Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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Proteomic and Metabolomic Mediators of Visceral Adiposity-Associated Chronic Kidney Disease: A Large-Scale Prospective Cohort Study

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Objectives : Visceral adipose tissue (VAT) is metabolically distinct from subcutaneous fat, but mechanistic pathways linking VAT expansion to chronic kidney disease (CKD) remain poorly characterized.
Methods : This study included 343,654 UK Biobank participants who had no CKD at baseline. The main predictor was VAT which was estimated using sex-specific prediction models validated against dual-energy X-ray absorptiometry. Associations between VAT and incident CKD were assessed using multivariable-adjusted Cox proportional hazards models. Mediation analyses (four-way decomposition) were conducted in proteomics (n=29,756) and metabolomics (n=77,945) subcohorts to identify mediating proteins and metabolites.
Results : Over a median follow-up of 13.8 years, 12,429 participants (3.6%) developed CKD. VAT showed a graded association with CKD risk. The adjusted hazard ratios (95% confidence intervals) for incident CKD were 1.16 (1.08–1.24), 1.32 (1.24–1.41), and 1.66 (1.56–1.76) for VAT quartiles 2 through 4, respectively. Proteomics analysis identified 35 protein mediators (explaining up to 71% of the VAT-CKD association) enriched in pathways related to angiogenesis, inflammation, and extracellular matrix remodeling. The adipocyte-derived protein FABP4 emerged as the predominant proteomic mediator. Metabolomics identified nine metabolite mediators, with docosahexaenoic acid and lipid unsaturation providing mechanistic evidence of lipid dysregulation.
Conclusions : Higher VAT was independently associated with an increased risk of incident CKD, with distinct proteomic and metabolomic signatures implicating angiogenic dysregulation, inflammation, and impaired lipid metabolism. These findings highlight VAT as a modifiable cardiometabolic risk factor and potential therapeutic target for CKD prevention.

Table.png

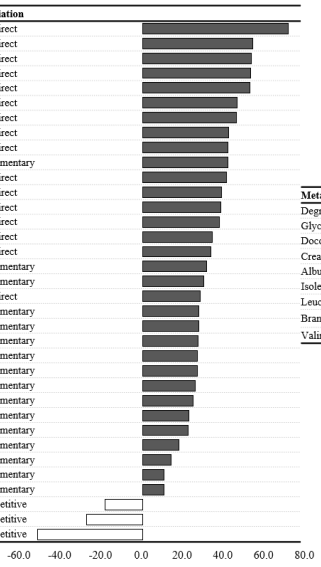
Table 1. The HRs for incident CKD according to the quartiles of VAT

	VAT	Events, n (%)	Person-years	Incidence rate 10,000 person-years	Unadjusted		Adjusted	
					HR (95% CI)	P	HR (95% CI)	P
Total	Quartile 1	1,366 (1.6)	1,177,759	11.6 (11.0-12.2)	reference		reference	
	Quartile 2	2,256 (2.6)	1,174,432	19.2 (18.5-20.0)	1.66 (1.55 - 1.78)	<0.001	1.16 (1.08 - 1.24)	<0.001
	Quartile 3	3,323 (3.9)	1,169,298	28.4 (27.5-29.4)	2.46 (2.31 - 2.62)	<0.001	1.32 (1.24 - 1.41)	<0.001
	Quartile 4	5,481 (6.4)	1,157,850	47.3 (46.1-48.6)	4.13 (3.90 - 4.39)	<0.001	1.66 (1.56 - 1.76)	<0.001
					P for trend	<0.001	P for trend	<0.001
Female	Quartile 1	549 (1.2)	605,476	9.1 (8.3-9.9)	reference		reference	
	Quartile 2	1,062 (2.4)	603,823	17.6 (16.6-18.7)	1.94 (1.75 - 2.15)	<0.001	1.28 (1.15 - 1.42)	<0.001
	Quartile 3	1,599 (3.6)	601,500	26.6 (25.3-27.9)	2.94 (2.67 - 3.24)	<0.001	1.43 (1.29 - 1.58)	<0.001
	Quartile 4	2,862 (6.5)	595,041	48.1 (46.4-49.9)	5.37 (4.90 - 5.88)	<0.001	1.89 (1.72 - 2.08)	<0.001
					P for trend	<0.001	P for trend	<0.001
Male	Quartile 1	817 (2.0)	572,283	14.3 (13.3-15.3)	reference		reference	
	Quartile 2	1,197 (2.9)	570,609	21.0 (19.8-22.2)	1.47 (1.35 - 1.61)	<0.001	1.09 (1.00 - 1.19)	0.056
	Quartile 3	1,724 (4.1)	567,799	30.4 (29.0-31.8)	2.14 (1.97 - 2.33)	<0.001	1.25 (1.15 - 1.36)	<0.001
	Quartile 4	2,619 (6.3)	562,809	46.5 (44.8-48.4)	3.30 (3.05 - 3.57)	<0.001	1.48 (1.36 - 1.61)	<0.001
					P for trend	<0.001	P for trend	<0.001

Note: Cox proportional hazard regression model was performed. The primary outcome was incident CKD, defined as the presence of ICD-10 or OPCS-4 codes in any primary care or inpatient hospital records. Adjustment for age, sex, smoking, history of hypertension, diabetes, and cardiovascular disease, eGFR, hs-CRP, total cholesterol. In the female and male subgroups, the adjustment for sex was excluded in the analysis. P for linear trend was calculated by treating quartiles as a continuous variable.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high sensitivity-C reactive protein; ICD, international classification of disease; OPCS, operating procedure codes supplement; VAT, visceral adipose tissue.

Table.png

Proteins	Proportion (%)	Mediation
FABP4	71.3	Indirect
ADM	54.1	Indirect
FSTL3	53.3	Indirect
CLMP	53.2	Indirect
COL6A3	52.6	Indirect
ADAMTS15	46.3	Indirect
COLEC12	46.0	Indirect
LGALS9	42.1	Indirect
MFAP5	41.9	Indirect
HSPG2	41.8	Complementary
HGF	41.3	Indirect
RBP5	38.7	Indirect
TNFRSF11A	38.5	Indirect
TGFBR2	37.7	Indirect
SEMA3F	34.3	Indirect
LAIR1	33.4	Indirect
IL1RN	31.3	Complementary
THY1	30.0	Complementary
SNCG	28.3	Indirect
EPHA1	27.6	Complementary
HNMT	27.6	Complementary
RARRES2	27.1	Complementary
LGALS1	27.1	Complementary
ASGR1	27.0	Complementary
DPT	26.0	Complementary
KRT18	24.7	Complementary
FGF21	22.6	Complementary
CPM	22.5	Complementary
IL18R1	17.9	Complementary
GOLM2	14.0	Complementary
ITGA5	10.7	Complementary
THBS4	10.5	Complementary
CHGB	-18.3	Competitive
COL4A1	-27.4	Competitive
IGFBP2	-51.4	Competitive



Metabolomics	Proportion (%)	Mediation
Degree of Unsaturation	13.7	Complementary
Glycoprotein Acetyls	9.2	Complementary
Docosahexaenoic Acid	6.9	Complementary
Creatinine	4.9	Complementary
Albumin	2.8	Complementary
Isoleucine	-13.7	Competitive
Leucine	-15.3	Competitive
Branched-Chain Amino Acids	-18.1	Competitive
Valine	-18.5	Competitive