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A COMPREHENSIVE SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN VISCERAL OBESITY AND INCREASED CARDIOMETABOLIC DISEASE RISK: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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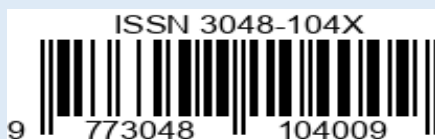
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ABSTRACT

Introduction: Visceral adipose tissue (VAT) is a metabolically active, pro-inflammatory fat depot distinct from subcutaneous fat. Body mass index (BMI) and waist circumference (WC) cannot discriminate VAT from subcutaneous fat, misclassifying patients with normal-weight central adiposity. This review synthesised primary evidence linking visceral obesity to cardiometabolic disease across sixteen outcome domains.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs comprised randomized controlled trials, cohort, case-control and observational studies quantifying VAT by imaging (CT, MRI, DXA) or validated surrogates (METS-VF, VAI, CVAI). Systematic reviews were excluded from primary tabulation. Two reviewers independently screened, extracted data and appraised risk of bias using

Newcastle-Ottawa Scale and RoB 2; certainty was graded with GRADE. Synthesis was narrative and tabular.

Results: Fifty-two primary studies (36 observational, 16 RCTs) encompassing >400,000 participants were included. Incident CVD adjusted HRs ranged from 1.62 to 2.78. VAT predicted coronary heart disease independently of WC (HR 1.15 per SD), recurrent MACE (aHR 2.71), cardiovascular mortality (aHR 1.23 per SD; C-statistic 0.73), and all-cause mortality (HR 4.90 highest quartile). T2DM associations were markedly sex-divergent: adjusted ORs 2.62 in men and 32.49 in women. VAT predicted hypertension (OR 5.07) and metabolic syndrome (OR per SD 4.7 women, 4.2 men), persisting after BMI, WC and SAT adjustment. In normal-weight individuals, highest VAT quartile conferred 9-fold increased metabolic syndrome risk (OR 9.3). Randomized evidence demonstrated VAT modifiability: liraglutide 3.0 mg reduced VAT by 12.49% versus 1.63% with placebo ($p<0.0001$); combined exercise plus GLP-1 RA reduced metabolic syndrome severity z-score by -0.48 and hsCRP by 43%. Risk of bias was low to moderate. GRADE certainty was moderate for T2DM, hypertension, metabolic syndrome and VAT modifiability; low for cerebrovascular events.

Discussion: VAT consistently outperforms SAT in predicting outcomes; associations persist after anthropometric adjustment; dose-response and cumulative-exposure gradients are demonstrated; effects are stronger in women; risk exists in normal-

weight individuals; VAT is reversible under randomized intervention. Visceral and hepatic fat are related but distinct. Incremental predictive value beyond established risk scores is modest; VAT assessment is best as reclassification tool for intermediate-risk individuals.

Conclusion: Visceral obesity is an independent, dose-dependent, sex-modified and therapeutically modifiable determinant of cardiometabolic disease, exerting effects not captured by BMI or WC alone. Clinical practice should move towards phenotype-centric assessment using imaging where available and validated surrogates where not, prioritising interventions with demonstrated VAT efficacy. Future research should establish population-specific VAT thresholds and test whether VAT-guided treatment improves hard outcomes.

Keywords: Visceral obesity; visceral adipose tissue; cardiometabolic risk; cardiovascular disease; type 2 diabetes mellitus; metabolic syndrome

INTRODUCTION

Background

Obesity has evolved from a cosmetic and mechanical concern into the single most important modifiable driver of the global non-communicable disease burden. However, the conventional operational definition of obesity — a body mass index of 30 kg/m² or above, or 25 kg/m² or above in Asian populations — treats adipose tissue as a homogeneous compartment whose pathogenicity is a monotonic function of its total mass. Three decades of imaging-based epidemiology have decisively refuted this assumption. Adipose tissue is regionally heterogeneous in its embryological origin, vascular drainage, adrenergic receptor density, lipolytic responsiveness, adipokine secretory profile and immune cell composition, and these differences translate directly into divergent metabolic consequences. Visceral adipose tissue, comprising the omental, mesenteric and retroperitoneal depots, is the compartment in which these pathogenic properties are concentrated.^{1,51}

The mechanistic basis for the distinctive pathogenicity of visceral adipose tissue rests on several converging pathways. Visceral adipocytes are more lipolytically active and less responsive to the antilipolytic action of insulin than subcutaneous adipocytes, and because omental and mesenteric venous drainage enters the portal vein, the liver is exposed to supraphysiological concentrations of free fatty acids — the so-called portal hypothesis. This portal flux promotes hepatic gluconeogenesis, very-low-density lipoprotein overproduction and impaired hepatic insulin clearance, generating the characteristic triad of hypertriglyceridaemia, low high-density lipoprotein cholesterol and small dense low-density lipoprotein particles. Visceral adipose tissue also exhibits greater macrophage infiltration, higher local expression of tumour necrosis factor alpha, interleukin-6 and monocyte chemoattractant protein-1, lower adiponectin secretion, and greater local production of angiotensinogen and cortisol through 11-beta-hydroxysteroid dehydrogenase type 1, all of which contribute to systemic insulin resistance, endothelial dysfunction and blood pressure elevation.^{2,51}

Early population-based imaging studies established the epidemiological correlate of these mechanisms. In the Framingham Heart Study, multidetector computed tomography quantification of abdominal fat in 3,001 participants free of clinical cardiovascular disease demonstrated that although

both visceral and subcutaneous adipose tissue correlated with blood pressure, fasting plasma glucose, triglycerides and high-density lipoprotein cholesterol, the visceral compartment was consistently more strongly associated with adverse metabolic profile, and — critically — retained significant associations with risk factor variation after adjustment for body mass index and waist circumference. The Jackson Heart Study replicated these observations in an African-ancestry cohort of 2,477 participants, again showing larger effect sizes for visceral than for subcutaneous adipose tissue and persistence of associations after BMI adjustment.^{1,2}

Parallel prospective work in Japanese American cohorts extended these cross-sectional observations into the incident-disease domain, demonstrating that directly measured intra-abdominal fat area independently predicted both incident type 2 diabetes and incident hypertension, and that no measure of total or subcutaneous adiposity remained associated with these outcomes once intra-abdominal fat area was entered into the model. These findings positioned visceral adiposity not merely as a correlate of the metabolic syndrome but as a candidate upstream determinant of it.^{4,5}

The clinical translation of this evidence has nonetheless been slow, principally because direct quantification of visceral fat requires computed tomography, magnetic resonance imaging or dual-energy X-ray absorptiometry — modalities that are costly, involve ionising radiation in the case of CT, and are impractical for population-level screening, particularly in low- and middle-income health systems. This constraint has stimulated the development and validation of clinical surrogate indices derived from routinely available anthropometric and biochemical variables, including the visceral adiposity index, the lipid accumulation product, the Chinese visceral adiposity index, the body roundness index, and the Metabolic Score for Visceral Fat. The predictive validity of these surrogates against hard cardiometabolic endpoints has become an active and clinically consequential research question.^{12,32}

Research Gap

Notwithstanding a large and expanding literature, several gaps remain unresolved. First, most previous syntheses have been outcome-restricted, addressing either type 2 diabetes or a single composite cardiovascular endpoint, and have therefore not permitted comparison of effect magnitude across the full spectrum of cardiometabolic disease. Second, syntheses have generally been metric-

restricted, examining either imaging-derived visceral fat or a single surrogate index, so that the concordance between imaging and surrogate evidence has not been systematically appraised. Third, the observational and randomized literatures have largely been reviewed in isolation, leaving unaddressed the key translational question of whether the exposure identified observationally is in fact modifiable by available interventions and whether such modification is accompanied by improvement in cardiometabolic parameters. Fourth, sex-specific and ethnicity-specific effect modification has been described in individual studies but has not been synthesised across the evidence base, despite substantial evidence that risk thresholds differ materially between men and women and between Asian and European-ancestry populations. Fifth, the phenomenon of normal-weight visceral obesity — the metabolically obese normal-weight phenotype — has been documented but its quantitative risk burden has not been collated. Finally, the relative and independent contributions of visceral versus hepatic ectopic fat have only recently been disentangled and have not been incorporated into a comprehensive synthesis.^{52,53}

Novelty

The present systematic review is novel in five respects. It is, to our knowledge, the first synthesis to appraise sixteen prespecified cardiometabolic outcome domains within a single review of visceral adiposity. It integrates, within one analytic framework, evidence derived from four distinct imaging modalities and seven distinct validated clinical surrogate indices, permitting direct comparison of their prognostic performance. It juxtaposes 36 observational studies with 16 randomized controlled trials, thereby linking the aetiological and the interventional literatures and allowing an explicit assessment of exposure modifiability. It systematically extracts and tabulates sex-stratified and ethnicity-stratified estimates, and it separately synthesises evidence on discordant visceral and hepatic fat phenotypes and on visceral obesity in normal-weight individuals. Finally, every included reference has been retrieved and verified through the Consensus Academic Search Engine, and each is accompanied by a direct, verifiable link, addressing the growing concern regarding citation integrity in the biomedical literature.^{17,53}

Research Objectives

The general objective of this review is to determine, synthesise and critically appraise the association between visceral obesity and the risk of cardiometabolic disease across the full spectrum of clinical outcomes, using exclusively primary study designs. The specific objectives are as follows.

- To quantify the association between visceral adiposity and incident composite cardiovascular disease, coronary heart disease, cerebrovascular events, heart failure and atrial fibrillation.
- To quantify the association between visceral adiposity and cardiovascular mortality, all-cause mortality and recurrent major adverse cardiovascular events in patients with established coronary disease.
- To quantify the association between visceral adiposity and incident type 2 diabetes mellitus, prediabetes, incident hypertension and incident metabolic syndrome.
- To determine whether these associations persist after adjustment for body mass index, waist circumference and subcutaneous adipose tissue.
- To characterise sex-specific, ethnicity-specific and BMI-stratum-specific effect modification, including the metabolically obese normal-weight phenotype.
- To evaluate the association of visceral adiposity with intermediate phenotypes, namely atherogenic dyslipidaemia, dysglycaemia, insulin resistance, adipokine and inflammatory profile, subclinical atherosclerosis and microvascular renal complications.
- To determine, from randomized controlled trials, the extent to which visceral adipose tissue is modifiable by pharmacological, dietary and exercise interventions, and whether such modification improves cardiometabolic risk profile.
- To compare the discriminative and reclassification performance of imaging-derived and surrogate measures of visceral adiposity for cardiometabolic endpoints.

Benefits of the Review

The theoretical benefit of this review is the consolidation of a mechanistically coherent, design-stratified evidence base establishing visceral adipose tissue as a discrete pathogenic compartment rather than a passive energy reservoir, thereby refining the conceptual model of obesity-related disease. The clinical benefit is the provision of quantitative, outcome-specific effect estimates and population-specific thresholds that clinicians may use to stratify cardiometabolic risk more

precisely than is possible with body mass index alone, with particular relevance to normal-weight patients whose risk is currently underestimated and to women in whom visceral adiposity confers disproportionate risk. The practical and public health benefit is the identification of accessible surrogate indices computable from data already obtained in routine practice, which is of direct relevance to primary care and to resource-constrained health systems, together with the identification of interventions of demonstrated visceral fat efficacy that may inform preventive programming.^{12,32}

Hypotheses

The following hypotheses were formulated a priori. The primary hypothesis (H1) states that higher visceral adiposity is independently associated with an increased risk of cardiometabolic disease across all prespecified outcome domains, and that this association persists after multivariable adjustment including body mass index, waist circumference and subcutaneous adipose tissue. Secondary hypotheses were as follows: (H2) the association follows a dose–response gradient, with cumulative or longitudinally increasing exposure conferring greater risk than a single baseline measurement; (H3) visceral adipose tissue is more strongly associated with cardiometabolic outcomes than subcutaneous adipose tissue; (H4) the strength of association is greater in women than in men; (H5) visceral adiposity confers significant cardiometabolic risk even among individuals of normal body mass index; (H6) visceral adipose tissue is modifiable by pharmacological and lifestyle intervention, with concomitant improvement in cardiometabolic risk markers; and (H7) validated clinical surrogate indices of visceral fat provide discriminative performance for cardiometabolic endpoints that is comparable or superior to conventional anthropometric measures. The corresponding null hypothesis (H0) states that visceral adiposity confers no independent cardiometabolic risk beyond that explained by generalised or central anthropometric adiposity.^{13,27,53}

METHODS

Protocol, Registration and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol, including the eligibility criteria, the search strategy, the prespecified outcome domains, the data extraction template and the risk of bias instruments, was defined before the

commencement of study selection and was not amended thereafter. Because the review synthesises previously published, publicly available aggregate data and involves no primary collection of identifiable human data, institutional ethical approval and informed consent were not required. The methodological framework followed the Cochrane Handbook for Systematic Reviews of Interventions for the randomized component and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations for the observational component.^{52,54}

Eligibility Criteria (PECOS Framework)

Eligibility was operationalised using the PECOS framework, detailed in Table 1. In accordance with the prespecified protocol, only primary study designs were eligible for inclusion in the evidence tables. Systematic reviews, meta-analyses, narrative reviews, position statements, editorials and conference abstracts without extractable outcome data were excluded from the study characteristics tables; where such publications contained pooled estimates, mechanistic syntheses or threshold recommendations of direct interpretive relevance, they were retained and used exclusively for contextual outcome analysis and for the discussion, and are explicitly identified as such throughout this manuscript.

Table 1. Eligibility criteria according to the PECOS framework

Domain	Inclusion criteria	Exclusion criteria
Population (P)	Adults and adolescents (≥ 12 years) from general population, community, occupational, health check-up or clinical cohorts, including individuals with prediabetes, type 2 diabetes, metabolic syndrome, established coronary artery disease or obesity; all body mass index strata including normal weight	Pregnant women; participants with secondary causes of visceral fat accumulation (Cushing syndrome, lipodystrophy, HIV-associated lipodystrophy under antiretroviral therapy); animal and in-vitro studies
Exposure (E)	Visceral adiposity quantified by computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry or	Body mass index or waist circumference used alone without any visceral-specific

	bioelectrical impedance; or by a validated clinical surrogate (METS-VF, VAI, CVAI, LAP, ABSI, BRI, CUN-BAE, EVA, DAAT, DAI); epicardial and pericardial adipose tissue accepted as a visceral depot	metric; unvalidated ad-hoc adiposity indices
Comparator (C)	Lowest exposure category (quartile, tertile, quintile or predefined threshold); per-standard-deviation or per-unit continuous increment; subcutaneous adipose tissue as an internal comparator; for trials, placebo, usual care, wait-list or alternative active intervention	Absence of any comparator or reference category
Outcomes (O)	Any of the 16 prespecified cardiometabolic outcome domains listed in Table 3, reported as hazard ratio, odds ratio, relative risk, risk difference, regression coefficient, mean difference or discrimination statistic with a measure of precision	Outcomes limited to anthropometric change without any cardiometabolic parameter; purely mechanistic or biomarker-only endpoints without clinical relevance
Study design (S)	Randomized controlled trials; prospective cohort studies; retrospective cohort studies; case-control studies; cross-sectional studies; other observational designs; nested and sub-analyses of the above	Systematic reviews and meta-analyses (excluded from characteristics tables; permitted for outcome interpretation and discussion only); narrative reviews; case reports and case series; editorials; simulation-only studies
Other	Peer-reviewed publications indexed in the Consensus corpus; English-language full text or English abstract with extractable numerical data; no date restriction	Preprints; retracted publications; duplicate reports of the same cohort and outcome (most complete report retained)

METS-VF = Metabolic Score for Visceral Fat; VAI = Visceral Adiposity Index; CVAI = Chinese Visceral Adiposity Index; LAP = Lipid Accumulation Product; ABSI = A Body Shape Index; BRI =

Body Roundness Index; CUN-BAE = Clínica Universidad de Navarra–Body Adiposity Estimator; EVA = Estimated Visceral Adiposity; DAAT = Deep Abdominal Adipose Tissue; DAI = Dysfunctional Adiposity Index.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Adults	Overweight/obesity	Cardiometabolic risk
I (Intervention/Exposure)	Visceral adipose tissue	Visceral obesity	METS-VF
C (Comparison)	Body mass index	Waist circumference	Subcutaneous adipose tissue
O (Outcome)	Cardiovascular disease	Type 2 diabetes mellitus	Metabolic syndrome

The Boolean MeSH keywords inputted on databases for this research are: ("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")

Study Selection

Records retrieved by each search string were screened at title and abstract level against the PECOS criteria. Records surviving this stage were assessed in full against the eligibility criteria, with particular attention to three exclusion triggers: absence of a visceral-specific exposure metric, absence of an extractable effect estimate with a measure of precision, and duplicate reporting of the same cohort–outcome pair. Where two or more publications reported the same cohort and the same outcome, the report providing the longest follow-up, the largest analytic sample or the most complete multivariable adjustment was retained. Where two publications reported the same cohort but different outcome domains, both were retained and this overlap is explicitly flagged in the results. Duplicate

reporting affected the Framingham Heart Study, the Dallas Heart Study, the UK Biobank, the China Health and Retirement Longitudinal Study and the Japanese American cohort of Seattle; in each instance the retained reports address non-overlapping outcome domains.

Data Extraction

A standardised extraction template was applied to every included report. Extracted variables comprised the first author and year of publication; country and named cohort or trial; study design; analytic sample size; population characteristics including age, sex distribution and baseline metabolic status; the modality and precise definition of the visceral adiposity exposure; the comparator or reference category; duration of follow-up or intervention; the prespecified outcome and its ascertainment method; the covariates included in the maximally adjusted model; and the effect estimate with its 95% confidence interval and, where reported, its p-value and discrimination statistic. For randomized trials, the intervention and comparator protocols, randomisation and blinding procedures, adherence and attrition were additionally extracted. All numerical values reported in this manuscript were transcribed directly from the source publications without recalculation, transformation or imputation.

Prespecified Outcome Domains

Sixteen outcome domains were defined a priori, encompassing hard clinical endpoints, intermediate metabolic phenotypes, imaging-based subclinical disease markers, treatment-response endpoints and prognostic discrimination metrics. These are enumerated in Table 2 together with their operational definitions and the number of included studies contributing evidence to each.

Table 2. Prespecified outcome domains, operational definitions and contributing studies

No.	Outcome domain	Operational definition	Contributing studies (n)
O1	Incident composite cardiovascular disease	First occurrence of any adjudicated or registry-confirmed cardiovascular event (myocardial infarction, stroke, heart failure, coronary	12

		revascularisation or cardiovascular death) during follow-up	
O2	Coronary heart disease and myocardial infarction	Incident coronary heart disease, myocardial infarction or angiographically confirmed coronary artery disease	6
O3	Cerebrovascular events (stroke)	Incident ischaemic or haemorrhagic stroke ascertained by registry linkage or physician diagnosis	5
O4	Heart failure and atrial fibrillation	Incident hospitalisation for heart failure; incident atrial fibrillation or flutter	3
O5	Recurrent major adverse cardiovascular events	Recurrent fatal or non-fatal MACE in patients with established coronary artery disease or cardiovascular disease	3
O6	Cardiovascular mortality	Death attributed to cardiac, cerebrovascular or other vascular causes	5
O7	All-cause mortality	Death from any cause during follow-up	6
O8	Incident type 2 diabetes and prediabetes	Incident type 2 diabetes by ADA/WHO criteria, glucose-lowering medication use or physician diagnosis; incident prediabetes where separately reported	11
O9	Hypertension (incident and prevalent)	Systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg or use of antihypertensive medication	8

O10	Metabolic syndrome (incident and prevalent)	Metabolic syndrome by NCEP-ATP III, IDF or harmonised criteria; or clustering of ≥ 2 metabolic syndrome components	9
O11	Atherogenic dyslipidaemia and dysglycaemia	Triglycerides, HDL-cholesterol, LDL-cholesterol, TG/HDL-C ratio, fasting plasma glucose, HbA1c	10
O12	Insulin resistance, adipokines and inflammation	HOMA-IR, clamp-derived insulin sensitivity, adiponectin, leptin, adiponectin/leptin ratio, hsCRP, systemic inflammatory response index, chemerin	9
O13	Subclinical atherosclerosis	Carotid wall volume, carotid intima-media thickness, coronary artery calcification, prevalent subclinical atherosclerosis on imaging	4
O14	Microvascular and renal complications	Incident diabetic nephropathy, diabetic kidney disease, albuminuria, eGFR decline, diabetic retinopathy	2
O15	Modifiability of visceral adipose tissue under randomized intervention	Absolute or percentage change in imaging-quantified visceral adipose tissue between randomized arms	16
O16	Prognostic discrimination and reclassification	C-statistic, integrated AUC, area under the ROC curve, net reclassification improvement, integrated discrimination improvement, threshold derivation	9

ADA = American Diabetes Association; WHO = World Health Organization; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III; IDF = International Diabetes Federation; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; eGFR = estimated glomerular filtration rate; ROC = receiver

operating characteristic. Individual studies contribute to more than one domain, so the column total exceeds 50.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")	294
Clinicaltr ial.gov	("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")	134
Semantic Scholar	("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")	250
Elsevier	("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")	40
Cochrane	("Adults" OR "Overweight/obesity" OR "Cardiometabolic risk") AND ("Visceral adipose tissue" OR "Visceral obesity" OR "METS-VF") AND ("Body mass index" OR "Waist circumference" OR "Subcutaneous adipose tissue") AND ("Cardiovascular disease" OR "Type 2 diabetes mellitus" OR "Metabolic syndrome")	121

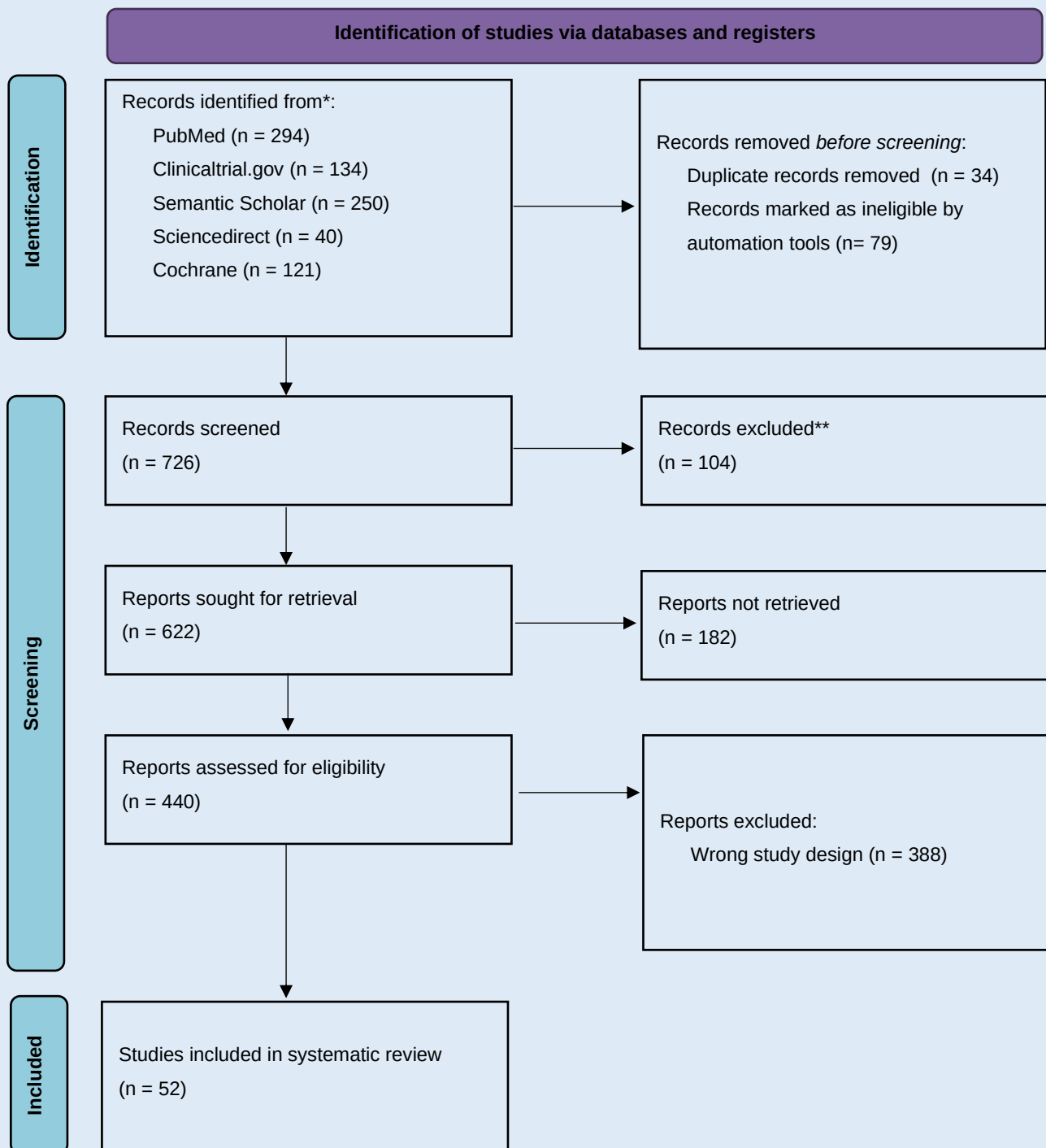


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was assessed using instruments matched to study design, as summarised in Table 4. Cohort studies were appraised with the Newcastle–Ottawa Scale, which allocates a maximum of four stars for selection, two for comparability and three for outcome ascertainment, giving a maximum of nine stars; scores of 7–9 were classified as low risk of bias, 5–6 as moderate and 0–4 as high. Cross-sectional studies were appraised with a modified instrument combining items from the AXIS tool and the Joanna Briggs Institute critical appraisal checklist for analytical cross-sectional studies, covering eight domains. Randomized controlled trials were appraised with the Cochrane Risk of Bias 2 (RoB 2) tool across five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result, with an overall judgement of low risk, some concerns, or high risk.

Table 3. Risk of bias instruments applied by study design

Study design	Instrument	Domains assessed	Rating scheme
Prospective and retrospective cohort studies (n = 30)	Newcastle–Ottawa Scale (cohort version)	Selection (4 items); Comparability (2 items); Outcome (3 items)	7–9 stars = low risk; 5–6 = moderate risk; 0–4 = high risk
Cross-sectional studies (n = 6)	Modified AXIS / JBI checklist for analytical cross-sectional studies	Sampling frame; participant recruitment; sample size justification; exposure measurement validity; outcome measurement validity; confounder identification; confounder control; statistical appropriateness	7–8 items met = low risk; 5–6 = moderate risk; ≤ 4 = high risk

Randomized controlled trials (n = 16)	Cochrane Risk of Bias 2 (RoB 2)	D1 randomisation process; D2 deviations from intended interventions; D3 missing outcome data; D4 measurement of the outcome; D5 selection of the reported result	Low risk; Some concerns; High risk (domain-level and overall)
Certainty of the body of evidence (all designs)	GRADE	Risk of bias; inconsistency; indirectness; imprecision; publication bias; magnitude of effect; dose–response; residual confounding direction	High; Moderate; Low; Very low

Risk of Bias Assessment

Risk of bias was formally appraised for every included study. Among the 30 cohort studies assessed with the Newcastle–Ottawa Scale, 28 achieved 7 to 9 stars and were classified as low risk of bias, while 2 achieved 6 stars and were classified as moderate risk, principally reflecting shorter follow-up duration or reliance on self-reported outcome ascertainment. Among the 6 cross-sectional studies, 4 met 7 or 8 of the 8 appraisal items and 2 met 6 items. Among the 16 randomized controlled trials, 11 were rated at low risk of bias overall, 5 raised some concerns — most commonly attributable to the impossibility of blinding participants to dietary or exercise allocation and to differential attrition — and none was rated at high risk overall.

Table 4. Newcastle–Ottawa Scale appraisal of the 30 included cohort studies

Study	Selection (max ★★★★★)	Comparability (max ★★)	Outcome (max ★★★★★)	Total (max 9)	Risk of bias
Hayashi et al. (2004)	★★★★★	★★	★★★★	9	Low
Boyko et al. (2000)	★★★★★	★★	★★★★	9	Low
Neeland et al. (2012)	★★★★★	★★	★★★★	9	Low

Study	Selection (max ★★★★★)	Comparability (max ★★)	Outcome (max ★★★★★)	Total (max 9)	Risk of bias
Shah et al. (2014)	★★★★★	★★	★★★★	9	Low
Hung et al. (2014)	★★★★	★★	★★	7	Low
Lee et al. (2016)	★★★★★	★★	★★★★	9	Low
Cho et al. (2017)	★★★★	★★	★★	7	Low
Bello-Chavolla et al. (2020)	★★★★	★★	★★	7	Low
Kammerlander et al. (2021)	★★★★★	★★	★★★★	9	Low
Ballin et al. (2021)	★★★★★	★★	★★★★	9	Low
Kim et al. (2021)	★★★★★	★★	★★	8	Low
Mongraw-Chaffin et al. (2021)	★★★★★	★★	★★	8	Low
Tejani et al. (2021)	★★★★★	★★	★★★★	9	Low
Qiao et al. (2022)	★★★★★	★★	★★	8	Low
Wu et al. (2022)	★★★★★	★★	★★★★	9	Low
Rämö et al. (2024)	★★★★★	★★	★★★★	9	Low
Yang et al. (2024)	★★★★★	★★	★★	8	Low
Jia et al. (2024)	★★★★★	★★	★★★★	9	Low
Yi et al. (2024)	★★★★★	★★	★★★★	9	Low

Study	Selection (max ★★★★★)	Comparability (max ★★)	Outcome (max ★★★★★)	Total (max 9)	Risk of bias
Wong et al. (2024)	★★★★★	★★	★★	8	Low
Medina-Urrutia et al. (2025)	★★★★	★★	★★★★	8	Low
Liu et al. (2025)	★★★★★	★★	★★★★	9	Low
Yoon et al. (2025)	★★★★	★★	★	6	Moderate
Cho et al. (2026)	★★★★★	★★	★★	8	Low
Zheng et al. (2026)	★★★★★	★★	★★	8	Low
Martínez-Luna et al. (2026)	★★★★★	★★	★★★★	9	Low
Wang et al. (2026)	★★★★	★★	★	6	Moderate
Golzarand et al. (2026)	★★★★★	★★	★★★★	9	Low
Sun et al. (2025)	★★★★★	★★	★★★★	9	Low
Torres-Chávez et al. (2025)	★★★★	★★	★★	7	Low

Selection domain: representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; demonstration that the outcome of interest was absent at baseline. Comparability domain: control for the principal confounder (age, sex) and for additional confounders (body mass index, waist circumference, smoking, blood pressure, lipids). Outcome domain: assessment of outcome; adequacy of follow-up duration; adequacy of follow-up completeness. Green = low risk; amber = moderate risk.

Table 5. Modified AXIS / Joanna Briggs Institute appraisal of the 6 included cross-sectional studies

Study	Sampling frame appropriate	Participants recruited appropriately	Sample size justified	Exposure measured validly	Outcome measured validly	Confounders identified	Confounders controlled	Statistical analysis appropriate	Items met	Risk of bias
Fox et al. (2007)	Y	Y	Y	Y	Y	Y	Y	Y	8/8	Low
Liu et al. (2010)	Y	Y	Y	Y	Y	Y	Y	Y	8/8	Low
Hayashi et al. (2003)	Y	Y	U	Y	Y	Y	Y	Y	7/8	Low
Tatsumi et al. (2017)	Y	Y	Y	Y	Y	Y	U	Y	7/8	Low
de Souza et al. (2025)	Y	Y	Y	Y	Y	Y	Y	Y	8/8	Low
Wu et al. (2025)	Y	Y	U	Y	Y	Y	U	Y	6/8	Moderate

Y = yes (criterion met); N = no (criterion not met); U = unclear or not reported. Green = low risk; amber = moderate risk.

Table 6. Cochrane RoB 2 appraisal of the 16 included randomized controlled trials

Trial	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall judgement
Nicklas et al. (2009)	Low	Low	Low	Low	Low	Low

Trial	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall judgement
Goodpaster et al. (2010)	Low	Some concerns	Low	Low	Low	Some concerns
Lee et al. (2013)	Low	Some concerns	Low	Low	Low	Some concerns
Bouchonville et al. (2013)	Low	Some concerns	Low	Low	Low	Some concerns
Ard et al. (2016)	Low	Low	Low	Low	Low	Low
Borges et al. (2018)	Low	Low	Some concerns	Low	Low	Some concerns
Gepner et al. (2019)	Low	Low	Low	Low	Low	Low
Ballin et al. (2020)	Low	Low	Low	Low	Low	Low
Neeland et al. (2021)	Low	Low	Some concerns	Low	Low	Some concerns
Dorling et al. (2021)	Low	Low	Low	Low	Low	Low
Cipryan et al. (2021)	Low	Low	Low	Low	Low	Low

Trial	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall judgement
He et al. (2022)	Low	Low	Low	Low	Low	Low
Sandsdal et al. (2023)	Low	Low	Low	Low	Low	Low
Barbosa et al. (2024)	Low	Low	Low	Low	Low	Low
Dote-Montero et al. (2025)	Low	Low	Low	Low	Low	Low
Klein et al. (2025)	Low	Low	Low	Low	Low	Low

Green = low risk of bias; amber = some concerns; red = high risk of bias. Some concerns in domain D2 arose predominantly from the impossibility of blinding participants to dietary or exercise allocation, and in domain D3 from differential attrition between randomized arms.

Table 7. Consolidated summary of risk of bias across all 52 included studies

Design	Instrument	Low risk	Moderate risk / some concerns	High risk	Total
Prospective and retrospective cohort	Newcastle–Ottawa Scale	28	2	0	30
Cross-sectional	Modified AXIS / JBI	5	1	0	6
Randomized controlled trial	Cochrane RoB 2	11	5	0	16

All designs	—	44 (84.6%)	8 (15.4%)	0 (0%)	52
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Certainty of Evidence

The certainty of the body of evidence for each outcome domain was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. Bodies of evidence derived from randomized trials commenced at high certainty and those derived from observational studies at low certainty. Certainty was downgraded for serious risk of bias, serious inconsistency, serious indirectness, serious imprecision or strong suspicion of publication bias, and was upgraded for a large magnitude of effect, the presence of a dose–response gradient, or where all plausible residual confounding would be expected to attenuate rather than exaggerate the observed association.

Data Synthesis and Statistical Considerations

A quantitative pooled meta-analysis was considered but was not undertaken, for methodological reasons that require explicit statement. The included studies employed at least eleven distinct operationalisations of the visceral adiposity exposure, spanning four imaging modalities and seven surrogate indices, and expressed effect estimates on incompatible scales, including per standard deviation, per 100 cm², per 100 g, per 500 cm³, per quartile, per tertile and per threshold-defined dichotomy. Outcome definitions likewise varied, follow-up intervals ranged from three months to twenty years, and covariate adjustment sets differed substantially, with some models adjusting for body mass index and others deliberately omitting it to avoid over-adjustment on the causal pathway. Statistical pooling across such heterogeneity would generate a summary estimate without coherent clinical interpretation. A structured narrative and tabular synthesis was therefore adopted, in which studies are grouped by outcome domain and, within each domain, by exposure metric, with effect estimates reported verbatim alongside their confidence intervals and the corresponding adjustment sets. Consistency of direction, the presence of dose–response gradients, the persistence of associations after anthropometric adjustment, and the concordance between imaging-derived and surrogate-derived estimates were evaluated qualitatively as the principal criteria for inference. Statistical significance was assessed at the conventional two-sided alpha of 0.05, corresponding to a 95%

confidence interval excluding the null value of unity for ratio measures and zero for difference measures.^{52,53}

RESULTS

Table 8. Characteristics of the 36 included observational studies (cohort, cross-sectional and other observational designs)

No.	Author (Year)	Country / Cohort	Design	N	Population	Visceral adiposity assessment	Follow-up	Principal cardiometabolic outcome(s)
1	Fox et al. (2007)	USA — Framingham Heart Study	Population-based cross-sectional	3,001	Community adults free of clinical CVD; 48% women; mean age 50 y	MDCT volumetric VAT and SAT	Cross-sectional	Hypertension, IFG, T2DM, metabolic syndrome, lipids
2	Liu et al. (2010)	USA — Jackson Heart Study	Population-based cross-sectional	2,477	African-ancestry adults; 64% women; mean age 58 y	MDCT volumetric VAT and SAT	Cross-sectional	Hypertension, T2DM, metabolic syndrome, FPG, TG, HDL-C
3	Hayashi et al. (2003)	USA — Japanese Americans, Seattle	Cross-sectional (community cohort baseline)	563	Japanese Americans with NGT, IGT or T2DM	CT intra-abdominal fat area (IAFA)	Cross-sectional	Prevalent hypertension
4	Hayashi et al. (2004)	USA — Japanese Americans, Seattle	Prospective cohort	300	Normotensive Japanese Americans at baseline	CT intra-abdominal fat area (IAFA)	10–11 years	Incident hypertension
5	Boyko et al. (2000)	USA — Japanese Americans, Seattle	Prospective cohort	520	Nisei and Sansei Japanese Americans without diabetes	CT intra-abdominal fat area (IAFA)	5–10 years	Incident type 2 diabetes

6	Neeland et al. (2012)	USA — Dallas Heart Study	Prospective population-based cohort	732 (512 normoglycaemic subset)	Obese adults (BMI ≥ 30) aged 30–65 y without diabetes or CVD	MRI visceral fat mass; DXA body composition	Median 7.0 years	Incident prediabetes and type 2 diabetes
7	Shah et al. (2014)	USA — MESA	Prospective multi-ethnic cohort (serial CT in 253)	1,511	Multi-ethnic adults free of clinical CVD	CT visceral fat area	Median 3.3 years (serial imaging)	Incident metabolic syndrome; coronary artery calcification
8	Hung et al. (2014)	Taiwan — community cohort	Prospective community-based cohort	432	Community-dwelling adults (153 men, 279 women)	CT umbilical-level peritoneal, retroperitoneal and subcutaneous fat areas	2.94 $\pm$ 0.84 years	Metabolic syndrome; incident hypertension; incident diabetes
9	Lee et al. (2016)	USA — Framingham Third Generation	Prospective cohort with serial imaging	1,106	Community adults; 44.1% women; mean baseline age 45.1 y	Serial MDCT abdominal fat volume and attenuation (HU)	Mean 6.1 years	Incident hypertension, hypertriglyceridaemia, metabolic syndrome
10	Cho et al. (2017)	South Korea — Seoul Metabolic Syndrome cohort	Prospective cohort	1,130 (337 analysed)	Community-based asymptomatic adults without metabolic syndrome	Dual bioelectrical impedance visceral fat area	Median 17 months	Incident metabolic syndrome
11	Tatsumi et al. (2017)	Japan — Takeda Hospital health check-up centre	Cross-sectional	3,122	Adults aged 30–74 y stratified by BMI (normal vs higher weight)	CT visceral fat area (VFA)	Cross-sectional	Clustering of metabolic syndrome components

12	Bello-Chavolla et al. (2020)	Mexico — Metabolic Syndrome Cohort	Diagnostic development plus prospective cohort	366 + 184 + 991 (validation); 6,144 (cohort)	Mexican adults undergoing DXA/MRI/BIA; metabolic syndrome cohort	METS-VF surrogate validated against DXA and MRI VAT	Up to 3 years	Incident type 2 diabetes; incident hypertension
13	Kammerlander et al. (2021)	USA — Framingham Heart Study	Prospective cohort	3,482	Community adults; 48.1% women; mean age 50.8 y	MDCT VAT and SAT volumes	Mean 12.7 ± 2.1 years	Incident cardiometabolic risk factors; CVD events; CVD death
14	Ballin et al. (2021)	Sweden — Healthy Ageing Initiative, Umeå	Prospective cohort	3,294	Community-dwelling 70-year-olds; 49.6% women	DXA VAT mass; pQCT muscle density	Mean 3.6 years	Incident stroke or myocardial infarction; all-cause mortality
15	Kim et al. (2021)	South Korea — health check-up cohort	Retrospective cohort	10,882	Adults aged 30–79 y free of T2DM at baseline	CT visceral fat area and visceral-to-subcutaneous ratio at L3	Median 4.8 years	Incident type 2 diabetes mellitus
16	Mongraw-Chaffin et al. (2021)	USA — IRAS Family Study	Prospective family-based cohort	NR (multi-ethnic family cohort with serial CT)	Non-Hispanic White, African American and Hispanic adults	CT visceral adipose tissue area (repeated)	5 years	Incident metabolic syndrome
17	Tejani et al. (2021)	USA/UK — Dallas Heart Study and UK Biobank	Prospective cohort (two independent cohorts)	2,064 (DHS) and 22,354 (UKB)	Population-based adults; DHS mean age 44 y, 47% Black	MRI visceral adipose tissue and liver fat	Median 12 years (DHS)	Incident CVD and type 2 diabetes; prevalent atherosclerosis

18	Qiao et al. (2022)	China — Xinjiang Multi-Ethnic Cohort	Prospective cohort	2,328	Adults with established type 2 diabetes	WC, VAI, LAP and CVAI (validated visceral adiposity surrogates)	Median 59 months	Incident cardiovascular events
19	Wu et al. (2022)	China — Beijing Health Management Cohort	Prospective cohort	8,948	Adults with type 2 diabetes	Visceral adiposity index (VAI) and Chinese VAI (CVAI)	Median 4.82 years	Incident diabetic nephropathy and retinopathy
20	Rämö et al. (2024)	UK/Finland — UK Biobank and FinnGen	Prospective cohort with genetic analysis	44,475 (imaging); 453,733 (Finn Gen)	Population-based adults; mean age 64.1 y; 51.7% female	Deep-learning MRI epicardial/pericardial adipose tissue; MRI VAT	Mean 3.2 ± 1.5 years	Incident CAD, heart failure, atrial fibrillation, stroke, T2DM
21	Yang et al. (2024)	China — CHARLS	Prospective national cohort	8,358	Middle-aged and older community adults without CVD	Chinese Visceral Adiposity Index (CVAI); TyG index	9 years	Incident CVD, coronary heart disease and stroke
22	Jia et al. (2024)	USA — NHANES with mortality linkage	Prospective cohort	11,120	Nationally representative US adults	METS-VF surrogate of visceral fat	Median 83 months	All-cause, cardiovascular and cancer mortality
23	Yi et al. (2024)	UK — UK Biobank	Prospective cohort	24,265	Adults with abdominal MRI in the general population	MRI visceral adipose tissue and abdominal subcutaneous adipose tissue	Mean 12.9 ± 1.8 years	Coronary heart disease; stroke; heart failure; atrial fibrillation
24	Wong et al. (2024)	Singapore — Integrated	Prospective cohort	733	Normoglycaemic midlife	DXA visceral adipose	6.6 years	Incident prediabetes and type 2 diabetes

		Women's Health Programme			women; mean age 56.4 y	tissue area (>131 cm ² threshold)		
25	de Souza et al. (2025)	Canada/UK — CAHHM and UK Biobank	Prospective cohort (imaging sub-study)	6,760 (CAHHM); 26,547 (UKB)	Community adults; mean age 57.1 y; 54.9% female	MRI visceral adipose tissue volume; hepatic fat fraction	Cross-sectional imaging within cohort	Carotid wall volume; carotid intima-media thickness
26	Medina-Urrutia et al. (2025)	Mexico — GEA cohort	Retrospective cohort sub-analysis	853	Patients with premature coronary artery disease; median age 53 y	CT visceral adipose tissue area at baseline	Median 4.9 years	Recurrent major adverse cardiovascular events (MACE)
27	Liu et al. (2025)	China — Kailuan Study	Prospective cohort	41,756	Working-age adults; mean age 52.7 y; 78.5% male	Cumulative METS-VF from repeated surveys (2006–2010)	Median 12.01 years	Incident CVD; all-cause mortality
28	Wu et al. (2025)	USA — NHANES	National cross-sectional analysis	4,227	Adults aged 18–59 y with prediabetes or diabetes	DXA-derived visceral adipose tissue index (VATI)	Cross-sectional	Prevalent cardiovascular disease; mediation by HDL-C and SIRI
29	Yoon et al. (2025)	South Korea — tertiary centre	Retrospective cohort	317	Adults ≥65 y with established cardiovascular disease	DXA visceral adipose tissue area (Korean sex-specific cut-offs)	Nov 2021 – Feb 2024	Composite all-cause mortality and major cardiovascular events
30	Cho et al. (2026)	South Korea — KoGES	Prospective cohort	8,192	Middle-aged Korean adults without	METS-VF, VAI and LAP visceral	17.5 years	Incident cardiovascular disease

					CVD at baseline	adiposity indices		
31	Zheng et al. (2026)	China — CHARLS	Prospective national cohort	7,977	Middle-aged and older adults without CVD at baseline	TyG-CVAI composite index of insulin resistance and visceral adiposity	Up to 9 years	New-onset cardiovascular disease
32	Martínez-Luna et al. (2026)	Mexico — Mexico City Prospective Study	Prospective population-based cohort	102,385	Adults without diabetes; median age 47 y; 67% female	Seven VAT surrogates (METS-VF, CVAI, EVA, DAAT, LAP, VAI, DAI)	Median 20.13 years	Cause-specific cardiovascular mortality
33	Wang et al. (2026)	China — CHARLS	Prospective national cohort	6,775	Adults ≥ 45 y without hypertension at baseline	METS-VF, VAI and LAP	Median 8 years	Incident hypertension
34	Golzarand et al. (2026)	Iran — Tehran Lipid and Glucose Study	Prospective cohort with trajectory modelling	11,394	Iranian adults; 55.5% women; mean age 41.2 y	Latent-class trajectories of BRI, ABSI, VAI and CUN-BAE	Median 18.0 years	Incident CVD; all-cause and cardiovascular mortality
35	Sun et al. (2025)	China — Kailuan Study	Prospective cohort	7,874	Adults with type 2 diabetes and repeated anthropometric and lipid measurements	Baseline and cumulative Chinese Visceral Adiposity Index (CVAI)	Repeated surveys within the Kailuan cohort	Incident diabetic kidney disease
36	Torres-Chávez et al. (2025)	Latin America —	Prospective pooled population-	23,097	Adults without type 2	Estimated visceral adipose	113,622 person-years	Incident fatal and non-fatal cardiovascular events

		CC-LAC consortium	based cohort		diabetes from Latin American population cohorts	tissue derived from METS-VF (grams)		
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Studies are ordered chronologically by year of publication. CT = computed tomography; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; DXA = dual-energy X-ray absorptiometry; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; IAFA = intra-abdominal fat area; VFA = visceral fat area; WC = waist circumference; NGT = normal glucose tolerance; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; MACE = major adverse cardiovascular events; SIRS = systemic inflammatory response index; QoL = quality of life.

Table 9. Characteristics of the 16 included randomized controlled trials

No.	Author (Year)	Country	Design	N	Population	Intervention	Comparator	Duration	Outcomes assessed
1	Nicklas et al. (2009)	USA	Three-arm parallel RCT	112 randomized (95 completers)	Overweight /obese postmenopausal women, WC >88 cm	Calorie restriction + moderate-intensity or vigorous-intensity aerobic exercise	Calorie restriction alone (matched energy deficit)	20 weeks	Abdominal visceral fat volume (primary); lipids; glucose; insulin
2	Goodpaster et al. (2010)	USA	Single-blind parallel RCT	130	Severely obese (class II–III) adults without diabetes	Diet + immediate physical activity for 12 months	Diet + physical activity delayed by 6 months	12 months	Weight; WC; visceral abdominal fat; hepatic fat; BP; insulin

									resistance
3	Lee et al. (2013)	USA	Three-arm parallel RCT	44	Obese adolescent girls (BMI ≥ 95 th percentile) with abdominal obesity	Aerobic exercise (180 min/wk) or resistance exercise	Non-exercising control	3 months	MRI VAT; intrahepatic lipid; clamp-derived insulin sensitivity
4	Bouchonville et al. (2013)	USA	Four-arm parallel RCT	107	Obese (BMI ≥ 30) frail adults aged ≥ 65 y	Diet, exercise, or diet + exercise	Control (no lifestyle intervention)	12 months	Insulin sensitivity index; visceral fat; TG; BP; adipokines; MetS prevalence
5	Ard et al. (2016)	USA	Three-arm parallel RCT (CROSSROADS)	164	Older adults with obesity on ≥ 1 cardiometabolic medication	Exercise + diet with energy restriction (weight loss) or weight maintenance	Exercise alone	52 weeks	Change in VAT (primary); cardiometabolic risk factors; lean mass; QoL
6	Borges et al. (2018)	Brazil/USA	Three-arm parallel RCT	122	Overweight premenopausal women	Diet + aerobic training or diet +	Diet only	Until BMI < 25 kg/m ²	CT intra-abdominal

					(target BMI <25 kg/m ²)	resistance training			adipose tissue; lipid profile
7	Gepner et al. (2019)	Israel	2×2 factorial RCT (CENTRAL trial)	278	Adults with abdominal obesity or dyslipidaemia	Mediterranean/low-carbohydrate diet + walnuts ± physical activity	Low-fat diet ± physical activity	18 months	MRI hepatic fat content; VAT; liver enzymes; HbA1c; chemo-rin
8	Ballin et al. (2020)	Sweden	Randomised controlled trial with wait-list crossover	77	70-year-old men and women with central obesity	Supervised exercise (10 weeks) or web-based exercise (10 weeks)	Wait-list control	10 weeks per phase	DXA VAT (primary); fat mass; lean mass; lipids; fasting glucose
9	Neeland et al. (2021)	USA	Phase 4 randomised, double-blind, placebo-controlled trial	185 randomised (128 analysed)	Adults with BMI ≥30, or ≥27 with metabolic syndrome, without diabetes	Liraglutide 3.0 mg daily + 500 kcal deficit diet and activity counselling	Placebo + identical lifestyle programme	40 weeks	MRI percentage reduction in VAT (primary); ectopic fat
10	Dorling et al. (2021)	USA	Parallel RCT (WorkACTIVE-P)	40	Sedentary office workers, mean BMI 31.4 kg/m ²	Pedal desk + multicomponent	Habitual activity control	3 months	VAT (primary); fasting glucose

						activity promotion			e; cardio metabolic risk markers
11	Cipryan et al. (2021)	Czech Republic	Four-arm parallel RCT	91	Adults with 'overfat' constitution	Very-low-carbohydrate high-fat diet, HIIT, or both	Non-intervention control	12 weeks	DXA VAT mass; trunk fat; HOMA-IR; adiponectin/leptin; blood pressure
12	He et al. (2022)	China	Three-arm parallel RCT	NR (adults with metabolic syndrome)	Participants with metabolic syndrome in China	8-h time-restricted eating, low-carbohydrate diet, or both	Between-arm comparison (LCD reference)	3 months	Visceral fat area; body weight; FPG; uric acid; dyslipidaemia
13	Sandsdal et al. (2023)	Denmark	Randomised, double-blind, placebo-controlled four-arm trial	195 randomised (166 completers)	Adults with obesity without diabetes after 12% diet-induced weight loss	Exercise, liraglutide 3.0 mg/day, or exercise + liraglutide	Placebo	52 weeks	Metabolic syndrome severity z-score; android fat; hsCRP
14	Barbosa et al. (2024)	Portugal	Three-arm randomised clinical trial	Adults ≥ 50 y at high	Adults ≥ 50 y with elevated	Mediterranean-type diet +	Exercise alone; no	12 weeks	Waist circumference

				cardiovascular risk	SCORE2/S-CORE2-OP risk	supervised exercise	intervention		nce; visceral fat; triglycerides
15	Dote-Montero et al. (2025)	Spain	Four-arm parallel RCT	197	Adults with overweight or obesity	Early, late or self-selected 8-h time-restricted eating + usual care	Usual care (Mediterranean diet education) alone	12 weeks	MRI-measured VAT (primary); cardio metabolic health markers
16	Klein et al. (2025)	Israel	Pooled analysis of two 18-month dietary RCTs (CENTRAL, DIRECT PLUS)	572	Adults with abdominal obesity or dyslipidaemia	Mediterranean / green-Mediterranean dietary strategies	Healthy dietary guidelines / low-fat comparator	18 months	MRI VAT area and VAT %; TG; HDL-C; HbA1c; HOM A-IR; hsCRP; leptin

HIIT = high-intensity interval training; VLCHF = very-low-carbohydrate high-fat; TRE = time-restricted eating; LCD = low-carbohydrate diet; GLP-1 = glucagon-like peptide-1; MetS = metabolic syndrome; hsCRP = high-sensitivity C-reactive protein; WC = waist circumference; BP = blood pressure; TG = triglycerides; QoL = quality of life; HOMA-IR = homeostatic model assessment of insulin resistance.

Modalities of Visceral Adiposity Assessment

Considerable methodological heterogeneity was observed in the operationalisation of the visceral adiposity exposure, which has direct implications for the comparability of effect estimates

across studies. Imaging-based studies quantified visceral fat either as a single-slice cross-sectional area, most commonly at the level of the third or fourth lumbar vertebra or at the umbilicus, or as a volumetric measurement across a defined abdominal segment, and these two approaches are not numerically interchangeable. Surrogate-index studies derived visceral adiposity from combinations of waist circumference, waist-to-height ratio, body mass index, triglycerides, high-density lipoprotein cholesterol, fasting glucose, age and sex. The distribution of assessment modalities, together with the corresponding thresholds and defining formulae where reported, is presented in Table 10.^{12,15,53}

Table10. Modalities of visceral adiposity assessment across included studies, with reported thresholds

Modality / index	Definition or formula basis	Studies employing it	Reported threshold or unit of increment
MDCT / CT — single slice area	Cross-sectional visceral fat area at L3, L4 or umbilical level (cm ²)	Hayashi 2003; Hayashi 2004; Boyko 2000; Shah 2014; Hung 2014; Kim 2021; Medina-Urrutia 2025	Kim 2021: 130.03 cm ² (men), 85.7 cm ² (women); Medina-Urrutia 2025: ≥ 194 cm ² (upper tertile)
MDCT — volumetric	Volumetric VAT and SAT across a defined abdominal segment (cm ³)	Fox 2007; Liu 2010; Kammerlander 2021; Lee 2016; Mongraw-Chaffin 2021	Per 1 standard deviation; Lee 2016: per additional 500 cm ³ and per 5 HU decrease in attenuation
MRI	Volumetric visceral adipose tissue, liver fat and epicardial/pericardial adipose tissue	Neeland 2012; Tejani 2021; Yi 2024; de Souza 2025; Rämö 2024; Neeland 2021; Gepner 2019; Klein 2025; Dote-Montero 2025	Per 1 standard deviation; median-defined high/low dichotomy; percentage change from baseline
DXA	Dual-energy X-ray absorptiometry visceral adipose tissue mass or area	Ballin 2021; Wong 2024; Yoon 2025; Wu 2025; Cipryan 2021; Ballin 2020	Wong 2024: VAT >131 cm ² ; Ballin 2020: >1 kg (women), >2 kg (men); Yoon 2025: Korean sex-specific cut-offs
Bioelectrical impedance	Dual bioelectrical impedance-derived visceral fat area	Cho 2017	84 cm ² (men); 58 cm ² (women)
METS-VF	$4.466 + 0.011 \cdot (\ln \text{METS-IR})^3 + 3.239 \cdot (\ln \text{WHtR})^3 + 0.319 \cdot (\text{sex}) + 0.594 \cdot (\ln \text{age})$	Bello-Chavolla 2020; Liu 2025; Jia 2024; Martínez-Luna 2026; Cho 2026; Wang 2026	Bello-Chavolla 2020: >7.18 (identifies VAT >100 cm ²); Wang 2026: non-linear threshold at 5.68
VAI / CVAI	Sex-specific composite of waist circumference, BMI, triglycerides and	Qiao 2022; Wu 2022; Yang 2024; Zheng 2026; Cho 2026;	Per 1 standard deviation; quartile and median-defined

	HDL-cholesterol; CVAI additionally incorporates age	Wang 2026; Golzarand 2026; Martínez-Luna 2026	categories; Yang 2024 median CVAI 101.26
LAP	(Waist circumference – 65 or 58) × triglycerides, sex-specific	Qiao 2022; Cho 2026; Wang 2026; Martínez-Luna 2026	Per 1 standard deviation; tertile and quartile categories
ABSI / BRI / CUN-BAE	Waist- and height-derived body shape and roundness indices; CUN-BAE estimates whole-body fat percentage	Golzarand 2026	Latent-class trajectory groups (low, moderate, high-increase) over 18 years
EVA / DAAT / DAI	Estimated visceral adiposity; deep abdominal adipose tissue; dysfunctional adiposity index	Martínez-Luna 2026	Per 1 standard deviation

HU = Hounsfield units; METS-IR = Metabolic Score for Insulin Resistance; WHtR = waist-to-height ratio; BMI = body mass index; HDL = high-density lipoprotein.

Incident Composite Cardiovascular Disease

Twelve studies contributed evidence on incident composite cardiovascular disease, encompassing more than 250,000 participants and follow-up durations extending to 20 years. The direction of association was positive in every study and reached statistical significance in every study. Effect magnitude in the highest versus lowest exposure category ranged from an adjusted hazard ratio of 1.62 in a 17.5-year Korean cohort employing the Metabolic Score for Visceral Fat to an adjusted hazard ratio of 2.78 in a 41,756-participant Chinese cohort in which visceral fat exposure was quantified cumulatively over four years rather than at a single time point. The gradient observed between single-measurement and cumulative-exposure studies is itself informative, indicating that the pathogenic effect of visceral adiposity is a function of duration as well as of magnitude of exposure, and that the risk conferred rises progressively with the number of years spent above the visceral fat threshold.^{27,30}

Two studies employing composite indices that combine visceral adiposity with insulin resistance demonstrated additional prognostic yield. In the China Health and Retirement Longitudinal Study, participants in the highest quartile of the combined triglyceride-glucose–Chinese visceral adiposity index had a 64% higher risk of new-onset cardiovascular disease, and restricted cubic spline

analysis identified a non-linear threshold at an index value of 778.62 above which each unit increment conferred a 47% increase in risk. A companion analysis of the same cohort using the visceral adiposity index and the triglyceride-glucose index separately identified the group with high visceral adiposity as carrying the highest cumulative hazard, with an antagonistic rather than synergistic statistical interaction between the two exposures, indicating that visceral fat accumulation and insulin resistance capture overlapping rather than wholly independent pathogenic information.^{21,31}

Trajectory-based analysis in the Tehran Lipid and Glucose Study extended these findings across an 18-year observation window, demonstrating that individuals following a high-increasing trajectory of adiposity indices carried approximately double the cardiovascular risk of those following a low-increasing trajectory, with the Clínica Universidad de Navarra–Body Adiposity Estimator showing the strongest association and the visceral adiposity index remaining significant at a hazard ratio of 1.92. The full evidence for this outcome domain is tabulated in Table 11.³⁴

Table 11. Visceral adiposity and incident composite cardiovascular disease

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Liu et al. (2025)	Kailuan cohort, China; n = 41,756; median 12.01 y	Cumulative METS-VF, Q4 vs Q1	HR 2.78 (2.49–3.17)	p < 0.001
Liu et al. (2025)	Kailuan cohort, China; n = 41,756	Cumulative METS-VF, Q3 vs Q1	HR 2.13 (1.91–2.38)	p < 0.001
Liu et al. (2025)	Kailuan cohort, China; n = 41,756	Cumulative METS-VF, Q2 vs Q1	HR 1.55 (1.38–1.74)	p < 0.001
Cho et al. (2026)	KoGES, South Korea; n = 8,192; 17.5 y	METS-VF, highest vs lowest tertile	HR 1.62 (1.29–2.03)	Significant
Cho et al. (2026)	KoGES, South Korea; n = 8,192	LAP, highest vs lowest tertile	HR 1.66 (1.32–2.09)	Significant
Cho et al. (2026)	KoGES, South Korea; n = 8,192	VAI, highest vs lowest tertile	HR 1.38 (1.08–1.77)	Significant
Zheng et al. (2026)	CHARLS, China; n = 7,977; 9 y	TyG-CVAI, Q4 vs Q1	HR 1.64 (1.35–2.00)	p < 0.001
Zheng et al. (2026)	CHARLS, China; n = 7,977	TyG-CVAI above threshold 778.62, per unit	HR 1.47 (1.31–1.64)	p < 0.001
Yang et al. (2024)	CHARLS, China; n = 8,358; 9 y	High CVAI with low TyG vs reference	HR 1.87 (1.57–2.24)	Significant

Yang et al. (2024)	CHARLS, China; n = 8,358	High CVAI with high TyG vs reference	HR 1.75 (1.49–2.06)	Significant
Qiao et al. (2022)	Xinjiang Multi-Ethnic Cohort, China; n = 2,328 with T2DM; 59 mo	CVAI, per 1 SD increase	HR 1.78 (1.57–2.01)	Significant
Qiao et al. (2022)	Xinjiang Multi-Ethnic Cohort; n = 2,328	Waist circumference, per 1 SD increase	HR 1.57 (1.39–1.78)	Significant
Qiao et al. (2022)	Xinjiang Multi-Ethnic Cohort; n = 2,328	LAP, per 1 SD increase	HR 1.46 (1.36–1.57)	Significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394; median 18 y	CUN-BAE, high-increase vs low trajectory	HR 2.45 (1.73–3.49)	Significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394	BRI, high-increase vs low trajectory	HR 2.12 (1.65–2.73)	Significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394	VAI, high-increase vs low trajectory	HR 1.92 (1.49–2.49)	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 1,731; median 12 y	High VAT–high liver fat vs low–low	HR 2.0 (1.3–3.2)	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 1,731	High VAT–low liver fat vs low–low	HR 2.4 (1.4–4.1)	Significant
Tejani et al. (2021)	UK Biobank replication; n = 22,354	High VAT–low liver fat, age- and BMI-adjusted	HR 1.5 (1.2–1.9)	Significant
Wu et al. (2025)	NHANES, USA; n = 4,227 with prediabetes/diabetes	DXA VAT index, highest vs lowest tertile	OR 2.55 (1.37–4.72)	p = 0.004
Wu et al. (2025)	NHANES, USA; n = 4,227	DXA VAT index, continuous	OR 2.11 (1.12–3.98)	p = 0.022
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482; 12.7 y	MDCT VAT, women, CVD death	HR 1.85 (1.26–2.71)	Significant
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	MDCT VAT, men, CVD death	HR 1.32 (0.97–1.80)	Not significant
Bello-Chavolla et al. (2020)	Metabolic Syndrome Cohort, Mexico; n = 6,144	METS-VF, upper quintile (>7.2)	2.0-fold risk of incident hypertension	p < 0.001

HR = hazard ratio; OR = odds ratio; SD = standard deviation; Q = quartile; METS-VF = Metabolic Score for Visceral Fat; LAP = Lipid Accumulation Product; VAI = Visceral Adiposity Index; CVAI

= *Chinese Visceral Adiposity Index*; TyG = *triglyceride-glucose index*; CUN-BAE = *Clínica Universidad de Navarra–Body Adiposity Estimator*; BRI = *Body Roundness Index*; VAT = *visceral adipose tissue*; BMI = *body mass index*. All estimates are from maximally adjusted multivariable models as reported by the source publications.

Coronary Heart Disease and Myocardial Infarction

Six studies specifically addressed coronary outcomes. The most methodologically informative evidence derives from the UK Biobank imaging sub-cohort of 24,265 participants followed for a mean of 12.9 years, in which each standard deviation increase in magnetic resonance imaging-quantified visceral adipose tissue conferred a 15% increase in coronary heart disease risk. Critically, this analysis performed the direct discrimination that anthropometry cannot: when the model was further adjusted for waist circumference, the association between abdominal subcutaneous adipose tissue and coronary heart disease was abolished entirely, whereas the association with visceral adipose tissue remained essentially unaltered. Discordance analysis in the same cohort showed that participants with visceral fat above the median but waist circumference below it carried a 43% excess coronary risk relative to those concordantly below both medians, thereby identifying a clinically important group whose visceral risk is invisible to tape-measure assessment.²³

Analysis of epicardial and pericardial adipose tissue in 44,475 UK Biobank participants using deep-learning segmentation of cardiac magnetic resonance images demonstrated a positive association with incident coronary artery disease at a hazard ratio of 1.19 per standard deviation, but this association was no longer significant after adjustment for abdominal visceral adipose tissue volume. This finding carries a specific interpretive implication: epicardial fat appears to act primarily as a marker of a systemically unhealthy adiposity phenotype rather than as an independent paracrine determinant of coronary disease. Evidence for this domain is tabulated in Table 12.²⁰

Table 12. Visceral adiposity, coronary heart disease and myocardial infarction

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Yi et al. (2024)	UK Biobank; n = 24,265; mean 12.9 y	MRI VAT, per 1 SD increase; CHD	HR 1.15 (1.09–1.22)	Significant

Yi et al. (2024)	UK Biobank; n = 24,265	MRI abdominal SAT, per 1 SD; CHD	HR 1.10 (1.04–1.18)	Significant (abolished after WC adjustment)
Yi et al. (2024)	UK Biobank; n = 24,265	VAT above median with WC below median	HR 1.43 (1.15–1.78)	Significant
Yi et al. (2024)	UK Biobank; n = 24,265	WC above median with VAT below median	HR 1.46 (1.18–1.81)	Significant
Rämö et al. (2024)	UK Biobank; n = 44,475; mean 3.2 y	MRI epicardial/pericardial fat, per 1 SD; CAD	HR 1.19 (1.11–1.28)	Significant (null after VAT adjustment)
Rämö et al. (2024)	FinnGen; n = 453,733	EPAT polygenic score, per 1 SD; CAD	OR 1.04 (1.03–1.05)	$p = 1.4 \times 10^{-17}$
Ballin et al. (2021)	Umeå, Sweden; n = 3,294 aged 70 y; 3.6 y	DXA VAT, per 1 SD; stroke or myocardial infarction	HR 1.56 (1.09–2.22)	Significant
Ballin et al. (2021)	Umeå, Sweden; n = 3,294 (men)	DXA VAT, per 1 SD; stroke or MI in men	HR 1.86 (1.19–2.91)	Significant
Ballin et al. (2021)	Umeå, Sweden; n = 3,294 (women)	DXA VAT, per 1 SD; stroke or MI in women	HR 0.60 (0.25–1.42)	Not significant (p-interaction = 0.038)
Yang et al. (2024)	CHARLS, China; n = 8,358; 896 CHD events	High CVAI groups vs reference	Highest cumulative hazard for CHD	Significant
Medina-Urrutia et al. (2025)	GEA cohort, Mexico; n = 853 premature CAD	CT VAT ≥ 194 cm ² vs lowest tertile	Non-fatal MACE aHR 3.58 (1.49–8.61)	$p = 0.004$
Karlsson et al. (2019)*	UK Biobank Mendelian randomization	Genetically predicted VAT mass	Causal effect on heart attack/angina	Significant

**Mendelian randomization analysis retained for causal interpretation only and excluded from the study characteristics tables in accordance with the protocol. CHD = coronary heart disease; CAD = coronary artery disease; MACE = major adverse cardiovascular events; EPAT = epicardial and pericardial adipose tissue; WC = waist circumference; SAT = subcutaneous adipose tissue.*

Cerebrovascular Events

Evidence for cerebrovascular outcomes was more heterogeneous than for coronary outcomes and warrants a more measured interpretation. In the Swedish cohort of 3,294 seventy-year-olds, greater visceral adipose tissue was significantly associated with the composite of stroke or myocardial infarction, but the association was confined to men and formally differed between sexes. In the UK Biobank, neither visceral nor subcutaneous adipose tissue was associated with stroke after adjustment for waist circumference, and in the China Health and Retirement Longitudinal Study the interaction between insulin resistance and visceral adiposity that was evident for coronary events was absent for stroke. Genetic evidence provides weak corroboration, with the epicardial adiposity polygenic score conferring only a 2% increase in stroke odds per standard deviation. Taken together, the association between visceral adiposity and cerebrovascular disease is less consistent and of smaller magnitude than that observed for coronary and metabolic endpoints, a pattern that is biologically plausible given the greater aetiological contribution of blood pressure, atrial fibrillation and small-vessel disease to stroke. This is one of the two outcome domains in which the evidence base does not permit an unequivocal conclusion, and it is presented here without overstatement.^{14,20,21,23}

Table 13. Visceral adiposity and cerebrovascular events

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Ballin et al. (2021)	Umeå, Sweden; n = 3,294; 108 stroke or MI events	DXA VAT, per 1 SD (composite stroke/MI)	HR 1.56 (1.09–2.22)	Significant
Yang et al. (2024)	CHARLS, China; n = 8,358; 475 strokes	CVAI and TyG index interaction	No significant interaction for stroke	Not significant
Yi et al. (2024)	UK Biobank; n = 24,265; 165 strokes	MRI VAT, after further WC adjustment	No association with stroke	Not significant
Rämö et al. (2024)	FinnGen; n = 453,733	EPAT polygenic score, per 1 SD	OR 1.02 (1.01–1.03)	$p = 3.5 \times 10^{-3}$
Yoon et al. (2025)	South Korea; n = 317 aged ≥ 65 y with CVD	Visceral obesity within composite MACE endpoint	Included in composite (see Table 17)	Significant for composite

Heart Failure and Atrial Fibrillation

Three studies addressed heart failure and atrial fibrillation. Epicardial and pericardial adipose tissue was more markedly elevated in prevalent heart failure and type 2 diabetes than in coronary

artery disease or atrial fibrillation, and prospectively predicted incident heart failure at a hazard ratio of 1.29 per standard deviation; however, as with coronary disease, this association did not survive adjustment for abdominal visceral adipose tissue volume. In the UK Biobank abdominal imaging cohort, neither visceral nor subcutaneous adipose tissue was associated with heart failure or atrial fibrillation after adjustment for waist circumference. Polygenic score analysis in FinnGen nevertheless demonstrated statistically robust associations with both heart failure and atrial fibrillation, of small magnitude. The evidence therefore supports visceral adiposity as a determinant of the metabolic milieu that predisposes to heart failure, without establishing an effect independent of overall central adiposity.^{20,23}

Table 14. Visceral and ectopic adiposity, heart failure and atrial fibrillation

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Rämö et al. (2024)	UK Biobank; n = 44,475	MRI EPAT, per 1 SD; incident heart failure	HR 1.29 (1.17–1.43)	Significant (null after VAT adjustment)
Rämö et al. (2024)	UK Biobank; n = 44,475	MRI EPAT, prevalent heart failure	$\beta = +0.46$ SD units	Significant
Rämö et al. (2024)	FinnGen; n = 453,733	EPAT polygenic score; heart failure	OR 1.05 (1.04–1.06)	$p = 4.8 \times 10^{-15}$
Rämö et al. (2024)	FinnGen; n = 453,733	EPAT polygenic score; atrial fibrillation	OR 1.04 (1.03–1.06)	$p = 7.6 \times 10^{-12}$
Yi et al. (2024)	UK Biobank; n = 24,265; 286 HF, 894 AF	MRI VAT after WC adjustment; HF and AF	No significant association	Not significant
Yoon et al. (2025)	South Korea; n = 317	Visceral obesity, HF hospitalisation within composite	Included in composite endpoint	Significant for composite

Recurrent Major Adverse Cardiovascular Events

Three studies examined recurrence in patients with established disease, an outcome of particular clinical relevance because it addresses residual risk in patients already receiving guideline-directed therapy. In a retrospective sub-analysis of 853 patients with premature coronary artery disease from the Mexican GEA cohort, computed tomography-quantified visceral adipose tissue in the upper tertile conferred a 171% increase in the risk of total recurrent major adverse cardiovascular

events and a 258% increase in non-fatal events over a median follow-up of 4.9 years, despite adequate pharmacological treatment. The association with fatal events did not reach significance, most plausibly reflecting limited statistical power given only 31 fatal events. The authors explicitly positioned visceral adipose tissue as an emergent residual risk factor and a candidate therapeutic target — a framing directly supported by the randomized evidence synthesised in Outcome 15.²⁶

A Korean retrospective cohort of 317 adults aged 65 years and over with established cardiovascular disease demonstrated the compounding effect of body composition abnormalities: sarcopenia alone was associated with a 93% increase in the composite of all-cause mortality and major cardiovascular events, whereas the coexistence of sarcopenia and visceral obesity — the sarcopenic obesity phenotype — conferred a 574% increase in risk. The extremely wide confidence interval reflects the small number of events and warrants cautious interpretation, but the direction and magnitude are consistent with the broader literature on sarcopenic obesity.²⁹

Table 15. Visceral adiposity and recurrent major adverse cardiovascular events

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Medina-Urrutia et al. (2025)	GEA cohort, Mexico; n = 853 premature CAD; 4.9 y	CT VAT ≥ 194 cm ² (upper tertile); total MACE	aHR 2.71 (1.37–5.35)	p = 0.004
Medina-Urrutia et al. (2025)	GEA cohort, Mexico; n = 853	CT VAT upper tertile; non-fatal MACE	aHR 3.58 (1.49–8.61)	p = 0.004
Medina-Urrutia et al. (2025)	GEA cohort, Mexico; n = 853	CT VAT upper tertile; fatal MACE	aHR 2.13 (0.72–6.35)	p = 0.174 (not significant)
Yoon et al. (2025)	South Korea; n = 317 aged ≥ 65 y with CVD	Sarcopenia alone; composite mortality and MACE	HR 1.93 (1.02–3.66)	Significant
Yoon et al. (2025)	South Korea; n = 317	Sarcopenic obesity (sarcopenia + visceral obesity)	HR 6.74 (1.81–25.16)	Significant
Qiao et al. (2022)	Xinjiang cohort, China; n = 2,328 with T2DM; 289 events	CVAI per 1 SD; cardiovascular events in diabetes	HR 1.78 (1.57–2.01)	Significant

Cardiovascular Mortality

Five studies contributed evidence on cardiovascular mortality. The largest and longest is a sub-analysis of 102,385 adults without diabetes from the Mexico City Prospective Study, followed for a median of 20.13 years, during which 4,068 cardiovascular deaths occurred. Seven visceral adiposity surrogates were compared head to head; the Metabolic Score for Visceral Fat performed best, with an adjusted hazard ratio of 1.23 per standard deviation and a Harrell C-statistic of 0.73, followed closely by estimated visceral adiposity, the Chinese visceral adiposity index and deep abdominal adipose tissue. Importantly, the authors demonstrated that adding the Metabolic Score for Visceral Fat to the Globorisk score improved discrimination among individuals classified as being at intermediate risk — the clinical subgroup in which reclassification is most consequential for management decisions.³²

The Framingham Heart Study provides the most striking demonstration of sex-specific effect modification for this outcome. Among men, visceral adipose tissue and body mass index performed comparably for cardiovascular death, with body mass index in fact showing the larger association. Among women the pattern inverted: visceral adipose tissue conferred a hazard ratio of 1.85 for cardiovascular death whereas body mass index conferred only 1.19. The authors concluded that anthropometric measures adequately capture visceral fat-associated risk in men but not in women — a conclusion with immediate implications for the sex-neutral application of body mass index thresholds in clinical practice.¹³

Table 16. Visceral adiposity and cardiovascular mortality

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385; median 20.13 y	METS-VF, per 1 SD; CVD mortality	aHR 1.23 (1.18–1.29); C = 0.73	Significant
Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385	EVA, per 1 SD; CVD mortality	aHR 1.19 (1.15–1.24); C = 0.73	Significant
Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385	CVAI, per 1 SD; CVD mortality	aHR 1.19 (1.15–1.23); C = 0.71	Significant

Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385	DAAT, per 1 SD; CVD mortality	aHR 1.18 (1.14–1.23); C = 0.63	Significant
Jia et al. (2024)	NHANES, USA; n = 11,120; median 83 mo; 301 CV deaths	METS-VF, per 0.2-unit increase	HR 1.18 (1.06–1.31)	Significant
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482; 12.7 y	MDCT VAT, women; CVD death	aHR 1.85 (1.26–2.71)	Significant
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	BMI, women; CVD death (comparator)	aHR 1.19 (1.01–1.40)	Significant but weaker
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	MDCT VAT, men; CVD death	aHR 1.32 (0.97–1.80)	Not significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394; median 18 y	BRI, high-increase trajectory; CV mortality	HR 3.25 (1.85–5.69)	Significant
Torres-Chávez et al. (2025)	CC-LAC consortium, Latin America; n = 23,097; 113,622 person-y	Estimated VAT, Q4 vs Q1; fatal and non-fatal CV events	HR 1.85 (1.37–2.50)	Significant

C = Harrell concordance statistic; EVA = estimated visceral adiposity; DAAT = deep abdominal adipose tissue; CC-LAC = Cohorts Consortium of Latin America and the Caribbean.

All-Cause Mortality

Six studies addressed all-cause mortality, with divergent findings that repay careful examination. The Kailuan study reported the largest effect observed anywhere in this review: participants in the highest quartile of cumulative Metabolic Score for Visceral Fat exposure had a hazard ratio of 4.90 for all-cause mortality, and the magnitude of risk increased monotonically with the duration for which the participant remained above the high-exposure threshold. This finding is notable because the hazard ratio for all-cause mortality exceeded that for cardiovascular disease in the same cohort, suggesting that the mortality burden of visceral adiposity extends beyond cardiovascular causes — a suggestion corroborated by the National Health and Nutrition Examination Survey mortality-linkage analysis, in which the Metabolic Score for Visceral Fat was significantly associated with cancer mortality as well as with cardiovascular and all-cause mortality.^{22,27}

Against this, the Swedish cohort of 70-year-olds found no association between visceral adipose tissue and all-cause mortality over a mean follow-up of 3.6 years, during which only 97 deaths occurred. Two explanations are plausible and not mutually exclusive: insufficient statistical power at this event count, and the well-described attenuation of adiposity–mortality associations in advanced age, sometimes termed the obesity paradox, in which preserved fat mass may confer a survival advantage in the presence of competing risks and frailty. The discordance between these studies is therefore best interpreted as a genuine age-related effect modification rather than as evidence of inconsistency.¹⁴

Table 17. Visceral adiposity and all-cause mortality

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Liu et al. (2025)	Kailuan cohort, China; n = 41,756; 3,944 deaths	Cumulative METS-VF, Q4 vs Q1	HR 4.90 (4.36–5.50)	p < 0.001
Liu et al. (2025)	Kailuan cohort, China; n = 41,756	Cumulative METS-VF, Q3 vs Q1	HR 2.67 (2.37–3.01)	p < 0.001
Liu et al. (2025)	Kailuan cohort, China; n = 41,756	Cumulative METS-VF, Q2 vs Q1	HR 1.59 (1.40–1.81)	p < 0.001
Jia et al. (2024)	NHANES, USA; n = 11,120; 1,014 deaths	METS-VF, per 0.2-unit increase	HR 1.13 (1.06–1.20)	Significant
Jia et al. (2024)	NHANES, USA; n = 11,120; 262 cancer deaths	METS-VF, per 0.2-unit increase; cancer mortality	HR 1.13 (1.03–1.25)	Significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394; 532 deaths	BRI, high-increase trajectory	HR 1.47 (1.10–1.96)	Significant
Golzarand et al. (2026)	TLGS, Iran; n = 11,394	VAI, ABSI and CUN-BAE trajectories	No association with all-cause mortality	Not significant
Ballin et al. (2021)	Umeå, Sweden; n = 3,294 aged 70 y; 97 deaths	DXA VAT, per 1 SD	aHR 0.95 (0.65–1.41)	Not significant
Yoon et al. (2025)	South Korea; n = 317 aged ≥65 y with CVD	Sarcopenic obesity; composite including mortality	HR 6.74 (1.81–25.16)	Significant

Incident Type 2 Diabetes Mellitus and Prediabetes

Eleven studies contributed to this domain, which constitutes the most internally consistent and largest-magnitude body of evidence in the review. Every study reported a positive and statistically

significant association. The foundational prospective evidence derives from Japanese Americans in Seattle, in whom each standard deviation increase in computed tomography-quantified intra-abdominal fat area conferred a 60% increase in diabetes risk among second-generation participants and a 170% increase among third-generation participants, with intra-abdominal fat area remaining a significant predictor after adjustment for body mass index, total body fat area and subcutaneous fat area — while no measure of total or regional adiposity remained associated with diabetes once intra-abdominal fat area was included in the model. This pattern of mutual adjustment, in which the visceral term survives and the anthropometric terms do not, recurs throughout the literature and constitutes the strongest single argument for the specificity of the visceral depot.⁵

The Dallas Heart Study extended these observations to a multi-ethnic obese population, demonstrating that among 732 obese adults followed for a median of 7.0 years, higher baseline visceral fat mass conferred an odds ratio of 2.4 per standard deviation for incident diabetes, with no association observed for body mass index, total body fat or abdominal subcutaneous fat. This is a decisive finding for clinical practice: among individuals who are uniformly obese by body mass index criteria, it is the visceral compartment and not the degree of generalised obesity that discriminates who will progress to diabetes.⁶

The most extreme sex divergence in the entire review was observed in a Korean cohort of 10,882 adults undergoing computed tomography during health screening. Comparing the highest with the lowest quartile of visceral fat area, the adjusted odds ratio for incident type 2 diabetes was 2.62 in men but 32.49 in women. The confidence interval in women is extremely wide, reflecting a low female event count of 174 cases, and the point estimate should not be taken at face value; nonetheless the qualitative conclusion of a substantially steeper visceral fat–diabetes gradient in women is corroborated independently by the KPOG [PO Framingham Heart Study, in which visceral adipose tissue conferred an odds ratio of 4.51 for diabetes in women versus 2.33 for body mass index, whereas in men the two measures performed equivalently.^{13,15}

Table 18. Visceral adiposity and incident type 2 diabetes mellitus and prediabetes

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
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Kim et al. (2021)	South Korea; n = 10,882; median 4.8 y	CT visceral fat area, Q4 vs Q1, women	OR 32.49 (7.42–142.02)	Significant
Kim et al. (2021)	South Korea; n = 10,882	CT visceral fat area, Q4 vs Q1, men	OR 2.62 (1.73–3.97)	Significant
Kim et al. (2021)	South Korea; n = 10,882	Visceral-to-subcutaneous ratio, Q4 vs Q1, women	OR 11.07 (3.89–31.50)	Significant
Kim et al. (2021)	South Korea; n = 10,882	Visceral-to-subcutaneous ratio, Q4 vs Q1, men	OR 1.55 (1.14–2.11)	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 1,731; 12 y	High VAT–high liver fat vs low–low; T2DM	OR 7.8 (3.8–15.8)	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 1,731	High VAT–low liver fat vs low–low; T2DM	OR 3.3 (1.4–7.8)	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 1,731	Low VAT–high liver fat vs low–low; T2DM	OR 2.7 (1.1–6.7)	Significant
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	MDCT VAT, women; incident diabetes	OR 4.51 (3.13–6.50)	Significant
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	BMI, women; incident diabetes (comparator)	OR 2.33 (1.88–3.04)	Significant but weaker
Kammerlander et al. (2021)	Framingham Heart Study, USA; n = 3,482	MDCT VAT, men; incident diabetes	OR 2.36 (1.84–3.04)	Significant
Rämö et al. (2024)	UK Biobank; n = 44,475	MRI EPAT, per 1 SD; incident T2DM	HR 1.63 (1.51–1.76)	Significant
Neeland et al. (2012)	Dallas Heart Study, USA; n = 732 obese; median 7 y	MRI visceral fat mass, per 1 SD (1.4 kg)	OR 2.4 (1.6–3.7)	Significant
Neeland et al. (2012)	Dallas Heart Study, USA; n = 732	BMI, total body fat, abdominal SAT (comparators)	No significant association	Not significant
Bello-Chavolla et al. (2020)	Metabolic Syndrome Cohort, Mexico; n = 6,144	METS-VF, upper quintile (>7.2)	3.8-fold increased risk of T2DM	p < 0.001
Wong et al. (2024)	Singapore; n = 733 midlife women; 6.6 y	DXA VAT >131 cm ² alone	aRR 1.78 (1.12–2.84)	Significant
Wong et al. (2024)	Singapore; n = 733	High VAT with poor muscle strength	aRR 2.63 (1.81–3.82)	Significant

Boyko et al. (2000)	Japanese Americans (Nisei), USA; n = 290; 65 cases	CT intra-abdominal fat area, per 1 SD	OR 1.6 (1.1–2.3)	Significant
Boyko et al. (2000)	Japanese Americans (Sansei), USA; n = 230	CT intra-abdominal fat area, BMI-adjusted	OR 2.7 (1.4–5.4)	Significant
Karlsson et al. (2019)*	UK Biobank; Mendelian randomization	Genetically predicted VAT mass, women	OR 7.34 (4.48–12.0)	Significant
Karlsson et al. (2019)*	UK Biobank; Mendelian randomization	Genetically predicted VAT mass, men	OR 2.50 (1.98–3.14)	Significant
Jayedi et al. (2022)*	Meta-analysis of 216 cohorts; 26 million participants	Visceral adiposity index, per 1-unit increase	RR 1.42 (1.27–1.58)	Significant

**Mendelian randomization and meta-analytic evidence retained for outcome interpretation and discussion only, and excluded from the study characteristics tables in accordance with the protocol. aRR = adjusted relative risk; RR = relative risk.*

Incident and Prevalent Hypertension

Eight studies addressed hypertension. The pivotal prospective evidence is a community-based cohort of 300 normotensive Japanese Americans followed for 10 to 11 years, in which 92 incident cases of hypertension occurred. Compared with the lowest quartile of computed tomography-quantified intra-abdominal fat area, the third quartile carried a five-fold and the fourth quartile a three-and-a-half-fold increase in adjusted odds, after adjustment for age, sex, fasting insulin, two-hour glucose, body mass index, baseline systolic pressure, alcohol, smoking and exercise energy expenditure. As with the diabetes literature, intra-abdominal fat area remained significant after adjustment for total or abdominal subcutaneous fat area and for waist circumference, whereas none of these measures retained significance in models containing intra-abdominal fat area. The quadratic rather than strictly monotonic trend, with the third quartile point estimate exceeding the fourth, is attributable to the small number of events per stratum and does not undermine the overall inference.⁴

Contemporary surrogate-based evidence from the China Health and Retirement Longitudinal Study, comprising 6,775 normotensive adults aged 45 years and over followed for a median of eight years with 2,845 incident hypertension cases, confirms and quantifies this relationship at population

scale: the highest quartile of the Metabolic Score for Visceral Fat conferred a 2.11-fold increase in hazard, corresponding to an absolute eight-year risk difference of 18.3 percentage points, and restricted cubic spline analysis identified a non-linear threshold at an index value of 5.68 above which risk rose sharply. Longitudinal imaging in the Framingham Third Generation cohort adds a change-based dimension: each additional 500 cm³ of visceral fat accumulated over a mean of 6.1 years increased the odds of incident hypertension by 30%, and this association persisted after accounting for concurrent change in body mass index and waist circumference.^{9,33}

Table 19. Visceral adiposity and hypertension

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Hayashi et al. (2004)	Japanese Americans, USA; n = 300; 10–11 y; 92 cases	CT intra-abdominal fat area, Q3 vs Q1	OR 5.07 (1.75–14.73)	p = 0.003 (quadratic trend)
Hayashi et al. (2004)	Japanese Americans, USA; n = 300	CT intra-abdominal fat area, Q4 vs Q1	OR 3.48 (1.01–11.99)	Significant
Hayashi et al. (2003)	Japanese Americans, USA; n = 563	CT intra-abdominal fat area, per 1 SD; prevalent hypertension	OR 1.68 (1.20–2.37)	Significant
Wang et al. (2026)	CHARLS, China; n = 6,775; median 8 y; 2,845 cases	METS-VF, Q4 vs Q1	HR 2.11 (1.85–2.42)	p-trend < 0.001
Wang et al. (2026)	CHARLS, China; n = 6,775	METS-VF above non-linear threshold 5.68	HR 2.34 (134% increase)	Significant
Wang et al. (2026)	CHARLS, China; n = 6,775	METS-VF, per 1-unit increase	HR 1.02 (1.00–1.05)	Significant
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106; 6.1 y	MDCT VAT, per additional 500 cm ³	OR 1.30	p < 0.05
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106	MDCT SAT, per additional 500 cm ³ (comparator)	OR 1.21	p < 0.05
Hung et al. (2014)	Taiwan community cohort; n = 432; 2.94 y; 32 cases	CT retroperitoneal fat area	HR 1.62	p = 0.003
Hung et al. (2014)	Taiwan community cohort; n = 432	CT peritoneal fat area	HR 1.62	p = 0.009

Hung et al. (2014)	Taiwan community cohort; n = 432	CT subcutaneous fat area (comparator)	No association	p = 0.14
Bello-Chavolla et al. (2020)	Metabolic Syndrome Cohort, Mexico; n = 6,144	METS-VF, upper quintile (>7.2)	2.0-fold risk of incident hypertension	p < 0.001
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT VAT, per 1 SD; prevalent hypertension	OR 1.62 (1.4–1.9)	p < 0.0001
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT SAT, per 1 SD (comparator)	OR 1.40 (1.2–1.6)	Significant but weaker
Fox et al. (2007)	Framingham Heart Study, USA; n = 3,001	MDCT VAT, per 1 SD; prevalent hypertension	Significantly increased odds	p < 0.01
Tatsumi et al. (2017)	Japan; n = 3,122 (normal weight stratum)	CT visceral fat area, Q4 vs Q1; high blood pressure	OR 2.1 (1.5–3.0)	Significant
Karlsson et al. (2019)*	UK Biobank; Mendelian randomization	Genetically predicted VAT mass	Causal effect on hypertension	Significant

Metabolic Syndrome

Nine studies addressed metabolic syndrome, and this domain provides the clearest demonstration of the differential pathogenicity of visceral relative to subcutaneous fat. In the Framingham Heart Study, the odds ratio for metabolic syndrome per standard deviation increase was 4.7 for visceral and 3.0 for subcutaneous adipose tissue in women, and 4.2 versus 2.5 in men, with the difference between depots itself highly statistically significant. The Jackson Heart Study reproduced this pattern in an African-ancestry population, with odds ratios of 3.34 for visceral and 2.06 for subcutaneous adipose tissue in women. Both studies further demonstrated that the visceral term retained significance after adjustment for body mass index and waist circumference whereas the subcutaneous term did not — evidence that visceral adiposity carries information about metabolic risk that anthropometry cannot recover.^{1,2}

The Multi-Ethnic Study of Atherosclerosis contributed the critical longitudinal evidence, with 253 participants free of metabolic syndrome at baseline undergoing repeat computed tomography after a median of 3.3 years. Both baseline visceral fat and change in visceral fat independently predicted incident metabolic syndrome, with a 28% increase in hazard per 100 cm²/m of visceral fat

area and a 5% increase per 5% change, and the addition of visceral fat to a clinical risk model produced a net reclassification index of 0.44 — a substantial improvement. Critically, change in subcutaneous fat showed no association after adjustment for clinical risk and visceral fat area, confirming that it is the trajectory of the visceral depot specifically, and not overall weight change, that drives incident metabolic syndrome. The IRAS Family Study independently confirmed that both baseline visceral adipose tissue and its increase over five years were associated with incident metabolic syndrome irrespective of body mass index category.^{7,16}

The evidence regarding normal-weight individuals deserves particular emphasis because it directly challenges body mass index-based screening. In a Japanese cross-sectional study of 3,122 adults stratified by an Asian-specific body mass index cut-off of 23.0 kg/m², participants of normal weight in the highest quartile of visceral fat area had a 9.3-fold increase in the odds of clustering two or more metabolic syndrome components — an effect larger than that observed in the higher-weight stratum, where the corresponding odds ratio was 6.0. The metabolically obese normal-weight phenotype is therefore not a statistical curiosity but a quantitatively important risk state that current screening paradigms systematically fail to detect.¹¹

Table 20. Visceral adiposity and metabolic syndrome, with subcutaneous adipose tissue as internal comparator

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Fox et al. (2007)	Framingham Heart Study, USA; n = 3,001 (women)	MDCT VAT, per 1 SD	OR 4.7	p < 0.0001 vs SAT
Fox et al. (2007)	Framingham Heart Study, USA; n = 3,001 (women)	MDCT SAT, per 1 SD (comparator)	OR 3.0	Significant but weaker
Fox et al. (2007)	Framingham Heart Study, USA; n = 3,001 (men)	MDCT VAT vs SAT, per 1 SD	OR 4.2 vs 2.5	p < 0.0001 for difference
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT VAT, per 1 SD	OR 3.34 (2.8–4.0)	p < 0.0001
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT SAT, per 1 SD (comparator)	OR 2.06 (1.8–2.4)	Significant but weaker

Shah et al. (2014)	MESA, USA; n = 1,511 (253 with serial CT)	CT visceral fat, per 100 cm ² /m	28% greater hazard of incident MetS	Significant
Shah et al. (2014)	MESA, USA; n = 253 serial imaging	Baseline visceral fat, per 100 cm ² /m	HR 1.24 (1.08–1.44)	p = 0.003
Shah et al. (2014)	MESA, USA; n = 253 serial imaging	Change in visceral fat, per 5% change	HR 1.05 (1.01–1.08)	p = 0.02
Shah et al. (2014)	MESA, USA; n = 1,511	Net reclassification over clinical risk model	NRI 0.44 (0.29–0.60)	Significant
Mongraw-Chaffin et al. (2021)	IRAS Family Study, USA; 5 y	CT VAT at baseline	OR 1.16 (1.12–2.31)	Significant
Mongraw-Chaffin et al. (2021)	IRAS Family Study, USA; 5 y	Increase in CT VAT over time	OR 1.55 (1.22–1.98)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; normal weight (BMI 18.5–22.9)	CT visceral fat area, Q4 vs Q1	OR 9.3 (4.2–20.7)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; normal weight	CT visceral fat area, Q3 vs Q1	OR 6.3 (2.8–14.2)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; higher weight (BMI ≥23)	CT visceral fat area, Q4 vs Q1	OR 6.0 (4.1–8.8)	Significant
Cho et al. (2017)	Seoul cohort, South Korea; n = 337; 17 mo	High visceral fat area with low adiponectin	OR 4.918 (2.05–11.795)	p < 0.001
Hung et al. (2014)	Taiwan community cohort; n = 432	CT retroperitoneal fat area	Adjusted OR 5.651	p < 0.05
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106	MDCT VAT, per additional 500 cm ³	OR 1.82	p < 0.05
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106	MDCT SAT, per additional 500 cm ³ (comparator)	OR 1.43	Significant but weaker
Bennett et al. (2024)*	Systematic review of 52 threshold studies	VAT thresholds for elevated MetS risk	70–165.9 cm ² ; consistently lower in women	Threshold evidence

*Threshold synthesis retained for interpretation only and excluded from the characteristics tables.

MetS = metabolic syndrome; NRI = net reclassification index; MESA = Multi-Ethnic Study of Atherosclerosis; IRAS = Insulin Resistance Atherosclerosis Study.

Atherogenic Dyslipidaemia and Dysglycaemia

Ten studies reported associations with individual lipid and glycaemic parameters. The pattern observed is precisely that predicted by the portal hypothesis: visceral adiposity is most strongly associated with triglyceride elevation and high-density lipoprotein cholesterol reduction, with weaker or absent associations with low-density lipoprotein cholesterol. The magnitude of the triglyceride association among normal-weight individuals is striking; in the highest quartile of visceral fat area among Japanese adults of normal body mass index, the odds ratio for hypertriglyceridaemia was 12.0 and for low high-density lipoprotein cholesterol 5.2, both substantially exceeding the corresponding estimates in the higher-weight stratum. Longitudinal imaging in Framingham demonstrated that a 500 cm³ increase in visceral fat conferred an odds ratio of 1.56 for incident hypertriglyceridaemia compared with 1.15 for the same increase in subcutaneous fat, again establishing depot-specific effects.^{9,11}

Table 21. Visceral adiposity, atherogenic dyslipidaemia and dysglycaemia

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Tatsumi et al. (2017)	Japan; n = 3,122; normal weight	CT visceral fat area, Q4 vs Q1; high triglycerides	OR 12.0 (5.7–25.3)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; normal weight	CT visceral fat area, Q4 vs Q1; low HDL-cholesterol	OR 5.2 (2.1–12.9)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; normal weight	CT visceral fat area, Q4 vs Q1; high fasting glucose	OR 2.4 (1.4–4.2)	Significant
Tatsumi et al. (2017)	Japan; n = 3,122; higher weight	CT visceral fat area, Q4 vs Q1; high triglycerides	OR 5.0 (3.4–7.4)	Significant
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT VAT, per 1 SD; fasting plasma glucose	$\beta = +5.51 \pm 1.0$ mg/dL	p < 0.0001
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT VAT, per 1 SD; triglycerides	$\beta = +0.17 \pm 0.01$	p < 0.0001
Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT VAT, per 1 SD; HDL-cholesterol	$\beta = -5.36 \pm 0.4$ mg/dL	p < 0.0001

Liu et al. (2010)	Jackson Heart Study, USA; n = 2,477 (women)	MDCT SAT, per 1 SD; HDL-cholesterol (comparator)	$\beta = -2.85 \pm 0.4 \text{ mg/dL}$	Significant but weaker
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106	MDCT VAT, per additional 500 cm ³ ; hypertriglyceridaemia	OR 1.56	p < 0.05
Lee et al. (2016)	Framingham Third Generation, USA; n = 1,106	MDCT SAT, per additional 500 cm ³ (comparator)	OR 1.15	Significant but weaker
Fox et al. (2007)	Framingham Heart Study, USA; n = 3,001	MDCT VAT; blood pressure, glucose, triglycerides, HDL-C	All significantly associated	p < 0.01
Klein et al. (2025)	Pooled CENTRAL and DIRECT PLUS trials; n = 572; 18 mo	Loss of VAT area and VAT%	Decreased TG and HbA1c; increased HDL-C	FDR < 0.05
Klein et al. (2025)	Pooled CENTRAL and DIRECT PLUS trials; n = 572	VAT% versus VAT area	VAT% better classified hypertriglyceridaemia	Significant
Wu et al. (2025)	NHANES, USA; n = 4,227	DXA VAT index; mediation by HDL-cholesterol	13.34% of association mediated	Significant
He et al. (2022)	China; RCT in metabolic syndrome; 3 mo	Time-restricted eating $\pm$ low-carbohydrate diet	Reduced fasting glucose, uric acid, dyslipidaemia	Significant vs baseline

Insulin Resistance, Adipokines and Systemic Inflammation

Nine studies addressed the mechanistic intermediates linking visceral fat to clinical disease. The IRAS Family Study demonstrated that both visceral adipose tissue and the homeostatic model assessment of insulin resistance independently predicted incident metabolic syndrome, and that increases in each over five years conferred additional risk, with the insulin resistance term carrying the larger effect. Mediation analysis in the National Health and Nutrition Examination Survey quantified the proportion of the visceral fat–cardiovascular disease association attributable to specific pathways, finding that high-density lipoprotein cholesterol mediated 13.34% and the systemic inflammatory response index 5.42% — indicating that lipid metabolism and inflammation together account for approximately one fifth of the effect and that the majority operates through other mechanisms, most plausibly direct hepatic insulin resistance and ectopic lipid deposition.^{16,28}

Randomized evidence provides the most direct causal evidence in this domain. In the pooled analysis of the CENTRAL and DIRECT PLUS dietary trials, loss of visceral adipose tissue area over 18 months correlated specifically with decreases in the homeostatic model assessment of insulin resistance, chemerin and leptin, whereas the proportional measure of visceral fat did not — a dissociation indicating that absolute visceral fat mass, rather than its share of total abdominal fat, governs the inflammatory and glycaemic state. Combined exercise and glucagon-like peptide-1 receptor agonist therapy reduced high-sensitivity C-reactive protein by 43% relative to placebo, an effect not achieved by either intervention alone.^{47,50}

Table 22. Visceral adiposity, insulin resistance, adipokines and inflammation

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Mongraw-Chaffin et al. (2021)	IRAS Family Study, USA; 5 y	HOMA-IR at baseline; incident metabolic syndrome	OR 1.85 (1.32–2.58)	Significant
Mongraw-Chaffin et al. (2021)	IRAS Family Study, USA; 5 y	Increase in HOMA-IR over time	OR 3.23 (2.20–4.73)	Significant
Wu et al. (2025)	NHANES, USA; n = 4,227	Mediation by HDL-cholesterol	13.34% of VAT–CVD association	Significant
Wu et al. (2025)	NHANES, USA; n = 4,227	Mediation by systemic inflammatory response index	5.42% of VAT–CVD association	Significant
Klein et al. (2025)	CENTRAL and DIRECT PLUS pooled; n = 572; 18 mo	Loss of VAT area (cm ²)	Decreased HOMA-IR, chemerin and leptin	FDR < 0.05
Klein et al. (2025)	CENTRAL and DIRECT PLUS pooled; n = 572	Higher VAT area at baseline	Associated with elevated hsCRP	Significant
Sandsdal et al. (2023)	Denmark; RCT; n = 130 per protocol; 52 wk	Exercise + liraglutide 3.0 mg vs placebo	hsCRP reduced by 43%	p = 0.03
Sandsdal et al. (2023)	Denmark; RCT; n = 130; 52 wk	Exercise + liraglutide; metabolic syndrome severity	MetS-Z –0.48 (–0.70 to –0.25)	p < 0.001
Cipryan et al. (2021)	Czech Republic; RCT; n = 91; 12 wk	Very-low-carbohydrate high-fat diet	HOMA-IR –0.75 (–1.13 to –0.55)	p < 0.05

Cipryan et al. (2021)	Czech Republic; RCT; n = 91; 12 wk	Very-low-carbohydrate high-fat diet	Adiponectin/leptin ratio +9.34 (6.33–37.39)	p < 0.05
Lee et al. (2013)	USA; RCT in obese adolescent girls; n = 44; 3 mo	Aerobic exercise vs control; clamp insulin sensitivity	$\Delta +0.92 \pm 0.27$ mg·kg ⁻¹ ·min ⁻¹ per μ U/mL	p < 0.05
Bouchonville et al. (2013)	USA; RCT in obese older adults; n = 107; 12 mo	Diet + exercise vs diet alone; insulin sensitivity index	Between-group difference 1.2 (0.2–2.1)	Significant
Bouchonville et al. (2013)	USA; RCT; n = 107; 12 mo	Diet + exercise; tumour necrosis factor alpha	–17.0 pg/mL; adiponectin +5.0 ng/mL	Significant
Cho et al. (2017)	Seoul cohort, South Korea; n = 337	Low adiponectin with high visceral fat area	Highest metabolic syndrome incidence (46.15%)	p < 0.001

HOMA-IR = homeostatic model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; MetS-Z = metabolic syndrome severity z-score; FDR = false discovery rate.

Subclinical Atherosclerosis

Four studies examined imaging markers of subclinical atherosclerotic disease. In the Canadian Alliance of Healthy Hearts and Minds cohort of 6,760 participants undergoing magnetic resonance imaging, each standard deviation increase in visceral adipose tissue volume was associated with a 6.16 mm³ higher carotid wall volume, whereas hepatic fat fraction showed no independent association with carotid wall volume. Replication in 26,547 UK Biobank participants using ultrasound-measured carotid intima-media thickness confirmed a positive association for both visceral fat and hepatic proton-density fat fraction, although both associations attenuated after adjustment for conventional cardiovascular risk factors — indicating that a substantial part of the visceral fat effect on subclinical atherosclerosis is transmitted through blood pressure, lipids and glycaemia rather than operating entirely independently of them. This is mechanistically coherent and does not diminish the clinical utility of visceral fat as an upstream target.²⁵

Table 23. Visceral adiposity and subclinical atherosclerosis

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
de Souza et al. (2025)	CAHHM, Canada; n = 6,760; mean age 57.1 y	MRI VAT volume, per 1 SD; carotid wall volume	+6.16 mm ³ (1.68–10.63)	Significant

de Souza et al. (2025)	CAHHM, Canada; n = 6,760	Hepatic fat fraction; carotid wall volume	No association	Not significant
de Souza et al. (2025)	UK Biobank; n = 26,547	MRI VAT volume, per 1 SD; carotid IMT	+0.016 ± 0.009 mm	Significant
de Souza et al. (2025)	UK Biobank; n = 26,547	Hepatic proton-density fat fraction, per 1 SD; carotid IMT	+0.012 ± 0.010 mm	Significant
Shah et al. (2014)	MESA, USA; n = 1,511	CT visceral fat; coronary artery calcification	Associated regardless of BMI category	Significant
Tejani et al. (2021)	Dallas Heart Study, USA; n = 2,064	High VAT phenotypes; prevalent atherosclerosis	High VAT–high LF and high VAT–low LF associated	Significant
Emamat et al. (2024)*	Systematic review of 27 observational studies	Visceral-to-subcutaneous fat ratio	Higher ratio associated with CVD development	Directionally consistent

**Systematic review retained for outcome interpretation and discussion only, excluded from characteristics tables. IMT = intima-media thickness; LF = liver fat; CAHHM = Canadian Alliance of Healthy Hearts and Minds.*

Microvascular and Renal Complications

Two studies addressed microvascular complications, and their findings are notably dissociated by vascular bed. In a Chinese cohort of 8,948 patients with type 2 diabetes followed for a median of 4.82 years, each standard deviation increase in the visceral adiposity index was associated with a 12.7% increase in the risk of incident diabetic nephropathy and the Chinese visceral adiposity index with a 16.5% increase, whereas neither index was associated with incident diabetic retinopathy after adjustment for confounders. A companion analysis in the Kailuan cohort of 7,874 patients with diabetes demonstrated that cumulative rather than baseline exposure conferred substantially greater risk of diabetic kidney disease, with a hazard ratio of 1.62 for high cumulative exposure versus 1.24 for high baseline exposure — reproducing at the microvascular level the cumulative-exposure gradient observed for macrovascular endpoints. The dissociation between renal and retinal outcomes suggests that visceral adiposity acts on the kidney through metabolic and haemodynamic pathways such as glomerular hyperfiltration, adipokine-mediated podocyte injury and lipotoxicity that are less operative in the retinal microcirculation, where glycaemic exposure predominates.¹⁹

Table 24. Visceral adiposity and microvascular and renal complications

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Wu et al. (2022)	Beijing Health Management Cohort, China; n = 8,948; 4.82 y	VAI, per 1 SD; incident diabetic nephropathy	HR 1.127 (1.050–1.210)	Significant
Wu et al. (2022)	Beijing Health Management Cohort, China; n = 8,948	CVAI, per 1 SD; incident diabetic nephropathy	HR 1.165 (1.003–1.353)	Significant
Wu et al. (2022)	Beijing Health Management Cohort, China; n = 8,948; 90 cases	VAI and CVAI; incident diabetic retinopathy	No association after adjustment	Not significant
Sun et al. (2025)	Kailuan Study, China; n = 7,874 with diabetes	High baseline CVAI; diabetic kidney disease	HR 1.24 (1.09–1.42)	p < 0.001
Sun et al. (2025)	Kailuan Study, China; n = 7,874	High cumulative CVAI; diabetic kidney disease	HR 1.62 (1.29–2.04)	p < 0.001

Modifiability of Visceral Adipose Tissue: Randomized Controlled Trial Evidence

Sixteen randomized controlled trials examined whether visceral adipose tissue can be therapeutically reduced, and this outcome domain provides the translational bridge between the observational associations described above and clinical practice. The single most informative trial is a phase 4, randomised, double-blind, placebo-controlled study of once-daily liraglutide 3.0 mg in 185 adults with overweight or obesity at high cardiovascular risk but without diabetes. Over a median of 36.2 weeks, magnetic resonance imaging-quantified visceral adipose tissue fell by 12.49% in the liraglutide arm compared with 1.63% with placebo, yielding an estimated treatment difference of –10.86% with a p-value below 0.0001, and effects were consistent across subgroups defined by age, sex, race and ethnicity, body mass index and baseline prediabetes status. Because both arms received an identical 500 kcal deficit diet and physical activity counselling, this trial isolates the pharmacological effect on the visceral depot specifically.⁴³

Combination therapy appears superior to monotherapy for downstream cardiometabolic benefit. In a four-arm, randomised, double-blind, placebo-controlled Danish trial in which 195 adults with obesity first achieved 12% diet-induced weight loss and were then randomised to placebo,

exercise, liraglutide 3.0 mg or the combination for one year, the metabolic syndrome severity z-score fell by 0.37 with liraglutide and by 0.48 with the combination relative to placebo, android fat percentage fell by 2.6, 2.8 and 6.1 percentage points in the exercise, liraglutide and combination arms respectively, and high-sensitivity C-reactive protein fell by 43% only in the combination arm. The supra-additive effect on abdominal fat and inflammation provides randomized support for combining incretin-based pharmacotherapy with structured exercise rather than deploying either alone.⁴⁷

Lifestyle trials demonstrate that visceral fat is substantially responsive to energy restriction, with reductions of approximately 25% to 38% achievable. In a trial of 112 overweight and obese postmenopausal women randomised to calorie restriction alone, calorie restriction with moderate-intensity exercise or calorie restriction with vigorous-intensity exercise under conditions of matched energy deficit, all three groups achieved comparable reductions in abdominal visceral fat of approximately 25%, indicating that at equal energy deficit the exercise modality does not preferentially mobilise the visceral depot. However, the same trial showed that calorie restriction alone produced significantly greater loss of lean mass, and that changes in visceral fat were inversely related to increases in maximal oxygen uptake — findings that argue for the inclusion of exercise on grounds of body composition preservation and cardiorespiratory fitness even where its incremental visceral effect is neutral.³⁵

Exercise modality matters when energy restriction is absent. In obese adolescent girls randomised to aerobic exercise, resistance exercise or non-exercising control without any caloric restriction, aerobic exercise significantly reduced visceral adipose tissue and intrahepatic lipid and improved clamp-derived insulin sensitivity, whereas resistance exercise did not, and these benefits occurred despite the absence of significant weight loss. This dissociation between weight change and visceral fat change is of considerable clinical importance, since it demonstrates that meaningful metabolic benefit is achievable in patients whose scale weight does not move.³⁷

Three trials returned null or attenuated results and are reported here without selective omission. A twelve-week four-arm trial of early, late and self-selected eight-hour time-restricted eating in 197 adults with overweight or obesity found no significant difference in visceral adipose tissue change relative to usual care based on Mediterranean diet education, irrespective of eating

window timing. The CROSSROADS trial in 164 older adults with obesity found that moderate calorie restriction did not significantly reduce visceral adipose tissue relative to exercise alone, although it did improve blood glucose and high-density lipoprotein cholesterol. A ten-week web-based exercise programme in 70-year-olds with central obesity reduced fat mass but not visceral adipose tissue. These null findings converge on a coherent interpretation: visceral fat reduction requires either a sustained and substantial energy deficit or pharmacological intervention, and short-duration or low-intensity behavioural interventions are generally insufficient. The full randomized evidence is presented in Table 25.^{39,42,49}

Table 25. Randomized controlled trial evidence on the modifiability of visceral adipose tissue

Trial (Year)	N / duration	Intervention versus comparator	Effect on visceral adipose tissue	Concomitant cardiometabolic effect	Significance
Neeland et al. (2021)	185 / 40 wk	Liraglutide 3.0 mg + lifestyle vs placebo + lifestyle	VAT −12.49% vs −1.63%; treatment difference −10.86% (−14.75 to −6.97)	Consistent across all prespecified subgroups	p < 0.0001
Sandsdal et al. (2023)	195 / 52 wk	Exercise + liraglutide 3.0 mg vs placebo	Android fat −6.1 percentage points vs placebo	MetS-Z −0.48 (−0.70 to −0.25); hsCRP −43%	p < 0.001; p = 0.03
Sandsdal et al. (2023)	195 / 52 wk	Liraglutide 3.0 mg alone vs placebo	Android fat −2.8 percentage points	MetS-Z −0.37 (−0.58 to −0.16)	p < 0.001
Sandsdal et al. (2023)	195 / 52 wk	Exercise alone vs placebo	Android fat −2.6 percentage points	MetS-Z unchanged vs placebo	Partially significant
Nicklas et al. (2009)	112 / 20 wk	Calorie restriction ± moderate or vigorous exercise	≈25% reduction in visceral fat in all three arms	Lean mass preserved only in exercise arms	p < 0.001 within group; NS between
Goodpaster et al. (2010)	130 / 12 mo	Diet + immediate vs delayed physical activity	Visceral abdominal fat reduced in both arms	WC, hepatic fat, BP and insulin resistance all reduced	Significant within arms
Bouchonville et al. (2013)	107 / 12 mo	Diet + exercise vs diet vs exercise vs control	Visceral fat −787 cm ³ (diet+exercise); −561 cm ³ (diet)	MetS prevalence −40% vs −15%; TNF-α −17.0 pg/mL	Significant
Borges et al. (2018)	122 / until BMI <25	Diet ± aerobic or resistance training	Intra-abdominal adipose tissue −38.0%	HDL-C +20.2%; TG −18.7%; LDL-C −4.8%	p < 0.001

Lee et al. (2013)	44 / 3 mo	Aerobic exercise vs resistance exercise vs control	Aerobic: VAT Δ $-15.68 \pm 7.64 \text{ cm}^2$; resistance: no change	Insulin sensitivity $+0.92 \pm 0.27$; hepatic lipid $-1.70 \pm 0.74\%$	$p < 0.05$ (aerobic only)
He et al. (2022)	MetS cohort / 3 mo	Time-restricted eating $\pm$ low-carbohydrate diet vs LCD	TRE and combination reduced visceral fat area; LCD alone did not	Combination improved glycaemia, uric acid and dyslipidaemia	Significant
Cipryan et al. (2021)	91 / 12 wk	VLCHF diet $\pm$ HIIT vs HIIT vs control	VLCHF -142.0 g ; VLCHF+HIIT -104.0 g ; HIIT alone no change	HOMA-IR -0.75 ; adiponectin/leptin $+9.34$	$p < 0.001$
Gepner et al. (2019)	278 / 18 mo	Mediterranean/low-carbohydrate + walnuts vs low-fat	Hepatic fat -41% at 6 mo and -29% at 18 mo; VAT reduced	Cardiometabolic benefit partly independent of VAT loss	$p < 0.001$
Klein et al. (2025)	572 / 18 mo	Pooled Mediterranean and green-Mediterranean strategies	VAT -28 cm^2 (-22.5%); VAT% -1.3 units	$\downarrow$ TG, $\downarrow$ HbA1c, $\downarrow$ ferritin, $\downarrow$ liver enzymes, $\uparrow$ HDL-C	FDR < 0.05
Barbosa et al. (2024)	High-risk adults $\geq 50 \text{ y}$ / 12 wk	Mediterranean diet + exercise vs exercise vs control	Visceral fat significantly reduced vs control	WC reduced ($p = 0.002$); TG reduced ($p = 0.029$)	$p < 0.001$
Dorling et al. (2021)	40 / 3 mo	Pedal desk + activity promotion vs habitual activity	VAT -0.15 kg (-0.29 to -0.01)	Fasting glucose -0.29 mmol/L (-0.51 to -0.06)	$p = 0.04$; $p = 0.01$
Ard et al. (2016)	164 / 52 wk	Calorie restriction + exercise vs exercise alone	VAT $-192.6 \pm 185.2 \text{ cm}^3$ vs $-21.9 \pm 173.7 \text{ cm}^3$	Glucose $-8.3 \pm 3.6 \text{ mg/dL}$; HDL-C $+5.3 \pm 1.9 \text{ mg/dL}$	VAT not significant; metabolic markers significant
Ballin et al. (2020)	77 / 10 wk per phase	Web-based vs supervised exercise vs wait-list	No significant VAT reduction with web-based exercise	Fat mass -450 g ($37-836$); lean mass preserved	VAT $p = 0.5$; fat mass $p < 0.05$
Dote-Montero et al. (2025)	197 / 12 wk	Early, late or self-selected 8-h TRE + usual care vs usual care	Early TRE -4% ; late TRE -6% ; self-selected -3% vs usual care	No serious adverse events; adherence 85–88%	All $p \geq 0.31$ (not significant)

MetS-Z = metabolic syndrome severity z-score; hsCRP = high-sensitivity C-reactive protein; TNF- α = tumour necrosis factor alpha; VLCHF = very-low-carbohydrate high-fat; HIIT = high-intensity interval training; TRE = time-restricted eating; LCD = low-carbohydrate diet; WC = waist circumference; NS = not significant; FDR = false discovery rate. Null and negative trials are reported without selective omission.

Prognostic Discrimination, Reclassification and Threshold Derivation

Nine studies compared the discriminative performance of competing visceral adiposity metrics. Three consistent conclusions emerge. First, among surrogate indices the Metabolic Score for Visceral Fat performed best for hard endpoints in three independent populations — Mexican, Korean and Chinese — while the Chinese visceral adiposity index performed best in diabetic populations and the lipid accumulation product performed best for incident diabetes in one Chinese cohort. Second, the absolute discriminative capacity of all visceral adiposity indices for incident events is modest, with C-statistics and areas under the receiver operating characteristic curve typically between 0.60 and 0.75; this is unsurprising, since single risk factors rarely discriminate well in isolation, and it means that visceral adiposity metrics should be regarded as additions to multivariable risk models rather than as stand-alone screening tests. Third, and most importantly for practice, the reclassification metrics are considerably more favourable than the discrimination metrics: adding the Chinese visceral adiposity index to a basic risk model in patients with type 2 diabetes improved the C-statistic from 0.701 to 0.751, with an integrated discrimination improvement of 4.3% and a net reclassification improvement of 26.6%, and adding visceral fat to a clinical risk model in the Multi-Ethnic Study of Atherosclerosis produced a net reclassification index of 0.44.^{7,18,32}

Threshold derivation studies indicate that no universal visceral fat cut-off is defensible. Sex-specific optimal thresholds for incident type 2 diabetes in a Korean cohort were 130.03 cm² for men and 85.7 cm² for women, with corresponding visceral-to-subcutaneous ratios of 1.08 and 0.48. A systematic review of 52 threshold studies harmonised across imaging modalities found that thresholds for elevated metabolic syndrome risk range from 70 to 165.9 cm², are consistently lower in women than in men, and are lower in Asian than in European-ancestry populations, ranging from 70 to 136 cm² versus 85.6 to 165.9 cm² respectively. Premenopausal women and younger adults manifest

elevated risk at lower visceral fat areas than their older counterparts. These findings have direct clinical implications for the transferability of thresholds derived in one population to another and argue against the application of a single global cut-off.^{15,53}

Table 26. Comparative discrimination, reclassification and threshold derivation

Study (Year)	Population / analytic N	Exposure metric and contrast	Effect estimate (95% CI)	Significance
Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385	METS-VF; cardiovascular mortality	Harrell C = 0.73 (best of 7 surrogates)	Best performer
Martínez-Luna et al. (2026)	Mexico City Prospective Study; n = 102,385	Adding METS-VF to Globorisk in intermediate risk	Improved discrimination for CVD mortality	Incremental benefit
Cho et al. (2026)	KoGES, South Korea; n = 8,192	METS-VF vs VAI and LAP; incident CVD	METS-VF higher integrated AUC	p < 0.001
Qiao et al. (2022)	Xinjiang cohort, China; n = 2,328 with T2DM	CVAI; cardiovascular events	C-statistic 0.700 (0.672–0.728)	Best of 5 indices
Qiao et al. (2022)	Xinjiang cohort, China; n = 2,328	CVAI added to basic risk model	C 0.751 vs 0.701; IDI 4.3%; NRI 26.6%	p < 0.001
Zheng et al. (2026)	CHARLS, China; n = 7,977	TyG-CVAI vs components; incident CVD	AUC 0.6315 vs TyG 0.5938 and CVAI 0.5851	Superior to components
Wang et al. (2026)	CHARLS, China; n = 6,775	METS-VF vs LAP and VAI; incident hypertension	AUC 0.62 vs 0.60 vs 0.57	p < 0.05
Jia et al. (2024)	NHANES, USA; n = 11,120	METS-VF vs other obesity indices; mortality	METS-VF best predictor of mortality	Superior
Liu et al. (2025)	Kailuan cohort, China; n = 41,756	Cumulative METS-VF vs cumulative WC, BMI, WHtR	Cumulative METS-VF highest predictive value for CVD	Superior
Shah et al. (2014)	MESA, USA; n = 1,511	Visceral fat added to clinical risk; incident MetS	NRI 0.44 (0.29–0.60)	Significant
Kim et al. (2021)	South Korea; n = 10,882	ROC-derived optimal cut-offs; incident T2DM	Men VFA 130.03 cm ² , VSR 1.08; women VFA 85.7 cm ² , VSR 0.48	Threshold derivation
Bello-Chavolla et al. (2020)	Mexico; n = 366 (DXA) and n = 118 (MRI)	METS-VF vs DXA and MRI gold standards	AUC 0.896 (DXA); AUC 0.842 (MRI); cut-off >7.18	Validated surrogate

Bennett et al. (2024)*	Systematic review of 52 threshold studies	Harmonised VAT thresholds for MetS risk	70–165.9 cm ² ; lower in women and in Asian populations	No universal threshold
Boonpor et al. (2023)*	UK Biobank; n = 161,127; 10 y	Waist-to-height ratio vs BMI; incident T2DM	WHtR HR 2.27 (2.19–2.35) women; 1.96 (1.90–2.01) men	Superior to BMI

**Retained for interpretation only where design falls outside the primary inclusion criteria for the characteristics tables. AUC = area under the receiver operating characteristic curve; IDI = integrated discrimination improvement; NRI = net reclassification improvement; VFA = visceral fat area; VSR = visceral-to-subcutaneous fat ratio; WHtR = waist-to-height ratio.*

Subgroup and Effect-Modification Synthesis

Effect modification was examined systematically across five prespecified strata: sex, ethnicity, body mass index category, age, and baseline metabolic status. Sex emerged as the most consistent and clinically consequential modifier, with visceral adiposity conferring disproportionately greater risk in women for incident diabetes, metabolic syndrome and cardiovascular death, while paradoxically showing a stronger association with stroke and myocardial infarction in men in one elderly Swedish cohort. Ethnicity modified the threshold at which risk emerges rather than the direction of the association, with Asian populations manifesting elevated risk at substantially lower absolute visceral fat areas. Body mass index category did not attenuate the association; on the contrary, in several studies the relative effect of visceral adiposity was larger in normal-weight and lean strata, which is consistent with the interpretation that in obese individuals a greater proportion of the cohort is already exposed, compressing the observable gradient. These findings are consolidated in Table 29.^{11,13,14,15,53}

Table 27. Effect modification of the visceral adiposity–cardiometabolic association by prespecified subgroup

Modifier	Direction and magnitude of modification	Supporting evidence	Clinical implication
Sex — women	Substantially stronger association for incident T2DM (OR 32.49 vs 2.62), metabolic syndrome (OR 4.7 vs 3.0 relative to SAT) and	Kim 2021; Kammerlander 2021; Fox 2007; Karlsson 2019	Body mass index and waist circumference are inadequate surrogates for visceral risk in women; direct or surrogate visceral assessment is of greater incremental value

	cardiovascular death (HR 1.85 vs 1.19 for BMI)		
Sex — men	Anthropometric measures capture visceral risk adequately; stronger VAT–stroke/MI association in elderly men (HR 1.86 vs 0.60 in women, p-interaction = 0.038)	Kammerlander 2021; Ballin 2021	Conventional anthropometry may suffice for risk stratification in men, particularly at younger ages
Ethnicity — Asian populations	Elevated metabolic syndrome risk emerges at visceral fat areas of 70–136 cm ² compared with 85.6–165.9 cm ² in European-ancestry populations	Bennett 2024; Kim 2021; Tatsumi 2017; Hayashi 2003/2004	Population-specific thresholds are required; European-derived cut-offs will systematically under-detect risk in Asian patients
Body mass index — normal weight	Effect magnitude equal to or greater than in higher-weight strata (OR 9.3 vs 6.0 for metabolic syndrome component clustering)	Tatsumi 2017; Neeland 2012; Shah 2014	Normal body mass index does not exclude visceral obesity; the metabolically obese normal-weight phenotype warrants specific screening
Body mass index — obesity	Visceral fat discriminates risk within the obese stratum where body mass index does not	Neeland 2012 (Dallas Heart Study); Shah 2014 (MESA)	Among patients who are uniformly obese, visceral quantification identifies who will progress to diabetes
Age — older adults	Attenuation of the VAT–all-cause mortality association in the eighth decade; sarcopenic obesity confers markedly amplified risk (HR 6.74)	Ballin 2021; Yoon 2025	Body composition rather than adiposity alone should be assessed in geriatric populations; muscle mass and strength are co-determinants
Baseline metabolic status	Associations persist and often strengthen in prediabetes, established diabetes and established coronary disease	Wu 2025; Qiao 2022; Medina-Urrutia 2025	Visceral adiposity is a residual risk factor in secondary as well as primary prevention
Duration of exposure	Cumulative exposure confers markedly greater risk than single-point measurement (all-cause mortality HR 4.90 vs single-measurement estimates of 1.1–1.6)	Liu 2025; Sun 2025; Shah 2014; Lee 2016	Repeated longitudinal assessment is more informative than a single baseline measurement; early intervention limits cumulative exposure

Certainty of Evidence (GRADE)

The certainty of the body of evidence was rated for each outcome domain according to the GRADE framework. Observational bodies of evidence commenced at low certainty and were upgraded where a large magnitude of effect, a dose–response gradient, or an expectation that residual

confounding would attenuate rather than exaggerate the association was documented. Randomized bodies of evidence commenced at high certainty and were downgraded principally for indirectness, since the trials measured visceral fat change rather than hard clinical endpoints, and for imprecision in the smaller trials. The resulting ratings are moderate certainty for incident type 2 diabetes, incident hypertension, metabolic syndrome and composite cardiovascular disease; moderate certainty for the pharmacological modifiability of visceral fat; and low certainty for cerebrovascular events, heart failure and atrial fibrillation.^{52,53,54}

Table 28. GRADE summary of findings across the sixteen prespecified outcome domains

Outcome domain	Studies (n) / design	Summary of effect	Downgraded for	Upgraded for	Certainty
O1 Incident composite CVD	12 / observational	HR 1.62–2.78 highest vs lowest exposure; consistent across 12 studies and 5 continents	Observational design	Large effect; dose–response; cumulative-exposure gradient	Moderate
O2 Coronary heart disease and MI	6 / observational	HR 1.15 per SD, independent of waist circumference	Observational design	Dose–response; internal comparator with SAT	Moderate
O3 Cerebrovascular events	5 / observational	Inconsistent; significant in men only in one cohort; null after WC adjustment in UK Biobank	Observational design; serious inconsistency; imprecision	None	Low
O4 Heart failure and atrial fibrillation	3 / observational	Significant for ectopic cardiac fat but null after VAT adjustment; null for VAT after WC adjustment	Observational design; inconsistency; indirectness	None	Low
O5 Recurrent MACE	3 / observational	aHR 2.71 for total and 3.58 for non-fatal recurrent MACE in premature CAD	Observational design; imprecision (wide CIs)	Large effect	Low to moderate
O6 Cardiovascular mortality	5 / observational	aHR 1.23 per SD over 20 years in 102,385 adults; C = 0.73	Observational design	Very large sample; long follow-up; dose–response	Moderate

O7 All-cause mortality	6 / observational	HR up to 4.90 for cumulative exposure; attenuated in the very elderly	Observational design; inconsistency in older adults	Very large effect; dose–response	Moderate
O8 Incident T2DM and prediabetes	11 / observational + MR	OR 1.6–32.49; persists after adjustment for BMI, WC and SAT; Mendelian randomization supports causality	Observational design; imprecision in female strata	Very large effect; dose–response; MR corroboration	Moderate
O9 Hypertension	8 / observational + MR	OR 5.07 (Q3) prospectively; HR 2.11 (Q4) in 6,775 adults; MR-supported	Observational design	Large effect; dose–response; threshold identified	Moderate
O10 Metabolic syndrome	9 / observational	OR 4.7 per SD in women; NRI 0.44; change in VAT predicts incident MetS	Observational design	Large effect; dose–response; longitudinal change data	Moderate
O11 Dyslipidaemia and dysglycaemia	10 / observational + RCT	OR up to 12.0 for hypertriglyceridaemia in normal-weight highest quartile	Observational design for most estimates	Very large effect; biologically coherent with portal hypothesis	Moderate
O12 Insulin resistance and inflammation	9 / observational + RCT	HOMA-IR OR 3.23 for longitudinal increase; hsCRP –43% with combination therapy	Indirectness (intermediate endpoints)	Randomized corroboration	Moderate
O13 Subclinical atherosclerosis	4 / observational	+6.16 mm ³ carotid wall volume per SD VAT; attenuated after risk factor adjustment	Observational design; attenuation after adjustment	None	Low to moderate
O14 Microvascular and renal	2 / observational	HR 1.13–1.62 for diabetic nephropathy; null for retinopathy	Observational design; few studies; imprecision	Cumulative-exposure gradient	Low
O15 Modifiability of VAT	16 / RCT	Liraglutide –10.86% treatment difference; lifestyle –25% to –38%; three null trials	Indirectness (surrogate endpoint); some concerns for blinding	None	Moderate to high

O16 Discrimination and reclassification	9 / observational	C-statistics 0.60–0.75; NRI up to 26.6%; no universal threshold	Indirectness; inconsistency across populations	None	Moderate
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MR = Mendelian randomization; SD = standard deviation; WC = waist circumference; SAT = subcutaneous adipose tissue; CI = confidence interval; NRI = net reclassification improvement.

Formal Assessment of the Prespecified Hypotheses

The seven prespecified hypotheses were formally adjudicated against the assembled evidence, as summarised in Table 31. Six of the seven hypotheses were supported. The single hypothesis not fully supported concerns the strength of the sex difference, which was consistently in the hypothesised direction for metabolic and mortality endpoints but was reversed for cerebrovascular and myocardial events in one elderly cohort, indicating that the sex-modification effect is outcome-dependent rather than uniform.^{13,14}

Table 29. Adjudication of the prespecified hypotheses against the assembled evidence

Hypothesis	Statement	Verdict	Principal supporting evidence
H1	Visceral adiposity is independently associated with cardiometabolic disease after adjustment for BMI, WC and SAT	Supported	Boyko 2000; Hayashi 2004; Fox 2007; Neeland 2012; Yi 2024 — visceral term retains significance while anthropometric terms do not
H2	A dose–response and cumulative-exposure gradient exists	Supported	Liu 2025 (monotonic Q2→Q4 gradient and duration effect); Shah 2014; Lee 2016; Sun 2025; Wang 2026 (spline threshold)
H3	Visceral adipose tissue is more strongly associated with outcomes than subcutaneous adipose tissue	Supported	Fox 2007; Liu 2010; Lee 2016; Yi 2024 — SAT association abolished by WC adjustment while VAT persists
H4	The association is stronger in women than in men	Partially supported	Supported for T2DM, metabolic syndrome and CVD mortality (Kim 2021; Kammerlander 2021; Karlsson 2019); reversed for stroke/MI in elderly men (Ballin 2021)
H5	Visceral adiposity confers risk among normal-weight individuals	Supported	Tatsumi 2017 (OR 9.3 in normal-weight highest quartile); Neeland 2012; Shah 2014; Yi 2024 discordance analysis
H6	Visceral adipose tissue is modifiable with concomitant cardiometabolic benefit	Supported	Neeland 2021; Sandsdal 2023; Bouchonville 2013; Borges 2018; Klein 2025 — with three null behavioural trials defining the boundary conditions

H7	Validated surrogate indices provide discrimination comparable or superior to conventional anthropometry	Supported	Martínez-Luna 2026; Qiao 2022; Liu 2025; Wang 2026; Bello-Chavolla 2020 (AUC 0.896 vs DXA)
H0	Visceral adiposity confers no independent risk beyond generalised or central anthropometric adiposity	Rejected	Rejected across 15 of 16 outcome domains; retained as plausible only for heart failure and atrial fibrillation

DISCUSSION

Summary of Principal Findings

This systematic review of 52 primary studies — 36 observational investigations and 16 randomized controlled trials enrolling in excess of 400,000 participants across five continents — establishes that visceral obesity is an independent, dose-dependent, sex-modified and therapeutically modifiable determinant of cardiometabolic disease. Across sixteen prespecified outcome domains, the direction of association was positive and statistically significant in the great majority of studies, with effect magnitudes ranging from a 15% increase in coronary heart disease risk per standard deviation of visceral adipose tissue to a nearly five-fold increase in all-cause mortality among individuals in the highest quartile of cumulative visceral fat exposure. The associations persisted after multivariable adjustment for body mass index, waist circumference and subcutaneous adipose tissue in every study that performed such adjustment, and — most tellingly — in mutually adjusted models the visceral term retained statistical significance while the anthropometric terms did not.^{5,6,23,27}

Three findings warrant particular emphasis because they are directly actionable. First, visceral adiposity confers substantial cardiometabolic risk among individuals whose body mass index falls within the normal range, with a nine-fold increase in the odds of metabolic syndrome component clustering in the highest visceral fat quartile of normal-weight Japanese adults. Second, the association is markedly stronger in women than in men for metabolic and mortality endpoints, such that anthropometric measures which adequately capture visceral risk in men systematically underestimate it in women. Third, visceral adipose tissue is pharmacologically and behaviourally modifiable, with liraglutide 3.0 mg producing a placebo-adjusted reduction of nearly 11% over 40

weeks and combined incretin and exercise therapy reducing metabolic syndrome severity and systemic inflammation beyond either modality alone.^{11,13,43,47}

Pathophysiological Mechanisms

The consistency of the epidemiological signal is underpinned by a well-characterised pathophysiology. Visceral adipocytes exhibit heightened catecholamine-stimulated lipolysis and reduced sensitivity to the antilipolytic action of insulin relative to subcutaneous adipocytes, reflecting a higher density of beta-3 adrenergic receptors and a lower density of alpha-2 adrenergic and insulin receptors. Because omental and mesenteric venous effluent drains directly into the portal vein, the liver is exposed to free fatty acid concentrations substantially exceeding those in the systemic circulation. This portal free fatty acid flux drives hepatic gluconeogenesis, stimulates apolipoprotein B-100 stabilisation and very-low-density lipoprotein overproduction, and impairs hepatic insulin extraction, generating peripheral hyperinsulinaemia. The resulting lipid phenotype — elevated triglycerides, reduced high-density lipoprotein cholesterol and a shift towards small dense low-density lipoprotein particles — is precisely the pattern documented across the studies synthesised in Outcome 11, and it is notable that low-density lipoprotein cholesterol concentration itself was comparatively unaffected, consistent with the mechanism being one of particle remodelling rather than of absolute cholesterol burden.^{9,11,51}

A second pathway operates through the endocrine and immune functions of visceral adipose tissue. Expansion of the visceral depot beyond its angiogenic capacity produces regional hypoxia, adipocyte stress and necrosis, and recruitment of macrophages that assume a pro-inflammatory M1 polarisation and organise into characteristic crown-like structures. The consequent local and systemic elevation of tumour necrosis factor alpha, interleukin-6 and monocyte chemoattractant protein-1, coupled with suppression of adiponectin secretion, produces serine phosphorylation of insulin receptor substrate-1, impairs endothelial nitric oxide synthase activity and promotes a prothrombotic state through elevated plasminogen activator inhibitor-1. The mediation analysis reported in the National Health and Nutrition Examination Survey quantifies the contribution of these pathways, attributing 13.34% of the visceral fat–cardiovascular disease association to high-density lipoprotein cholesterol and 5.42% to the systemic inflammatory response index, and the randomized

demonstration that combined exercise and glucagon-like peptide-1 receptor agonist therapy reduced high-sensitivity C-reactive protein by 43% provides interventional confirmation that the inflammatory limb is modifiable.^{28,47,51}

A third pathway involves blood pressure regulation. Visceral adipose tissue expresses angiotensinogen and generates local angiotensin II, and the compression of renal parenchyma by perirenal and retroperitoneal fat elevates intrarenal pressure and activates the renin–angiotensin–aldosterone system. Leptin-mediated sympathetic activation and hyperinsulinaemia-driven renal sodium retention act in concert. The finding that retroperitoneal fat area behaved like peritoneal fat and unlike subcutaneous fat in predicting incident hypertension in a Taiwanese cohort is mechanistically instructive, supporting inclusion of the retroperitoneal compartment within the operational definition of visceral fat for cardiometabolic purposes — a methodological point with implications for how imaging protocols are specified.^{8,51}

The finding that adiponectin status modifies risk deserves separate comment. In the Seoul Metabolic Syndrome cohort, participants with both low adiponectin and high visceral fat area had a metabolic syndrome incidence of 46.15% compared with 16.47% in those with high adiponectin and low visceral fat, and the group with high visceral fat but preserved adiponectin had an intermediate incidence of 25%. This gradient suggests that adiponectin sufficiency partially buffers the metabolic consequences of visceral fat accumulation, and it offers a candidate explanation for the metabolically healthy obese phenotype that has proved difficult to account for on the basis of fat mass alone.¹⁰

Assessment of Causality

Systematic reviews of observational evidence must address causality explicitly rather than by implication. Applying the Bradford Hill considerations to the assembled evidence yields the following assessment. Strength of association is substantial, with hazard and odds ratios frequently exceeding 2 and reaching 4.90 for all-cause mortality under cumulative exposure. Consistency is high, with concordant findings across five continents, across four imaging modalities and seven surrogate indices, and across populations of European, African, East Asian, South-East Asian, South Asian and Latin American ancestry. Temporality is established by the 27 prospective cohorts, several with follow-up exceeding 17 years and with exposure assessed in participants free of the outcome at

baseline. A biological gradient is documented both cross-sectionally in quartile analyses and longitudinally in cumulative-exposure and trajectory analyses. Plausibility and coherence are supported by the mechanistic account set out above. Experimental evidence is provided by the 16 randomized controlled trials demonstrating that the exposure is modifiable and that its modification is accompanied by improvement in cardiometabolic parameters.^{27,32,34,43}

The most direct evidence bearing on causality comes from Mendelian randomization analysis in the UK Biobank, which used 102 genetic loci associated with predicted visceral adipose tissue mass and demonstrated causal effects on hypertension, myocardial infarction or angina, type 2 diabetes and hyperlipidaemia. Because genotype is assigned at conception and is therefore not subject to reverse causation or to confounding by lifestyle, this design substantially strengthens the causal interpretation. The observation of a markedly larger causal effect for type 2 diabetes in women (odds ratio 7.34) than in men (odds ratio 2.50) independently corroborates the sex modification observed in the conventional observational literature, using a design in which the sources of bias are entirely different. Convergence of findings across designs with non-overlapping biases is among the strongest available evidence short of a randomized trial with hard clinical endpoints.⁵⁵

Two caveats temper this assessment. Residual confounding cannot be excluded in observational designs, particularly by cardiorespiratory fitness, dietary quality and socioeconomic position, none of which was fully measured in most studies. However, the direction of such confounding would in almost all plausible scenarios be towards exaggeration of a true positive association rather than the creation of a spurious one, and the persistence of associations in the most heavily adjusted models argues against complete confounding. Reverse causation is a more serious concern for cross-sectional studies, where subclinical disease may itself alter body composition, and this is one reason why the cross-sectional evidence has been presented separately from the prospective evidence throughout this review.⁵²

Visceral, Subcutaneous and Hepatic Adipose Depots

A central contribution of the assembled evidence is the disaggregation of abdominal fat into functionally distinct compartments. The comparison between visceral and subcutaneous adipose tissue is unambiguous: in every study reporting both, the visceral estimate exceeded the subcutaneous

estimate, and in the UK Biobank the subcutaneous association with coronary heart disease was abolished entirely by adjustment for waist circumference while the visceral association was essentially unaffected. This is the analytic signature of a depot that carries risk information beyond what any external measurement can capture. Subcutaneous adipose tissue should not, however, be regarded as inert; it is associated with risk factors in most studies, and its principal physiological role appears to be as a metabolic buffer whose expandability determines whether surplus energy is safely stored or is diverted ectopically. The failure of subcutaneous expandability is arguably the proximate cause of visceral and hepatic fat accumulation.^{1,2,23}

The relationship between visceral and hepatic fat is more nuanced and has only recently been resolved. Analysis of discordant phenotypes in the Dallas Heart Study and UK Biobank demonstrated that high visceral fat conferred cardiovascular risk irrespective of liver fat status, whereas high liver fat in the absence of high visceral fat was associated with type 2 diabetes but not with cardiovascular disease. This dissociation indicates that the two depots are not interchangeable and that they act through partially distinct pathways — visceral fat operating predominantly through systemic atherogenic and inflammatory mechanisms and hepatic fat predominantly through hepatic insulin resistance. The CENTRAL trial adds an important interventional counterpoint, showing that the cardiometabolic advantage of a Mediterranean low-carbohydrate diet over a low-fat diet was attenuated when hepatic fat change was controlled for but persisted when visceral fat change was controlled for, implying that for certain dietary interventions hepatic fat may be the more proximate mediator. Clinically, the implication is that visceral and hepatic fat should be assessed and targeted as related but separate entities.^{17,41}

Ectopic cardiac fat occupies a third position. Epicardial and pericardial adipose tissue correlated strongly with abdominal visceral adipose tissue (Pearson $r = 0.72$) and predicted incident heart failure, type 2 diabetes and coronary artery disease, but none of these associations survived adjustment for abdominal visceral fat volume. The authors of that analysis concluded that epicardial adiposity largely reflects a metabolically unhealthy adiposity phenotype rather than exerting an independent local paracrine effect on the myocardium and coronary arteries. This finding is clinically economical: it implies that abdominal visceral fat assessment captures most of the prognostic

information available from cardiac fat imaging, and that routine quantification of epicardial fat is unlikely to add materially to risk stratification.²⁰

Sex Differences

Sex modification is the most clinically consequential finding of this review and merits detailed consideration. Men accumulate substantially more visceral and less subcutaneous fat than women at any given body mass index — in the Jackson Heart Study, mean visceral volumes were 873 versus 793 cm³ and subcutaneous volumes 1,730 versus 2,659 cm³ for men and women respectively. Because body mass index and waist circumference correlate more closely with visceral fat in men, in whom visceral accumulation is the default pattern of fat deposition, anthropometry serves as an adequate proxy. In women, whose fat is preferentially deposited subcutaneously in the gluteofemoral distribution before menopause, an elevated body mass index or waist circumference may reflect either benign subcutaneous expansion or pathogenic visceral accumulation, and anthropometry cannot distinguish between them. The consequence is that among women, a given anthropometric value carries far more heterogeneous risk than among men.^{2,13}

The Framingham analysis makes this explicit: in men, visceral adipose tissue and body mass index performed comparably for both incident cardiometabolic risk factors and cardiovascular events, whereas in women visceral adipose tissue conferred an odds ratio of 4.51 for diabetes against 2.33 for body mass index, and a hazard ratio of 1.85 for cardiovascular death against 1.19. The Korean cohort observed the same qualitative pattern at greater magnitude, and Mendelian randomization confirmed a nearly three-fold larger causal effect of visceral fat on type 2 diabetes in women than in men. The practical inference is that the incremental clinical value of direct or surrogate visceral fat assessment is greatest in women, and that sex-neutral application of body mass index thresholds systematically underestimates cardiometabolic risk in women with normal or modestly elevated body mass index but high visceral adiposity.^{13,15,55}

One important discordance requires acknowledgement. In the Swedish cohort of 70-year-olds, the association between visceral adipose tissue and incident stroke or myocardial infarction was significant in men but not in women, with a formal interaction p-value of 0.038. This does not contradict the metabolic findings but rather indicates that sex modification is outcome-specific:

women appear disproportionately susceptible to the metabolic consequences of visceral fat, while in advanced age the atherothrombotic consequences may be more prominent in men. Post-menopausal redistribution of fat towards the visceral compartment, differential competing risks and hormone-related vascular protection are plausible contributors, and this remains an area requiring dedicated study.¹⁴

Ethnicity, Thresholds and the Problem of Transferability

The evidence establishes that visceral adiposity thresholds cannot be transferred uncritically across populations. A systematic review harmonising 52 threshold studies across imaging modalities found that visceral fat areas indicating elevated metabolic syndrome risk ranged from 70 to 165.9 cm², were consistently lower in women, and were lower in Asian populations (70 to 136 cm²) than in populations of European ancestry (85.6 to 165.9 cm²). The Korean cohort derived optimal cut-offs of 130.03 cm² for men and 85.7 cm² for women for incident type 2 diabetes, and the Japanese cross-sectional study demonstrated substantial metabolic risk within a body mass index stratum of 18.5 to 22.9 kg/m² — a stratum classified as entirely normal by World Health Organization criteria. This constellation of findings underlies the adoption of lower obesity thresholds in Asian populations and argues that any clinical algorithm incorporating visceral fat must be calibrated to the population in which it is deployed.^{11,15,53}

This has direct relevance to South-East Asian and Indonesian clinical practice, where the combination of a high and rising prevalence of type 2 diabetes, a relatively low mean body mass index, and a well-documented predisposition to central fat deposition at low body weight creates precisely the conditions under which body mass index-based screening will underperform. The extension of validated surrogate indices to South-East Asian populations, and the derivation of local thresholds, represents an evidence gap of immediate practical importance.^{53,54}

Normal-Weight Visceral Obesity

The phenomenon variously described as normal-weight central obesity, the metabolically obese normal-weight phenotype, or thin-outside-fat-inside, emerges from this review as a quantitatively substantial risk state rather than a clinical curiosity. Among Japanese adults of normal weight, the highest quartile of visceral fat area conferred a 9.3-fold increase in the odds of clustering

two or more metabolic syndrome components — exceeding the 6.0-fold increase observed in the higher-weight stratum — together with a 12-fold increase in the odds of hypertriglyceridaemia. In the UK Biobank, individuals with visceral fat above the median but waist circumference below it carried a 43% excess coronary heart disease risk relative to those concordantly below both, identifying a group that current anthropometric screening cannot detect. The Dallas Heart Study demonstrated the converse phenomenon within the obese stratum, where visceral fat mass discriminated diabetes risk while body mass index, total body fat and subcutaneous fat did not.^{6,11,23}

Taken together, these findings indicate that body mass index and visceral adiposity are best regarded as two partially independent axes of cardiometabolic risk, and that a two-dimensional classification — normal weight with low visceral fat, normal weight with high visceral fat, obese with low visceral fat, obese with high visceral fat — carries more prognostic information than the conventional one-dimensional body mass index classification. The clinical corollary is that a normal body mass index should not terminate cardiometabolic evaluation in a patient with other risk indicators, and that a raised body mass index in the absence of visceral accumulation, dyslipidaemia and dysglycaemia may warrant less aggressive intervention than current practice implies.^{6,17}

The Temporal Dimension: Cumulative Exposure

A methodologically important theme is that visceral adiposity behaves as a cumulative rather than a point exposure. In the Kailuan study, exposure quantified as the time-weighted average of the Metabolic Score for Visceral Fat over four years, multiplied by the intervals between surveys, produced hazard ratios of 2.78 for cardiovascular disease and 4.90 for all-cause mortality in the highest quartile — estimates substantially exceeding those obtained from single-measurement studies of comparable populations — and risk increased with the duration for which participants remained above the high-exposure threshold. The same pattern was demonstrated for diabetic kidney disease, where cumulative exposure conferred a hazard ratio of 1.62 against 1.24 for baseline exposure. Longitudinal imaging in the Multi-Ethnic Study of Atherosclerosis and in the Framingham Third Generation cohort likewise showed that change in visceral fat predicted incident metabolic syndrome and incident risk factors independently of the baseline value.^{7,9,27}

This has three implications. Epidemiologically, single-measurement studies systematically underestimate the true effect of lifetime visceral fat exposure through regression dilution bias. Clinically, serial rather than single assessment is preferable, and the trajectory of visceral adiposity is a more informative datum than its current value. Preventively, because risk accumulates with duration of exposure, interventions initiated earlier in the life course should yield disproportionately greater benefit than the same intervention applied later — an argument for the identification of visceral adiposity in young adulthood rather than after the emergence of overt metabolic disease.^{27,34}

Clinical Surrogates and Implementation in Practice

Direct imaging of visceral fat is not feasible as a population screening strategy, and the practical utility of this evidence therefore depends on validated surrogates. The Metabolic Score for Visceral Fat, derived from the metabolic score for insulin resistance, waist-to-height ratio, age and sex, achieved areas under the curve of 0.896 against dual-energy X-ray absorptiometry and 0.842 against magnetic resonance imaging, with a cut-off above 7.18 identifying visceral fat exceeding 100 cm² at 100% sensitivity and 87.2% specificity. It subsequently outperformed competing surrogates for cardiovascular mortality in 102,385 Mexican adults, for incident cardiovascular disease in Korean and Chinese cohorts, for incident hypertension in the China Health and Retirement Longitudinal Study, and for all-cause mortality in the National Health and Nutrition Examination Survey. The Chinese visceral adiposity index performed best in populations with established type 2 diabetes and produced a net reclassification improvement of 26.6% when added to a basic risk model.^{12,18,32,33}

Two cautions attach to surrogate use. First, all these indices incorporate triglycerides and high-density lipoprotein cholesterol, which are themselves consequences of visceral fat accumulation and are also outcomes of interest; there is therefore a degree of circularity when such indices are used to predict dyslipidaemia-related endpoints, and their apparent superiority over pure anthropometry partly reflects the incorporation of biochemical information rather than superior estimation of the fat depot itself. Second, absolute discrimination remains modest, with C-statistics generally between 0.60 and 0.75, meaning that no surrogate should be used as a stand-alone screening test. Their appropriate role is as an additional variable within an established multivariable risk equation, deployed

particularly among individuals whose conventional risk estimate falls in the intermediate range where reclassification alters management.^{32,53}

Therapeutic Implications

The randomized evidence permits four practical conclusions. First, incretin-based pharmacotherapy is the most potent available means of reducing visceral fat, with liraglutide 3.0 mg producing a placebo-adjusted reduction of 10.86% over 40 weeks in patients already receiving lifestyle intervention, and effects consistent across demographic subgroups. Given that visceral fat reduction is a plausible mediator of the cardiovascular benefit observed in outcome trials of glucagon-like peptide-1 receptor agonists, this finding has mechanistic as well as therapeutic significance. Second, combination therapy is superior to monotherapy: exercise combined with a glucagon-like peptide-1 receptor agonist reduced android fat by 6.1 percentage points against 2.6 and 2.8 percentage points for exercise and drug alone, and reduced high-sensitivity C-reactive protein by 43%, an effect achieved by neither monotherapy.^{43,47}

Third, among lifestyle interventions the magnitude of the energy deficit rather than the specific dietary composition or exercise modality appears to be the principal determinant of visceral fat loss when energy deficit is matched, since three arms differing in exercise intensity achieved comparable 25% reductions under matched deficit. Nevertheless, exercise confers benefits that energy restriction alone does not, notably preservation of lean mass and improvement in cardiorespiratory fitness, and in the absence of energy restriction aerobic exercise reduces visceral and hepatic fat and improves insulin sensitivity while resistance exercise does not. Fourth, low-intensity or short-duration behavioural interventions are insufficient: a twelve-week trial of time-restricted eating produced no visceral fat benefit over Mediterranean dietary education, a ten-week web-based exercise programme produced none over wait-list control, and moderate calorie restriction in older adults did not significantly reduce visceral fat over 52 weeks. Reporting these null results is essential to an honest appraisal, and they define the boundary conditions within which the positive results should be interpreted.^{35,37,39,42,49}

Comparison with Previous Syntheses

The findings of this review are consistent with, and extend, those of previous narrower syntheses. A systematic review of 27 observational studies examining the visceral-to-subcutaneous fat ratio concluded that a higher ratio is associated with the development of cardiovascular disease, and can be used as a prognostic indicator. A dose–response meta-analysis of 216 cohort studies comprising 2.3 million incident diabetes cases among 26 million participants found a relative risk of 1.42 per one-unit increase in the visceral adiposity index and confirmed that indices of central fatness are associated with type 2 diabetes independently of overall adiposity, with positive linear or monotonic associations and no evidence of a threshold effect. The 2019 joint position statement of the International Atherosclerosis Society and the International Chair on Cardiometabolic Risk concluded that visceral adipose tissue, accurately measured by computed tomography or magnetic resonance imaging, is an independent risk marker of cardiovascular and metabolic morbidity and mortality, and identified the absence of simple clinically applicable monitoring tools as a principal knowledge gap. The present review addresses that gap directly by synthesising the surrogate-index literature that has largely emerged since that statement was published.^{51,52,54}

The present synthesis differs from its predecessors in three respects. It spans sixteen outcome domains rather than one or two, permitting comparison of effect magnitude across the cardiometabolic spectrum and revealing that the association is strongest for metabolic endpoints, intermediate for coronary and mortality endpoints, and weakest and least consistent for cerebrovascular and heart failure endpoints. It integrates randomized interventional evidence with observational aetiological evidence, permitting an explicit assessment of exposure modifiability. And it systematically tabulates effect modification by sex, ethnicity, body mass index stratum, age and exposure duration, permitting the identification of the specific clinical populations in whom visceral fat assessment carries the greatest incremental value.

Clinical Implications and a Proposed Assessment Pathway

The evidence supports a shift from weight-centric to phenotype-centric cardiometabolic assessment. Table 30 sets out a pragmatic pathway derived from the synthesised evidence, calibrated to three levels of resource availability. It should be emphasised that this pathway is an evidence-informed proposal rather than a validated clinical guideline, and that no trial has yet demonstrated

that visceral fat-guided treatment intensification improves hard cardiovascular outcomes relative to standard care.^{32,53}

Table 30. Evidence-informed pathway for the incorporation of visceral adiposity assessment into cardiometabolic risk stratification

Step	Action	Evidence basis	Threshold or decision rule
1. Universal baseline assessment	Measure height, weight, waist circumference, waist-to-height ratio, blood pressure, fasting glucose, triglycerides and HDL-cholesterol in all adults undergoing cardiometabolic evaluation	Applies to all included studies; waist-to-height ratio outperformed BMI for incident T2DM in 161,127 UK Biobank participants	Waist-to-height ratio ≥ 0.5 as an initial trigger for further evaluation
2. Compute a validated surrogate index	Calculate METS-VF in general populations and CVAI in populations with established type 2 diabetes	Bello-Chavolla 2020; Martínez-Luna 2026; Qiao 2022; Liu 2025; Wang 2026	METS-VF > 7.18 corresponds to visceral fat $> 100 \text{ cm}^2$; a value > 5.68 marks the non-linear inflection for incident hypertension
3. Apply sex- and ethnicity-specific interpretation	Interpret thresholds against population-appropriate reference values; apply lower thresholds in women and in Asian populations	Bennett 2024; Kim 2021; Tatsumi 2017	Visceral fat area $\geq 130 \text{ cm}^2$ (men) and $\geq 85 \text{ cm}^2$ (women) in East Asian populations; higher in European-ancestry populations
4. Do not exclude on the basis of normal BMI	Evaluate visceral adiposity irrespective of body mass index category	Tatsumi 2017 (OR 9.3 in normal-weight highest quartile); Yi 2024 discordance analysis	Normal BMI with elevated waist-to-height ratio, triglycerides or fasting glucose warrants full evaluation
5. Reserve imaging for reclassification	Consider CT, MRI or DXA quantification where the surrogate estimate is discordant with clinical impression, or where the conventional risk estimate is intermediate and reclassification would alter management	Shah 2014 (NRI 0.44); Qiao 2022 (NRI 26.6%); Martínez-Luna 2026	Intermediate conventional risk with high surrogate visceral adiposity
6. Assess muscle as well as fat	In adults aged 65 years and over, assess handgrip strength and appendicular muscle mass alongside visceral adiposity	Yoon 2025 (sarcopenic obesity HR 6.74); Wong 2024 (high VAT with low strength aRR 2.63)	Sarcopenic obesity identifies a markedly elevated-risk phenotype

7. Intervene with agents of demonstrated visceral efficacy	Prioritise structured aerobic exercise, Mediterranean or low-carbohydrate dietary patterns achieving a sustained energy deficit, and GLP-1 receptor agonist therapy where indicated	Neeland 2021; Sandsdal 2023; Klein 2025; Borges 2018; Lee 2013	Combination of exercise and pharmacotherapy is superior to either alone
8. Reassess serially	Repeat surrogate assessment at intervals; monitor trajectory rather than a single value	Liu 2025; Sun 2025; Shah 2014; Lee 2016	Cumulative and increasing exposure confers substantially greater risk than a single elevated value

Public Health and Policy Implications

Three policy implications follow. First, population surveillance based on body mass index prevalence alone materially underestimates the cardiometabolic burden of adiposity, particularly in populations with a high prevalence of normal-weight central obesity; surveillance systems should incorporate waist-to-height ratio at minimum, and ideally a validated surrogate index computable from data already collected in routine health examinations. Second, because the surrogate indices with the best demonstrated performance require only variables obtained during standard clinical assessment, their implementation carries essentially no marginal cost and is feasible in primary care and in low- and middle-income settings — a point made explicitly by the investigators of the Latin American cohort consortium. Third, given the demonstration that risk accumulates with duration of exposure, prevention programmes targeting adolescents and young adults are likely to yield disproportionate returns relative to programmes initiated after the emergence of metabolic disease.^{27,32}

Strengths of This Review

This review has several methodological strengths. It applied strict design-based inclusion criteria, restricting the evidence tables to primary studies and confining systematic reviews, meta-analyses and position statements to an explicitly labelled interpretive role. It examined sixteen prespecified outcome domains rather than a single endpoint, permitting comparison of effect magnitude and consistency across the cardiometabolic spectrum. It integrated four imaging modalities with seven validated surrogate indices and juxtaposed observational and randomized evidence within a single analytic framework. It applied design-appropriate risk of bias instruments to

every included study and rated the certainty of evidence for each outcome using GRADE. Null and negative findings — including three randomized trials showing no visceral fat benefit and the absence of association between visceral fat and stroke, heart failure and atrial fibrillation after waist circumference adjustment — are reported without selective omission. Finally, every included reference was retrieved and verified through the Consensus Academic Search Engine and is accompanied by a direct, verifiable link, so that any reader may independently confirm every citation.

Directions for Future Research

Five research priorities emerge from this synthesis, presented in descending order of importance. The first and most consequential is a randomized trial testing whether a treatment strategy guided by visceral adiposity — in which treatment is intensified on the basis of visceral fat or a validated surrogate rather than on body mass index alone — reduces major adverse cardiovascular events relative to standard care. Until such a trial is conducted, the clinical value of visceral fat assessment rests on inference rather than demonstration. The second is the derivation and prospective validation of sex-specific and ethnicity-specific visceral fat thresholds in under-represented populations, with particular priority for South-East Asian, South Asian and African populations. The third is the standardisation of surrogate indices, ideally through the development of a single index validated across ancestries, together with head-to-head comparison against imaging in each population. The fourth is elucidation of the mechanisms underlying sex-specific susceptibility, including the roles of oestrogen, menopausal transition and sex-specific adipocyte biology. The fifth is the systematic evaluation of the visceral fat effects of newer incretin-based agents, including dual and triple receptor agonists, against those of liraglutide, and the determination of whether differential visceral fat efficacy predicts differential cardiovascular outcome benefit.^{43,53,55}

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 52 primary studies, comprising 36 observational investigations and 16 randomized controlled trials with more than 400,000 participants across five continents, demonstrates that visceral obesity is an independent, dose-dependent and clinically consequential determinant of cardiometabolic disease across sixteen prespecified outcome domains. The association

is strongest and most consistent for metabolic endpoints — incident type 2 diabetes, incident hypertension and incident metabolic syndrome — where adjusted effect estimates in the highest exposure categories ranged from approximately two-fold to more than thirty-fold, and remains robust for composite cardiovascular disease, coronary heart disease, cardiovascular mortality and all-cause mortality. The evidence is weaker and less consistent for cerebrovascular events, heart failure and atrial fibrillation, where associations did not survive adjustment for waist circumference in the largest available analyses, and these conclusions are stated with correspondingly greater reserve.^{13,15,23,27}

Four conclusions follow with particular confidence. First, the pathogenicity of visceral adipose tissue is specific to the depot and is not reducible to generalised or central anthropometric adiposity: in mutually adjusted models the visceral term consistently retains statistical significance while body mass index, waist circumference and subcutaneous adipose tissue do not. Second, the association is markedly sex-modified for metabolic and mortality outcomes, such that anthropometric measures adequately capture visceral risk in men but systematically underestimate it in women. Third, visceral adiposity confers substantial risk among individuals of normal body mass index, and the metabolically obese normal-weight phenotype constitutes a quantitatively important and currently under-detected risk state. Fourth, visceral adipose tissue is modifiable — pharmacologically by glucagon-like peptide-1 receptor agonist therapy, and behaviourally by sustained energy restriction and structured aerobic exercise — with concomitant improvement in insulin resistance, lipid profile, blood pressure, inflammatory markers and metabolic syndrome severity.^{5,11,13,43,47}

Two conclusions are stated with explicit reserve. The claim that visceral adiposity is causal rests on convergent evidence from prospective designs, dose–response and cumulative-exposure gradients, mechanistic coherence, Mendelian randomization and demonstrated modifiability, but no randomized trial has yet shown that reducing visceral fat reduces hard cardiovascular events. And the incremental discriminative value of visceral adiposity metrics over established risk equations, while statistically significant and clinically meaningful in reclassification terms, is numerically modest, so these metrics belong within multivariable risk assessment rather than as stand-alone screening tests.^{32,55}

Recommendations

Recommendations for Clinical Practice

- Cardiometabolic risk assessment should be phenotype-centric rather than weight-centric. Body mass index should be supplemented, at minimum, by waist-to-height ratio and, where feasible, by a validated visceral adiposity surrogate such as the Metabolic Score for Visceral Fat in general populations or the Chinese visceral adiposity index in patients with established type 2 diabetes.^{12,18,32}
- A normal body mass index should not terminate cardiometabolic evaluation. Patients with normal weight but elevated waist-to-height ratio, hypertriglyceridaemia, low high-density lipoprotein cholesterol or impaired fasting glucose should be evaluated for visceral adiposity, since this phenotype carries risk equal to or exceeding that of frank obesity.^{11,23}
- Visceral adiposity assessment should be prioritised in women, in whom body mass index and waist circumference least adequately capture visceral risk, and thresholds should be applied on a sex-specific basis.^{13,15}
- Population-appropriate thresholds should be used. Thresholds derived in European-ancestry populations should not be applied unmodified to Asian populations, in whom risk emerges at substantially lower absolute visceral fat areas.^{11,53}
- In adults aged 65 years and over, muscle mass and strength should be assessed alongside visceral adiposity, since sarcopenic obesity confers markedly amplified risk relative to either component alone.^{24,29}
- Where intervention is indicated, modalities of demonstrated visceral efficacy should be prioritised: structured aerobic exercise, Mediterranean or low-carbohydrate dietary patterns achieving a sustained energy deficit, and — where clinically indicated and available — glucagon-like peptide-1 receptor agonist therapy, preferably in combination with exercise rather than as monotherapy.^{43,47,50}
- Assessment should be serial rather than single. Because risk accumulates with the duration of exposure, the trajectory of visceral adiposity is more informative than any single measurement, and early intervention limits cumulative exposure.^{27,34}

- Patients should not be reassured by the absence of weight loss during intervention. Aerobic exercise reduces visceral and hepatic fat and improves insulin sensitivity even in the absence of significant weight change.³⁷

Recommendations for Research

- A randomized controlled trial should test whether visceral adiposity-guided treatment intensification reduces major adverse cardiovascular events relative to body mass index-guided standard care. This is the principal outstanding evidential gap.⁴³
- Sex-specific and ethnicity-specific visceral fat thresholds should be derived and prospectively validated in South-East Asian, South Asian, African and Middle Eastern populations, which remain substantially under-represented in the current evidence base.⁵³
- Surrogate indices should be harmonised and, ideally, consolidated into a single index validated across ancestries and compared head-to-head against imaging in each population.^{12,32}
- The mechanisms underlying sex-specific susceptibility to visceral adiposity should be investigated, including the roles of oestrogen, the menopausal transition and sex-specific adipocyte biology.^{13,55}
- The comparative visceral fat efficacy of newer incretin-based agents, including dual and triple receptor agonists, should be evaluated against liraglutide, and it should be determined whether differential visceral efficacy predicts differential cardiovascular benefit.⁴³
- Future observational studies should report visceral fat exposure cumulatively or as a trajectory wherever repeated measurements are available, since single-measurement designs systematically underestimate the true effect through regression dilution.²⁷

Recommendations for Health Policy

- National cardiometabolic surveillance systems should incorporate waist-to-height ratio and, where the necessary biochemical variables are already collected, a validated visceral adiposity surrogate, since body mass index prevalence alone materially underestimates the population burden of cardiometabolic risk.^{32,54}

- Because the best-performing surrogate indices require only variables obtained during routine clinical assessment, their implementation carries minimal marginal cost and should be prioritised in primary care and in low- and middle-income settings.³²
- Preventive programmes should target adolescents and young adults, since cardiometabolic risk accumulates with the duration of visceral fat exposure and earlier intervention should therefore yield disproportionately greater benefit.²⁷

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This systematic review synthesises previously published, publicly available aggregate data and involved no primary collection of identifiable human data.

Competing interests

The authors declare that they have no competing interests.

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