1 Appendices

1.1 Appendix 1: Supplementary methods

1.1.1 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.

1.1.2 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 ($\sim$100 mg/dL) was maintained by a variable infusion of 20% dextrose; arterialized blood samples using a hot box were obtained every 10 minutes during the final 30 minutes of the EHC to determine glucose and insulin concentrations. Insulin sensitivity was determined by the glucose infusion rate or M-value during the final 30 minutes adjusted for fat-free mass (MFFM) obtained by dual X-ray energy absorciometry (DXA) with a GE Lunar iDXA$^{®}$ densitometer.[?]

1.2 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/m²]	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 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 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 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		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)	Adiponectin	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 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.

1.3 Appendix 3: Supplementary figures
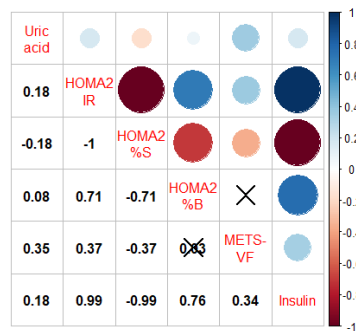
(a) NHANES-ENSANUT joint cohort.
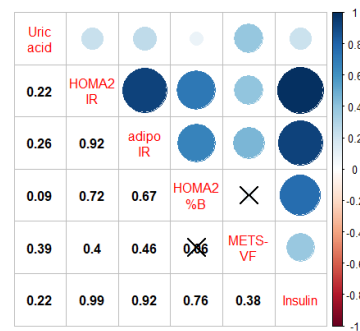
(b) NHANES adipoIR cohort.

Figure 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.
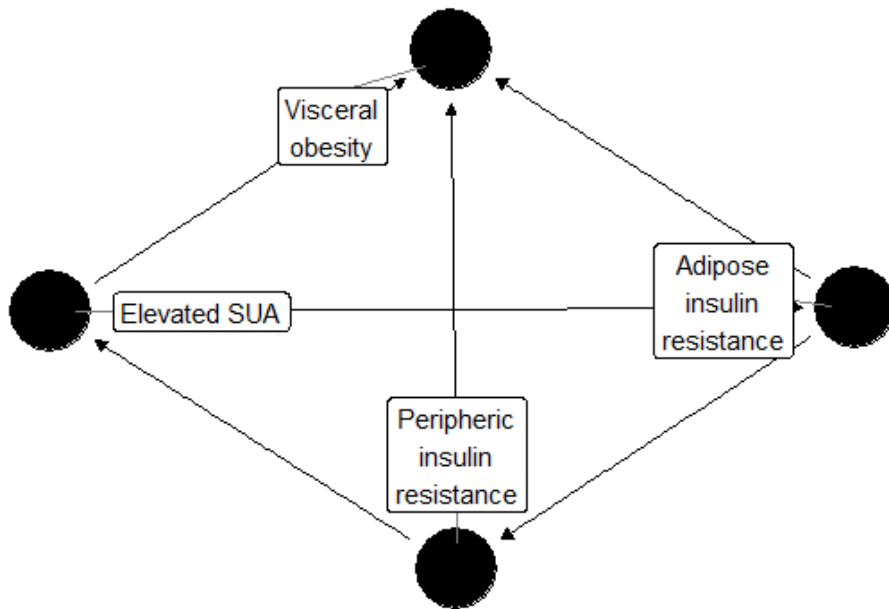

Figure 2: Directed Acyclic Graph which illustrates the strongest direction of causality for the mechanism.