclinical atherosclerosis for prediction of atherosclerotic CVD. The study also had some limitations, including the cross-sectional study design, which may constrain any assessment of causality. Approximately 97% of participants reported White race, which may reduce the generalizability of the findings of the present study to other racial or ethnic groups, since adiposity measures and CIMT also vary by race and ethnicity.[46,56] Because the mechanisms underlying these associations of adiposity and CIMT are not fully understood, one cannot exclude the possibility of residual confounding or reverse causality bias.[57] However, the findings were largely unaltered in sensitivity analyses, which assessed the potential impact of reverse causality. Repeat measurements of cholesterol and glycated hemoglobin were not available for participants in the imaging survey, which limited additional adjustment for these potential intermediate factors. Lastly,

the findings of this study may only be applicable to lower levels of CIMT because at higher levels of CIMT, intimal thickening and CIMT plaque equivalents may subsequently result in subclinical atherosclerosis to a greater extent. Moreover, carotid plaques were not evaluated in UK Biobank participants. Using other imaging modalities including dual energy x-ray absorptiometry, computed tomography, and magnetic resonance imaging may enhance the understanding of the associations of visceral adipose tissue or subcutaneous adipose tissue and muscle mass with CIMT. Overall, the present study demonstrated that fat-free mass index was the single adiposity measure most strongly associated with CIMT, which suggests that CIMT may be influenced to a greater extent by compensatory remodeling of the arterial wall rather than subclinical atherosclerosis. The findings suggest that carotid ultrasound examinations should consider including screening for carotid plaques in addition to CIMT when screening for subclinical atherosclerosis.

ARTICLE INFORMATION

Received May 5, 2022; accepted November 15, 2022.

Affiliation

Nuffield Department of Population Health, University of Oxford, UK.

Acknowledgments

The authors gratefully acknowledge the contribution of all participants and staff involved in the UK Biobank.

Sources of Funding

The UK Biobank was supported by grants from Wellcome Trust and Medical Research Council (MRC). Dr Clarke and S. Lewington were also supported by grants from BHF and MRC. The study was also supported by core grants to CTSU (Clinical Trial Service Unit) from the Medical Research Council (Clinical Trial Service Unit A310) and the British Heart Foundation (CH/1996001/9454 [J.C., H.T., S.L.]) and by the NIHR Oxford Biomedical Research Centre (J.C., S.L.).

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

REFERENCES

1. Fantuzzi G, Mazzone T. Adipose tissue and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2007;27:996–1003. doi: 10.1161/ATVBAHA.106.131755
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
3. World Health Organization. Obesity and overweight. 2018. Available at: https://www.who.int/news-room/fact-sheets/detail/obesityand-overweight. Accessed 15 December 2022.
4. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27. doi: 10.1056/NEJMoa1614362
5. Health Survey for England. Overweight and obesity in adults and children. 2019. Available at: https://healthsurvey.hscic.gov.uk/supportguidance/public-health/health-survey-for-england-2019/overweight-and-obesity-in-adult-and-children.aspx. Accessed 15 December 2022.
6. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377:1085–1095. doi: 10.1016/S0140-6736(11)60105-0
7. Cornier M-A, Després J-P, Davis N, Grossniklaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge MP, Towfighi A, et al. Assessing adiposity. *Circulation*. 2011;124:1996–2019. doi: 10.1161/CIR.0b013e318233bc6a
8. Knowles R, Carter J, Jebb SA, Bennett D, Lewington S, Piernas C. Associations of skeletal muscle mass and fat mass with incident cardiovascular disease and all-cause mortality: a prospective cohort study of UK biobank participants. *J Am Heart Assoc*. 2021;10(9):e019337. doi: 10.1161/JAHA.120.019337
9. Rider OJ, Francis JM, Ali MK, Byrne J, Clarke K, Neubauer S, Petersen SE. Determinants of left ventricular mass in obesity; a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2009;11:1–9. doi: 10.1186/1532-429X-11-9
10. Bella JN, Devereux RB, Roman MJ, O'Grady MJ, Welty TK, Lee ET, Fabsitz RR, Howard BV. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. *Circulation*. 1998;98:2538–2544. doi: 10.1161/01.cir.98.23.2538
11. Fenger-Grøn M, Overvad K, Tjønneland A, Frost L. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. *J Am Coll Cardiol*. 2017;69:2488–2497. doi: 10.1016/j.jacc.2017.03.558
12. O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima–media thickness. *Eur Heart J*. 2010;31:1682–1689. doi: 10.1093/eurheartj/ehq185
13. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen T-P, Sander D, Plichart M, Catapano AL, Robertson CM, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet*. 2012;379:2053–2062. doi: 10.1016/S0140-6736(12)60441-3
14. Magnussen CG. Carotid artery intima-media thickness and hypertensive heart disease: a short review. *Clin Hypertens*. 2017;23:1–4. doi: 10.1186/s40885-017-0063-3
15. Simova I. Intima-media thickness: appropriate evaluation and proper measurement. *J Cardiol Pract*. 2015;13:1–4.
16. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging*. 2014;7:1025–1038. doi: 10.1016/j.jcmg.2013.11.014
17. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovasc Dis*. 2012;34:290–296. doi: 10.1159/000343145
18. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2010;122:e584–e636. doi: 10.1161/CIR.0b013e3182051b4c
19. Members ATF, Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eht151
20. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128–133. doi: 10.1016/j.atherosclerosis.2011.06.044
21. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol*. 2010;30:182–185. doi: 10.1161/ATVBAHA.109.196980
22. Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis risk in communities (ARIC) study investigators. *Stroke*. 1994;25:66–73. doi: 10.1161/01.STR.25.1.66

23. Yan RT, Yan AT, Anderson TJ, Buithieu J, Charbonneau F, Title L, Verma S, Lonn EM. The differential association between various anthropometric indices of obesity and subclinical atherosclerosis. *Atherosclerosis*. 2009;207:232–238. doi: 10.1016/j.atherosclerosis.2009.03.053
24. Zhang Z-q, He L-p, Xie X-y, Ling W-h, Deng J, Su Y-x, Chen Y-m. Association of simple anthropometric indices and body fat with early atherosclerosis and lipid profiles in Chinese adults. *PLoS One*. 2014;9:e104361. doi: 10.1371/journal.pone.0104361
25. Arnold M, Linden A, Clarke R, Guo Y, Du H, Bian Z, Wan E, Yang M, Wang L, Chen Y, et al. Carotid intima-media thickness but not carotid artery plaque in healthy individuals is linked to lean body mass. *J Am Heart Assoc*. 2019;8:e011919. doi: 10.1161/JAHA.118.011919
26. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell JD, Boultwood C, Collins R, Conroy MC, et al. The UK biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun*. 2020;11:2624. doi: 10.1038/s41467-020-15948-9
27. Nuffield Department of Population Health, University of Oxford. Dataaccess. Available at: https://www.ndph.ox.ac.uk/data-access. Accessed July 16, 2022.
28. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779
29. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, et al. The UK biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562:203–209. doi: 10.1038/s41586-018-0579-z
30. UK Biobank Anthropometry. Available at: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Anthropometry.pdf. Accessed 15 December 2022.
31. Coffey S, Lewandowski AJ, Garratt S, Meijer R, Lynum S, Bedi R, Paterson J, Yaqub M, Noble JA, Neubauer S, et al. Protocol and quality assurance for carotid imaging in 100,000 participants of UK biobank: development and assessment. *Eur J Prev Cardiol*. 2017;24:1799–1806. doi: 10.1177/2047487317732273
32. Office for National Statistics; National Records of Scotland; Northern Ireland Statistics and Research Agency; UK Data Service. Doi: 10.5257/census/aggregate-2011-2.
33. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire. Available at: https://www.physio-pedia.com/images/c/c7/Quidelines_for_interpreting_the_IPAQ.pdf. Accessed 15 December 2022.
34. Chiesa ST, Charakida M, Georgiopoulos G, Dangardt F, Wade KH, Rapala A, Bhowruth DJ, Nguyen HC, Muthurangu V, Shroff R, et al. Determinants of intima-media thickness in the young: the ALSPAC study. *J Am Coll Cardiol Img*. 2021;14:468–478. doi: 10.1016/j.jcmg.2019.08.026
35. Azarbal F, Stefanick ML, Assimes TL, Manson JE, Bea JW, Li W, Hlatky MA, Larson JC, ES LB, Albert CM, et al. Lean body mass and risk of incident atrial fibrillation in post-menopausal women. *Eur Heart J*. 2016;37(20):1606–1613. doi: 10.1093/eurheartj/ehv423
36. Nattel S. Atrial fibrillation and body composition: is it fat or lean that ultimately determines the risk? *J Am Coll Cardiol*. 2017;69:2498–2501. doi: 10.1016/j.jacc.2017.03.566
37. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803. doi: 10.1001/jama.2012.9630
38. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221. doi: 10.1056/NEJMoa1012592
39. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid intima-media thickness task force endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111. doi: 10.1016/j.echo.2007.11.011
40. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1001/jama.2012.9624
41. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987-1993. *Am J Epidemiol*. 1997;146:483–494. doi: 10.1093/oxfordjournals.aje.a009302
42. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
43. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G. Carotid wall thickness is predictive of incident clinical stroke: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol*. 2000;151:478–487. doi: 10.1093/oxfordjournals.aje.a010233
44. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, Becher H, Sillesen H. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33:917–933. doi: 10.1016/j.echo.2020.04.021
45. Ren C, Zhang J, Xu Y, Xu B, Sun W, Sun J, Wang T, Xu M, Lu J, Wang W, et al. Association between carotid intima-media thickness and index of central fat distribution in middle-aged and elderly Chinese. *Cardiovasc Diabetol*. 2014;13:139. doi: 10.1186/s12933-014-0139-2
46. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev*. 2002;3:141–146. doi: 10.1046/j.1467-789x.2002.00065.x
47. Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, Dahlqvist Leinhard O. Advanced body composition assessment: from body mass index to body composition profiling. *J Investig Med*. 2018;66:1–9. doi: 10.1136/jim-2018-000722
48. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care*. 2004;7:271–277. doi: 10.1097/00075197-200405000-00006
49. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. *Physiol Rev*. 2015;95:549–601. doi: 10.1152/physrev.00035.2013
50. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam study. *Stroke*. 1997;28:2442–2447. doi: 10.1161/01.STR.28.12.2442
51. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, Alderman MH, Devereux RB. Parallel cardiac and vascular adaptation in hypertension. *Circulation*. 1992;86:1909–1918. doi: 10.1161/01.CIR.86.6.1909
52. Najjar SS, Scuteri A, Lakatta EG. Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension*. 2005;46:454–462. doi: 10.1161/01.HYP.0000177474.06749.98
53. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, Liao X, Lonn E, Gerstein HC, Yusuf S, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation*. 2020;142:621–642. doi: 10.1161/CIRCULATIONAHA.120.046361
54. Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML, METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical Atherosclerosis: the METEOR trial. *JAMA*. 2007;297:1344–1353. doi: 10.1001/jama.297.12.1344
55. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues–the biology of pear shape. *Biol Sex Differ*. 2012;3:1–2. doi: 10.1186/2042-6410-3-13
56. Rush EC, Goedecke JH, Jennings C, Micklesfield L, Dugas L, Lambert EV, Plank LD. BMI, fat and muscle differences in urban women of five ethnicities from two countries. *Int J Obes*. 2007;31:1232–1239. doi: 10.1038/sj.ijo.0803576
57. Santos IS, Alencar AP, Rundek T, Goulart AC, Barreto SM, Pereira AC, Benseñor IM, Lotufo PA. Low impact of traditional risk factors on carotid intima-media thickness: the ELSA-Brasil cohort. *Arterioscler Thromb Vasc Biol*. 2015;35:2054–2059. doi: 10.1161/ATVBAHA.115.305765

SUPPLEMENTAL MATERIAL

Table S1. Characteristics of female participants in UK Biobank

	Fifths of carotid intima-media thickness, micrometres					
Characteristics	324-<570	570-<622	622-<675	675-<748	748-<1298	All
Number of participants	4 124	4 118	4 124	4 096	4 109	20 571
Socio-demographic factors						
Age, mean (SD), years	58.0 (6.6)	61.2 (6.8)	63.2 (6.9)	65.6 (6.9)	68.0 (6.5)	63.0 (8.0)
Race, n (%)						
White	3 977 (96.4)	3 975 (96.5)	4 003 (97.1)	3 988 (97.4)	3 995 (97.2)	19 938 (96.9)
Mixed	31 (0.8)	38 (0.9)	24 (0.6)	15 (0.4)	20 (0.5)	128 (0.6)
Indian	53 (1.3)	33 (0.8)	38 (0.9)	21 (0.5)	26 (0.6)	168 (0.8)
Black	19 (0.5)	18 (0.4)	26 (0.6)	34 (0.8)	39 (1.0)	136 (0.7)
Chinese	14 (0.3)	27 (0.7)	8 (0.2)	13 (0.3)	10 (0.2)	72 (0.4)
Other	30 (0.7)	27 (0.7)	25 (0.6)	25 (0.6)	22 (0.5)	129 (0.6)
Townsend deprivation, median (IQR)	-2.4 (3.7)	-2.6 (3.5)	-2.5 (3.4)	-2.6 (3.3)	-2.5 (3.5)	-2.5 (3.4)
Medical history, n (%)						
Hypertension *	1 461 (35.4)	1 836 (44.6)	2 129 (51.6)	2 418 (59.0)	2 763 (32.8)	10 607 (52)
Diabetes	93 (2.3)	117 (2.8)	145 (3.5)	169 (4.1)	177 (4.3)	701 (3)
Self-reported medication use						
Anti-hypertensive	435 (10.6)	553 (13.4)	687 (16.7)	849 (20.7)	1 012 (24.6)	3 536 (17)
Statin	343 (8.3)	454 (11.0)	548 (13.3)	690 (16.9)	874 (21.3)	2 909 (14)
Family history of CVD	2 318 (56.2)	2 448 (59.5)	2 501 (60.7)	2 497 (61.0)	2 615 (63.6)	12 379 (60)
Lifestyle behaviours, n (%)						
Current smoker	149 (3.6)	147 (3.6)	110 (2.7)	112 (2.7)	95 (2.3)	613 (3)
Daily/almost daily alcohol intake	508 (12.3)	518 (12.6)	585 (14.2)	568 (13.9)	555 (13.5)	2 734 (13)
Moderate physical activity (10-50 MET hrs/week)	2 230 (54.1)	2 206 (53.6)	2 150 (52.1)	2 157 (52.7)	2 142 (52.1)	10 885 (53)
Clinical measures, mean (SD)						
Systolic blood pressure, mmHg †	126.7 (16.3)	131.5 (17.1)	135.9 (18.1)	140.0 (18.8)	145.0 (20.0)	136.0 (19.0)
Adiposity measures, mean (SD)						
Height, cm	163.3 (6.2)	163.3 (6.2)	163.4 (6.1)	163.2 (6.1)	163.3 (6.2)	163.0 (6.2)
Weight, kg	67.6 (12.2)	68.6 (12.1)	69.6 (12.5)	69.9 (12.7)	71.0 (12.9)	69.0 (13.0)
Body mass index, kg/m^2	25.6 (4.7)	25.8 (4.5)	26.0 (0)	26.2 (4.8)	26.5 (4.8)	26.0 (4.7)
Waist circumference, cm	81.3 (11.5)	81.9 (11.6)	82.7 (11.7)	83.1 (12.0)	84.4 (11.8)	82.7 (11.8)
Fat mass index, kg/m^2	9.4 (3.4)	9.5 (3.4)	9.7 (3.4)	9.8 (3.5)	9.9 (3.5)	9.6 (3.4)
Fat-free mass index, kg/m^2	16.3 (1.6)	16.3 (1.5)	16.4 (1.6)	16.4 (1.6)	16.5 (1.7)	16.4 (1.6)
Carotid measures, median (IQR)						
Carotid intima-media thickness, um	537.8 (39.9)	597.0 (26.3)	646.8 (25.9)	706.8 (35)	809.5 (93.5)	650 (140)

Table S2. Characteristics of male participants in UK Biobank

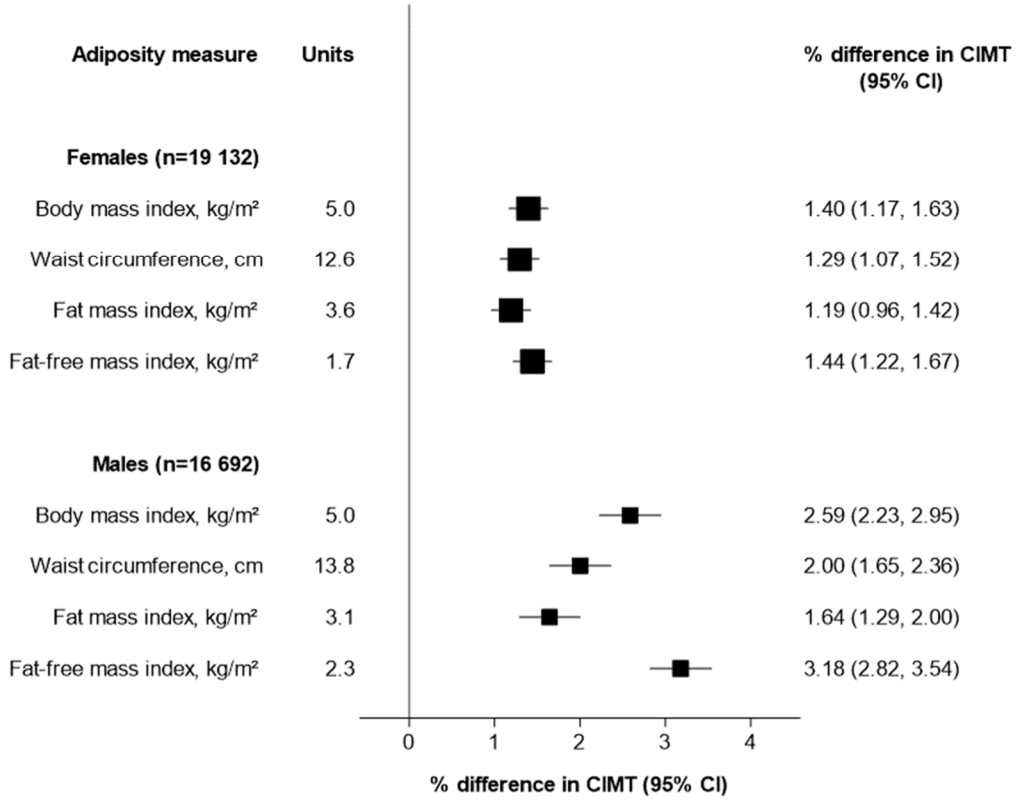
	Fifths of carotid intima-media thickness, micrometres					
Characteristics	315-<590	590-<654	654-<724	724-<814	814-<1295	All
Number of participants	3 774	3 749	3 764	3 756	3 753	18 796
Socio-demographic factors						
Age, mean (SD), years	59.7 (7.3)	62.4 (7.4)	64.7 (7.5)	66.1 (7.2)	68.3 (6.8)	64.0 (8.0)
Race, n (%)						
White	3 601 (95.4)	3 636 (96.9)	3 644 (96.8)	3 658 (97.4)	3 645 (97.1)	18 180 (96.7)
Mixed	24 (0.6)	4 (0.1)	13 (0.4)	12 (0.3)	12 (0.3)	65 (0.4)
Indian	86 (2.3)	53 (1.4)	53 (1.4)	35 (0.9)	39 (1.0)	266 (1.4)
Black	21 (0.6)	27 (0.7)	22 (0.6)	23 (0.6)	35 (0.9)	128 (0.7)
Chinese	11 (0.3)	11 (0.3)	16 (0.4)	7 (0.2)	6 (0.2)	51 (0.3)
Other	31 (0.8)	22 (0.6)	16 (0.4)	21 (0.6)	16 (0.4)	106 (0.6)
Townsend deprivation, median (IQR)	-2.5 (3.6)	-2.6 (3.4)	-2.7 (3.3)	-2.7 (3.4)	-2.8 (3.2)	-2.7 (3.4)
Medical history, n (%)						
Hypertension *	1 850 (49.0)	2 134 (56.9)	2 415 (64.2)	2 549 (67.9)	2 809 (74.9)	11 757 (63)
Diabetes	189 (5.0)	208 (5.6)	245 (6.5)	271 (7.2)	321 (8.6)	1234 (7)
Self-reported medication use						
Anti-hypertensive	792 (21.0)	921 (24.6)	999 (26.5)	1 110 (29.6)	1 213 (32.3)	5 035 (27)
Statin	787 (20.9)	993 (26.5)	1 077 (28.6)	1 198 (31.9)	1 304 (34.8)	5 359 (29)
Family history of CVD	1 948 (51.6)	1 996 (53.2)	2 021 (53.7)	2 054 (54.7)	2 072 (55.2)	10 091 (54)
Lifestyle behaviours, n (%)						
Current smoker	151 (4.0)	166 (4.4)	152 (4.0)	140 (3.7)	170 (4.5)	779 (4)
Daily/almost daily alcohol intake	664 (17.6)	742 (19.8)	785 (20.9)	823 (21.9)	873 (23.3)	3 887 (21)
Moderate physical activity (10-50 MET hrs/week)	2 056 (54.5)	2 022 (53.9)	1 965 (52.2)	2 001 (53.3)	1 961 (52.3)	10 005 (53)
Clinical measures, mean (SD)						
Systolic blood pressure, mmHg †	135.2 (14.9)	139.2 (16.1)	142.5 (16.9)	144.8 (17.6)	148.1 (18.0)	142.0 (17.0)
Adiposity measures, mean (SD)						
Height, cm	176.7 (6.5)	176.7 (6.2)	176.7 (6.5)	176.6 (6.6)	176.8 (6.5)	176.0 (6.6)
Weight, kg	82.8 (12.9)	83.7 (12.7)	84.3 (12.5)	85.1 (12.8)	86.2 (12.8)	83.0 (13.2)
Body mass index, kg/m^2	25.6 (3.8)	26.7 (3.8)	26.9 (3.8)	27.1 (3.8)	27.3 (3.9)	26.9 (3.8)
Waist circumference, cm	92.5 (10.6)	93.3 (10.4)	94.0 (10.4)	94.6 (10.6)	95.5 (10.7)	94.0 (10.6)
Fat mass index, kg/m^2	6.7 (2.4)	6.8 (2.4)	7.0 (2.4)	7.1 (2.4)	7.3 (2.5)	7.0 (2.4)
Fat-free mass index, kg/m^2	19.8 (1.8)	19.9 (1.8)	19.9 (1.8)	20.0 (1.8)	20.1 (1.9)	19.9 (1.8)
Carotid measures, median (IQR)						
Carotid intima-media thickness, um	550 (50.5)	622 (31.9)	688 (35.3)	765 (44.3)	886 (104)	688 (182)

Table S3. Odds ratio of CIMT above the sex-specific 75th percentile per increase of each adiposity measure after mutual adjustment for other adiposity measures

	Females		Males	
Adiposity measure	Basic adjustment OR (95% CI)	Mutual adjustment OR (95% CI)	Basic adjustment OR (95% CI)	Mutual adjustment OR (95% CI)
Body mass index, kg/m^2	1.18 (1.14, 1.23)	1.09 (1.02, 1.17)	1.31 (1.25, 1.37)	1.38 (1.26, 1.51)
Waist circumference, cm	1.18 (1.14, 1.23)	1.09 (1.02, 1.17)	1.24 (1.19, 1.30)	1.24 (1.19, 1.30)
Fat mass index, kg/m^2	1.15 (1.11, 1.20)	1.03 (0.98, 1.08)	1.19 (1.14, 1.24)	0.95 (0.89, 1.00)
Fat-free mass index, kg/m^2	1.20 (1.16, 1.24)	1.18 (1.12, 1.24)	1.41 (1.34, 1.47)	1.46 (1.37, 1.54)

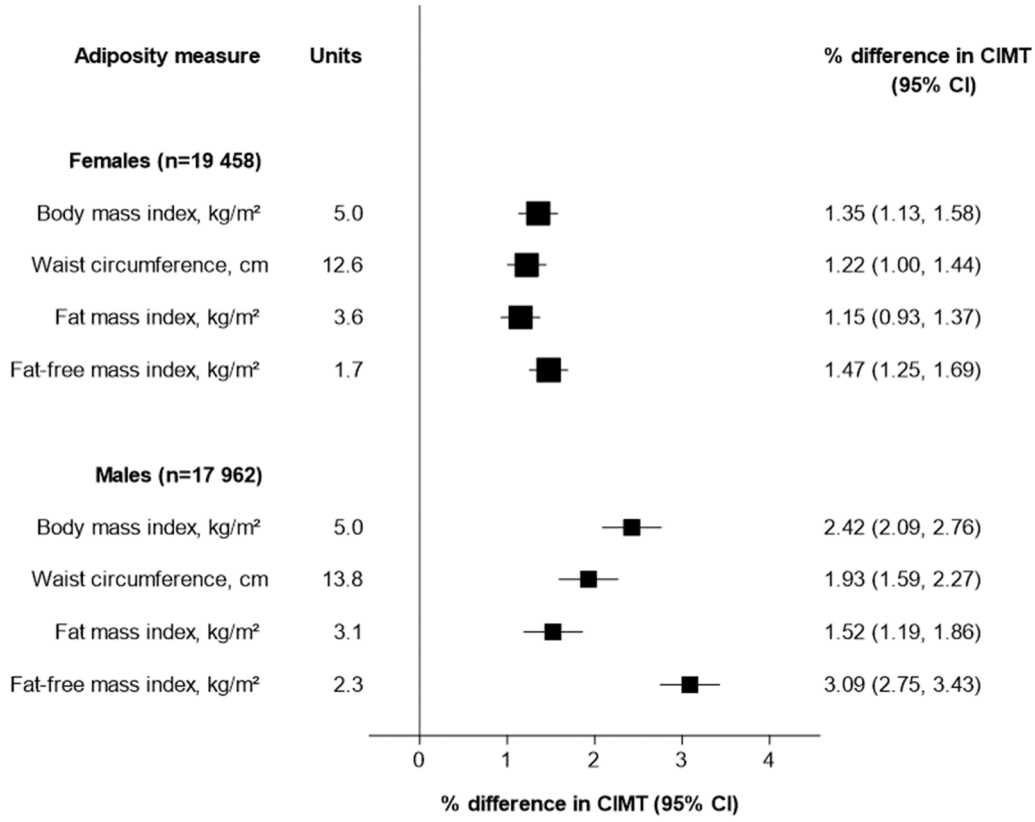
Basic adjustment: Adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of CVD.
Mutual adjustment: body mass index and waist circumference, fat mass index and fat-free mass index mutually adjusted.
OR, odds ratio

Figure S1. Mean percentage difference in carotid-intima media thickness (CIMT) per specified unit increase in adiposity measures after further exclusions, by sex.



All models adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease. Further exclusions were current smokers, and participants with emphysema or diabetes. Point estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Horizontal lines represent 95% confidence intervals (CIs).

Figure S2. Mean percentage difference in carotid-intima media thickness (CIMT) per specified unit increase in adiposity measures with complete case analysis, by sex.



All models were adjusted for age, ethnicity, Townsend deprivation, smoking status, alcohol intake, physical activity, and family history of cardiovascular disease. Point estimates are plotted as squares, with the size of each square proportional to the amount of statistical information. Horizontal lines represent 95% confidence intervals (CIs).