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Visceral adipose tissue and hepatic fat as determinants of carotid atherosclerosis

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Abstract

Background: Visceral adipose tissue (VAT) and hepatic fat (HF) contribute to multiple health risks, including diabetes, hypertension, cardiovascular disease, cognitive decline, and cancer. The objective of this study is to determine whether VAT and HF are associated with carotid atherosclerosis beyond traditional cardiovascular risk factors.

Methods: Participants in the Canadian Alliance of Healthy Hearts and Minds (CAHHM) cohort study ($n = 6760$; average age= 57.1; 54.9% female) underwent MRI for VAT volume, hepatic fat fraction (HFF), and carotid atherosclerosis assessed by carotid wall volume (CWV). Regression models were used to assess the associations of VAT and HF with carotid atherosclerosis, separately in males and females, controlling for other cardiovascular risk factors. Associations of VAT and proton-density hepatic fat fraction (PDFF) with ultrasound-measured carotid-intima media thickness (CIMT) were also assessed in the UK Biobank (UKB; n = 26,547; average age = 54.7; 51.9% female).

Results: In CAHHM, we show that a 1-SD higher VAT volume is associated with a 6.16 mm^3 higher CWV (95% CI: 1.68 to 10.63), but there is no association between HFF and CWV. In the UK Biobank cohort, a 1-SD higher VAT volume is associated with a 0.016 ± 0.009 mm higher CIMT, and a 1-SD higher PDFF is associated with a 0.012 ± 0.010 mm higher CIMT. After adjustment for CV risk factors, these associations are attenuated. A pooled analyses of CAHHM and UKB support a direct, positive association of VAT and HFF with subclinical atherosclerosis in both sexes, albeit slightly weaker for hepatic fat.

Conclusion: Visceral fat, and to a lesser extent, hepatic fat, are associated with increased carotid atherosclerosis.

Plain language summary

Visceral fat, a type of fat stored in the abdomen, and buildup of fat within the liver are known to increase type 2 diabetes, high blood pressure, and heart disease risk. This study aims to see how these types of fat affect artery health. We studied 6760 Canadian adults to examine how visceral and liver fat relate to the buildup of fatty plaque deposits in arteries, and 26,547 adults from the United Kingdom to see how these fats affect artery thickness. Combined results confirm that narrowed arteries and plaque buildup are strongly related to visceral fat, and to a lesser extent liver fat. These results suggest that lowering visceral fat may prevent or slow the progression of atherosclerosis.

In 2022, more than 2.5 billion adults aged 18 years and older were overweight (43% of men and 44% of women), defined as having a body mass index [BMI; weight (kg) divided by height (m^2)] ≥ 25.0 kg/m^2, and of these, over 890 million were obese (BMI ≥ 30 kg/m^2; 16%)[1]. The worldwide prevalence of adult obesity has more than doubled since 1990. At least 2.8 million people die each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) of global disability-adjusted life years are caused by overweight or obesity[2].

A 2023 expert commentary on current clinical challenges surrounding obesity listed six top issues clinicians must deal with, one of which is the need for a better measure of obesity than BMI[3,4]. Abdominal obesity has stronger associations with cardiometabolic risk than overall obesity assessed by BMI[5,6]. A measure of abdominal obesity is waist circumference, which is more closely linked to the accumulation of fat around the visceral organs (visceral adipose tissue; VAT) than BMI[7], and independent of total adiposity, VAT is associated with atherosclerosis progression, even after accounting cardiovascular risk factors[8,9]. The presence of fat within the liver,

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known as hepatic fat (HF), is also associated with the presence of cardiovascular (CV) risk factors and there is some data suggesting it is also related to atherosclerosis. The presence of VAT and or HF likely drives the development of numerous health conditions, including type 2 diabetes mellitus (T2DM), hypertension, elevated cholesterol, increased inflammation, CVD, reduced cognitive function, certain cancers, and increased death[10–15].

This study sought to determine if VAT and HF are associated with carotid atherosclerosis over and above traditional CV risk factors in adult males and females assessed in two cohort studies using two different modalities to measure carotid atherosclerosis: MRI and ultrasound. The Canadian Alliance for Healthy Hearts and Minds (CAHHM) study collected health information, physical measurements, and a magnetic resonance imaging (MRI) scan of the abdomen and carotid arteries in a cross-sectional sample of middle-aged adults and investigated the associations of VAT and hepatic fat fraction (HF) with carotid wall volume (CWV), an index of carotid atherosclerosis[16]. The association of VAT and HF with an ultrasound measure of atherosclerosis (carotid intima-media thickness [CIMT]) collected in the UK Biobank (UKB) was also tested[17]. Pooling data from CAHHM and UKB, visceral and hepatic fat are associated with CV risk factors and carotid atherosclerosis. Adjustment for CV risk factors does not eliminate the association of visceral or hepatic fat with carotid atherosclerosis.

Methods

The CAHHM study enrolled males and females (80% self-identified as "white") between the ages of 35–69 from 8 Canadian cohort studies to undergo a detailed CV assessment including MRI as previously described[18]. Participants were excluded if they had any contraindications to undergoing an MRI scan. Selection of participants from each cohort was stratified to ensure that less than 20% had known CVD, approximately 50% were female, and age was balanced across age strata of 35–45 years, 46–55 years, and 56–69 years. At the time of questionnaire administration, participants were asked to identify as either "male" or "female," therefore the term "sex" is used in this manuscript, but the authors acknowledge that biological sex is not always the same as gender identity. All participants provided written informed consent for completion of study procedures. The CONSORT flow diagram for CAHHM is presented as Supplementary Fig. 1. Research ethics approval was granted by the Hamilton Integrated Research Ethics Board (HiREB #13-255), with consent obtained at each collaborating site as per site-specific regulations prior to participation in the study. This study complied with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data collection

Clinical assessment

The clinical assessment for CAHHM participants consisted of (a) completion of questionnaires, (b) physical measurements, (c) collection of blood samples in some participants, and (d) an MRI scan of the brain, heart, carotid artery, and abdomen. Details of each component have been previously described[16]. Personal and medical history were collected using standardized questions including family history, and health behaviors[16].

Hypertension, dyslipidemia, and diabetes

The presence of these conditions was assessed from self-report on questionnaires, or, for hypertension, also including physical measures taken at the clinic visit[16]. A history of hypertension was defined as either self-reported history of high blood pressure on treatment, or a clinic visit with measured SBP > = 140 mmHg or DBP > = 90 mmHg. A history of dyslipidemia was defined as either self-reported daily use of a cholesterol-lowering medication (e.g., statin) or a self-reported history of high blood cholesterol. A history of diabetes was defined as self-reported history of diabetes mellitus (either type 1 or type 2) on treatment.

Physical measures

Participants' height (stadiometer), weight (scale), waist and hip circumferences (tape measure), and blood pressure (automated OMRON cuff) were collected using a standardized protocol[16]. A measure of percent body fat was determined using biolectrical impedance (BIA) with a Tanita Ironman, Innerscale BC-554. Resistance is measured and input into validated Tanita equations to calculate body composition measurements.

INTERHEART Risk Score (IHRS)

Global CV risk was assessed using a validated score that includes data on age, sex, smoking history, exposure to second-hand smoke, diabetes, high blood pressure, family history of myocardial infarction, waist-to-hip ratio (WHR), stress, depression, diet, and physical activity. The non-lab-based version of the IHRS that did not include data on lipid levels was calculated for each participant[19,20]. Scores range from 0 to 48, with higher scores indicating a greater risk-factor burden. A score of 9 or less was classified as low risk, a score of 10 to 15 as medium risk, and a score of 16 and higher as high risk[19,21]. The development and validation of the IHRS have been previously described[19,21,22].

Modified Framingham Risk Score (mFRS)

In a subset of participants in whom blood was collected ($n = 3597$), apolipoproteins A1 and B (apo A1 and apo B) were measured. The mFRS was calculated using age and sex-specific prediction equations. To incorporate surrogates of high-density lipoprotein, and total cholesterol, these were estimated from measured apo B and A1 values[18,23]. Participants were scored and then categorized into sex-specific risk categories as per the published FRS[23].

Magnetic resonance imaging in CAHHM

The MRI protocol for this study has been described in previous publications[16,18]. The protocol used validated standard techniques and provided information on morphology, function, and tissue characteristics. Briefly, participants underwent a short non-contrast-enhanced scan using a 1.5 or 3.0 Tesla magnet. Each of the 11 local (and 1 mobile) MRI centers underwent a test scan for quality assurance, which was evaluated and validated by the four MRI core labs (heart, carotid, liver, and brain). The MRI outcomes of this study were defined and measured as follows:

Visceral adipose tissue (VAT). VAT volume (mL) was determined by sequences heavily weighted for T1, providing a bright signal for fat. Fat, as defined by anatomically matching high signal intensity areas, was quantified using clinically certified software in axial T1w turbo spin echo (TSE) images positioned across L4-L5. VAT and SAT volumes were analyzed by the core lab, and sex-stratified quartiles were derived.

Hepatic fat fraction (HFF). The HFF (expressed as a percentage, %) was measured on dual- and triple-echo gradient-recalled echo sequences of a standarized abdominal magnetic resonance protocol performed on a 3 T MRI system with a body coil, analyzed and reported by the core lab; and sex-stratified quartiles were derived for analysis.

Carotid Wall Volume (CWV). Carotid artery vessel wall volume (mm^3) (left and right) within a 32-mm vessel length centered on each carotid bifurcation (to include distal common and proximal internal carotid arteries) was measured by subtracting lumen volume from total vessel volume. Carotid vessel wall volume data included in our analyses was defined as the greater of the left and right carotid vessel wall volumes and was used as a quantitative marker for atherosclerosis[24]. Fig. 1 depicts the measurement approach and differences between CWV and carotid intima-media thickness (cIMT) measurements.

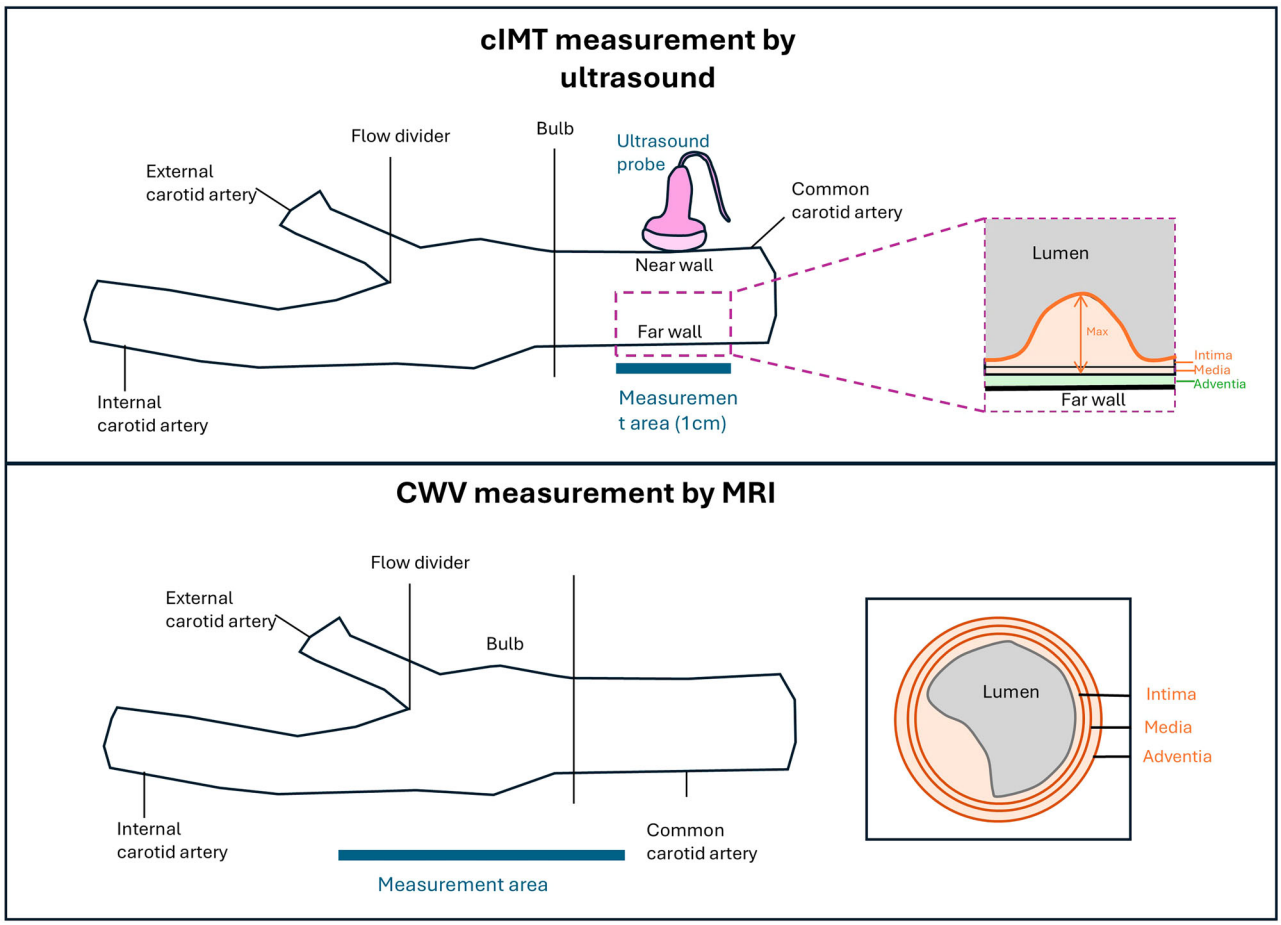

Fig. 1 | Schematic overview of carotid intima-media thickness (cIMT) measurement using ultrasound (top) and carotid wall volume (CWV) measurement using magnetic resonance imaging (MRI; bottom). Anatomical landmarks include the common carotid artery, bifurcation, and internal/external branches. Insets illustrate the vessel wall layers evaluated by each modality.

The UK Biobank

External replication analyses of the associations between VAT, proton-density hepatic fat fraction (PDFF), and carotid atherosclerosis were conducted using data from the UK Biobank (UKB), a prospective cohort of over 500,000 individuals aged 40–69 years, recruited between 2006 and 2010 from centers across the United Kingdom[17]. UK Biobank received ethical approval from the National Health Service (NHS) North West Centre for Research Ethics Committee (Ref11:/NW/0382). Participants attended baseline assessment centers across England, Scotland, and Wales, where they provided informed consent. Data for the present study were accessed under application #15255. UKB individual-level data are available through application (https://www.ukbiobank.ac.uk/register-apply/); aggregate data for this manuscript are presented in text and its Supplementary Information.

From the May 2023 data release, participants who underwent imaging assessments—including carotid ultrasonography and abdominal MRI—were selected if they had valid VAT measurements (mL) and PDFF (%). Carotid ultrasound was used to acquire intima-media thickness at two predefined angles per carotid artery (right: 150°, 120°; left: 210°, 240°), yielding four measurements per participant. For each angle, mean, maximum, and minimum cIMT values were recorded (initially in micrometers, expressed in millimeters for analysis). The highest mean cIMT values at each angle were retained, yielding an analytic sample of 26,547 participants (Supplementary Fig. 2).

Abdominal MRI was used to derive average liver PDFF across three to nine regions of interest. VAT was defined as intra-abdominal adipose tissue, excluding adipose tissue located outside skeletal muscles and posterior to the spine.

Additional data collected during imaging visits included waist and hip circumferences and self-reported lifestyle and health information via touchscreen questionnaire. Variables used in analyses included smoking status (never vs. current/former), alcohol consumption frequency (six-level categorical variable), self-identified ethnicity, and presence of diabetes, hypertension, and dyslipidemia (based on self-reported diagnoses or medication use).

Statistics and reproducibility

Generalized mixed models with an unstructured covariance matrix are used to describe associations of VAT and HFF with CWV, the continuous measure of atherosclerosis, in CAHHM. Models are constructed separately for males and females. Additionally, values of VAT and HFF are each placed into quartiles, and linear contrasts are used to evaluate trends across quartiles of VAT or HFF.

Five models are fitted to account for known and suspected confounders of the associations between adiposity and atherosclerosis measures. Model 1 includes only a random intercept to account for cohort-level clustered effects that may induce variation, such as location (i.e., there were 10 centers across Canada), and characteristics of the MRI machine used at a given site (i.e., brand and magnet strength). The minimally adjusted model adds age and ethnicity, both of which are associated with adiposity and CVD, as fixed covariates (Model 2)[25–27]. This model is then additionally adjusted for the IHRS, which is a single summary measure of several risk factors that together predict CVD, and is correlated with measures of obesity[22] (Model 3;

Table 1 | Associations of sex-specific VAT quartiles with carotid wall volume (mm^3) in the CAHHM cohort

	Carotid Wall Volume, mm^3 in Visceral Adipose Quartiles				
	Q1	Q2	Q3	Q4	*P*-trend
Overall (*N* = 5546)					
N	1428	1401	1397	1320	
No fixed covariates	897.6 (876.8, 918.4)	907.4 (886.6, 928.2)	907.0 (886.2, 927.9)	917.8 (896.9, 938.8)	0.003
Minimally adjusted	899.3 (877.7, 921.0)	902.8 (881.2, 924.5)	903.9 (882.3, 925.6)	911.7 (890.0, 933.5)	0.05
+ IHRS	900.1 (878.7, 921.5)	903.1 (881.8, 924.4)	903.7 (882.4, 925.0)	910.6 (889.0, 932.2)	0.12
+HFF	899.5 (877.7, 921.3)	902.8 (881.3, 924.4)	903.9 (882.4, 925.4)	911.4 (889.3, 933.5)	0.12
Minimal + IHRS without WHR	900.1 (878.5, 921.7)	903.6 (882.0, 925.1)	904.6 (883.0, 926.2)	912.4 (890.6, 934.2)	0.06
Females (*N* = 3054)					
N	800	749	772	733	
No fixed covariates	837.4 (815.5, 859.2)	843.8 (821.7, 865.8)	844.8 (822.8, 866.8)	848.1 (826.0, 870.2)	0.14
Minimally adjusted	842.9 (821.3, 864.5)	844.5 (822.8, 866.1)	842.9 (821.3, 864.5)	843.6 (821.9, 865.3)	0.99
+ IHRS	844.5 (822.8, 866.2)	845.4 (823.7, 867.0)	843.1 (821.6, 864.7)	841.9 (819.9, 863.8)	0.69
+HFF	843.6 (821.8, 865.4)	844.9 (823.3, 866.5)	843.5 (822.1, 865.0)	843.7 (821.3, 866.1)	0.97
Minimal + IHRS without WHR	844.0 (822.4, 865.6)	845.1 (823.4, 866.7)	843.1 (821.5, 864.6)	842.5 (820.7, 864.4)	0.80
Males (*N* = 2492)					
N	628	652	625	587	
No fixed covariates	966.6 (943.4, 989.9)	973.3 (950.1, 996.4)	977.0 (953.6, 1000)	996.8 (973.0, 1021)	0.003
Minimally adjusted	967.6 (945.2, 990.1)	973.7 (951.6, 995.8)	976.5 (954.2, 998.8)	993.2 (970.5, 1016)	0.01
+ IHRS	968.0 (945.4, 990.6)	973.8 (951.7, 995.8)	976.2 (953.9, 998.6)	992.6 (969.4, 1016)	0.03
+HFF	967.3 (944.2, 990.5)	973.4 (951.3, 995.5)	976.4 (954.0, 998.7)	993.1 (969.3, 1017)	0.04
Minimal + IHRS without WHR	967.3 (944.7, 989.9)	973.6 (951.4, 995.7)	976.7 (954.3, 999.1)	993.8 (970.7, 1017)	0.01

Data within each cell are the adjusted least-squared means derived from a mixed model using all participants falling into that sex-specific quartile of VAT. Each mean and (95% confidence interval) is adjusted for the covariates presented in the first column. The minimally adjusted model contains a random effect for centre; as well as fixed effects for age and ethnicity. A linear contrast was used to assess the *P*-trend, using values of 1–4 across the quartiles. *P*- sex interaction > 0.28.
VAT visceral adipose tissue, *IHRS* INTERHEART Risk Score, *HFF* hepatic fat fraction, *WHR* waist-to-hip ratio.

the primary model), and HF (where VAT is the primary exposure) or VAT (where HF is the primary exposure) to estimate the independent association of each measure with the CWV, because of their high intercorrelation within our dataset ($r = 0.53$) (Model 4). These models were also repeated treating VAT and HF as continuous variables, and associations expressed per 1-SD unit. Four sensitivity analyses were conducted. First, the IHRS in Model 3 was replaced with a version excluding WHR, due to the strong correlation of both VAT and HF with WHR. The remaining three analyses used the base minimally adjusted model, restricted to participants with available lipid level data ($n = 3597$; 58% female). These analyses assessed the association across quartile of VAT and HFF, incorporating different covariate sets: (1) the non-laboratory-based IHRS and the Apo B:A1 ratio, (2) the laboratory-based IHRS, and (3) the Apo B:A1 ratio.

As with the primary analyses in CAHHM, models are constructed separately for males and females in UKB. Additionally, values of VAT and PDFF are each placed into quartiles, and linear contrasts are used to evaluate trends across quartiles of ectopic fat. Models are performed (1) without adjustment; and (2) adjusted for age, ethnicity; (3) and waist-to-hip ratio, smoking status, alcohol consumption frequency, hypertension, diabetes, dyslipidemia status; (4) as well as VAT (for PDFF) or PDFF (for VAT).

In a pooled analysis of CAHHM and UKB data, to improve the robustness of the association of VAT and HFF with measures of atherosclerosis, values of CWV and CIMT are standardized within each cohort, and quartile-specific adjusted means are then meta-analyzed using a fixed-effect approach. A value of 0 is interpreted as 1 standard unit of atherosclerosis measure, calculated for each individual as $\frac{x-\bar{x}}{SD}$, where x = individual CIMT or CWV measure, $\bar{x}$ = cohort and sex-specific mean, and SD = cohort and sex-specific SD.

CAHHM analyses were completed in SAS (version 9.2; Cary, NC), and UKB analyses completed in r (https://www.r-project.org/). A fixed effect meta-analysis was used to pool CAHHM and UKB data, and trends across quartiles in the pooled analyses were assessed using variance-weighted least squares estimation on pooled data, implemented in STATA (version 12.1, College Station, TX). A random effects meta-regression model was used to test interactions between sex and quartile of VAT and HFF with atherosclerosis.

Results

The CAHHM analytic cohort consisted of 6760 individuals (54.9% female), with a mean age of 57.1 (SD = 8.8) years. Most participants were white European (79.9%), had a university degree (54.9%), worked full or part-time (72.2%), and never smoked (61.5%). The mean blood pressure of the cohort was 129 (17)/80 (10) mm Hg, with 37.2% reporting a history of hypertension, 36.1% of high cholesterol, and 4.7% of treated diabetes. The prevalence of these conditions was higher in males (Supplementary Data 1). Males had more VAT than females [82.8 (39.3) vs. 60.8 (29.9) mL] and a higher HFF [6.5 (6.0) vs. 5.0 (5.4) %], higher CV risk score [IHRS: 11.5 (5.8) vs. 8.7 (5.4)] and more carotid atherosclerosis by CWV [973 (168) vs. 838 (136) mm^3] (Supplementary Data 1). The distributions of VAT, HFF, and CWV by age and sex; as well as the interrelationships between measures of adiposity are shown in Supplementary Tables 1 and 2. VAT, body fat %, CWV, IHRS, and FRS increased with age in both sexes, while HFF was only increased with age in males. In both sexes, VAT was correlated with HFF, and HFF and VAT were correlated with percent body fat.

VAT, HF and cardiovascular risk factors

VAT and HFF were each associated with higher CV risk factor burden, measured by the IHRS (with or without WHR included in the IHRS), and with the mFRS (Supplementary Fig. 3). Those without lipid measurements for mFRS calculation were more likely to be female (58.2% vs. 52.0%), and white (88.7% vs. 72.2%). They were similar in all other respects (Supplementary Table 3).Consistent with this finding, each 1 sex-specific SD higher

Table 2 | Associations of sex specific HFF quartiles with carotid wall volume (mm^3) in the CAHHM cohort

	Carotid Wall Volume, mm^3 in Hepatic Fat Quartiles				
	Q1	Q2	Q3	Q4	*P*-trend
Overall (*n* = 5546)					
N	1415	1388	1399	1344	
No fixed covariates	903.2 (882.9, 923.5)	905.3 (884.9, 925.7)	911.8 (891.5, 932.1)	908.0 (887.6, 928.4)	0.29
Minimally adjusted	903.3 (881.8, 924.8)	900.6 (879.0, 922.1)	908.4 (886.9, 929.8)	905.2 (883.7, 926.7)	0.45
+ IHRS	904.0 (882.7, 925.3)	901.2 (879.8, 922.5)	908.0 (886.7, 929.3)	903.3 (881.8, 924.8)	0.81
+VAT	907.2 (885.4, 929.0)	903.2 (881.4, 924.9)	907.6 (886.0, 929.2)	899.0 (876.9, 921.1)	0.36
Minimal + IHRS without WHR	903.5 (882.1, 924.9)	900.7 (879.3, 922.2)	908.1 (886.8, 929.5)	904.4 (882.8, 925.9)	0.59
Females (*N* = 3054)					
N	791	758	777	728	
No fixed covariates	841.7 (820.1, 863.4)	843.0 (821.2, 864.9)	847.4 (825.7, 869.1)	840.9 (819.1, 862.7)	0.93
Minimally adjusted	845.2 (823.7, 866.8)	843.6 (821.9, 865.3)	845.9 (824.3, 867.5)	839.9 (818.2, 861.6)	0.54
+ IHRS	846.1 (824.7, 867.4)	844.6 (823.1, 866.1)	845.9 (824.6, 867.2)	837.7 (816.1, 859.3)	0.30
+VAT	848.3 (826.7, 870.0)	846.3 (824.5, 868.0)	845.7 (824.3, 867.1)	833.9 (811.5, 856.2)	0.10
Minimal + IHRS without WHR	845.8 (824.4, 867.2)	844.3 (822.7, 865.8)	845.9 (824.5, 867.2)	838.4 (816.7, 860.0)	0.36
Males (*N* = 2492)					
N	624	630	622	616	
No fixed covariates	974.5 (952.2, 996.9)	971.2 (948.8, 993.5)	984.2 (962.0, 1007)	980.1 (957.7, 1002)	0.32
Minimally adjusted	973.7 (951.7, 995.6)	970.1 (948.2, 992.0)	983.5 (961.6, 1005)	982.0 (960.0, 1004)	0.19
+ IHRS	974.5 (952.5, 996.6)	970.7 (948.7, 992.6)	982.9 (961.1, 1005)	980.5 (958.2, 1003)	0.34
+VAT	979.0 (956.0, 1002)	972.9 (950.4, 995.5)	982.1 (959.7, 1004)	975.6 (952.2, 999.0)	0.98
Minimal + IHRS without WHR	973.7 (951.7, 995.8)	970.2 (948.2, 992.1)	983.6 (961.7, 1005)	982.1 (959.8, 1004)	0.21

Data within each cell are the adjusted least-squared means derived from a mixed model using all participants falling into that sex-specific quartile of VAT. Each mean and (95% confidence interval) is adjusted for the covariates presented in the first column. The minimally adjusted model contains a random effect for centre; as well as fixed effects for age and ethnicity. A linear contrast was used to assess the P-trend, using values of 1–4 across the quartiles. *P*-sex interaction > 0.41.

VAT visceral adipose tissue, *IHRS* INTERHEART Risk Score, *HFF* hepatic fat fraction, *WHR* waist-to-hip ratio.

VAT volume or HFF was associated with 1.5 to 2-fold higher odds of each of hypertension, diabetes, and dyslipidemia (Supplementary Table 4) in both sexes.

VAT and HF and carotid atherosclerosis

In CAHHM, a 1-SD higher VAT volume was associated with a 6.16 mm^3 higher CWV (95% CI: 1.68 to 10.63), which persisted after adjustment for CV risk factors [5.67 mm^3 higher CWV (95% CI: 0.75 to 10.58)] and driven by the effect in males (Supplementary Table 5). These trends are reflected in the analyses across quartiles of VAT (Table 1 and Supplementary Fig. 4). For HFF, a 1-SD increase was not associated with a higher CWV (1.80 mm^3 per SD; 95% CI: −2.24 to 5.84), which did not change after adjustment for CV risk factors (Supplementary Table 6). There were no trends across quartiles of HFF for males ($P = 0.36$) or females ($P = 0.24$) (Table 2 and Supplementary Fig. 4). The sensitivity analyses in the smaller subset of participants with measured lipids ($n = 1727$ men; 1,870 women) show no associations with CWV across quartiles of VAT (Supplementary Table 7) and HFF (Supplementary Table 8).

The UKB cohort

The UKB analytic cohort consisted of 26,547 individuals (51.9% female), with a mean age of 54.7 (SD = 7.4) years. Most participants were white British (92.8%) and never smoked (63.3%). A total of 22.9% reported prevalent hypertension, 23.3% reported prevalent dyslipidemia, and 5.2% reported prevalent diabetes, and the prevalence of these conditions was higher in males (Supplementary Data 1). Males had more VAT than females [4,823 (2,283) vs. 2593 (1483) mL] and a higher PDFF [4.7 (4.0) vs. 3.8 (3.7) %], and more carotid atherosclerosis by CIMT [0.81 (0.18) vs. 0.74 (0.15) mm].

The study confirms a positive, direct association between VAT volume and CIMT (0.016 ± 0.0009 mm per 1-SD higher VAT; $p < 0.0001$) in minimally adjusted models, and after adjustment for CV risk factors (0.014 ± 0.0012; $p < 0.0001$). These were of similar magnitude in males (0.012 mm per 1-SD increase in VAT; $P < 0.0001$) and females (0.011 mm per 1-SD increase in VAT; $P < 0.0001$) (Supplementary Table 9). The analyses by quartile were consistent with the continuous associations (Supplementary Fig. 4, Supplementary Table 10). There was a positive, direct association between HFF and CIMT in minimally-adjusted models (0.012 ± 0.0010 mm per 1-SD higher PDFF; $p < 0.0001$), as well as after adjustment for CV risk factors (0.009 ± 0.0010 mm per 1-SD higher PDFF; $p < 0.0001$), in males and females (mean higher CIMT of 0.0089 mm per 1-SD higher PDFF, $P < 0.0001$ in males; vs. 0.0086 mm per 1-SD increase in hepatic fat, $P < 0.0001$ in females; Supplementary Table 11). The analyses by quartile were consistent with the continuous associations for males and females (Supplementary Fig. 5, Supplementary Table 12). Pooled analyses of CAHHM and UKB supported a positive association of VAT and HFF with subclinical atherosclerosis in the full cohorts even after adjustment for CV risk factors (Fig. 2, Supplementary Fig. 6, and Supplementary Table 13).

Discussion

Using data from two independent cohorts of middle-aged adults in Canada and the United Kingdom, visceral and hepatic fat are associated with CV risk factors and carotid atherosclerosis. Adjustment for CV risk factors does not eliminate the association of visceral or hepatic fat with carotid atherosclerosis.

Pooling CAHHM with UKB data showed a consistent positive association of visceral and hepatic fat with atherosclerosis. This approach overcame the CAHHM cohort's low power to detect small degrees of carotid atherosclerosis because the large size of UK Biobank could detect a 0.01-mm difference in CIMT per 1 SD higher VAT. In CAHHM, detecting a similar difference in atherosclerosis measure (i.e., 1.3% = 11.7 mm^3) with 90% power, given the observed SD of CWV = 166 mm^3

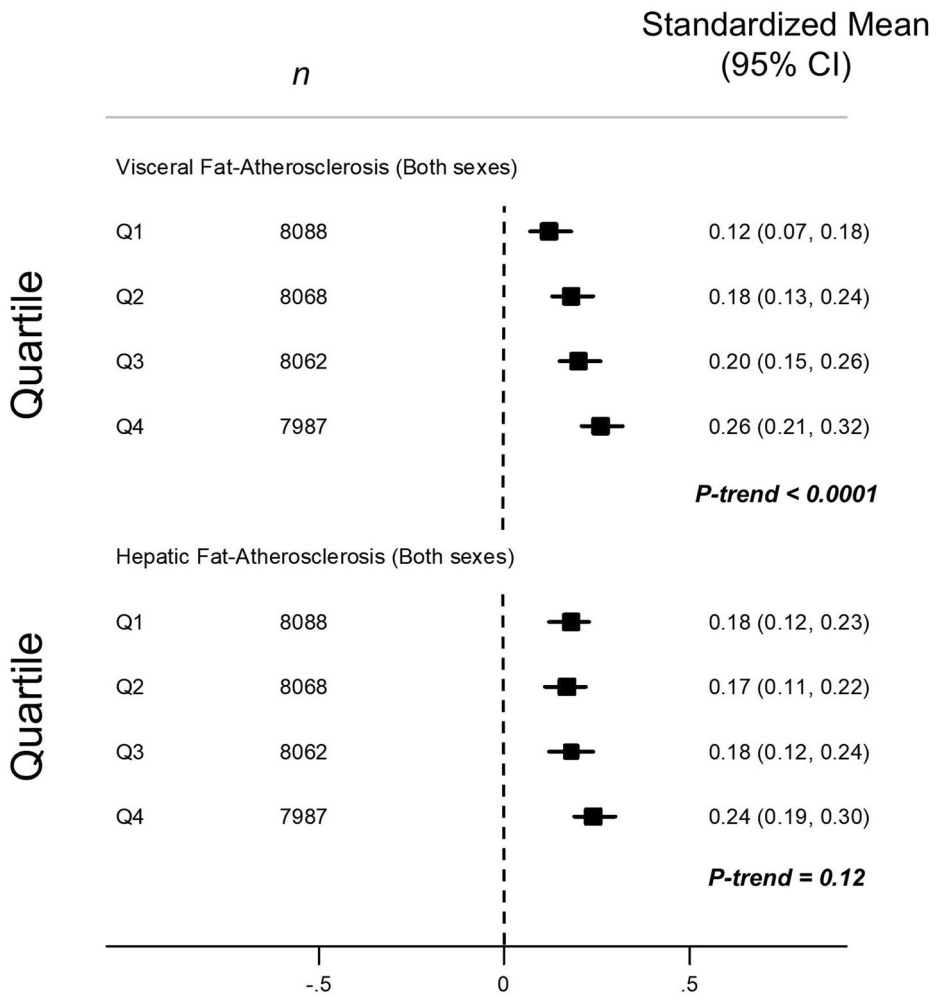

Fig. 2 | Forest plot of pooled (CAHHM with UKB) associations of measures of visceral and hepatic fat with atherosclerosis (standardized means). Squares represent point estimates, and horizontal lines are the bounds of the 95% CI. STM, standardized mean. A value of 0 is interpreted as 1 standard unit of atherosclerosis measure, calculated for each individual as $\frac{x-\bar{x}}{SD}$, where x = individual CIMT or CWV measure, $\bar{x}$ = cohort and sex-specific mean CIMT or CWV measure, and SD = cohort and sex-specific SD of CIMT or CWV measure. CAHHM models adjusted for: age, ethnicity, IHRS, VAT (for HFF) or HFF (for VAT). UKB models adjusted for age, ethnicity, smoking, alcohol, hypertension, diabetes, dyslipidemia, WHR, and VAT (for PDFF) or PDFF (for VAT). *P*-trend for pooled data assessed using variance-weighted least squares (n= 32, 185 for visceral fat; n= 32, 185 for hepatic fat).

would have required 8482 participants. A meta-analysis of 119 RCTs (n = 100,667 participants) found that reducing CIMT progression by 0.010 mm/y was associated with a relative risk reduction of 16% in composite CVD (MI, stroke, revascularization, or fatal CVD); and a 0.020 mm/y reduction with a 24% reduction per year. The observed effect size in the UKB of 0.016 mm CIMT per SD VAT therefore reflects non-trivial change in CVD risk (~19–32%)[28].

In CAHHM, visceral and hepatic fat were linked to higher CVD risk scores, and 1.3 to 2.2-fold higher odds of hypertension, diabetes mellitus, and dyslipidemia. These findings support prior associations between higher visceral and hepatic fat and hyperglycemia, dyslipidemia, and hypertension[29–39]. The International Atherosclerosis Society and International Chair on Cardiometabolic Risk Working Group on Visceral Obesity hold the position that among adiposity measures, visceral fat is the strongest predictor of adverse CV risk[9,40,41], and is a better predictor of subclinical atherosclerosis than waist circumference[42]. In the multicultural community health assessment trial (M-CHAT), which included 794 men and women of Indigenous, Chinese, European, and South Asian ancestries, VAT was associated with CIMT, plaque area, and total area after adjusting for demographics, family history, smoking, and percent body fat in men and women[8]. Although some of the increased risk visceral fat confers is through risk factors like hypertension, diabetes, and dyslipidemia, these risk factors do not fully explain the pathway. Follow-up of the CAHHM cohort will test visceral fat's association with incident CVD in future analyses.

Prospective studies of hepatic fat and development of CVD are inconsistent[33,43–45]. In the Framingham and MESA studies, hepatic fat was not associated with clinical CVD after adjusting for obesity, metabolic syndrome components, and traditional risk factors[44,46]; but in MESA and the Rotterdam study, hepatic fat was associated with greater coronary artery calcification[43,47]. In the Oulu Project Elucidating Risk of Atherosclerosis (OPERA) cohort, severe hepatic fat (~13–17% PDFF[48]) was associated with 74% higher 20-year multivariable risk of cardiovascular events (HR 1.74, CI 1.16 to 2.63)[45]. Further, HF was shown to be associated with metabolic syndrome, an important risk constellation for CVD, and CIMT in a study of 485 obese adults[49].

The mechanisms by which visceral and hepatic fat may promote atherosclerosis independently of traditional CV risk factors are not established. The "fat overflow" theory suggests visceral fat accumulation occurs only when subcutaneous storage capacity is exceeded[50–52]. This expanding visceral fat depot becomes inflamed due to macrophage infiltration of hypertrophied adipocytes, increasing cytokines that influence metabolic, inflammatory, and vascular pathways involved in atherosclerosis progression[53–58]. Also proposed is a theory that excess visceral fat is a consequence of an activated hypothalamic-pituitary-adrenal axis, which increases glucocorticoid control of carbohydrate and lipid metabolism. Visceral adipocytes express more glucocorticoid receptors than subcutaneous adipocytes, which may promote preferential fat deposition in this depot, and insulin resistance in the liver and muscle[59,60].

Hepatic fat may increase CV risk through local overexpression of inflammatory markers that cause endothelial damage, and mediate blood pressure[61]. NAFLD is associated with higher inflammatory, lipid, and coagulation markers[33,62–64]. Accumulation of lipid metabolites in the liver may cause insulin resistance, and promote inflammation through activation of proinflammatory receptors[65]; rendering the liver less able to suppress intrahepatic gluconeogenesis and lipolysis[66].

It has also been proposed that fatty liver is a byproduct of fat deposition in the viscera, caused by triglyceride-rich blood draining into the liver[67,68]. This may result in de novo lipogenesis, and fatty acid esterification and storage as cytoplasmic triglycerides or VLDL. These particles can form atherogenic small, dense lipoproteins, cholesterol-rich VLDL, and TG-rich HDL[69,70].

These analyses show that an adiposity phenotype characterized by excessive accumulation of visceral adipose tissue is associated with carotid atherosclerosis, irrespective of hepatic fat content. However, a high hepatic fat content is not associated with carotid atherosclerosis without excess visceral fat. Those pursuing therapeutic approaches to reduce liver fat should also consider targeting excess visceral adiposity.

Behavior modification is the primary therapeutic approach to reducing visceral and hepatic fat. Prevailing dietary advice includes adopting a Mediterranean diet rich in fiber, omega-3 and mono-unsaturated fats (e.g., fish and seafood, fruits, whole grains, nuts, olive oil, vegetables, and legumes), avoiding fried foods, saturated fat, red and processed meat, and foods with refined/added sugar[71]. Smaller studies support various popular diet regimes to reduce both visceral and hepatic fat, including time restricted eating[72], very low calorie ketogenic diets[73], and low-fat vegan diets[74]. Additional beneficial lifestyle modifications include exercise[75]; and achieving and maintaining a healthy body weight[71]. In 2024, the U.S. Food and Drug Administration approved Rezdiffra (resmetirom) for the treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced fibrosis, as an adjunct to diet and exercise[76]. Pharmacological treatments for reducing VAT include liraglutide[77], and Orlistat[78].

The strengths of this study include its large sample size with representation of middle-aged and older males and females from 10 provinces across Canada, and the UK[16,17]; and the quantification of atherosclerosis using standardized MRI and ultrasound protocols[16,79]. MRI-assessed CWV may be a more sensitive measure of early plaque than CIMT[80]. Visceral and hepatic fat by MRI allows for precise quantification compared to indirect measures of visceral fat and fatty liver disease, such as waist circumference or elevated liver function tests, which have low sensitivity.

The main limitation is the cross-sectional analysis, which precludes assessment of a temporal relationship between ectopic fat, vascular risk factors, and clinical CVD[16]. The datasets also could not be limited to those who did not drink alcohol excessively, because the highest alcohol intake response categories for both the CAHHM and UKB questionnaires included safe consumption ranges. Secondly, because of the precision limitations of measuring CIMT in clinical practice, extrapolating changes in CIMT to CV event risk must be done cautiously[81]. Finally, the pooled analysis combined heterogeneous measurements (CIMT and CWV), which warrants cautious interpretation of the conclusions drawn.

In conclusion, visceral fat, and to a lesser extent, hepatic fat, are associated with increased carotid atherosclerosis. These results highlight the importance of assessing and targeting excess visceral adiposity for the optimal management of CVD risk, and that approaches to reduce visceral adiposity may influence progression of atherosclerosis, independent of effects on other risk factors. Strategies to reduce visceral adiposity may reduce risk of atherosclerosis, over and above controlling other established risk factors for CVD.

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Author contributions

The study was conceptualized by Russell J de Souza and Sonia S Anand. The original draft of the manuscript was written by Russell J. de Souza. The study methodology was developed by Russell J de Souza, Marie E Pigeyre, Karleen M Schulze, and Joseph Beyene. The software used to analyze the data was used by Russell J de Souza, Marie E Pigeyre, Karleen M Schulze, Joseph Beyene. Formal data analyses (statistical) were conducted by Karleen M Schulze, Russell J de Souza, Marie E Pigeyre, and Joseph Beyene. The investigations described in the study were conducted by Russell J de Souza, Marie E Pigeyre; with participant data collected in CAHHM and UKB by respective study staff. Data visualization was created by Russell J. de Souza, Marie E Pigeyre, and Amel Lamri. Data was curated by Karleen M Schulze. The manuscript was reviewed and edited by Marie E Pigeyre, Karleen M Schulze, Amel Lamri, Baraa Al-Khazraji, Philip Awadalla, Joseph Beyene, Dipika Desai, Jean-Pierre Despres, Trevor Dummer, Matthias Friedrich, Jason Hicks, Vikki Ho, Eric Larose, Scott A Lear, Douglas S Lee, Jonathon A Leipsic, Guilliaume Lettre, Alan R Moody, Michael D Noseworthy, Guillaume Pare, Grance Parraga, Paul Poirier, Jean-Claude Tardif, Salim Yusuf, Jennifer Vena, and Sonia S. Anand. Sonia S. Anand provided supervision and oversight.

Additional information

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