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Relationship between bmi and glomerular filtration rate in a large cohort initiating a weight loss program: differential contributions of fat mass, fat-free mass, and abdominal fat compartments

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Abstract

Background The relationship between BMI and chronic kidney disease is controversial, likely due to the inability of BMI to accurately define body composition and adipose tissue distribution. Our objective was to evaluate the synergistic contribution of fat-free mass, fat mass, visceral (VAT) and subcutaneous (SAT) adipose tissue, to glomerular filtration rate (GFR) in a large cohort of subjects.

Methods A cross-sectional study of 9704 subjects (72% female, median age 47y, median BMI 28.1 kg/m^2) was carried out. Each patient underwent an anthropometric assessment (weight, height, waist circumference, % of body fat by body skinfolds), an ultrasound measurement of VAT and SAT and blood sampling to measure metabolic syndrome (MS) parameters and serum creatinine. GFR was estimated using the EPI-CKD equation. MS was defined according to the harmonized criteria.

Results Among 9,704 subjects, 61.1% had a normal renal function, while 29.3% reported a reduction, from slightly to severely. The BMI was initially negatively associated with GFR in the univariate model (β = -0.32, 95% CI: -0.39, -0.25), but after adjusting for %body fat, the association was lost. We then split the BMI into its two components, Fat Mass Index (FMI) and Fat Free Mass Index (FFMI), and observed that FMI (β = -1.23, 95% CI: -1.35, -1.12) and FFMI (β = 0.79, 95% CI: 0.65, 0.92) were associated with a decrease and an increase in GFR, respectively. VAT (β = -1.83, 95% CI: -2.00, -1.67) and SAT (β = 3.21, 95% CI: 2.86, 3.57) were independently associated with a decrease and an increase in GFR, respectively. Similar results were obtained when studying the association between BMI, body composition, adipose tissue distribution, and the risk of reduced GFR (<90 ml/min/1.73 m^2). Stratification by sex and MS did not substantially alter the results. A significant association between VAT and reduced GFR was observed only in women.

Conclusions Our study highlights the importance of considering body composition and fat distribution when assessing renal function.

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Keywords Obesity, Chronic kidney disease, BMI, Glomerular filtration rate, Body composition, Visceral and subcutaneous fat, Metabolic syndrome

Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by a gradual and irreversible decline in kidney function. It has become an escalating global public health concern due to its increasing prevalence. Current estimates indicate that approximately 8–16% of the global population is affected by CKD [1]. This issue is further compounded by the association of CKD with an elevated risk of cardiovascular disease and increased mortality rates [2, 3]. The glomerular filtration rate (GFR) is defined as the volume of blood filtered by the glomeruli per unit time and is considered the gold standard for assessing kidney function [4].

Obesity is a significant risk factor for the development and progression of CKD [5]. However, the relationship between obesity and CKD is complex and multifaceted. Numerous studies have established that obesity significantly contributes to both the onset of CKD [6–8] and progression to end-stage renal disease [9]. Nonetheless, some research indicates that a higher body mass index (BMI), the most commonly used metric for defining obesity, is associated with hyperfiltration [10, 11], a condition in which the kidney filters blood at a rate faster than normal, which can lead to kidney damage over time [12]. In contrast, other work has failed to detect an association between BMI and the development and progression of CKD [13, 14]. Finally, additional work found that high BMI was associated with a reduced risk of deterioration of renal function in diabetic patients with stage 3 or 4 CKD [15].

The discrepancy between these findings may be attributed to a methodological issue, specifically the inability of BMI to differentiate between fat mass and fat-free mass. It has indeed been suggested that these two components contribute differently to kidney function [16]. Moreover, BMI does not reflect fat distribution, which is another crucial factor in renal function impairment risk. Visceral adipose tissue (VAT) has more pronounced metabolic and inflammatory effects than subcutaneous adipose tissue (SAT) and can significantly impact renal function [17]. Excess VAT is a major risk factor for the development of metabolic syndrome, hypertension, and type 2 diabetes [18] — all of which are well-established risk factors for CKD and reduced GFR. In contrast, the role of SAT is less clear, with some evidence suggesting it may have a protective effect against cardiometabolic risk [19].

These observations suggest that a more detailed assessment of body composition, beyond BMI, may be necessary to fully understand the complex relationship between obesity and CKD and to guide more effective preventive and therapeutic strategies. Nevertheless, studies that have evaluated the synergistic contributions of body composition and adipose tissue distribution to GFR, while considering the metabolic profile, are limited.

Therefore, the aim of this epidemiological study is to investigate the contributions of fat mass, lean mass, and adipose tissue distribution to glomerular filtration rate in a large cohort of subjects with a wide range of BMI values.

Materials and methods

Study design and participants selection

A total of 11,364 patients spontaneously attending the International Center for Nutritional Status Assessment (ICANS) at the University of Milan were recruited between September 2010 and September 2022. To be enrolled, patients had to be at least 18 years old. Participants were excluded if they had a diagnosis of diabetes, cardiovascular disease, cancer within the last 5 years, neurological or gastrointestinal diseases, or any history of cardiac, liver, or pulmonary failure, as well as those taking anti-obesity medications or drugs known to cause lipodystrophy (such as steroids and antiretroviral medications). 1,660 subjects met at least one of the exclusion criteria and were therefore excluded. The final analysis was conducted on 9,704 subjects. Each patient underwent a medical examination to evaluate their medical history, current pharmacological treatments, and engagement in at least two hours per week of structured physical activity. An abdominal ultrasound was performed during the medical examination to quantify SAT and VAT. Participants also underwent a nutritional examination during which anthropometric measurements were taken. Additionally, a blood sample was obtained from each subject for the measurement of hematochemical parameters necessary for the definition of metabolic syndrome and for the calculation of GFR. The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and each participant read and signed a written informed consent form. The Ethics Committee of the University of Milan approved the study procedures (study protocol No. 23/2016).

Anthropometric measurements

Anthropometric measurements were collected following international guidelines [20]. Body weight and height were measured using a calibrated column scale with an approximation of 0.1 kg and a stadiometer with an approximation of 0.5 cm, respectively. Participants were asked to wear only underwear and socks during these measurements. The Body Mass Index (BMI) was calculated using the formula: weight (kg)/height^2 (m^2) and classified according to the World Health Organization (WHO) guidelines [21]. Waist circumference (WC) and skinfold thicknesses (triceps, biceps, subscapular, and suprailiac) were also recorded. WC was measured with an accuracy of 0.5 cm using a nonelastic tape placed at the midpoint between the last rib and the iliac crest. The thicknesses of the four skinfolds were measured using a skinfold caliper (Holtan Ltd., Crymych, Wales). Skinfold measurements were taken at specific anatomical landmarks on the non-dominant side of each patient. Each skinfold was measured three times, and the mean value was used for analysis. Body density was assessed using sex- and age-specific Durnin and Womersley equations [22]. The percentage of body fat (BF) was calculated using Siri's formula: %BF = (4.95/body density—4.50) × 100 [23]. Fat mass index (FMI) and fat-free mass index (FFMI) were calculated using the formula: fat mass or fat-free mass (kg)/height^2 (m^2). The intra- and inter-operator coefficient of variation were 2.5% and 2.9%, respectively [24].

Abdominal ultrasound

A trained physician conducted ultrasound measurements of abdominal VAT and SAT using a Logiq 3 Pro ultrasound system. This system was equipped with both a 7.5 MHz linear probe and a 3.5 MHz convex-array probe (GE Healthcare, Chicago, IL, United States). Measurements were taken 1 cm above the umbilicus at the end of expiration. SAT was measured with the 7.5 MHz linear probe and defined as the distance from the epidermis to the external surface of the rectus abdominis muscle. VAT, measured with the 3.5 MHz convex-array probe, was defined as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominis muscle [25, 26]. The within-day intra-operator coefficient of variation for repeated measures of VAT and SAT in our laboratory is 0.8% [26].

Blood pressure and laboratory assessment

A physician measured blood pressure according to international guideline [27]. Blood samples were collected from each patient between 6:30 and 9:30 a.m., while fasting. The samples were analyzed on the same day. The following parameters were measured: blood glucose, HDL cholesterol, triglycerides, and creatinine. GFR was estimated using the CKD-EPI equation [28], which incorporates four main parameters: creatinine, age, sex, and ethnicity.

GFR values were classified as follows [29]:

- GFR ≥ 90 ml/min/1.73 m^2: Normal or high renal function
- GFR 89–60 ml/min/1.73 m^2: Slightly decreased renal function
- GFR 59–45 ml/min/1.73 m^2: Slightly to moderately decreased renal function
- GFR 44–30 ml/min/1.73 m^2: Moderately to severely decreased renal function
- GFR 29–15 ml/min/1.73 m^2: Severely decreased renal function
- GFR < 15 ml/min/1.73 m^2: Kidney failure

Metabolic syndrome

Metabolic syndrome (MS) was diagnosed according to the harmonized criteria [30]. MS was identified based on the presence of at least three of the following criteria:

- Waist circumference ≥ 102 cm in men or ≥ 88 cm in women
- Fasting blood glucose ≥ 100 mg/dl or use of antidiabetic therapy
- Fasting triglycerides ≥ 150 mg/dl or use of hypotriglyceridemic therapy
- HDL cholesterol < 40 mg/dl in men or < 50 mg/dl in women of use of or drug treatment for reduced HDL
- Blood pressure ≥ 130/85 mmHg or use of antihypertensive medication

Statistical analysis

Continuous variables are presented as median and interquartile range due to the non-normal distribution of some variables. Categorical variables are expressed as frequency and percentage. We used multiple linear regression models with different levels of adjustment to isolate the independent association of BMI and various body composition components on GFR. Six models with the following predictor combinations were utilized:

1. Univariate: exposure variables: BMI (continuous, kg/m.^{2})
2. Multivariate: exposure variables: BMI (continuous, kg/m.^{2}), BF (continuous, %)
3. Multivariate: exposure variables: FMI (continuous, kg/m^2), FFMI (continuous, kg/m^2).

4. Multivariate: exposure variables: FMI (continuous, kg/m^2), FFMI (continuous, kg/m^2), VAT (continuous, cm), SAT (continuous, cm).
5. Multivariate: exposure variables: FMI (continuous, kg/m^2), FFMI, (continuous, kg/m^2), VAT (continuous, cm), SAT (continuous, cm); covariates: MS (categorical; 0 = no, 1 = yes)
6. Multivariate: exposure variables: FMI (continuous, kg/m^2), FFMI (continuous, kg/m.^{2}), VAT (continuous, cm), SAT (continuous, cm); covariates: sex (categorical; 0 = woman, 1 = man), impaired fasting glucose (categorical; 0 = no, 1 = yes), high blood pressure (categorical; 0 = no, 1 = yes), high triglycerides (categorical; 0 = no, 1 = yes), low HDL cholesterol (categorical; 0 = no, 1 = yes), structured physical activity (categorical; 0 = no, 1 = yes)

The first model included only BMI to assess the crude association. In the second model, we adjusted for BF percentage to isolate the role of body composition. The third model replaced BMI and fat mass (%) with FMI and FFMI to clarify the specific contribution of each body mass component. The fourth model further incorporated VAT and SAT to evaluate the impact of abdominal fat distribution. Finally, the fifth and sixth models accounted for MS, its components, and physical activity as confounders, ensuring the robustness of the associations with body composition and abdominal fat distribution. We conducted a collinearity analysis assessed using the Variance Inflation Factor (VIF) for each predictor and for the overall model to rule out the presence of multicollinearity. All VIF values were consistently < 5, indicating a low degree of collinearity and ensuring that the estimated coefficients are not inflated or misleading. We used the Akaike Information Criterion (AIC) to assess the model's goodness of fit and to reduce the risk of overadjustment due to the inclusion of unnecessary variables. Lower AIC values indicate a better balance between model complexity and fit to the data. Homoscedasticity and potential violations of the linearity assumption between continuous predictors and the dependent variable were assessed both graphically, using residual-versus-fitted plots, and through statistical tests. The Breusch-Pagan test was applied to check for heteroscedasticity. No violations of homoscedasticity were found. Multivariable fractional polynomials were used to model nonlinear associations between continuous predictors and outcomes. However, no significant improvements were observed. The association between reduced GFR (< 90 ml/min/1.73 m^2) and the various predictors of interest was assessed using logistic regression models with the combinations of predictors described above. The goodness of fit (GOF) of the models was assessed using the Hosmer-Lemeshow test. However, no significant results were found, indicating that the model adequately fits the observed data. None of the subjects had missing values for the variables of interest or the confounding factors. To explore potential interaction effects and reduce the risk of overadjustment, stratified analyses were conducted based on sex and MS status. Stratification by sex was performed because sex is already included in the CKD-EPI equation, and its addition to the model could lead to excessive adjustment. Similarly, stratification by MS was conducted as this condition may act as an effect modifier, influencing the association between the studied variables and the outcome. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA software, version 18.5 (StataCorp LP).

Results

The final sample included 9704 subjects (72% women) with a median age of 47 years (IQR: 37–55 years old) and a median BMI of 28.1 (IQR 25.1–31.8 kg/m^2). Table 1 report the characteristics of the patients.

61.1% of the patients had a GFR between 90 and 120 ml/min/1.73 m^2. 29.3% of the subjects had a reduced GFR (< 90 ml/min1.73 m^2), with 27.7% exhibiting a slight reduction in GFR (60–89 ml/min1.73 m^2), 1.3% showing a moderate reduction (30–59 ml/min1.73 m^2), and 0.1% presenting a severe reduction in GFR (< 30 ml/min1.73 m^2).

Table 2 shows the association of BMI, body composition and abdominal fat distribution with GFR. In the univariate model (M1), BMI was significantly associated with a reduction in GFR (β = −0.32, 95% CI: −0.39, −0.25). However, after including the percentage of fat mass (M2), the association of BMI with GFR was lost, suggesting that the relationship between BMI and GFR was driven by differences in body composition. We then split BMI into its two components (FMI and FFMI) (M3). An increase of one unit in FMI was associated with a reduction of 1.23 ml/min/1.73 m^2 (95% CI: −1.35, −1.12) in GFR, while an increase of one unit in FFMI was associated with an increase of 0.79 ml/min/1.73 m^2 (95% CI: 0.65, 0.92) in GFR. Incorporating abdominal adipose tissue distribution (M4) revealed an inverse relationship between VAT and GFR (β = −1.83, 95% CI: −2.00, −1.67), while SAT was linked to an increase in GFR (β = 3.21, 95% CI: 2.86, 3.57). The inclusion of MS (M5) and its components (M6) did not alter the association between body composition, abdominal fat distribution, and GFR.

Table 3 shows the association of BMI, body composition and abdominal fat distribution with the risk of reduced GFR. In the univariate model (M1), BMI was significantly associated with an increased risk of low GFR (OR = 1.02, 95% CI: 1.01, 1.03). However, after including

Table 1 Characteristics of patients

	Women			Men			Total		
	n = 7012			*n* = 2692			*n* = 9704		
	Median	P25	P75	Median	P25	P75	Median	P25	P75
Age (years)	47	37	55	47	38	56	47	37	55
BMI (kg/m^2)	27.5	24.5	31.2	29.6	26.9	32.7	28.1	25.1	31.8
Body fat (%)	39	35.4	41.8	31.4	27.5	35.3	37.2	32.4	40.8
FMI (kg/m^2)	10.7	8.8	13	9.3	7.6	11.3	10.3	8.4	12.5
FFMI (kg/m^2)	16.8	15.6	18.4	20.2	18.9	21.8	17.7	16	19.9
Waist circumference (cm)	91.5	83.2	101	105.2	97.4	113	95.3	86	105
VAT (cm)	3.9	2.8	5.6	6.9	5	8.7	4.6	3.1	6.7
SAT (cm)	2.6	1.8	3.4	2.5	1.8	3.3	2.6	1.8	3.4
Glucose (mg/dl)	92	86	99	98	91	105	94	87	101
Triglycerides (mg/dl)	82	61	113	113	80	162	89	65	126
HDL (mg/dl)	64	55	75	48	41	56	59	49	71
Systolic blood pressure (mm Hg)	120	110	130	130	120	135	120	110	130
Diastolic blood pressure (mm Hg)	75	70	80	80	76	86	80	70	82
Creatinine (mg/dl)	0.7	0.6	0.8	0.9	0.8	1	0.8	0.7	0.9
GFR (ml/min/1.73 m^2)	101.4	88.1	112	97.9	86.2	108	100.4	87.5	111
	N	%		N	%		N	%	
BMI classes									
Normal weight	2066	29.5		314	11.7		2380	24.5	
Overweight	2736	39		1125	41.8		3861	39.8	
Obesity	2210	31.5		1253	46.5		3463	35.7	
High waist circumference (102 cm M/88 cm F)	4321	61.6		1627	60.4		5948	61.3	
High triglycerides (150 mg/dl or treatment)	948	13.5		826	30.7		1774	18.3	
High blood pressure (130/85 mm Hg or treatment)	2581	36.8		1755	65.2		4336	44.7	
Impaired fasting glucose (100 mg/dl or treatment)	1611	23		1142	42.4		2753	28.4	
Low HDL (< 50 F/40 M mg/dl or treatment)	1125	16		631	23.4		1756	18.1	
Metabolic syndrome	1473	21		1153	42.8		2626	27.1	
GFR stages									
Normal or increased GFR (> 90 ml/min/1.73 m^2)	5049	72		1810	67.2		6859	70.7	
Mild reduction in GFR (60–89 ml/min/1.73 m^2)	1864	26.6		823	30.6		2687	27.7	
Moderate reduction in GFR (45–59 ml/min/1.73 m^2)—A	79	1.1		48	1.8		127	1.3	
Moderate reduction in GFR (30–44 ml/min/1.73 m^2)—B	14	0.2		10	0.4		24	0.2	
Severe reduction in GFR (15–29 ml/min/1.73 m^2)	4	0.1		1	0		5	0.1	
Kidney failure (GFR < 15 ml/min/1.73 m^2 or dialysis)	2	0		0	0		2	0	

Abbreviations: *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue

the BF percentage (M2) the association was lost. Splitting BMI in FMI e FFMI (M3), we observed that an increase of one unit in FMI was associated with a 9% increase in the risk of reduced GFR (OR = 1.09, 95% CI: 1.07, 1.11), while an increase of one unit in FFMI was associated with a 6% reduction in the risk of reduced GFR (OR = 0.94, 95% CI: 0.93, 0.96). Including abdominal fat distribution (M4), we observed that VAT (OR = 1.17, 95% CI: 1.14, 1.20) and SAT (OR = 0.72, 95% CI: 0.69, 0.76) were associated with a higher and lower risk of reduced GFR, respectively. The inclusion of MS (M5) and its components (M6) did not change the direction of these associations.

We also conducted a stratified analysis by sex and MS. BMI and GFR showed opposite linear associations depending on the presence of metabolic syndrome (Table 4, M1). However, after adjusting for BF percentage, BMI was positively associated with GFR (M2). Separating FMI and FFMI (M3) and including abdominal adipose tissue distribution (M4) confirmed previous findings, except for the loss of association between VAT

Table 2 Contribution of body composition and abdominal fat distribution to glomerular filtration rate

	M1	M2	M3	M4	M5	M6
BMI (kg/m^2)	−0.32***	0.05				
	[−0.39,−0.26]	[−0.03,0.12]				
Body fat (%)		−0.59***				
		[−0.64,−0.53]				
FMI (kg/m^2)			−1.23***	−1.41***	−1.31***	−1.30***
			[−1.35,−1.12]	[−1.55,−1.27]	[−1.44,−1.16]	[−1.43,−1.16]
FFMI (kg/m^2)			0.79***	1.35***	1.42***	1.49***
			[0.65,0.92]	[1.19,1.51]	[1.26,1.57]	[1.34,1.65]
VAT (cm)				−1.83***	−1.57***	−1.28***
				[−2.00,−1.67]	[−1.75,−1.40]	[−1.45,−1.10]
SAT (cm)				3.21***	3.14***	3.01***
				[2.86,3.57]	[2.78,3.50]	[2.66,3.36]
Metabolic syndrome (yes)					−4.33***	
					[−5.17,−3.50]	
Impaired fasting glucose (yes)						−3.08***
						[−3.80,−2.35]
High triglycerides (yes)						−1.73***
						[−2.60,−0.86]
High blood pressure (yes)						−7.23***
						[−7.92,−6.55]
Low HDL cholesterol (yes)						1.60***
						[0.74,2.46]
Structured physical activity (≥ 2 h/w)						−2.55***
						[−3.18,−1.93]
Constant	108.06***	118.59***	97.53***	89.81***	87.52***	89.22***
	[106.11,110.02]	[116.43,120.75]	[95.35,99.70]	[87.47,92.16]	[85.15,89.89]	[86.90,91.54]
Observations	9704	9704	9704	9704	9704	9704
VIF	-	1.38	1.34	1.85	1.8	1.50
AIC	82,504	82,162	82,192	81,213	81,110	80,591

Values are regression coefficients and 95% confidence intervals obtained from multivariable linear regression models

M1: univariate: BMI (continuous)

M2: multivariate: M1 + total body fat (continuous)

M3: multivariate: FMI (continuous), FFMI (continuous)

M4: multivariate: M3 + VAT (continuous), SAT (continuous)

M5: multivariate: M4 + metabolic syndrome (discrete)

M6: multivariate: M4 + impaired fasting glucose (discrete), high blood pressure (discrete), high triglycerides (discrete), low HDL-cholesterol (discrete) and physical activity (discrete)

Abbreviations: *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VIF* Variance Inflation Factor, *AIC* Akaike Information Criterion

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

and GFR in men. Including MS components and physical activity (M5) did not alter the direction of associations.

The risk of reduced GFR was initially inversely associated with BMI only in individuals with metabolic syndrome (Table 5, M1), but after adjusting for BF percentage, this was observed across all groups. FMI and FFMI separation (M3) and abdominal fat distribution inclusion (M4) confirmed unstratified analysis results, except for the loss of VAT-GFR risk association in men. After including MS components and physical activity (M5), the FMI-reduced GFR association disappeared only in women with MS, while other associations remained unchanged.

Table 3 Contribution of body composition and abdominal fat distribution to the risk of reduced glomerular filtration rate

	M1	M2	M3	M4	M5	M6
BMI (kg/m^2)	1.02***	1.00				
	[1.01,1.03]	[0.99,1.01]				
Body fat (%)		1.05***				
		[1.04,1.06]				
FMI (kg/m^2)			1.09***	1.12***	1.11***	1.11***
			[1.07,1.11]	[1.10,1.14]	[1.09,1.13]	[1.09,1.13]
FFMI (kg/m^2)			0.94***	0.90***	0.89***	0.88***
			[0.93, 0.96]	[0.87,0.92]	[0.87,0.91]	[0.86,0.90]
VAT (cm)				1.17***	1.14***	1.11***
				[1.14,1.20]	[1.11,1.17]	[1.09,1.14]
SAT (cm)				0.72***	0.73***	0.73***
				[0.69,0.76]	[0.69,0.77]	[0.69,0.77]
Metabolic syndrome (yes)					1.52***	
					[1.35,1.70]	
Impaired fasting glucose (yes)						1.31***
						[1.18,1.46]
High triglycerides (yes)						1.15
						[1.02,1.31]
High blood pressure (yes)						1.96***
						[1.77,2.17]
Low HDL cholesterol (yes)						0.88
						[0.78,1.00]
Structured physical activity (at least 2 h/w)						1.34***
						[1.22,1.47]
Observations	9704	9704	9704	9704	9704	9704
VIF	-	1.26	1.24	1.71	1.69	1.71
AIC	11,716	11,614	11,628	11,211	11,262	10,960

Values are odds ratios and 95% confidence intervals obtained from multivariable logistic regression models

M1: univariate: BMI (continuous)

M2: multivariate: M1 + total body fat (continuous)

M3: multivariate: FMI (continuous), FFMI (continuous)

M4: multivariate: M3 + VAT (continuous), SAT (continuous)

M5: multivariate: M4 + metabolic syndrome (discrete)

M6: multivariate: M4 + impaired fasting glucose (discrete), high blood pressure (discrete), high triglycerides (discrete), low HDL-cholesterol (discrete) and physical activity (discrete)

Abbreviations: *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VIF* Variance Inflation Factor, *AIC* Akaike Information Criterion

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Discussion

In this large epidemiological study, we investigated the relationship between BMI and GFR. Although BMI was generally associated with reduced GFR, after adjustment for BF, BMI was found to be no longer associated or associated with increased GFR. This change indicates that BMI alone may not adequately capture the complex interaction between the various components of body composition and their respective impact on renal function. Therefore, we separately assessed the contributions of fat-free mass and fat mass, observing that they had different effects on GFR. On one hand, fat mass was associated with a reduction in GFR, while on the other hand, fat-free mass contributed to an increase in GFR. Additionally, the distribution of abdominal adipose tissue was independently associated with GFR, with different contributions depending on the adipose tissue compartment. VAT contributed to a reduction in GFR, particularly in women,

Table 4 Contribution of body composition and abdominal fat distribution to glomerular filtration rate after stratification by sex and metabolic syndrome

	Women									
	No metabolic syndrome					Metabolic syndrome				
	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5
BMI (kg/m^2)	−0.18***	0.94***				0.20***	0.53***			
	[−0.27,−0.09]	[0.82,1.06]				[0.01,0.39]	[0.31,0.75]			
Body fat (%)		−1.41***					−1.08***			
		[−1.52,−1.29]					[−1.48,−0.69]			
FMI (kg/m^2)			−2.88***	−3.45***	−3.14***			−1.59***	−1.46***	−1.18**
			[−3.10,−2.67]	[−3.74,−3.17]	[−3.42,−2.86]			[−2.20,−0.98]	[−2.12,−0.80]	[−1.84,−0.52]
FFMI (kg/m^2)			3.72***	3.46***	3.21***			2.18***	1.80***	1.59***
			[3.43,4.01]	[3.17,3.75]	[2.93,3.50]			[1.53,2.83]	[1.18,2.41]	[0.99,2.19]
VAT (cm)				−0.68***	−0.62***				−0.89***	−0.85***
				[−0.98,−0.38]	[−0.91,−0.32]				[−1.35,−0.42]	[−1.32,−0.37]
SAT (cm)				3.71***	3.43***				4.25***	4.08***
				[3.21,4.20]	[2.95,3.90]				[3.26,5.24]	[3.09,5.07]
Impaired fasting glucose (yes)					−3.39***					−1.67
					[−4.65,−2.12]					[−3.87,0.54]
High triglycerides (yes)					0.29					−2.09*
					[−2.09,1.51]					[−4.05,−0.13]
High blood pressure (yes)					−5.92***					−7.82***
					[−6.90,−4.93]					[−10.34,−5.32]
Low HDL cholesterol (yes)					2.30**					0.12
					[0.87,3.73]					[1−88,2.13]
Structured physical activity (≥ 2 h/w)					−3.03***					−0.95
					[−3.83, −2.23]					[−2.63,0.73]
Constant	106.17***	128.18***	68.18***	71.49***	76.17***	86.46***	121.17***	73.97***	71.54***	80.15***
	[103,64,108.71]	[124.96,131.39]	[64.72,71.63]	[68.02,74.95]	[72.71,79.62]	[80.25,92.67]	[106.75,135.59]	[67.02,80.91]	[64.91,78.17]	[72.49,87.80]
Observations	5539	5539	5539	5539	5539	1473	1473	1473	1473	1473
VIF	-	2.04	2.30	2.45	1.78	-	1.36	2.80	2.34	1.77
AIC	46,842	46,267	46,135	45,864	45,634	12,636	12,596	12,584	12,451	12,405
	Men									
	No metabolic syndrome					Metabolic syndrome				
	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5
BMI (kg/m^2)	−0.23*	1.12***				0.47***	1.22***			
	[−0.44,−0.02]	[0.84,1.40]				[0.26,0.68]	[0.99,1.45]			
Body fat (%)		−1.35***					−1.35***			

Table 4 (continued)

		[−1.53,−1.18]					[−1.58,−1.12]			
FMI (kg/m^2)			−2.29***	−2.82***	−2.62***			−1.42***	−1.66***	−1.51***
			[−2.63,−1.94]	[−3.28,−2.36]	[−3.07,−2.15]			[−1.81,−1.04]	[−2.09,−1.24]	[−1.93,−1.08]
FFMI (kg/m^2)			2.45***	1.90***	1.83***			2.65***	2.01***	1.94***
			[2.02,2.88]	[1.45,2.35]	[1.38,2.29]			[2.24,3.06]	[1.56,2.46]	[1.50,2.40]
VAT (cm)				−0.35	−0.39				−0.09	−0.07
				[−0.78, 0.08]	[−0.82,−0.04]				[−0.53,0.36]	[−0.51,0.38]
SAT (cm)				4.17***	3.96*				3.64***	3.47***
				[3.30,5.05]	[3.09,4.84]				[2.80,4.48]	[2.63,4.34]
Impaired fasting glucose (yes)					−2.24*					−1.81
					[−3.98,−0.49]					[−3.88,0.25]
High triglycerides (yes)					−2.54					0.38
					[−4.92,−0.16]					[−1.57,2.33]
High blood pressure (yes)					−4.51***					−5.03**
					[−6.08,−2.93]					[−7.93,−2.13]
Low HDL cholesterol (yes)					1.60					1.94*
					[−1.16,4.35]					[0.05,3.84]
Structured physical activity (≥ 2 h/w)					−2.43**					−0.82
					[−3.97,−0.88]					[−2.55,0.91]
Constant	106.17***	106.53***	69.44***	76.34***	80.81***	78.43***	99.81***	52.70***	59.37***	64.39***
	[103,64,108.71]	[101.02,112.04]	[61.73,77.16]	[68.62,84.07]	[72.93,88.72]	[71.43,85.43]	[92.09,107.53]	[45.04,60.37]	[51.55,67.19]	[55.47,73.30]
Observations	1539	1539	1539	1539	1539	1153	1153	1153	1153	1153
VIF	-	1.89	1.33	1.86	1.45	-	1.36	1.28	1.51	1.86
AIC	12,947	12,729	12,755	12,652	12,612	9734	9612	9610	9530	9514

Values are regression coefficients and 95% confidence intervals obtained from multivariable linear regression models

M1: univariate: BMI (continuous)

M2: multivariate: M1 + total body fat (continuous)

M3: multivariate: FMI (continuous), FFMI (continuous)

M4: multivariate: M3 + VAT (continuous), SAT (continuous)

M5: multivariate: M4 + impaired fasting glucose (discrete), high blood pressure (discrete), high triglycerides (discrete), low HDL-cholesterol (discrete) and physical activity (discrete)

Abbreviations: *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VIF* Variance Inflation Factor, *AIC* Akaike Information Criterion

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 5 Contribution of body composition and abdominal fat distribution to the risk of reduced glomerular filtration rate after stratification by sex and metabolic syndrome

	Women									
	No metabolic syndrome					Metabolic syndrome				
	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5
BMI (kg/m^2)	1.01	0.93***				0.98*	0.96**			
	[1.00,1.02]	[0.91,0.94]				[0.96,1.00]	[0.94,0.98]			
Body fat (%)		1.11***					−1.06**			
		[1.10,1.14]					[1.02,1.11]			
FMI (kg/m^2)			1.24***	1.30***	1.26***			1.08*	−1.08*	1.06
			[1.19,1.28]	[1.24,1.36]	[1.21,1.32]			[1.01,1.15]	[1.00,1.16]	[0.98,1.14]
FFMI (kg/m^2)			0.75***	0.76***	0.78***			0.88***	0.90**	0.92*
			[0.71,0.79]	[0.72,0.80]	[0.74,0.82]			[0.82,0.94]	[0.84,0.97]	[0.85,0.98]
VAT (cm)				1.10***	1.10***				1.07*	1.07*
				[1.05,1.15]	[1.05,1.15]				[1.01,1.13]	[1.01,1.13]
SAT (cm)				0.67***	0.69***				0.68***	0.69***
				[0.62,0.73]	[0.63,0.74]				[0.60,0.77]	[0.61,0.78]
Impaired fasting glucose (yes)					1.38**					1.07
					[1.14,1.68]					[0.82,1.40]
High triglycerides (yes)					0.29					1.07
					[0.94,1.27]					[0.84,1.37]
High blood pressure (yes)					1.77***					1.62**
					[1.52,2.05]					[1.17,2.24]
Low HDL cholesterol (yes)					0.72*					0.95
					[0.55,0.94]					[0.75,1.23]
Structured physical activity (at least 2 h/w)					1.40***					1.23
					[1.23,1.59]					[0.99,1.54]
Observations	5539	5539	5539	5539	5539	1473	1473	1473	1473	1473
VIF	-	1.73	1.92	2.21	1.66	-	1.25	2.22	2.10	1.40
	6215	6063	6037	5904	5809	1979	1972	1971	1911	1905
	Men									
	No metabolic syndrome					Metabolic syndrome				
	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5
BMI (kg/m^2)	1.02	0.91***				0.96**	0.90***			
	[1.00,1.05]	[0.88,0.95]				[0.936,0.99]	[0.87,0.93]			
Body fat (%)		1.12***					1.11***			
		[1.09,1.16]					[1.08,1.15]			
FMI (kg/m^2)			1.21***	1.27***	1.25***			1.12***	1.15***	1.14***

Table 5 (continued)

			[1.15,1.28]	[1.19,1.37]	[1.17,1.35]			[1.06,1.18]	[1.08,1.22]	[1.07,1.21]
FFMI (kg/m^2)			0.81***	0.85***	0.85***			0.80***	0.83***	0.84***
			[0.76,0.87]	[0.79,0.91]	[0.79,0.92]			[0.75,0.85]	[0.78,0.89]	[0.77,0.90]
VAT (cm)				1.04	1.04				0.99	0.99
				[0.97,1.11]	[0.97,1.12]				[0.94,1.06]	[0.93,1.06]
SAT (cm)				0.67***	0.68***				0.72***	0.74***
				[0.57,0.78]	[0.58,0.79]				[0.64,0.83]	[0.65,0.84]
Impaired fasting glucose (yes)					1.25					1.24
					[0.94,1.66]					[0.91,1.68]
High triglycerides (yes)					1.43					1.04
					[0.99,2.08]					[0.79,1.36]
High blood pressure (yes)					1.78***					1.69*
					[1.39,2.28]					[1.04,2.77]
Low HDL cholesterol (yes)					1.03					0.82
					[0.66,1.62]					[0.62,1.07]
Structured physical activity (at least 2 h/w)					1.44**					1.07
					[1.12,1.87]					[0.83,1.38]
Observations	1539	1539	1539	1539	1539	1153	1153	1153	1153	1153
VIF	-	1.65	1.27	1.73	1.43	-	1.30	1.23	1.44	1.30
AIC	1840	1770	1779	1741	1720	1532	1491	1488	1463	1460

Values are odds ratios and 95% confidence intervals obtained from multivariable logistic regression models

M1: univariate: BMI (continuous)

M2: multivariate: M1 + total body fat (continuous)

M3: multivariate: FMI (continuous), FFMI (continuous)

M4: multivariate: M3 + VAT (continuous), SAT (continuous)

M5: multivariate: M4 + impaired fasting glucose (discrete), high blood pressure (discrete), high triglycerides (discrete), low HDL-cholesterol (discrete) and physical activity (discrete)

Abbreviations: *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VIF* Variance Inflation Factor, *AIC* Akaike Information Criterion

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

whereas SAT contributed to an increase in GFR. These results remained substantially unchanged after consideration for MS, its components and physical activity.

Obesity is defined as an excessive accumulation of adipose tissue that can negatively impact health [31]. In clinical practice and research, BMI is commonly used to define obesity. However, BMI does not differentiate between fat-free mass and fat mass, nor does it provide information on fat distribution. This limitation often leads to inconsistent and controversial results. Previous studies have reported varying findings regarding the relationship between BMI and GFR. Our study confirms that this discrepancy may stem from the fact that the two main components of body composition—fat mass and fat-free mass—have opposing effects on GFR.

We found that total fat mass and VAT are independently associated with a reduction in GFR. It is well established that excess adipose tissue, particularly VAT, is associated with an increased risk of MS [32], which in turn contributes to a reduction in GFR [33]. Specifically, consistent with previous studies [34, 35], we observed that elevated blood pressure was the main MS component to be associated with reduced GFR, as it was consistently associated despite adjustments and stratifications. Interestingly, our results reveal that fat mass and VAT are associated with reduced GFR despite adjustment for metabolic profile. This suggests that both contribute to kidney function not only through the MS but also through direct mechanisms. Indeed, adipose tissue is a significant source of inflammatory mediators, oxidative stress, adipocyte-specific proteins (such as adiponectin, leptin, and resistin), and elements of the renin-angiotensin-aldosterone system. All of these factors would appear to contribute to the development of obesity-associated kidney disease [36, 37]. Interestingly, when we stratified our analysis by sex and MS the inverse association between VAT and GFR was confirmed only in women, whereas in men this association was absent. In addition, in women with MS, the association between FMI and reduced GFR was no longer significant, suggesting that, in this subgroup, abdominal fat distribution, particularly VAT, may be the main determinant of renal function decline. This result aligns with a previous study, which found that each unit increase in VAT was associated with a greater likelihood of fatty liver in women compared to men [38]. Our findings also suggest that an increase in SAT is linked to an increase in GFR. SAT is generally considered less metabolically active than VAT, which makes its contribution to cardiometabolic risk somewhat controversial. Some researchers argue that the expandability of SAT, particularly in the leg region, is beneficial for metabolic health and the preservation of insulin sensitivity [19]. It is plausible that individuals with greater SAT expandability are less likely to store excess energy as VAT, thereby mitigating the negative impact of VAT on kidney health. However, it should be noted that the magnitude of the association between SAT and GFR suggests that high SAT levels could lead to glomerular hyperfiltration. Over time, if left untreated, this could increase the risk of GFR reduction and the development of CKD. This phenomenon may partially explain the higher CKD risk observed among individuals with obesity and MS compared to those with so-called metabolically healthy obesity [39], who generally exhibit greater SAT expandability [19]. Nonetheless, these individuals still have a higher risk of CKD compared to healthy normal-weight individuals [40].

The relationship between fat-free mass and GFR is of opposite sign to that of fat mass. Our findings indicate that higher fat-free mass is associated with increased GFR and a lower risk of reduced GFR. This result can be attributed to several mechanisms. Greater muscle mass has been previously associated to a better insulin sensitivity, lower metabolic syndrome risk, and reduced systemic inflammation [41, 42]. Given that insulin resistance and other metabolic complications are well-known contributors to kidney damage, the healthier metabolic characteristics associated with increased muscle mass may help to prevent the decline in kidney function. Additionally, recent research has identified skeletal muscle as an endocrine organ that releases peptides known as myokines. These myokines have been shown to influence kidney function, a process referred to as muscle–kidney crosstalk [43]. Notably, irisin, a significant myokine, has been found to enhance kidney energy metabolism and protect against kidney damage in animal models. The beneficial effect of lean mass on renal function may explain the increased risk of CKD observed in individuals with sarcopenic obesity compared to those with obesity alone [44, 45].

Our study has certain limitations. First, body composition was assessed using skinfold measurements, which are not considered the gold standard and only provide an estimate of fat-free mass and fat mass quantities. However, in routine clinical practice, gold standard methods are often impractical due to their cost, time requirements, and need for highly specialized personnel. Skinfold measurement, in contrast, is quicker and simpler to perform. Moreover, at our center, the intra- and inter-operator coefficient of variation is very low [46]. Second, ultrasound, used for evaluating abdominal adipose tissue, is also not a gold standard method. Reference methods such as computed tomography and magnetic resonance imaging are not feasible as routine clinical examinations. Nonetheless, several studies have reported good correlations between ultrasound measurements and adipose

areas measured by gold standard methods [25, 47]. Third, the GFR was estimated using a predictive formula rather than direct measurement. However, we employed the CKD-EPI equation, which has been validated and is recommended by the KDIGO guidelines for assessing kidney function [29]. Fourth, we recruited subjects who voluntarily decided to start a dietary program aimed at weight loss or maintenance. This aspect may introduce selection bias, as participants might have specific characteristics (e.g., greater health awareness or a different metabolic profile) that influence the relationship between body composition and renal function. Fifth, the lack of consideration of dietary habits may represent potential confounders in the observed associations. Adherence to specific dietary patterns, such as the Mediterranean diet, could influence metabolic health and kidney function, potentially contributing to residual confounding. Sixth, although we accounted for key medications affecting metabolic parameters and renal function, including lipid-lowering drugs, antihypertensives, and antidiabetic medications, we acknowledge that the influence of other unconsidered medications cannot be ruled out. This may represent a source of residual confounding in our findings. Finally, as with any observational study, potential residual confounding could not be ruled out.

Our study also has several strengths. Firstly, the large sample size allowed us to obtain more precise estimates, as demonstrated by the narrow confidence intervals. Secondly, this is one of the few studies that have examined the contributions of body composition, adipose tissue distribution, and metabolic profile within the same population. This comprehensive approach enabled us to determine the independent effects of each predictor.

In conclusion, our study highlights the importance of considering body composition and fat distribution when assessing renal function. BMI alone does not adequately reflect the nuanced contributions of different body compartments to kidney health. Our study suggests that a more comprehensive evaluation of body composition, including the assessment of fat-free mass and the distribution of adipose tissue, is crucial for a more accurate understanding of the relationship between obesity and renal function. This approach could enhance the development of targeted strategies for the prevention and management of chronic kidney disease.

Abbreviations

BF	Body fat
CKD	Chronic kidney disease
FFMI	Fat-free mass index
FMI	Fat mass index
GFR	Glomerular filtration rate
MS	Metabolic syndrome
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue
WC	Waist circumference

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Authors' contributions
Conceptualization, A.L. and A.B.; methodology, A.L., S.B. and A.B.; formal analysis, A.L.; investigation, F.M., L.V., R.D., A.F., F.S. and A.L.; data curation, A.L.; writing—original draft preparation, A.L.; writing—review and editing, A.L. and A.B. All authors have read and agreed to the published version of the manuscript.

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Data availability
The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and each participant read and signed a written informed consent form. The Ethics Committee of the University of Milan approved the study procedures (study protocol No. 23/2016).

Competing interests
The authors declare no competing interests.

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