Elevated serum uric acid is a facilitating mechanism for insulin resistance mediated accumulation of visceral adipose tissue

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Abstract

BACKGROUND: Serum uric acid (SUA) has a relationship with cardiometabolic conditions such as insulin resistance (IR) and visceral adipose tissue (VAT) accumulation. Here, we aimed to clarify the nature of this relationship and the underlying causality mechanism.

METHODS: We conducted a population-based cross-sectional study comprising 8,504 subjects joining both NHANES 2003-2004 and 2011-2012 cycles and ENSANUT Medio Camino 2016. We performed mixed effects linear regression models using HOMA2-IR, adipoIR, and METS-VF as indicators of IR and VAT accumulation. Furthermore, we performed mediation analyses to assess a potential causal mechanism and ROC curves to establish cut-off points for identification of IR and visceral obesity using SUA. Finally, with an additional dataset comprised of 226 subjects with both euglycemic hyperinsulinemic clamp (EHC) and dual X-ray absorptiometry (DXA) measurements for IR and VAT accumulation, we performed a network of confirmatory mediation analyses.

RESULTS: We found that SUA has a mediating role inside the bidirectional relationship between IR and visceral obesity, and it is part of an underlying causality mechanism which includes adiponectin. The proportion of the mechanism mediated by SUA is greater when stated that IR (in either peripheral or adipose tissue) leads to VAT accumulation (14.90%[13.20%-17.00%] and 15.54%[13.61% - 18.00%] to 4.88%[3.06%-7.00%] and 8.13%[5.91% - 10.00%]) instead of the opposite direction. This result was confirmed by mediation analyses using gold-standard measurements.

CONCLUSIONS: Elevated SUA acts as mediator inside the bidirectional relationship between IR and VAT accumulation. Its role appears to be larger when considering adipose tissue IR as the promoter for VAT accumulation.

Keywords: Serum uric acid, Insulin resistance, Visceral obesity, Mediation

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[8]*Abbreviations*: IR: insulin resistance. VAT: Visceral adipose tissue. SUA: Serum uric acid. T2D: Type 2 Diabetes.

1. Introduction

Uric acid is a heterocyclic puric compound and the final product of purine oxidative metabolism, which can be found in extracellular fluids as sodium urate given its properties as a weak acid.[1] Urate comprises two-thirds of serum antioxidant capacity and it is a strong reducing agent.[2,3] Serum uric acid (SUA) levels are dependent on age and sex, given that they are mainly controlled by hepatic production. Impairments in urate metabolism are related to several cardiometabolic conditions including cardiovascular disease (CVD), nephrolithiasis, gout, arterial hypertension, dyslipidemias,[3,4,5] and loss of plasmatic antioxidant capacity.[6,7]

Two particular cardiometabolic conditions which have been linked to SUA-related metabolic impairments include insulin resistance (IR) and increased visceral adipose tissue (VAT) accumulation. Independently, IR and VAT accumulation have a bidirectional causality relationship, which has been thoroughly explored.[8,9,10,11] Additionally, VAT has endocrine functions such as adipokine secretion, which can be altered due to its excessive accumulation leading towards further decrease in cardiometabolic health.[12] Ultimately, IR can be caused by metabolic deregulation due to excessive VAT accumulation,[13] and at the same time IR can cause this same VAT accumulation.[8] Both phenomena have been studied as interlinked conditions to SUA metabolism, as it is related to both IR and VAT accumulation through different physiopathological pathways. These pathways mainly involve oxidative stress,[14,15] electrolyte equilibrium, immunometabolic regulators[16,17,18] and specific enzymatic deregulation.[19,5] Nevertheless, SUA has only been hypothesized to be a part of an underlying causality mechanism linking both IR and VAT in *in vitro* environments.[20]

Mechanistic, population-based studies which focus in determining the nature of the relationship that SUA has with both IR and VAT accumulation are currently scarce. Identifying a causal and mediating role of SUA inside the relationship which links both IR and VAT would allow to further strengthen the importance for its identification in clinical practice as related phenomena, that will ultimately promote cardiometabolic health prevention in general population. Hence, in this study we attempt to clarify a mediating physiopathological pathway relating VAT accumulation and IR, where SUA acts as a link between both phenomena using national-based surveys in two countries.

2. Methods

2.1. Population analysis

We analyzed an ethnically diverse joint cohort comprised of Mexican (ENSANUT Medio Camino 2016) and American (NHANES 2003-2004 and 2011-2012 cycles) subjects. The goal of both cohorts was to assess the health and nutritional general status in each country based on a comprehensive sample of subjects of each population. Further sampling and stratification methodology of the sampling and methods for ENSANUT and NHANES cohorts are published elsewhere.[21,22,23] A subset of NHANES 2003-2004 and 2011-2012 cycles were analysed using fasting plasmatic free fatty acid quantification to further explore a pathophysiological mediating relationship between adipose tissue IR, VAT and elevated SUA.

Finally, in order to confirm a possible mediating relationship, an additional dataset of Mexican subjects was recruited from the SIGMA Cohort study and a subset of metabolically-healthy obese individuals.[24] IR was assessed in subjects using euglycemic hyperinsulinemic clamp (EHC) and VAT accumulation with Dual X-Ray Absorptiometry (DXA). Complete methodology of SIGMA-cohort is presented in supplementary material. Briefly, we recruited patients with T2D and glycated hemoglobin (A1c) concentration <8%, who were not receiving insulin and were treated only with metformin and healthy subjects without underlying comorbidities amongst which we included metabolically healthy obese subjects. We excluded subject with

active smoking, T2D complications (nephropathy, neuropathy and retinopathy), cardiovascular diseases, chronic kidney disease, or with an acute infections from all analyses.

2.2. Laboratory and anthropometric measurements

For the ENSANUT-cohort, anthropometric measurements, such as height, weight, and waist circumference were measured by trained professionals to one significant digit. Clinical sampling, as well as the complete analysis methodology can be found in supplementary material. For the NHANES-cohort, anthropometric measurement methods, as well as the standardized DXA procedures, are specified for both (2004)[21] and (2012) cycles.[22] BMI categorization was done according to the following benchmarks: Underweight: <18.5 kg/m^2, normal weight: 18.5-25.0 kg/m^2, overweight: 25.1 - 29.9 kg/m^2, obese: 30.0 - 39.9 kg/m^2, morbidly obese: >40 kg/m^2.

2.3. Definitions of metabolic related conditions

2.3.1. Elevated SUA

Subjects with elevated SUA were those with SUA>5.5 mg/dL, given as this cut-off describes the midpoint between hypouricemia[25,26] and serum solubility,[3] thus weighing its inverted J-shaped antioxidant behavior. For categorized analyses, elevated SUA for females was assigned at SUA>4.7 mg/dL; and at SUA>5.9 mg/dL for males, again weighing hormetic behavior.

2.3.2. Insulin resistance

For the NHANES and ENSANUT-cohorts, insulin resistance was estimated using the HOMA2-IR index. Insulin sensitivity and estimated pancreatic secretion was estimated using HOMA2-%B and HOMA2-%S indexes, respectively. These estimates were calculated using the Oxford Centre Diabetes Trial Unit calculator spreadsheet[27] Version 2.3.3. We defined as peripheral insulin resistant subjects with HOMA2-IR > 2.5. To explore the role of adipose tissue IR, we calculated the adipoIR index by multiplying palmitate (µmol/L) by fasting insulin (pmol/L) by four:[28]

$$(\text{Palmitate}\,[\mu mol/L] \times \text{Fasting insulin}\,[pmol/L]) \times 4$$

We classified subjects as adipose tissue insulin resistant with $\log_{10}$adipoIR> 4.6,[28] averaging cut-off points for male and female subjects.

In the SIGMA-cohort, we performed a EHC according to the standardized methods described in Supplementary Material. IR using EHC was defined as M-value [mg/min/kg] $\leq$ 4.7.[29]

2.3.3. Visceral obesity

We estimated VAT using the clinical surrogate METS-VF (Metabolic Score for Visceral Fat), as stated by Bello-Chavolla et. al.[30] METS-VF was calculated using by the following equation:

$$\text{METS-VF} = 4.466 + 0.011[(\text{Ln}(\text{METS-IR}))^3] + 3.239[(\text{Ln}(\text{WHtr}))^3] + 0.319(\text{Sex}) + 0.594(\text{Ln}(\text{Age}))$$

We defined as visceral obese, subjects with METS-VF > 7.18 in NHANES and ENSANUT-cohorts. In the SIGMA-cohort, we performed DXA VAT assessments according to the standardized methods described in the Supplementary Material. Visceral obese subjects were classified by DXA > 1000g.

2.4. Statistical analysis

Categorical variables are presented in frequency distribution with their respective percentage. Continuous variables are presented in mean (±standard deviation) or median (interquartile range), wherever appropriate. Differences amongst groups of subjects with hyperuricemia were tested using two-by-two Chi-Squared tests for categorical variables and Mann-Whitney U or T-tests for continuous variables, wherever appropriate.

2.4.1. Association among SUA with IR and VAT

To ensure the best symmetry in variables, we performed logarithmic, Ordered Quantile (ORQ) normalization, and square root transformations wherever appropriate. To establish that SUA has a correlation with IR and VAT, together with its direction, we performed a Pearson's Correlation test. Correlation matrices can be found in supplementary material. Further on, we explored the effect of IR and VAT on SUA according to every possible direction using linear mixed effect regression models. The best models were chosen with Bayesian Information Criteria (BIC) criteria; model assumptions were verified by analyzing standardized residuals. Fits and coefficients can be found in supplementary material.

2.4.2. SUA mediation in IR and VAT accumulation

To explore a possible mechanistic mediation model of SUA on IR and VAT, we performed adjusted linear mediation analysis using linear mixed effects models which specified cohort of origin as a random effect and logistic mixed effects models with phenotype categorization. These models depict all plausible mediation mechanisms inside the relationship. All mediation analyses were adjusted for age, sex, and ethnicity. We also performed mediation analyses stratified by sex.

For the confirmatory mediator analysis, a joint mediator between adiponectin and uric acid was calculated according to the following equation:

$$\text{Joint mediator} = \ln\left(\frac{\ln(\text{uric acid } [mg/dL])}{\ln(\text{Adiponectin } [\mu g/mL])}\right)$$

2.4.3. ROC curves

To evaluate the utility of SUA as a clinical identification tool for IR and VAT accumulation, ROC curves were fitted according to categorization phenotypes and sex was established as covariate. All statistical analyses and data management were done with RStudio version 4.0.0. A p value <0.05 was considered as statistically significant.

3. Results

3.1. Population analysis

Our final dataset was comprised of 8,054 patients (ENSANUT = 1,941; NHANES = 6,113) from two national based surveys. Sociodemographic, biochemical, and anthropometrical measurments are presented in Table 6.1. Briefly, our data-set is comprised primarily of young adult women, from which 4.76% were diagnosed with T2D. In this enhanced cohort, all included parameters were different, but when analyzing the ENSANUT cohort alone some non-significant differences between the uric acid-based groups were observed, such as T2D prevalence, HOMA2-IR, HOMA2-%S, and total cholesterol (Supplementary material, Table 7.1).

3.2. Difference in SUA levels in IR and visceral obesity

We observed a positive correlation between increased values of SUA with HOMA2-IR and METS-VF in the joined cohort. These positive correlations were observed also when each cohort was analyzed separately (**Supplementary Figure 7.1**). As expected, we noted differences in SUA levels attributable to sex, which were increased in subjects with visceral obesity. Furthermore, it was also noted that increasing BMI categories had an ascending trend in SUA levels, which were independent of visceral obesity status. Similarly this trend was observed in all groups, except for subjects who were viscerally obese but not insulin resistant (Figure 6.1). In order to elucidate a reasonable pathway for the relationship of the studied variables, a joint indicator was established considering both phenomena (IR and visceral obesity), and it was weighed again against SUA levels. We found a positive association between IR, visceral obesity and both phenomena with increasing SUA levels. Interestingly, those subjects with visceral obesity but not IR had increased SUA compared with those with IR alone. This ultimately suggests a possible interaction between the joint effect of IR and visceral obesity with SUA. (Figure 6.2).

3.3. SUA acts as predictor for IR and visceral adipose tissue

Regression models with every possible combination between SUA, IR and visceral fat were explored. Linear regression models showed that the chosen adjustment for all the individual regressions fits varied between linear, quadratic, and cubic. (Supplementary material). The variety in fits opens the hypothesis towards that a potential mediation mechanism is taking place, given the observed directions of the correlations and regressions. To further strengthen this hypothesis, we analyzed a third cohort in which the gold standard methods were used to measure insulin action and abdominal adiposity. AdipoIR was used as a marker for adipose tissue IR. The correlation between individual variables when using adipoIR as an adipose tissue IR marker is stronger than HOMA2-IR as peripheral IR marker and provides a first indication towards the approach of a mediating pathway for this mechanism. The presence of non-linear models in the dataset accounts for the existence of bidirectional relationships. With this information, a bidirectional mediation model was proposed in which it was hypothesized that elevated SUA could act as a mediator in IR-mediated visceral adipose tissue accumulation (Figure 6.3a).

3.4. SUA mediates a bidirectional relationship between IR and VAT accumulation

Several mediation analyses were developed with the aforementioned relationships. Guided by our proposed mediation model, a total of four mediation pathways were developed. The hypothesis which stated that peripheral IR leads to VAT accumulation showed a greater mediated proportion than the opposite direction (14.90% [95% CI: 13.20% - 17.00%] to 4.88% [95% CI: 3.06% - 7.00%]) (Table 6.2). Both directions describing relationships between IR and VAT accumulation for the mediation models were significant. Moreover, elevated SUA was observed to act as a mediator between peripheral IR and visceral fat. The same models were explored with adipoIR, and the results were similar. The observed mediated proportion with both hypotheses increased when compared to HOMA2-IR estimator (15.54% and 8.13%, Table 6.2), indicating a grater role of adipose tissue IR inside the mechanism. Also, when adjusting for T2D in evaluated subjects as a covariate, or excluding patients with diabetes, we observed no significant differences in model estimates and fit.

A Directed Acyclic Graph (Supplementary Figure 7.2) was built in order to accurately represent the proposal for the directions of this mechanism. It holds regarding potential causality with both phenomena. Elevated SUA acts as a stronger mediator inside the relationship when quantifying adipose tissue IR instead of peripheral IR.

3.5. Adiponectin has a physiopathological role in the relationship linking elevated SUA, IR, and visceral obesity

It is well known that visceral fat has extensive metabolic and endocrine activity. Adiponectin is secreted by visceral adipose tissue and when depleted, it is related to a decrease in insulin sensitivity. With elevated SUA, adiponectin secretion is decreased.[31,13] In order to test the strength of the proposed mechanisms, a confirmatory analysis was performed using a third dataset. This data-set measured IR using EHC measurements and VAT accumulation using DXA scan. Characteristics of this dataset are included in supplementary material. We first confirmed the aforementioned bidirectional mechanism using EHC and DXA. Then, a new multi-directional mediation model was proposed where adiponectin plays a role within the previously hypothesized mediation models (Figure 6.3b). A set of 10 mediation models were developed, including two with a joint mediator which accounts for SUA units per unit of serum adiponectin. Our original models yielded significant mediated proportions in both directions (8.60% and 12.52%, respectively). When assessing the joint mediator, it yielded a greater mediated proportion as elevated SUA alone in the original dataset for both directions (16.32% [8.84% - 26.00%] and 12.52% [3.23% - 23.00%], Supplementary table 7.4). The relationship between SUA and adiponectin is an important mediator inside the bidirectional mechanism relating peripheral IR and visceral fat accumulation.

Given these observations, adiponectin partly mediates the relationship between elevated SUA and both peripheral IR and VAT accumulation in both directions. With the relationship between peripheral IR and VAT alone, adiponectin has a smaller mediated proportion, suggesting that the adipokine is indeed involved in the relationship between elevated SUA and both peripheral IR and visceral fat accumulation, and that this effect takes place in both directions.

3.6. SUA as a marker of IR and VAT accumulation

The proposed mechanism is established as bidirectional, and given the strength of the mediated proportions, ROC analyses were fitted to assess if SUA levels could be used to identify or predict peripheral and adipose IR, and visceral obesity. For our joint cohort, the cut-off value for both phenotypes varied for male sex, respectively (6.1 mg/dL for IR and 7.0 mg/dL for visceral obesity), while females observed the same cut-off for all phenotypes (4.8 mg/dL). None of these models showed SUA to be a strong predictor for its corresponding outcome, given their specificity and sensitivity, but all have a high negative predictive value (87.2%, 88.5%, 70.2%, 86.1% respectively) meaning that a SUA below the cut-off values could help discard IR and visceral obesity. For the NHANES data-set alone, the same analysis was performed for adipose tissue IR identification. Both of these models yielded different cut-off points for males (7.0 mg/dL) and females (5.0 mg/dL), with a high negative predictive value for both sexes (89.0% for males and 93.1% for females) (Supplementary table 7.3).

4. Discussion

Here, we described the mediating role of elevated SUA in the relationship between IR and visceral obesity, as well as a strong assumption on its causal relationship towards a possible clinical application using representative, population-based cross-sectional data. This is relevant given that SUA is a routine, easy, and reproducible laboratory examination. Its role in maintaining body homeostasis has been widely proven and discussed, while not causally linked to these mechanisms. Our research aimed to link together known mechanisms, such as the relationship between IR and uric acid,[32,19,33] uric acid and VAT accumulation,[34,35,36] the connection between IR and visceral adiposity,[8,9,10,11,37] and how elevated SUA links together both phenomena through a mediating mechanism using population-based data. Additionally, our population-based results

were further strengthened by a confirmatory sub-analysis using gold-standard measurements for both IR and VAT accumulation, while also accounting for the involvement of adiponectin, which also leads towards a more mechanistic description of the metabolic pathways behind the main relationships. Inside the confirmatory sub-analysis cohort the fact that both mediated proportions were not significantly different despite its modest sample size, further accounts for the existence of a bidirectional mechanism.

There is a bidirectional nature in the relationship between IR and VAT accumulation as stated by our results and evidence from previous studies.[38] Nevertheless, elevated SUA levels has a larger mediating effect when stated that IR leads to visceral fat accumulation. Subjects who have a normal BMI can be viscerally obese as well as IR, and IR can then lead towards greater VAT accumulation. Even though the link between SUA levels and IR in this direction has been the least studied, it has been shown that IR does lead to hyperuricemia through an increase in renal Na^+ proximal resorption[19] and a shift in renal electrolytic balance through URAT1 transporter.[39] Elevated SUA leads to VAT accumulation through three known mechanisms:[5] (1) through the increase of uric acid-dependent intracellular and mitochondrial oxidative stress via NADPH oxidase activation,[40] (2) through the inhibition of AMP-activated protein kinase by low intracellular phosphate levels, which decreases transformation rate of AMP to IMP, to inosine and uric acid, and (3) through the activation of the nuclear transcription factor, carbohydrate responsive element-binding protein and increased ketohexokinase expression, responding to fructose abundance and avoiding phosphate depletion.[41]

Even though our results from the joint cohort point towards a causal mechanism in which VAT accumulation leads to IR, exemplified in our DAG graph (Supplementary Figure 7.2), we should not ignore its bidirectionality. Mediation analyses inside ENSANUT cohort had negative signs in the mediated effect when stating that IR leads to VAT accumulation, but these disappear in the joint cohort analysis. This leads towards a hypothesis saying that there is indeed a mediation effect in this direction (IR to VAT accumulation), but it is relatively smaller compared to the mechanism involving IR leading to VAT accumulation. Biologically, there is more evidence supporting this sequence of events; in which VAT accumulation leads to IR mediated by elevated SUA. Elevated SUA is known to precede IR[19, 17, 42] through different mechanisms, both metabolic and immunological, and VAT accumulation can cause elevated SUA through an increased expression of xantine oxidorreductase[43] of adipose tissue, commonly found in obesity upstream from PPAR-γ, which is a regulator of adipogenesis.[42] This particular phenomenon can account for why elevated SUA is a stronger mediator inside this relationship when quantifying adipose tissue IR instead of peripheral IR. Correlation of visceral fat with HOMA2%B was not statistically significant, but it had significant differences when comparing subjects with and without elevated SUA. Elevated SUA can cause pancreatic β-cell dysfunction through the NF-$\varkappa$B signaling pathway and NO synthase induction, but it is through a mechanism that does not correlate with VAT accumulation directly,[17] although VAT accumulation can still be responsible for the rising in SUA levels. Similarly, based on the signs of the mediated proportions, a hypothesis stating that the causality of this mechanism depends more on the previous metabolic state of the subject could be feasible; both directions can occur at the same time but not with the same intensity. VAT accumulation could lead to IR when the subject is not yet insulin resistant, but IR could lead to further VAT accumulation once the threshold for IR has been met when the process is mediated by elevated SUA, with possible biochemical and immunometabolical players illustrated in Figure 6.4.

As the confirmatory sub-analysis suggests, adiponectin has a strong relationship inside this mechanism when considered together with elevated SUA. It has been previously shown that the relationship that this adipokine has with both insulin sensitivity in adipose tissue and uric acid secretion.[44, 31, 45] Our results

suggest that adiponectin acts as a significant mediator inside our proposed mediation model, which confirms that the endocrinometabolic regulation arising from VAT is partially responsible for the role uric acid plays inside this relationship, as pictured in Figure 6.3b and previously proven in an *in vitro* environment.[20]

The last step of this analysis consisted in finding a clinical application for these findings. Elevated SUA has been previously related with cardiometabolic conditions.[32,19,38,5,4,46] Even so, a threshold for IR or visceral obesity identification had not yet been estimated; the observed specificities and sensitivities for SUA cannot support its routine use as a reliable diagnostic tool. Even so, elevated SUA should not be ignored when looking for indicators of IR or visceral obesity in clinical practice; although we observed a better performance in the ROC curves with female patients, further evaluations of underlying hormonal and physiological assessments should be performed to estimate differential sex-based impacts of SUA on whole-body metabolism. Limitations of this study include its cross-sectional nature; although hypothesized, just potential causality based on biological plausibility and previous findings but not temporality of the mechanisms could be established. Further considerations for sex should be made if this were to be applied in a clinical environment. Also, given the different sources for the data, not all measurements were done the same way accounting for some uncertainty; however this was addressed considering this variability within a mixed effects framework. Strengths of our study include the heterogeneity of the population studied, the use of ethnically diverse, representative population-based data, which allowed for precise estimates of the relationship between these phenomena. Furthermore, we conducted a confirmatory sub-analysis using gold-standard measurements for IR and VAT assessment which reproduced our previous observations and allowed for a characterization of the role of adiponectin within our causality framework. Overall, our approach allowed the elucidation of a relationship which had not yet been entirely established.

In conclusion, elevated SUA acts as a mediator inside a bidirectional relationship between IR and VAT accumulation. The role of elevated SUA appears to be larger when considering adipose tissue IR as a promoter of VAT accumulation. Adiponectin appears to be involved as a modifier of the role of elevated SUA within these mechanisms. These observations position SUA as a potential marker to evaluate metabolic health from a pathophysiological and mechanistic perspective. Further longitudinal population-based studies should be performed to clarify the hypothesized temporality and the possible immunometabolic pathways underlying this relationship.

5. Supplementary information

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DATA AVAILABILITY

All data sources and R code are available for reproducibility of results at `https://github.com/oyaxbell/hyperuricemia_ir_vat`.

AUTHOR CONTRIBUTIONS

Research idea and study design LFC, CAAS, OYBC; data acquisition: OYBC, PAV, DGV, TLVR, RR, CAAS; data analysis/interpretation: LFC, OYBC, NEAV, AVV, PAV, CAAS; statistical analysis: LFC,

OYBC; manuscript drafting: LFC, OYBC, NEAV, AVV, PAV, RR, TLVR, CAAS; supervision or mentorship: OYBC, CAAS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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6. Tables and Figures

	General population	Elevated SUA	Normal SUA	p-values
n	8054	4491	3563	
Age [years]	42.46 (±20.78)	45.67 (±20.67)	39.91 (±20.50)	<0.001
Male sex	3789 (47.04%)	2455 (68.92%)	3157 (70.30%)	<0.001
Glucose [mg/dL]	104.63 (±37.08)	105.54 (±31.21)	103.94 (±41.13)	0.047
Insulin [µU/mL]	9.20 (9.56)	10.60 (11.34)	8.43 (8.17)	<0.001
TGL [mg/dL]	113.00 (98.00)	132.00 (109.00)	100.00 (86.00)	<0.001
cHDL [mg/dL]	50.17 (±15.47)	46.64 (±14.40)	52.96 (±15.76)	<0.001
Total cholesterol [mg/dL]	187.77 (±42.87)	190.21 (±42.84)	185.82 (±42.80)	<0.001
BMI [kg/m^2]	27.78 (±6.51)	29.41 (±6.70)	26.47 (±6.02)	<0.001
WHR	0.58 (±0.10)	0.60 (±0.10)	0.56 (±0.10)	<0.001
METS-VF	6.57 (±0.94)	6.86 (±0.82)	6.34 (±0.97)	<0.001
Visceral obese [METS-VF>7.18]	2452 (100%)	1514 (61.75%)	932 (38.25%)	<0.001
HOMA2-%B	90.45 (60.60)	93.05 (63.80)	88.40 (58.50)	<0.001
HOMA2-%S	81.00 (82.30)	70.90 (75.07)	88.50 (85.50)	<0.001
HOMA2-IR	1.23 (1.29)	1.41 (1.51)	1.12 (1.10)	<0.001
Insulin resistant [HOMA2-IR>2.5]	1398 (100%)	794 (56.80%)	605 (43.20%)	<0.001
Type 2 Diabetes	387 (100%)	236 (60.98%)	151 (39.02%)	<0.001

Table 6.1: General characteristics of studied cohort (NHANES-ENSANUT). Patients with elevated SUA are those with a serum concentration greater than 5.5 mg/dL. *Abbreviations*: BMI: Body Mass Index. cHDL: Cholesterol-high density lipoprotein. HOMA2-IR: Homeostatic Model for Insulin Resistance. HOMA2-%S: Homeostatic Model for Insulin Resistance for pancreatic β cell sensitivity. HOMA2-%B: Homeostatic Model for Insulin Resistance for functionality of pancreatic β cells. HUA: Hyperuricemia. n-HUA: Non-hyperuricemia. METS-VF: Metabolic Score for Visceral Fat. WHR: Waist-height ratio.

Causality model	Efector	Mediator	Result	ACME	ADE	Total effect	% Mediated
H2-IR n=8054	IR (HOMA2-IR)	Elevated SUA	Visceral fat (METS-VF)	0.079 (0.070 - 0.090)	0.452 (0.425 - 0.480)	0.532 (0.504 - 0.560)	14.90% (13.20% - 17.00%)
adipoIR n=4801	IR (AdipoIR)			0.086 (0.076 - 0.100)	0.470 (0.439 - 0.500)	0.555 (0.526 - 0.580)	15.54% (13.61% - 18.00%)
H2-IR$_{log}$ n=8054	IR (HOMA2-IR>2.5)	Elevated SUA (SUA>5.5 mg/dL)	Visceral fat (METS-VF>7.18)	0.032 (0.026 - 0.040)	0.267 (0.237 - 0.290)	0.296 (0.268 - 0.330)	10.98% (8.84% - 13.00%)
AdipoIR$_{log}$ n=4801	IR ($\log_{10}$(adipoIR))			0.049 (0.039 - 0.380)	0.293 (0.250 - 0.330)	0.342 (0.298 - 0.340)	14.28% (11.21% - 18.00%)
H2-IR' n=8054	Visceral fat (METS-VF)	Elevated SUA	IR (HOMA2-IR)	0.014 (0.008 - 0.020)	0.271 (0.255 - 0.290)	0.285 (0.270 - 0.300)	4.88% (3.06% - 7.00%)
AdipoIR' n=4801			IR (adipoIR)	0.033 (0.024 - 0.040)	0.372 (0.349 - 0.390)	0.405 (0.384 - 0.430)	8.13% (5.91% - 10.00%)
H2-IR'$_{log}$ n=8054	Visceral fat (METS-VF>7.18)	Elevated SUA (SUA>5.5mg/dL)	IR (HOMA2-IR>2.5)	0.014 (0.009 - 0.060)	0.192 (0.166 - 0.220)	0.206 (0.180 - 0.230)	6.87% (4.57% - 9.00%)
adipoIR'$_{log}$ n=4801			IR ($\log_{10}$(adipoIR))	0.016 (0.010 - 0.020)	0.165 (0.109 - 0.230)	0.181 (0.119 - 0.250)	8.75% (5.97% - 12.00%)

Table 6.2: Mediation analyses for general bidirectional mechanisms.*Abbreviations*: ACME: Average Causal Mediation Effect. ADE: Average Direct Effect. AdipoIR: Adipose Insulin Resistance index. H2-IR: Homeostatic Model for Insulin Resistance. METS-VF: Metabolic Score for Visceral Fat.

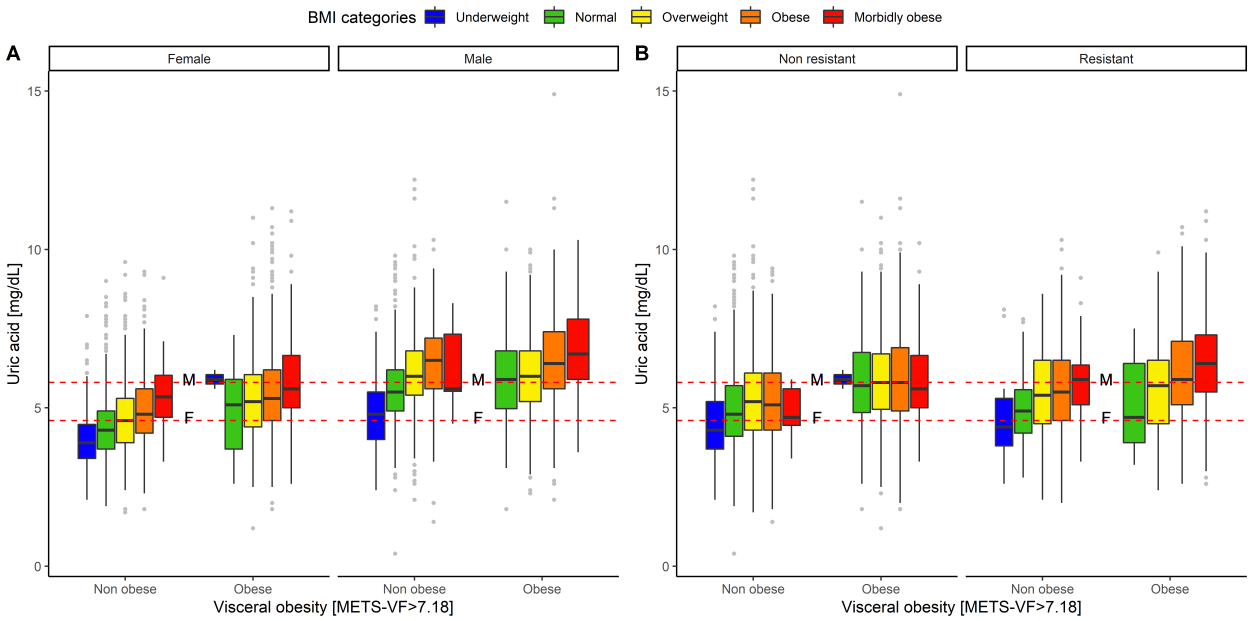


Figure 6.1: Box plot graph comparing serum uric acid values against visceral obesity in male, female, insulin resistant, and non-insulin resistant population for NHANES-ENSANUT cohort. Horizontal lines represent limit for elevated SUA in males (M, 5.9 mg/dL) and in females (F, 4.7 mg/dL). Insulin resistance was established as HOMA2-IR>2.5. *Abbreviations*: METS-VF: Metabolic Score for Visceral Fat.

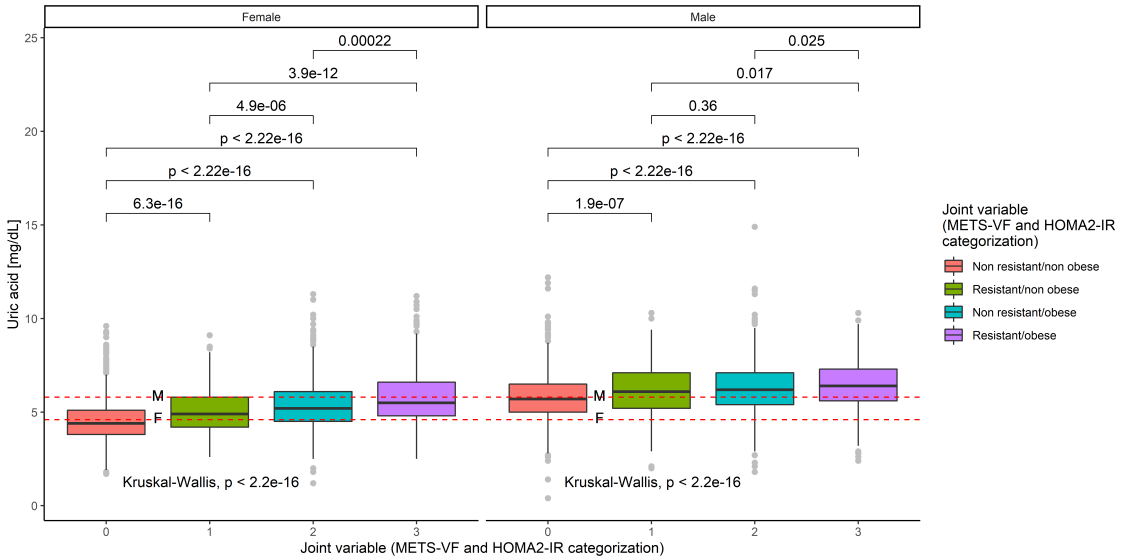
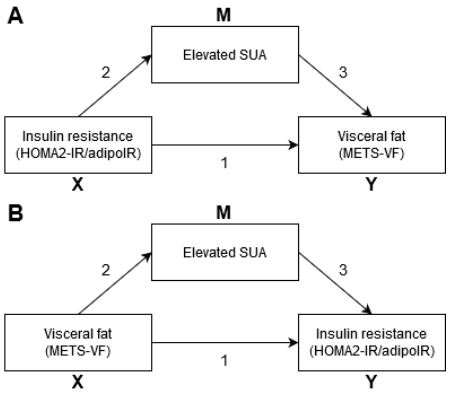
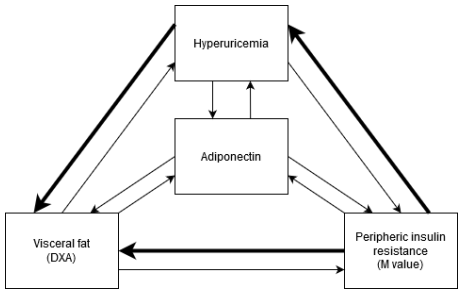


Figure 6.2: Box plot graph comparing serum uric acid values against joint variable in male and female population for NHANES-ENSANUT cohort. Horizontal lines represent limit for elevated SUA in males (M, 5.9 mg/dL) and in females (F, 4.7 mg/dL). *Abbreviations*: HOMA2-IR: Homeostatic Assessment Model for Insulin Resistance. METS-VF: Metabolic Score for Visceral Fat.



(a) Bidirectional mediation analysis.



(b) Confirmatory mediation analysis.

Figure 6.3: Mediation diagrams depicting general and confirmatory mediation analyses.*Abbreviations*: adipoIR: Adipose Insulin Resistance index. DXA: Dual X-Ray absorptiometry. HOMA2-IR: Homeostatic Assessment Model for Insulin Resistance. SUA: Serum uric acid.

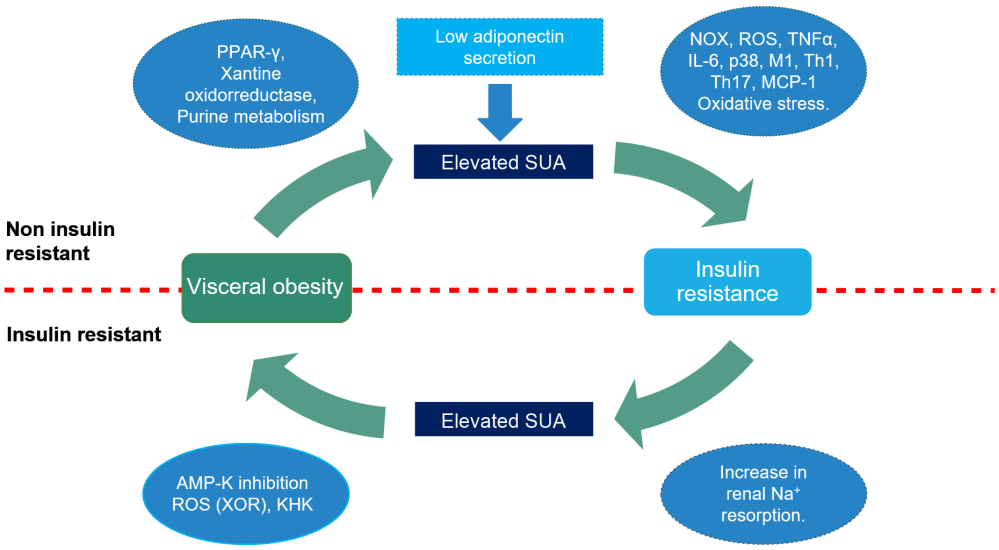


Figure 6.4: Illustration summary of possible biochemical and immunological causal players inside proposed mechanisms.

7. Appendices

7.1. Appendix 1: Supplementary methods

7.1.1. Fasting biochemical and anthropometric evaluations in ENSANUT

Subjects were weighed on calibrated scales and height was determined with a floor scale stadiometer; BMI was calculated as weight in kg divided by the squared product of height in meters. Blood was obtained between 8:00 and 9:00 am after 8-12 hour fast. Plasma glucose concentration was measured by an automated glucose analyzer (Yellow Springs Instruments Co.), serum insulin concentration was measured by using a chemiluminescent immunoassay (Beckman Coulter Access 2), and A1c levels using high performance liquid chromatography (HPLC) (Variant II Turbo, BIORAD). Lipid concentrations (cholesterol, triglycerides, and HDL cholesterol), uric acid, creatinine, and hepatic enzymes were measured using colorimetric assays (Unicel DxC 600 Synchron Clinical System Beckman Coulter). LDL-cholesterol was calculated with the Friedewald equation when triglycerides were <250 mg/dL.

7.1.2. Euglycemic-hyperinsulinemic clamp and body composition analysis in SIGMA cohort

In the SIGMA cohort, we performed a one-stage EHC in subjects who underwent a 12-hour fast; subjects with T2D were instructed to suspend treatment three days in advance. The study was not performed if fasting glucose concentrations were >250 mg/dL. A priming dose of 200 mU/m^2/min of insulin was infused for 5 min, followed by 100 mU/m^2/min for 5 min; subsequently, insulin was infused at a rate of 50 mU/m^2 body surface area (BSA)/min. Euglycemia (∼100 mg/dL) was maintained by a variable infusion of 20% dextrose; arterialized blood samples using a hot box were obtained every 10 minutes during the final 30 minutes of the EHC to determine glucose and insulin concentrations. Insulin sensitivity was determined by the glucose infusion rate or M-value during the final 30 minutes adjusted for fat-free mass (MFFM) obtained by dual X-ray energy absorciometry (DXA) with a GE Lunar iDXA® densitometer.[47]

7.2. Appendix 2: Supplementary Tables

	General population	Elevated SUA	Normal SUA	p-values
n	1940	1051	889	
Age [years]	47.11 (±15.95)	48.32 (±16.39)	46.09 (15.51)	0.002
Male sex	734 (100%)	506 (68.94%)	228 (31.06%)	<0.001
Glucose [mg/dL]	110.22 (±49.06)	105.04 (±34.25)	114.61 (±58.40)	<0.001
Insulin [µU/mL]	11.47 (10.66)	12.30 (11.79)	10.78 (9.55)	0.002
TGL [mg/dL]	209.12 (167.58)	219.96 (149.66)	199.95 (180.93)	0.008
c-HDL [mg/dL]	38.61 (±10.45)	37.02 (±10.19)	39.95 (±10.49)	<0.001
Total cholesterol [mg/dL]	189.45 (40.65 ±)	189.96 (40.05 ±)	189.02 (41.17 ±)	**0.611**
BMI [kg/m^2]	28.63 (±5.54)	29.57 (±5.54)	27.84 (±5.41)	<0.001
WHR	0.61 (±0.09)	0.62 (±0.09)	0.60 (±0.09)	<0.001
METS-VF	6.96 (±0.57)	7.11 (±0.52)	6.84 (±0.58)	<0.001
Visceral obese [METS-VF>7.18]	784 (100%)	444 (56.63%)	340 (43.37%)	<0.001
HOMA2-IR	1.65 (3.23)	1.71 (3.30)	1.60 (3.16)	**0.442**
HOMA2-%S	111.77 (96.56)	108.22 (94.39)	114.77 (98.31)	**0.135**
HOMA2-%B	95.43 (58.10)	100.27 (59.18)	91.33 (56.88)	0.001
Insulin resistant [HOMA2-IR>2.5]	282 (100%)	145 (51.42%)	137 (48.58%)	**0.634**
Type 2 diabetes	100 (100%)	51 (51.00%)	49 (49.00%)	**0.841**

Table 7.1: General characteristics of ENSANUT cohort. Patients with elevated SUA are those with a serum concentration greater than 5.5 mg/dL. *Abbreviations*: BMI: Body Mass Index. cHDL: colesterol high density lipoprotein. HOMA2-IR: Homeostatic Model for Insulin Resistance. HOMA2-S: Homeostatic Model for Insulin Resistance for pancreatic β cell sensitivity. HOMA2-B: Homeostatic Model for Insulin Resistance for functionality of pancreatic β cells. HUA: Hyperuricemia. n-HUA: Non-hyperuricemia. Insulin resistance. METS-VF: Metabolic Score for Visceral Fat. WHR: Waist-height ratio.

	General population	Elevated SUA	Normal SUA	p-values
n	226	94	132	
Age [years]	39.84 (±14.70)	42.84 (±15.42)	37.70 (±13.83)	0.011
Male sex	53 (100%)	36 (67.92%)	17 (32.08%)	<0.001
Glucose [mg/dL]	98.77 (±21.91)	103.38 (±25.83)	95.48 (±18.02)	0.012
Insulin [µU/mL]	8.45 (8.57)	11.10 (10.38)	7.00 (6.05)	<0.001
TGL [mg/dL]	120.50 (73.50)	134.00 (77.25)	110.00 (64.25)	0.001
cHDL [mg/dL]	45.32 (±11.82)	40.27 (±9.12)	48.92 (±12.23)	<0.001
Total cholesterol [mg/dL]	177.56 (±33.63)	177.50 (±34.89)	177.60 (±32.84)	**0.983**
VAT mass [g]	1168.36 (±860.25)	1502.61 (±842.62)	930.34 (±793.56)	<0.001
Visceral obese [DXA>1000g]	124 (100%)	69 (56.10%)	55 (43.90%)	<0.001
BMI [kg/m^2]	31.29 (±10.50)	33.85 (±10.81)	29.46 (±9.92)	0.002
WHR	0.72 (±0.17)	0.72 (±0.18)	0.71 (±0.17)	**0.633**
METS-VF	7.11 (±0.84)	7.46 (±0.53)	6.87 (±0.94)	<0.001
Visceral obese [METS-VF>7.18]	142 (100%)	72 (50.70%)	70 (9.30%)	<0.001
Adiponectin [µg/mL]	7.76 (5.20)	6.82 (3.86)	9.43 (6.06)	<0.001
Leptin [µg/mL]	18.72 (38.05)	19.17 (69.01)	18.64 (22.49)	**0.908**
Mvalue [mg/min/kg]	5.97 (4.78)	5.08 (4.53)	6.70 (4.98)	0.001
Insulin resistant [Mvalue<4.6]	87 (100%)	45 (52.33%)	42 (47.67%)	<0.001
HOMA2-IR	1.12 (1.16)	1.51 (1.58)	0.94 (0.81)	<0.001
HOMA2-%B	91.40 (50.28)	96.15 (60.95)	89.75 (44.17)	**0.256**
HOMA2-%S	88.40 (84.75)	66.10 (71.93)	106.00 (82.35)	<0.001
Insulin resistant [HOMA2-IR>2.5]	40 (17.70%)	24 (60.00%)	16 (40.00%)	0.004
Type 2 Diabetes	102 (100%)	53 (51.96%)	49 (48.04%)	<0.001

Table 7.2: General characteristics of SIGMA cohort. Patients with elevated SUA are those with a serum concentration greater than 5.5 mg/dL. *Abbreviations*: BMI: Body Mass Index. cHDL: colesterol high density lipoprotein. HOMA2-IR: Homeostatic Model for Insulin Resistance. HOMA2-S: Homeostatic Model for Insulin Resistance for pancreatic β cell sensitivity. HOMA2-B: Homeostatic Model for Insulin Resistance for functionality of pancreatic β cells. METS-VF: Metabolic Score for Visceral Fat. WHR: Waist-height ratio.

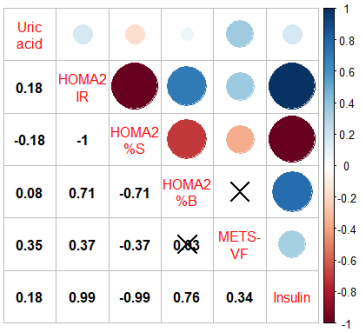
Parameter	AUC	Cut-off	Se	Sp	PPV	NPV
IR (Male) (HOMA2-IR)	0.571 (0.571 - 0.621)	6.1	59.1% (55.2% - 62.9%)	57.3% (55.6% - 59.0%)	22.1% (20.9% - 25.0%)	87.2% (85.3% - 87.9%)
IR (Female) (HOMA2-IR)	0.647 (0.625 - 0.669)	4.8	65.6% (62.09% - 69.0%)	56.5% (54.9% - 58.1%)	24.4% (23.2% - 27.4%)	88.5% (86.8% - 89.1%)
IR (Male) (adipoIR)	0.631 (0.597 - 0.665)	7.0	38.2% (33.0% - 43.7%)	81.9% (80.2% - 83.6%)	25.7% (23.6% - 30.3%)	89.0% (86.6% - 90.1%)
IR (Female) (adipoIR)	0.709 (0.679 - 0.739)	5.0	67.3% (61.7% - 72.5%)	63.3% (61.2% - 65.3%)	20.8% (19.4% - 25.2%)	93.1% (91.4% - 93.6%)
Visceral obesity (Male) (METS-VF)	0.618 (0.599 - 0.637)	6.4	47.2% (44.5% - 49.9%)	70.3% (68.4% - 72.1%)	47.3% (45.1% - 50.0%)	70.2% (67.9% - 72.0%)
Visceral obesity (Female) (METS-VF)	0.704 (0.686 - 0.722)	4.8	71.3% (68.5% - 74.0%)	60.8% (59.0% - 62.5%)	38.2% (36.6% - 41.5%)	86.1% (84.5% - 87.0%)

Table 7.3: ROC curves estimated with categorized variables in joint population NHANES-ENSANUT against SUA as a continuous predictor. *Abbreviations*: AdipoIR: Adipose Insulin Resistance index. AUC: Area under curve. HOMA2-IR: Homeostatic Model for Insulin Resistance. IR: Insulin resistance. METS-VF: Metabolic Score for Visceral Fat. NPV: Negative predictive value. PPV: Positive predictive value. Se: Sensibility. Sp: Specificity.

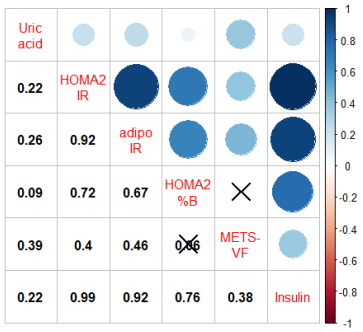
Causality model	Efector	Mediator	Result	ACME	ADE	Total effect	% Mediated
1	IR (Mvalue*kg)	Elevated SUA	Visceral fat (DXA)	-0.003 (-0.006 - 0.000)	-0.035 (-0.042 - -0.030)	-0.038 (-0.045 - -0.030)	8.60% (2.85% - 16.00%)
2	Visceral fat (DXA)		IR (Mvalue*kg)	-0.008 (-0.016 - 0.000)	-0.058 (-0.095 - -0.040)	-0.066 (-0.103 - -0.040)	12.52% (3.66% - 23.00%)
3	Elevated SUA	Adiponectin	Visceral fat (DXA)	0.319 (0.134 - 0.540)	0.766 (0.332 - 1.240)	1.085 (0.673 - 1.550)	29.40% (12.90% - 55.00%)
4	Visceral fat (DXA)		Elevated SUA	0.020 (0.003 - 0.004)	0.069 (0.031 - 0.110)	0.089 (0.056 - 0.120)	22.19% (4.01% - 49.00%)
5	IR (Mvalue*kg)		Visceral fat (DXA)	-0.104 (-0.170 - -0.050)	-0.666 (-0.810 - -0.530)	-0.771 (-0.898 - -0.650)	13.50% (6.37% - 23.00%)
6	Visceral fat (DXA)		IR (Mvalue*kg)	-0.047 (-0.088 - -0.010)	-0.390 (-0.491 - -0.300)	-0.437 (-0.531 - -0.350)	10.70% (2.08% - 21.00%)
7	IR (Mvalue*kg)		Elevated SUA	-0.027 (-0.126 - -0.010)	-0.077 (0.425 - -0.030)	-0.104 (-0.151 - -0.050)	25.90% (7.53% - 57.00%)
8	Elevated SUA		IR (Mvalue*kg)	-0.221 (-0.379 - -0.090)	-0.500 (-0.854 - -0.160)	-0.721 (-1.096 - -0.360)	30.60% (13.50% - 60.00%)
9	IR (Mvalue*kg)	Joint mediator	Visceral fat (DXA)	-0.126 (-0.191 - -0.070)	-0.645 (-0.790 - -0.510)	-0.771 (-0.898 - -0.65)	16.32% (8.84% - 26.00%)
10	Visceral fat (DXA)		IR (Mvalue*kg)	-0.055 (-0.101 - -0.021)	-0.382 (-0.485 - -0.290)	-0.437 (-0.531 - -0.350)	12.52% (3.23% - 23.00%)

Table 7.4: Mediation analyses network for confirmatory subanalysis. *Abbreviations*: ACME: Average Causal Mediation Effect. ADE: Average Direct Effect. DXA: Dual X-Ray absorptiometry. IR: Insulin resistance.

7.3. *Appendix 3: Supplementary figures*



(a) NHANES-ENSANUT joint cohort.



(b) NHANES adipoIR cohort.

Figure 7.1: Correlation matrices for different cohorts. *Abbreviations*: AdipoIR: Adipose Insulin Resistance index. HOMA2-IR: Homeostatic Model for Insulin Resistance. HOMA2-S: Homeostatic Model for Insulin Resistance for pancreatic β cell sensitivity. HOMA2-B: Homeostatic Model for Insulin Resistance for functionality of pancreatic β cells. METS-VF: Metabolic Score for Visceral Fat.

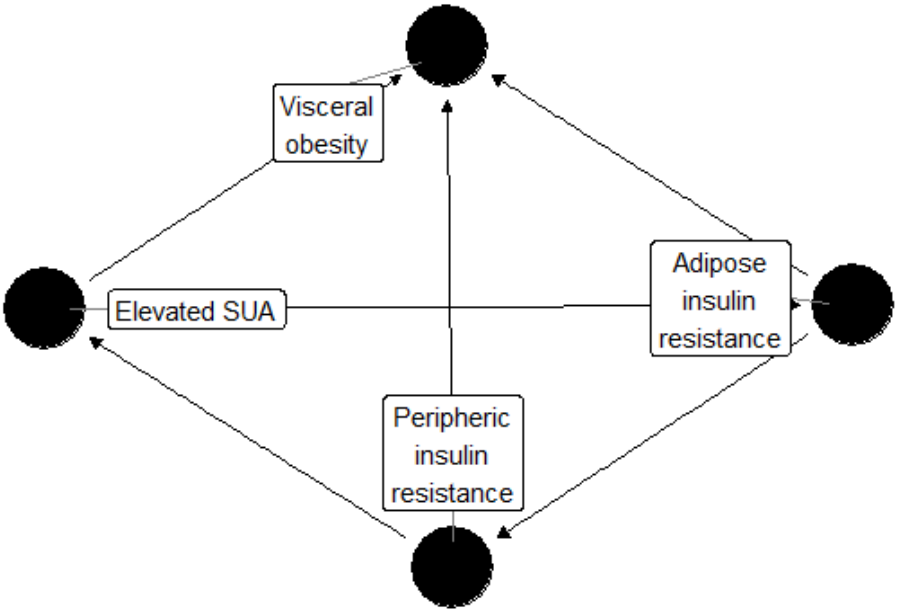


Figure 7.2: Directed Acyclic Graph which illustrates the strongest direction of causality for the mechanism.

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