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The Association of Red Meat Intake with Inflammation and Circulating Intermediate Biomarkers of Type 2 Diabetes Is Mediated by Central Adiposity

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Abstract

We explored the role of lipid accumulation products and visceral adiposity on the association between red meat consumption and markers of insulin resistance (IR) and inflammation in US adults. Data on red meat consumption, and health outcome measurements were extracted from the 2005-2010 US National Health and Nutrition Examination Surveys. Overall 16,621 participants were included in the analysis (mean age = 47.1 years, 48.3% men). Analysis of covariance and “conceptus causal mediation” models were applied, while accounting for survey design. In adjusted models, a lower red meat consumption was significantly associated with a cardio-protective profile of IR and inflammation. Body mass index (BMI) had significant mediation effects on the associations between red meat consumption and C-reactive protein (CRP), Apolipoprotein-B, fasting glucose (FBG), insulin, homeostatic model assessment (HOMA) IR and β -cell function, glycated haemoglobin (HbA1c), triglyceride to high density lipoprotein (TG:HDL) ratio and triglyceride-glucose (TyG) index (all $p < 0.05$). Both waist circumference and anthropometrically predicted visceral adipose tissue (apVAT) mediated the association between red meat consumption with CRP, FBG, HbA1c, TG: HDL ratio and TyG index (all $p < 0.05$). Our findings suggest that adiposity, particularly the accumulation of abdominal fat, accounts for a significant proportion of the associations between red meat consumption IR and inflammation.

Keywords: Meat Intake, Inflammation, Glucose Haemostasis, Insulin Resistance, Adiposity.

Introduction

Red meat consumption has been associated with a pro-inflammatory status, which in turn has been related to a higher risk for type 2 diabetes (1), metabolic syndrome (2) and coronary heart disease (2). The Multi-Ethnic Cohort Study and Nurses’ Health Study reported that a high red meat consumption was linked to approximately 40% greater risk of type 2 diabetes over a follow-up time of 14 and 4 years, respectively (3, 4). However, findings are not consistent across studies as a non-significant association was also found between risk of type 2 diabetes and red meat intake, especially for unprocessed red meat and diabetes risk(5, 6).

Despite the conflicting literature surrounding red meat consumption and risk of type 2 diabetes, there is evidence to suggest that increased red meat consumption is associated with increased whole-body and central adiposity (7). These findings may contribute to explaining the significant association between red meat consumption and type 2 diabetes as central adiposity is a more sensitive predictor of type 2 diabetes and other obesity-related chronic diseases compared to BMI (8).

The role of visceral fat as a causal factor connecting obesity and weight gain to the pathogenesis of insulin resistance and atherosclerosis is established (9). Waist circumference has been proposed as a rapid and simple measurement for the assessment of abdominal adiposity but, like body mass index (BMI), is not able to discriminate between subcutaneous and visceral abdominal fat depots (10). Hence, additional simple and integrated indexes have been recently proposed by combining physical (i.e., waist circumference, BMI, thigh circumference, age) and biochemical measures [(i.e., triglycerides, blood glucose or high density lipoproteins (HDL)]. The lipid accumulation product (LAP) index is a marker of central fat accumulation, derived from the measurements of waist circumference and circulating triglycerides (11), which has been proposed as a predictor of insulin resistance (IR), metabolic syndrome (MetS), type 2 diabetes mellitus and cardiovascular diseases (12, 13). The visceral adiposity index (VAI) is another indicator of adipose tissue distribution which has been used in the stratification of adult obesity phenotypes (14) and to improve the prediction of cardio-metabolic risk (15).

Regression analysis is frequently used to evaluate the association between dietary factors and disease risk but it may be characterised by a limited capacity to identify putative biological mechanisms which could possibly explain the association between red meat intake and risk of high inflammation and impaired glucose control (16). Mediation analysis is a more sensitive statistical approach that can be used to explore and quantify the extent to which the relationship between an exposure and an outcome of interest occurs through the effect of a third variable (16, 17). The traditional approach to mediation analysis tends to produce a bias when the interaction between exposure and mediator is undefined (18, 19). In addition, unbiased valid estimates of direct and indirect effects can be obtained with the use of the counterfactual framework in causal mediation analysis (18, 19). It is unclear to what extent the adjustment for adiposity, modifies or attenuates the association between meat consumption and cardio-protective parameters. Mediation analysis could clarify the role of adiposity underlying the relation between meat consumption and cardio-protective factors.

Previous studies have investigated the association between red meat intake with biomarkers of inflammation and glucose/insulin metabolism with mixed results (20-23); however, none of these studies has attempted to identify which intermediate factors connect the exposure to red meat with the selected health outcomes. The present analysis aims to specifically investigate the link between red meat intake with CRP and glucose/insulin haemostasis and identify adiposity factors that may mediate these associations. These factors include markers of adiposity [WC, BMI, visceral adipose tissue (VAT)], lipid accumulation products (LAP) and visceral adiposity index (VAI) in a representative population of US adults by using National Health and Nutrition Examination Survey (NHANES) database. We hypothesized that a higher red meat intake would be associated with unfavourable concentrations of inflammatory and glucose/insulin haemostasis biomarkers among adults and that these associations would be partly or fully mediated by adiposity markers.

Methods

Population characteristics

The NHANES programme is implemented by the US National Center for Health Statistics (NCHS) (24). NHANES uses a complex, multistage and stratified sampling design to select a representative sample of the civilian and non-institutionalized resident population of the US. The NCHS Research Ethics Review Board approved the NHANES protocol and consent was obtained from all participants (24). The current study was based on analysis of data collected from 2005 to 2010. Data collection on demographics occurs through in-home administered questionnaires, while anthropometric and biochemistry data are collected by trained personnel using mobile exam centers (MEC). More detailed information is available elsewhere (24, 25).

For the assessment of height and weight during the physical examination, participants were dressed in underwear, disposable paper gowns and foam slippers. A digital scale ('Mettler Toledo, Panther') was used to measure weight to the nearest 100 g, a fixed stadiometer was used to measure height to the nearest millimetre. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Waist circumference (WC) was measured at the iliac crest to the nearest millimetre (25).

A blood specimen was drawn from the participant's antecubital vein by a trained phlebotomist. Glycated haemoglobin (HbA1c) was measured using a Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer. Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer. Insulin was measured using an ELISA immunoassay (Merocodia, Uppsala, Sweden) (26). Other laboratory-test details are available in the NHANES Laboratory/ Medical Technologists Procedures Manual (27). Apolipoprotein-B was

measured by radial immunodiffusion (RID) (25). Details on the measurement of C-reactive protein (CRP) concentrations are available elsewhere (25). Homeostatic model assessment of insulin resistance (HOMA-IR), β -cell function (HOMA-B) and insulin sensitivity (HOMA-IS) were calculated as follows: HOMA-IR = [FBG (nmol/L) * insulin (mU/mL)/22.5], and HOMA-B=[20 * insulin (μ U/ml)]/[FBG (mmol/l) - 3.5] (28). The triglyceride-glucose (TyG) index was calculated as the \ln [triglyceride (TG,mg/dl) \times FBG (mg/dl)/2](29). Visceral adipose tissue (apVAT) was predicted with sex-specific validated equations that included age, BMI, and circumferences of the waist and thigh (30). The equation for men was: $6 * WC - 4.41 * \text{proximal thigh circumference} + 1.19 * \text{age} - 213.65$; and the equation for women was: $2.15 * WC - 3.63 * \text{proximal thigh} + 1.46 * \text{age} + 6.22 * \text{BMI} - 92.713$ (30). VAI was calculated using sex-specific formulas: males [WC/39.68 + (1.88 \times BMI)] \times (TGs/1.03) \times (1.31/high density lipoprotein (HDL)); females: [WC/36.58 + (1.89 \times BMI)] \times (TGs/0.81) \times (1.52/HDL), where both TGs and HDL levels are expressed in mmol/L (15). LAP was calculated as [WC-65] \times [TG] in men, and [WC-58] \times [TG] in women (11). Smoking status was self-reported and participants classified as current smoker or not. Metabolic equivalent of task (MET) is used to measure the intensity level of physical activity and indicated the rate of energy consumption for a specific activity. A MET is defined as 1 kcal/kg/hour that is roughly equal to the energy cost of being at rest. Physical activity was categorized into three intensity levels upon MET score: light, moderate and vigorous (31). Subjects with diabetes were excluded from the study.

Red meat consumption

Dietary intake was assessed via a 24-hour recall obtained by a trained interviewer during the MEC visit, with the use of a computer-assisted dietary interview system with standardized probes, i.e. the United States Department of Agriculture Automated Multiple-Pass Method (AMPM) (32, 33). Briefly, the type and quantity of all foods and beverages consumed in a single 24-hour period before the dietary interview (from midnight to midnight) were collected with the use of the AMPM. AMPM is designed to enhance complete and accurate data collection while reducing respondent burden (33, 34). Detailed descriptions of the dietary interview methods are provided in the NHANES Dietary Interviewer's Training Manual (35). The MyPyramid Equivalent Database for USDA Survey Food Codes was used to calculate red meat consumption (35). In the current study red meat intake was calculated as the sum of beef, pork, lamb, veal and game consumption and expressed as grams per day.

Statistical analysis

Analyses were conducted using the SPSS software (version 22, Chicago, IL, USA) according to the guidelines set forth by the center for disease and prevention (CDC) for analysis of complex NHANES datasets, accounting for the masked variance and using the proposed weighting methodology (36). We used means and standard error mean for continuous measures (analysis of variance) and percentages for categorical variables (Chi-square). Analysis of covariance (ANCOVA) was used to compute age, race, energy intake, and sex-adjusted means of markers of insulin resistance or inflammation across quartiles of meat consumption.

The counterfactual framework assessed the total, direct, and indirect effects of red meat consumption on markers of insulin resistance or inflammation with BMI, WC, apVAT, VAI and LAP as a mediator (37, 38). In this approach, the “total effect” can be decomposed into a “direct effect” (not mediated by BMI, WC, apVAT, VAI and LAP, sup Fig1) and an “indirect effect” (mediated by BMI, WC, apVAT, VAI and LAP, sup Fig1). The analysis was conducted using the SPSS Macro developed by Preacher and Hayes (39). A product-of-coefficients test was used as it has the potential to detect significant mediation effects in the absence of a significant intervention effect (37, 38). In brief, the macro generates outputs that include the following steps. Firstly, the “total effect” (γ coefficient) of the exposure on the outcome variable (i.e., markers of insulin resistance or inflammation) is estimated by regressing the markers of insulin resistance or inflammation (outcomes) on red meat consumption (independent variable) while adjusting for the covariates used in the first step, but without adjusting for mediators. The “action theory” test is then used to examine the effect of the exposure (meat consumption) on the hypothesized mediators (α coefficient, BMI, WC, apVAT, VAI and LAP, sup Fig1). The “conceptual theory” test examines the association between changes in the hypothesized mediators and changes in outcome variables (i.e., markers of insulin resistance or inflammation; β coefficient, sup Fig 1). The program also estimates the direct (γ' coefficient) and indirect ($\alpha\beta$ product of coefficients) effects. The proportion of the mediation effect was calculated using the following equation [$\alpha\beta / (\alpha\beta + \gamma)$]. Full or complete mediation is present when the total effect (the γ' -path) is significant, the direct effect (the γ' -path) is not significant and $\alpha\beta$ is significant, whereas partly or incomplete mediation is present when the direct effect (the γ' -path) is also significant. Inconsistent mediation is present when neither total nor direct effect is significant and $\alpha\beta$ is significant(40). All estimates were adjusted for age, sex, race/ethnicity, educational, smoking and level of physical activity.

Results

General characteristics

A total of 16,621 subjects met the criteria for inclusion in the current analyses. Overall 8,607 (48.3%) participants were men and the mean age was 47.1 years. Non-Hispanic white (69.4%) was the largest racial group and other Hispanic (4.5%) the smallest racial group. Furthermore, 56.1% of the participants were married, while 56.4% had achieved more than high school education. Mean and standard error for BMI, WC, apVAT were 28.7 ± 0.05 kg/m², 98.2 ± 0.12 cm and 179.2 ± 1.18 , respectively. Overall, 20.1% were current smokers including 24.7% of men and 15.7% of women. Participants engaging in vigorous physical activity represented 5.2% of the participants, and those engaging in little/no physical activity represented 24.3%. Age, sex, and race-adjusted mean of markers of insulin resistance and inflammation (hs-CRP, apolipoprotein B, FBG, insulin, HOMA-IR, HOMA-B and TyG index) significantly increased across quartiles of red meat consumption (all $p < 0.001$, **Table 1**); HbA1c was not associated with red meat consumption (**Table 1**).

Red meat intake, anthropometry, insulin resistance and inflammation

Action theory: After covariates adjustment, there was a significant association between red meat intake and BMI (β : 0.345, $p < 0.001$), WC (β : 0.912, $p < 0.001$), apVAT (β : 3.27, $p < 0.001$), VAI (β : 0.054, $p < 0.001$) and LAP (β : 0.066, $p < 0.001$) (**Table 2**).

Total effect: This was calculated by examining the association between red meat intake and markers of insulin resistance or inflammation in multivariate models without adjusting for potential mediators. Results showed that, with the exception of HbA1c and HOMA-B, all the markers of insulin resistance or inflammation were positively and significantly associated with red meat intake (all $p < 0.04$, **Table 2**).

Conceptual theory: This analysis tested the association between mediators (BMI, WC, apVAT, VAI and LAP) and markers of insulin resistance or inflammation; all potential mediators had significant and positive associations with markers of insulin resistance or inflammation (all $p < 0.001$, **Table 3**).

Direct and indirect effects of red meat consumption on insulin resistance and inflammation

Table 4 shows the “direct effect”, “indirect effect”, proportion of mediation effect, and Sobel statistics for testing indirect effects. Both BMI and WC significantly mediated the association between markers of insulin resistance and inflammation and red meat intake (all $p < 0.001$); BMI and WC showed the greatest effect on FBG ($\beta = 0.312$, $\beta = 0.371$, respectively). apVAT was a significant mediator for the association between red meat intake with CRP, FBG, HbA1c and TyG index (all $p < 0.001$); similarly FBG was the variable with the strongest association with apVAT ($\beta = 0.293$). Both

VAI and LAP mediated the association between red meat intake and markers of insulin resistance and inflammation (all $p < 0.001$); Serum Apolipoprotein (B) was the variable with the strongest association with VAI and LAP ($\beta = 0.682$, $\beta = 0.808$, respectively).

Discussion:

In the current study we demonstrated that red meat intake was significantly associated with all anthropometric outcomes (BMI, WC, apVAT, VAI and LAP) in fully adjusted models. Red meat intake was also significantly associated with markers of insulin resistance, (except for HbA1c and HOMA-B), and with inflammation. In addition, mediation analyses suggested that these significant associations were partly or fully mediated by central adiposity.

A systematic review reported a significant link between red meat intake, especially processed varieties, with risk of breast cancer (41). Existing observational and intervention studies testing the association between red meat consumption and CRP levels have reported mixed results. Findings were significant in some studies (20, 22) (42) which is in line with what was found in this study. However other studies have findings contradictory to what our study showed demonstrating that while processed meat was positively associated with CRP, red meat consumption alone was not (23) and in another study where lean red meat was not associated with levels of CRP (43). The cholesterol (44), iron (45) and saturated fatty acid (44, 46) content of red meat has been suggested, to some extent, to explain the association between red meat and adverse health outcomes. (47, 48). Previous studies on the effect of meat consumption on glucose/insulin homeostasis have been inconsistent, with some finding an association, in line with our study (49-52), and other failing to show such an association (21, 22). It has been reported that red meat consumption may have impact on glucose/insulin metabolism through iron-related metabolic pathways (53). Iron is a strong pro-oxidant that catalyses several cellular reactions involved in the production of reactive oxygen species, and hence increases the level of oxidative stress (54). This can cause damage to cellular structures, including pancreatic beta cells, and high body iron stores have been shown to be associated with an elevated risk of diabetes (54). Once iron accumulated in the liver, it could interrupt with role of insulin and also constrain the glucose production (55). Increased iron accumulation might lead to insulin resistance by constraining glucose uptake in different tissues (53). Clinical studies have shown no significant effect of iron supplementation on CRP levels (45). Additionally, the effect of red meat on uric acid levels could constitute another pathway linking this dietary component with glucose/insulin homeostasis dysregulation (56). It has been reported that uric acid could play a role in oxidative stress (57) and inflammatory factors (57), which are both linked to the progress of unfavourable glucose/Insulin homeostasis (56, 57). Further, an experiment

in animal models reported that fructose-induced hyperuricemia plays a pathogenic role in developments of cardio-metabolic risk factors (58).

A prolonged intake of saturated fatty acids is correlated metabolic syndrome and is known to contribute to weight gain and inflammation if consumed in excess (59, 60). In particular saturated fatty acids are known to contribute to increases in influence white adipose tissue increasing inflammatory response (61-63). Hence, we hypothesised that a high energy diet which contains excess red meat consumption and is high in saturated fatty acids may be associated with weight gain and thus increased adiposity and subsequently contribute to developing unfavourable glucose/insulin homeostasis enhancing low grade inflammation which is strongly linked to the pathogenesis of CVD and other non-communicable disease. The role of dietary factors, such as excess refined sugar or saturated fat intake, on triggering low grade chronic inflammatory response has received further scientific support recently, reiterating the link with age- related chronic conditions. These inflammatory responses are thought to interact with the ageing process and, if persisted could play a key role in the pathogenic mechanisms leading to the onset of chronic metabolic and cardiovascular diseases (64).

The main strength of the present study is the investigation of the mediation effects using various markers of adiposity including not only BMI and WC, which are the markers of general and abdominal obesity, but also apVAT, VAI and LAP. Moreover we have used a randomly selected, large and representative sample and our results can be extrapolated to the general population. Lastly, the analyses included extensive adjustment for potential confounders which reduces the chance of the residual confounders.

The study has limitations. The study is cross sectional and focused on adults only. Cohort studies may better address the causal relation between red meat intake and relevant health outcomes, but may not be feasible because of the nature of the exposure and ethical issues. Consumption reported associations do not necessarily mean causation. Consumption of red meat in different life stages (childhood, adolescents adulthood and during ageing) has been previously shown to affect risk estimates (65). Furthermore, different patterns of exposure over time could also affect the results. Cooking methods and variations in animal farming and meat preparation, can alter the quality as well as the health effects of red meats (66, 67). This introducing additional residual confounding into the analyses (68-70). This information was not available and therefore could not be controlled. The mediating effect of WC may be affected by BMI, or vice versa, because of the high colinearity between these two variables. This issue could be resolved by adding BMI and WC simultaneously to the mediation model (45). However, this approach was not possible in our analyses because of the complex survey design of the present study. Hence, in an attempt to overcome this limitation, we

have added other validated adiposity factors to the models such as apVAT, LAP and VAI, which provides an independent evaluation of the mediating role of central adiposity between red meat intake and markers of diabetes risk. Lastly, although BMI and WC are regularly applied to determine adiposity, these indicators are still imprecise and can lead to bias in determining obesity. For instance, BMI, is usually limited compared to direct measures of obesity due to the fact that it does not consider age, sex, bone structure, fat distribution or muscle mass into (71). However, we also used other markers of adiposity (apVAT and LAP) which are sensitive to the age, and sex.

Conclusion:

Our study finding suggests that high red meat consumption could negatively affect glucose/insulin homeostasis and inflammatory profile, via mechanisms involving central fat accumulation. Future research is warranted to explore the effect of reducing red meat intake on glucose/insulin homeostasis, which in turn could inform dietary strategies to reduce the risk of T2DM.

Availability of data and material: all the data are from public access database.

Abbreviations:

Red meat consumption (RMC)

insulin resistance (IR)

Homeostatic model assessment (HOMA)

C-reactive protein (CRP)

Body mass index (BMI)

anthropometrically predicted visceral adipose tissue (apVAT)

triglyceride-glucose (TyG)

fasting glucose (FBG)

high density lipoprotein (TG:HDL)

glycated haemoglobin (HbA1c)

lipid accumulation product (LAP)

metabolic syndrome (MetS)

high density lipoproteins (HDL)

visceral adiposity index (VAI)

National Center for Health Statistics (NCHS)

mobile exam centers (MEC)

National Health and Nutrition Examination Survey (NHANES)

Metabolic equivalent of task (MET)

Agriculture Automated Multiple-Pass Method (AMPM)

center for disease and prevention (CDC)

Analysis of covariance (ANCOVA)

Competing financial interests:

The corresponding author is responsible for submitting a competing financial interest statement on behalf of all authors of the paper. The authors declare no competing financial interests.

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Author Contributions:

MM: Study conception and design, Analysis and interpretation of data. Drafting of manuscript.

APK, ESG and MS: Critical revision and interpretation of data.

Declarations:

Ethics approval and consent to participate: for the data collection and physical examination of the NHANES, informed consent was obtained from all adult participants, and the National Centre for Health Statistics Research Ethics Review Board approved the protocol

Consent for publication: for the data collection and physical examination of the NHANES, informed consent (publication) was obtained from all adult participants, and the National Centre for Health Statistics Research Ethics Review Board approved the protocol.

Availability of data and material: all the data are from public access database.

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Supplementary Figure legend:

Supplementary FIGURE 1. Mediation model for the association between red meat consumption and Insulin/Glucose Haemostasis and inflammation; with body mass index (BMI), waist circumference (WC) and anthropometrically-predicted visceral adipose tissue (apVAT), visceral adipose tissue (VAI) and Lipid accumulation product (LAP) as mediators. Path α represents the regression coefficient for the association of red meat consumption with BMI, WC, apVAT, VAI and LAP "*action theory*". Path β represents the regression coefficient for the association of BMI, WC, apVAT, VAI and LAP with Insulin/Glucose Haemostasis and inflammation "*conceptual theory*". The product of regression coefficients α and β represents the mediated effect (indirect effect) of BMI, WC, apVAT, VAI and LAP ($\alpha\beta$). Path γ' represents the direct effect of red meat consumption with Insulin/Glucose Haemostasis and inflammation, after adjustment for BMI, WC, apVAT, VAI and LAP "*direct effect*". Path γ represents the simple total effect of red meat consumption on Insulin/Glucose Haemostasis and inflammation, without adjustment for BMI, WC, apVAT, VAI and LAP "*total effect*".

Table 1. Age-, sex-, and race-adjusted mean of markers of insulin resistance and inflammation across quartiles of red meat consumption

Variables	Quartiles of red meat consumption				p – value ^a
	1	2	3	4	
N,	4153	4158	4166	4144	
Median (25th–75th percentiles) Meat Consumption (g/day)	5.5 (2.2-7.8)	11.1 (9.8-19.7)	32.4(27.6-41.9)	58.4 (46.3-66.9)	
Serum Hs-CRP (mg/dl)	0.29±0.01	0.36±0.01	0.39±0.03	0.48±0.01	<0.001
Serum Apolipoprotein (B) (mg/dL)	91.3±0.86	93.9±0.82	96.4±0.98	97.1±1.04	<0.001
Fasting blood glucose (mg/dl)	97.4±0.65	97.6±0.82	100.2±0.49	102.3±0.76	<0.001
Plasma Insulin (µU/mL)	1.86±0.01	1.93±0.02	2.06±0.01	2.19±0.01	<0.001
HOMA-IR	0.69±0.03	0.89±0.01	1.06±0.01	1.18±0.01	<0.001
HOMA-B	4.29±0.01	4.41±0.01	4.62±0.02	4.79±0.01	<0.001
HbA1c (%)	5.44±0.02	5.49±0.01	5.34±0.01	5.28±0.02	0.28
TyG index	8.46±0.01	8.59±0.01	8.71±0.03	8.89±0.01	<0.001

HOMA-IR, Homeostatic model assessment of insulin resistance ; HOMA-B, Homeostatic model assessment of β -cell function; TyG index, triglyceride-glucose index; hsCRP; high sensitivity C-reactive protein; HbA1c haemoglobin A1c. Values expressed as estimated mean and standard error.

^a p-values for linear trend across quartiles of hs-CRP. Variables were compared across quartiles of red meat consumption using analysis of covariance (ANCOVA) test.

Table 2. Estimates of regression coefficients (95% CIs) for the association between red meat consumption (g/day), BMI, WC, apVAT, VAI and LAP (action theory), and markers of insulin resistance and inflammation (total effect) among US adults in NHANES

Mediator	Estimate	95% CI	P
BMI	0.34	(0.21-0.48)	<0.001
WC	0.91	(0.59-1.24)	<0.001
apVAT	3.27	(0.95-5.42)	<0.001
LAP	0.06	(0.04-0.08)	<0.001
VAI	0.05	(0.03-0.07)	<0.001
Outcome			
Serum Hs-CRP (mg/dl)	0.03	(0.02 - 0.07)	0.01
Serum Apolipoprotein (B) (mg/dL)	0.96	(0.45-1.12)	0.01
Fasting blood glucose (mg/dl)	0.69	(0.33-1.01)	0.04
Plasma Insulin (uU/mL)	0.03	(0.02 - 0.06)	<0.001
HOMA_IR	0.04	(0.02 - 0.07)	<0.001
HOMA_B	0.01	(-0.005- 0.04)	0.14
HbA1c (%)	0.01	(-0.003- 0.04)	0.12
TyG index	0.04	(0.03-0.06)	<0.001

Abbreviations: *BMI: body mass index, WC, waist circumference, apVAT, Anthropometrically-predicted visceral adipose tissue, HOMA_IR, Homeostatic model assessment of insulin resistance; HOMA_B, Homeostatic model assessment of β -cell function HOMA_S; Homeostatic model assessment of insulin sensitivity, TyG index, triglyceride-glucose index Hs-CRP; high senility C-reactive protein, HbA1c Glycated haemoglobin. All estimates were adjusted for age, sex, race/ethnicity, education, smoking and level of physical activity. Estimates for mediator and outcomes correspond to the regression coefficients α and β , respectively, in Figure 1.*

Table 3. Estimates of regression coefficients (95% CIs) for the association between BMI, WC, apVAT, VAI and LAP with markers of insulin resistance and inflammation (conceptual theory) among US adults

Outcomes	BMI			WC			apVAT			VAI			LAP		
	Estimate	95% CI	P	Estimate	95% CI	P	Estimate	95% CI	P	Estimate	95% CI	P	Estimate	95% CI	P
Serum Hs-CRP (mg/dl)	0.08	0.00-0.085	<0.001	0.03	0.006-0.038	<0.001	0.09	0.009-0.0096	<0.001	0.40	0.38-0.42	<0.001	0.56	0.52-0.56	<0.001
Serum Apolipoprotein (B) (mg/dL)	0.54	0.46-0.630	<0.001	0.29	0.26-0.330	<0.001	0.09	0.073-0.102	<0.001	14.23	13.95-15.26	<0.001	13.6	12.52-14.63	<0.001
Fasting blood glucose (mg/dl)	0.77	0.69-0.880	<0.001	0.36	0.32-0.400	<0.001	0.07	0.064-0.095	<0.001	8.25	7.62-9.12	<0.001	7.42	6.39-8.54	<0.001
Plasma Insulin(uU/mL)	0.05	0.04-0.059	<0.001	0.02	0.024-0.026	<0.001	0.06	0.005-0.007	<0.001	0.40	0.38-0.42	<0.001	0.44	0.43-0.46	<0.001
HOMA_IR	0.06	0.061-0.065	<0.001	0.02	0.028-0.030	<0.001	0.07	0.006-0.008	<0.001	0.47	0.44-0.49	<0.001	0.51	0.49-0.52	<0.001
HOMA_B	0.03	0.034-0.039	<0.001	0.01	0.016-0.018	<0.001	0.04	0.003-0.005	<0.001	0.23	0.21-0.25	<0.001	0.28	0.26-0.30	<0.001
HbA1c (%)	0.02	0.023-0.027	<0.001	0.01	0.010-0.012	<0.001	0.02	0.001-0.003	<0.001	0.21	0.19-0.23	<0.001	0.20	0.19-0.22	<0.001
TyG index	0.02	0.027-0.031	<0.001	0.01	0.013-0.015	<0.001	0.04	0.003-0.005	<0.001	0.77	0.72-0.80	<0.001	0.64	0.63-0.66	<0.001

Abbreviations: BMI: body mass index, WC, waist circumference, apVAT, Anthropometrically-predicted visceral adipose tissue, HOMA_IR, Homeostatic model assessment of insulin resistance; HOMA_B, Homeostatic model assessment of β -cell function HOMA_S; Homeostatic model assessment of insulin sensitivity, TyG index, triglyceride-glucose index, Hs-CRP; high senility C-reactive protein. All estimates were adjusted for age, sex, race/ethnicity, educational, smoking and level of physical activity. Regression coefficient β is shown in Figure 1.

Table 4. Direct and indirect effects of red meat consumption on markers of insulin resistance and inflammation with BMI, WC, apVAT, VAI and LAP as mediators among US adults

Mediator and outcomes	Direct effect (β)		Indirect effect (αβ)		Proportion of mediation, %
	Estimate	P	Estimate	Sobel test statistic	
BMI					
Serum Hs-CRP (mg/dl)	0.004	0.692	0.029	<0.001	82.1%
Serum Apolipoprotein (B) (mg/dL)	0.888	0.023	0.201	<0.001	21.1%
Fasting blood glucose (mg/dl)	0.382	0.312	0.312	<0.001	27.2%
Plasma Insulin (uU/mL)	0.016	0.079	0.022	<0.001	66.9%
HOMA_IR	0.020	0.032	0.025	<0.001	58.1%
HOMA_B	0.002	0.795	0.013	<0.001	12.3%
HbA1c (%)	0.055	0.623	0.009	<0.001	26.1%
TyG index	0.039	<0.001	0.010	<0.001	5.3%
WC					
Serum Hs-CRP (mg/dl)	0.008	0.865	0.034	<0.001	69.1%
Serum Apolipoprotein (B) (mg/dL)	0.695	0.046	0.266	<0.001	22.3%
Fasting blood glucose (mg/dl)	0.203	0.562	0.371	<0.001	23.1%
Plasma Insulin (uU/mL)	0.014	0.112	0.024	<0.001	52.1%
HOMA_IR	0.019	0.043	0.028	<0.001	46.5%
HOMA_B	0.001	0.956	0.015	<0.001	4.23%
HbA1c (%)	0.001	0.846	0.011	<0.001	20.4%
TyG index	0.033	<0.001	0.013	<0.001	34.5%
apVAT					
Serum Hs-CRP (mg/dl)	-0.023	0.336	0.030	<0.001	95.1%
Serum Apolipoprotein (B) (mg/dL)	-0.022	0.762	0.212	0.166	72.1%
Fasting blood glucose (mg/dl)	0.112	0.623	0.293	<0.001	16.3%
Plasma Insulin (uU/mL)	0.031	0.042	0.016	0.166	40.6%
HOMA_IR	0.030	0.109	0.019	0.143	36.1%
HOMA_B	0.022	0.245	0.011	0.145	33.1%
HbA1c (%)	0.003	0.831	0.009	<0.001	13.1%
TyG index	0.020	0.032	0.013	<0.001	20.1%

VAI					
Serum Hs-CRP (mg/dl)	0.016	0.205	0.021	<0.001	6.2%
Serum Apolipoprotein (B) (mg/dL)	0.215	0.563	0.682	<0.001	43.1%
Fasting blood glucose (mg/dl)	0.105	0.777	0.452	<0.001	4.1%
Plasma Insulin (uU/mL)	0.021	0.039	0.018	<0.001	3.7%
HOMA_IR	0.021	0.019	0.022	<0.001	3.4%
HOMA_B	0.007	0.653	0.011	<0.001	6.2%
HbA1c (%)	0.001	0.635	0.11	<0.001	2.9%
TyG index	0.005	0.038	0.042	<0.001	19.7%
LAP					
Serum Hs-CRP (mg/dl)	0.003	0.865	0.036	<0.001	16.2%
Serum Apolipoprotein (B) (mg/dL)	0.101	0.723	0.808	<0.001	16.2%
Fasting blood glucose (mg/dl)	0.033	0.986	0.542	<0.001	8.2%
Plasma Insulin (uU/mL)	0.011	0.214	0.027	<0.001	18.6%
HOMA_IR	0.016	0.123	0.031	<0.001	14.8%
HOMA_B	0.001	0.865	0.017	<0.001	31.2%
HbA1c (%)	-0.011	0.911	0.014	<0.001	6.3%
TyG index	0.004	0.320	0.043	<0.001	6.32%

Abbreviations: BMI: body mass index, WC, waist circumference, apVAT, Anthropometrically-predicted visceral adipose tissue, HOMA_IR, Homeostatic model assessment of insulin resistance; HOMA_B, Homeostatic model assessment of β -cell function HOMA_S; Homeostatic model assessment of insulin sensitivity, TyG index, triglyceride-glucose index Hs-CRP; high senility C-reactive protein. All estimates were adjusted for age, sex, race/ethnicity, educational, smoking and level of physical activity. Regression coefficients α , β , and \mathcal{E} are shown in Figure 1.