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Original Article

Menopause is associated with a reduction in glomerular filtration rate, independent of body composition and metabolic syndrome

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A B S T R A C T

Objectives: This study examines the relationship between menopause and glomerular filtration rate (GFR), independent of body composition and metabolic profile, both known risk factors for GFR decline.
Study design: Cross-sectional study involving 3918 women aged 40–55 years.
Main outcome measures: Participants provided information about medical history, menopausal status, and current medication use. Participants underwent nutritional and anthropometric assessments. Blood samples were collected to measure biochemical parameters. Menopause was defined as no menstrual cycle for 12 months or more. GFR was estimated using the EPI-CKD formula, and metabolic syndrome was identified using harmonized criteria. Premenopausal and postmenopausal women were matched by age, body composition, and metabolic syndrome factors to assess the menopause–GFR association.
Results: Postmenopausal women exhibited higher fat mass, lower fat-free mass, and reduced GFR compared with premenopausal women. They also had higher rates of hypertension, impaired fasting glucose, and metabolic syndrome. After matching for age, fat mass index, fat-free mass index, and components of the metabolic syndrome, menopause was independently associated with a GFR reduction of 2.32 ml/min/1.73m^2 (95 % CI: −3.81, −0.83). Additionally, menopause was linked to a 51 % higher risk of GFR <90 ml/min/1.73m^2 (OR = 1.51; 95 % CI 1.12, 2.02).
Conclusions: Menopause represents an independent risk factor for GFR decline, beyond the effects related to body composition and metabolic risk factors.

Abbreviations

BF	body fat
BMI	body mass index
CKD	chronic kidney disease
FFMI	fat-free mass index
FMI	fat mass index
GFR	glomerular filtration rate
NO	nitric oxide
RAAS	Renin–Angiotensin–Aldosterone System
ROS	reactive oxygen species

Keywords

Menopause
Glomerular filtration rate
Renal function
Body composition
Metabolic syndrome

1. Introduction

Menopause represents a critical phase in a woman's life, marked by the cessation of ovarian function and the consequent decline in sex hormone levels. This endocrine transition, typically occurring between ages 45 and 52, triggers a range of physiological changes that directly

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impact long-term health [1,2].

Menopause is characterized by distinct physiological patterns, including a reduction in basal metabolic rate [3], increased body weight, and a redistribution of adipose tissue with a tendency toward visceral fat accumulation [4,5]. Additionally, metabolic changes are observed, such as reduced insulin sensitivity [6], elevated blood lipid levels [7,8], and an increase of blood pressure [9,10]. Consequently, postmenopausal women face a higher risk of obesity [11], metabolic syndrome [12], cardiovascular disease [13], and diabetes [14], all of which are known risk factors for alterations in glomerular filtration rate (GFR) [15] that may contribute to the development of chronic kidney disease (CKD).

Indeed, it has been suggested that postmenopausal women have an increased risk of CKD [16]. However, it remains unclear whether this elevated risk can be attributed solely to increased cardiometabolic risk. Some observations suggest that the decline in estrogen levels during menopause may have a direct impact on renal dysfunction through mechanisms involving hemodynamic alterations and changes in inflammatory and oxidative processes [17].

Estrogen has been widely recognized for its protective role in kidney health, as demonstrated in both animal models [18] and observational studies in women [19,20]. In particular, experimental data highlight its ability to reduce glomerulosclerosis in ovariectomized mice following estrogen replacement therapy [21,22]. These findings are further supported by epidemiological studies showing an increased risk of CKD in women undergoing bilateral oophorectomy before the age of 45 [23], as well as studies demonstrating beneficial effects of estrogen on renal function [24,25]. However, conflicting evidence exists, with some studies reporting a potential detrimental effect of estrogen on kidney health [26,27].

It is important to acknowledge that the regulation of glomerular dynamics is a complex process involving multiple interacting factors, not solely estrogen. The inflammatory status, modulated by various cytokines, significantly impacts kidney function. Menopause-related changes in estrogen levels can influence cytokine production and activity, contributing to altered renal hemodynamics and potentially impacting GFR [28]. The renin-angiotensin-aldosterone system (RAAS), a critical regulator of blood pressure and fluid balance, also plays a key role in kidney function. Hormonal fluctuations during menopause, as well as metabolic disturbances, can affect RAAS activity, thereby influencing GFR [29].

It is therefore plausible to hypothesize that renal function may be at risk during menopause, independently of physiological changes related to body composition and metabolic profile. Nonetheless, epidemiological studies in this area remain limited.

Therefore, the objective of this study was to investigate the association between menopause and GFR, independently of body composition and metabolic profile.

2. Materials and methods

2.1. Study design and sample selection

We conducted a cross-sectional study involving 3918 women who attended the International Center for the Assessment of Nutritional Status (ICANS) between September 2010 and September 2022. ICANS is a university-affiliated, urban clinical and research center specialized in the dietary management of obesity and its related comorbidities, as well as in nutritional education aimed at maintaining a healthy body weight. Participants were recruited if they were aged 40–55 years. Diagnoses of diabetes, cardiovascular disease, neurological, gastrointestinal, cardiac, or pulmonary failure, cancer within the last 5 years, and acute illness, as well as the use of drugs known to cause lipodystrophy, including steroids and antiretroviral agents, were reasons for exclusion. Each participant underwent a medical evaluation to assess their medical history, current medication and menopausal status. A nutritional assessment was also performed to collect anthropometric measurements. In addition, a blood sample was collected from each participant to measure biochemical parameters useful to define metabolic syndrome and calculate GFR. The study adhered to the ethical standards outlined in the Helsinki Declaration, and all participants provided written informed consent. The study protocol was approved by the Ethics Committee of the University of Milan (protocol No. 23/2016).

2.2. Clinical assessment and evaluation of menopausal status

A physician conducted a medical examination to gather information on the patient's medical history, chronic pharmacological therapies (including oral contraceptives and hormone replacement therapies), and menopausal status, the latter defined as the absence of a menstrual cycle for at least 12 months.

2.3. Anthropometric measurements

Anthropometric measurements were performed following the international guidelines set by Lohman et al. [30]. Weight and height were measured respectively using a special column scale, with a precision of 0.1 kg, and a stadiometer, accurate to 0.5 cm. Participants were asked to wear only undergarments and socks. The body mass index (BMI) was obtained using the standard formula: weight (kg) divided by height (m^2). According to World Health Organization (WHO) classifications, BMI values were categorized as underweight (BMI $<$18.5 kg/m^2), normal weight (BMI 18.5–25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obesity (BMI $\geq$30 kg/m^2). Circumferences were measured using a suitable non-elastic measuring tape. Body skinfolds were measured by a caliper with an accuracy of 0.2 mm. Skinfold thickness of the triceps, biceps, subscapular, and suprailiac regions was recorded for each participant. The final values represented the average of three measurements taken at each site on the nondominant side of each participant. Finally, body density (ρ) was calculated using the Durnin and Womersley Eqs. [31], depending on sex and age. Body fat (BF) percentage was determined using Siri's formula [32] $BF = (4.95 / \rho - 4.50) \times 100$. Fat mass index (FMI) and fat-free mass index (FFMI) were calculated using the formula: fat mass or fat-free mass (kg)/height (m^2).

2.4. Blood pressure and laboratory evaluation

A physician measured blood pressure in accordance with international guidelines [33].

Blood samples were drawn from each patient between 6:30 and 9:30 a.m., following an overnight fast, to measure serum glucose, HDL cholesterol, triglycerides, and creatinine levels. GFR was estimated using the CKD-EPI Eq. [34] and a value $\geq$90 ml/min/1.73 m^2 was considered normal [35].

2.5. Definition of metabolic syndrome

Metabolic syndrome was diagnosed using harmonized criteria [36], based on the presence of at least three of the following factors: waist circumference $\geq$ 102 cm in men or $\geq$ 88 cm in women, blood pressure $\geq$ 130/85 mmHg or use of antihypertensive treatment, fasting glucose $\geq$100 mg/dl or ongoing antidiabetic treatment, triglycerides $\geq$150 mg/dl or use of triglyceride-lowering therapy, HDL cholesterol $<$40 mg/dl in men or $<$ 50 mg/dl in women.

2.6. Statistical analysis

Most continuous variables had non-Gaussian distributions and are reported as the 25th, 50th, and 75th percentiles. Discrete variables are reported as counts and proportions. The Mann-Whitney and Chi-squared tests were used to compare the distribution of continuous variables and the distribution of categorical variables, respectively, based on menopausal status. To reduce the confounding effect of metabolic syndrome

and body composition on GFR, the association between menopause and GFR was assessed by matching premenopausal women with postmenopausal women. Coarsened exact matching (CEM) [37] was used to match premenopausal and postmenopausal women based on age, FMI, FFMI, and the presence of individual metabolic syndrome factors. To verify the success of the matching, the distribution of continuous variables between the two groups of women was assessed at the 25th, 50th, and 75th percentiles using quantile regression. The association between menopausal status and GFR was evaluated using a linear regression model adjusted for age, FMI, FFMI, number of births, use of oral contraceptives or a hormone replacement therapy, and metabolic syndrome parameters. Confounders were added to the model despite the matching to account for any residual confounding. A multivariable logistic regression model was then used to assess the association between menopausal status and the risk of GFR <90 ml/min/1.73m^2. Marginal probabilities were obtained from the model to determine the prevalence of GFR <90 ml/min/1.73m^2 by menopausal status. Matching was accounted for by using CEM-related weights and robust 95 % CIs in all regression models. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA version 18.5 (StataCorp).

3. Results

Table 1 reports the characteristics of the 3918 women recruited for the study according to the menopausal status (61.4 % premenopausal women).

Compared to premenopausal women, postmenopausal women were older, had higher FMI and lower FFMI, and exhibited lower GFR. Additionally, postmenopausal women had a lower likelihood of maintaining a normal GFR and a higher prevalence of hypertension, impaired fasting glucose, and, consequently, metabolic syndrome compared to premenopausal women. Fig. 1 illustrates the most common combinations of metabolic syndrome parameters in both premenopausal and postmenopausal women. All combinations are presented in Supplementary Table S1.

Given that premenopausal and postmenopausal women presented different body composition and cardiometabolic risk, both factors influencing GFR, we matched the two groups of women by age, body composition, and individual metabolic syndrome factors, as described above. We thus matched 928 premenopausal women with 649 postmenopausal women. Table 2 presents the nutritional and metabolic characteristics of premenopausal and postmenopausal women after matching. The two groups of women were comparable in terms of age, body composition, metabolic parameters (except for 25th percentile of HDL), and had identical prevalence of metabolic syndrome and its individual components.

We then investigated the contribution of menopause to GFR. Even after adjusting for age, FFMI, FMI, and individual metabolic syndrome parameters, menopause was significantly associated with a reduction of 2.32 ml/min/1.73m^2 (95 % CI: −3.81, −0.83) (Fig. 2).

Menopause was also significantly associated with an increased risk of GFR <90 ml/min/1.73m^2. Compared to premenopausal women, postmenopausal women had a 51 % higher risk (OR = 1.51, 95 % CI: 1.12, 2.02), independent of age, body composition, and metabolic status (Fig. 3). The prevalence of GFR <90 ml/min/1.73m^2 was 31.5 % (95 % CI: 27.9, 35.1) in postmenopausal women compared to 23.7 % (95 % CI: 19.6, 27.8) in premenopausal women.

Table 1.
Characteristics of women according to the menopausal status.

	Premenopausal			Menopausal			
	P25	P50	P75	P25	P50	P75	*P* value
Age (years)	42	45	48	48	51	54	<0.001
BMI (kg/m^2)	24.5	27.5	30.9	24.5	27.4	31.0	0.566
Body fat (%)	36.2	39.2	41.6	37.6	40.5	42.8	<0.001
FMI (kg/m^2)	9.0	10.8	12.8	9.3	11.1	13.2	<0.001
FFMI (kg/m^2)	15.5	16.8	18.4	15.1	16.3	17.9	<0.001
Waist circumference (cm)	83.7	91.2	99.3	84.6	92.0	100.5	0.078
Glucose (mg/dl)	86	92	98	87	93	100	<0.001
Triglycerides (mg/dl)	60	79	109	64	84	112	<0.001
HDL (mg/dl)	54	64	73	55	65	76	<0.001
Systolic blood pressure (mm Hg)	110	120	128	110	120	130	0.001
Diastolic blood pressure (mm Hg)	70	76	80	70	80	80	0.008
Creatinine (mg/dl)	0.6	0.7	0.8	0.6	0.7	0.8	<0.001
GFR (ml/min/1.73m^2)	91.5	104.2	109.5	85.1	98.8	104.4	<0.001

	N	%	N	%	P value
Oral contraceptive/Hormone Replacement Therapy	217	9.0	82	5.4	<0.001
BMI classes					0.547
Normal weight	698	29.0	454	30.0	
Overweight	961	39.9	613	40.5	
Obesity	747	31.0	445	29.4	
High waist circumference	1488	61.8	975	64.5	0.096
High triglycerides (≥150 mg/dl or treatment)	313	13.0	205	13.6	0.621
High blood pressure (≥130/85 mmHg or treatment)	775	32.2	600	39.7	<0.001
Impaired fasting glucose (≥100 mg/dl or treatment)	453	18.8	416	27.5	<0.001
Low HDL (≤50F/40M mg/dl or treatment)	392	16.3	225	14.9	0.238
Metabolic syndrome	422	17.5	339	22.4	<0.001
CKD stage					<0.001
Normal or increased GFR (>90 ml/min/1.73 m^2)	1867	77.6	993	65.6	
Mild reduction in GFR (60–89 ml/min/1.73 m^2)	533	22.2	506	33.5	
Moderate reduction in GFR (45–59 ml/min/1.73 m^2) - A	4	0.2	8	0.5	
Moderate reduction in GFR (30–44 ml/min/1.73 m^2) - B	1	0.0	4	0.3	
Severe reduction in GFR (15–29 ml/min/1.73 m^2)	0	0.0	1	0.1	
Kidney failure (GFR < 15 ml/min/1.73 m^2 or dialysis)	1	0.0	0	0.0	

Abbreviations: P25, 25th percentile, P50, 50th percentile, P75, 75th percentile.

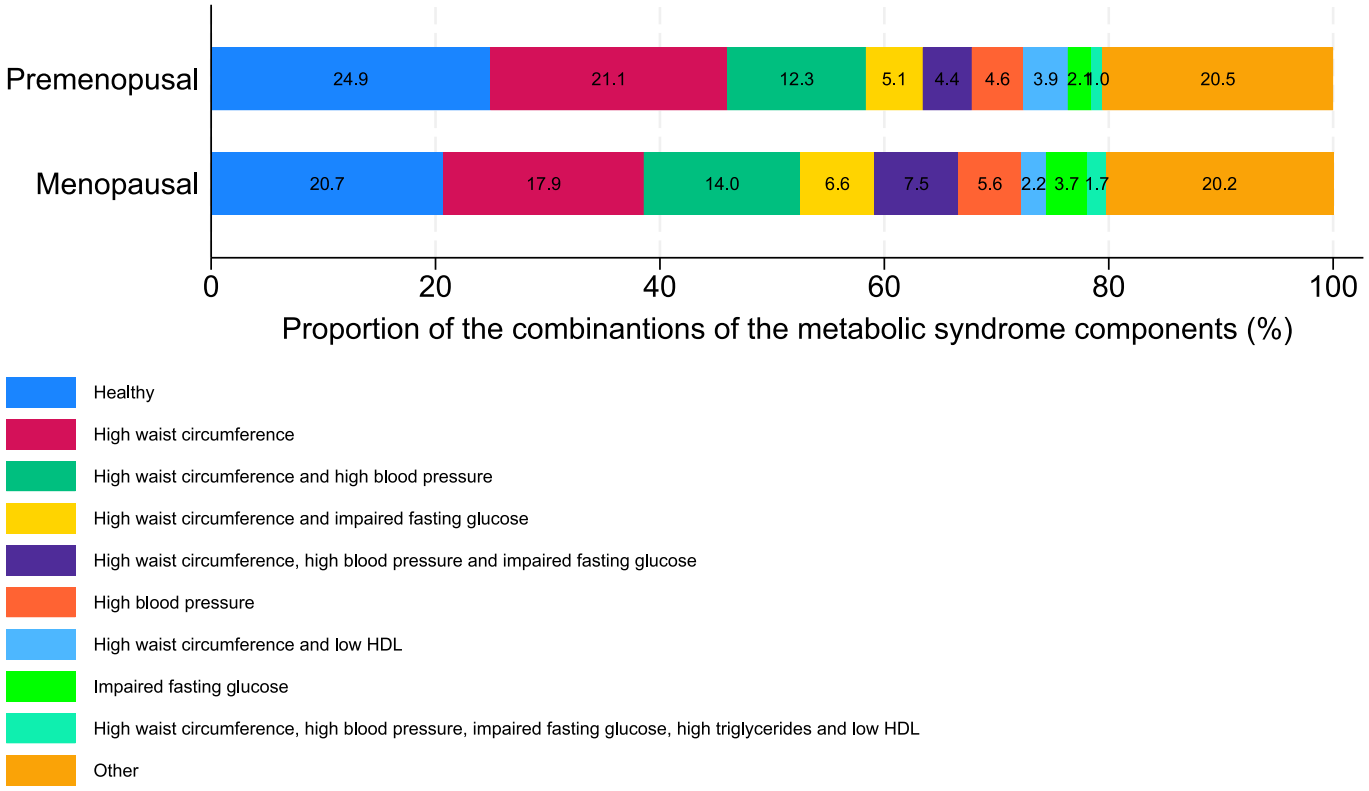

Fig. 1. Proportion of major combinations of metabolic syndrome factors.

Table 2
Characteristics of women after matching.

	Premenopausal			Menopausal			P value		
	P25	P50	P75	P25	P50	P75	P25	P50	P75
Age (years)	46	49	52	46	49	52	>0.999	>0.999	>0.999
BMI (kg/m^2)	24.1	26.5	29.2	24.1	26.6	29.2	0.965	0.710	0.781
Body fat (%)	36.7	39.9	42.2	36.7	39.7	42.1	0.990	0.457	0.735
FMI (kg/m^2)	8.9	10.6	12.1	8.9	10.6	12.2	0.964	0.993	0.863
FFMI (kg/m^2)	15.0	16.0	17.1	15.1	16.0	17.3	0.544	0.684	0.277
Waist circumference (cm)	82.9	90.3	97.0	83.2	89.7	97.2	0.732	0.485	0.809
Glucose (mg/dl)	86	91	96	86	91	96	>0.999	>0.999	>0.999
Triglycerides (mg/dl)	61	78	97	59	76	97	0.185	0.350	>0.999
HDL (mg/dl)	57	66	76	60	67	78	0.004	0.351	0.219
Systolic blood pressure (mm Hg)	110	120	124	110	120	122	>0.999	>0.999	0.402
Diastolic blood pressure (mm Hg)	70	75	80	70	75	80	>0.999	>0.999	>0.999
Creatinine (mg/dl)	0.6	0.7	0.77	0.65	0.7	0.8	0.002	>0.999	<0.001
GFR (ml/min/1.73m^2)	93	102	107	86	100	106	<0.001	0.007	0.191

	N	%	N	%	P value
Oral contraceptive/Hormone Replacement Therapy	63	6.8	31	4.8	0.107
High waist circumference	542	58.4	379	58.4	>0.999
High triglycerides (≥150 mg/dl or treatment)	29	3.1	20	3.1	>0.999
High blood pressure (≥130/85 mmHg or treatment)	263	28.4	184	28.4	>0.999
Impaired fasting glucose (≥100 mg/dl or treatment)	112	12.0	78	12.0	>0.999
Low HDL (≤50F/40M mg/dl or treatment)	47	5.1	33	5.1	>0.999
Metabolic syndrome	60	6.5	42	6.5	>0.999

Abbreviations: P25, 25th percentile, P50, 50th percentile, P75, 75th percentile.

4. Discussion

The results of this study confirm that menopause is significantly associated with a reduction in GFR and that this association persists even when accounting for body composition and metabolic syndrome risk factors. These findings suggest an independent role of menopause and estrogen reduction in impairing renal function, beyond the effects typically attributed to changes in body composition, adipose tissue redistribution, and metabolic alterations occurring during the menopausal transition.

Previous studies have shown that the onset of menopause, whether natural or induced, can impair renal health. A study conducted within the Women's Health Initiative cohort indicated that early menopause occurs more frequently among women with CKD [38]. More recently, a

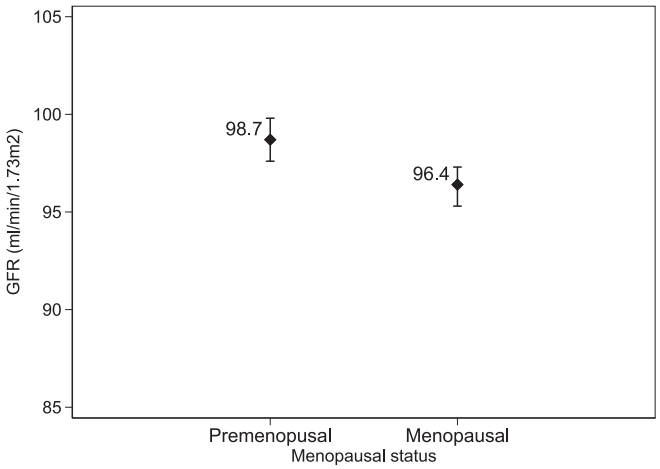

Fig. 2. Association of menopausal status with GFR. Values are linear regression coefficients and 95 % confidence intervals obtained from a multivariable linear regression models adjusted for age, FFMI, FMI, waist circumference, triglycerides, HDL, glucose, systolic and diastolic blood pressure, number of pregnancies and use of oral contraceptives and hormone replacement therapy.

study in the National Health and Nutrition Examination Survey cohort found that early menopause is associated with an increased risk of CKD [39]. Similarly, it has been reported that women who undergo oophorectomy have a higher risk of CKD. Given the protective role of estrogen on cardiovascular health and insulin resistance, reduced lifetime exposure to endogenous estrogen may be the primary contributing factor [17].

It is well known that menopause is associated with changes such as increased fat mass, particularly visceral fat, and increased risk of metabolic syndrome, both of which may contribute to reduced GFR [40–42]. Our data confirm the increased cardiometabolic risk in postmenopausal women. Specifically, we observed that compared to premenopausal women, postmenopausal women exhibited a higher amount of fat mass, particularly abdominal fat, as indicated by a larger waist circumference, along with a higher risk of hypertension and impaired fasting glucose, resulting in an elevated risk of metabolic syndrome. However, our study demonstrates that even when controlling for these factors, menopause remains significantly associated with a decline in GFR. This observation suggests that menopause may negatively impact kidney function, potentially due to the reduction of estrogen's protective effects on renal health. Supporting this hypothesis, several studies have reported that hormone replacement therapy in postmenopausal women is associated with improvements in renal function, as evidenced by an increase in GFR [43,44].

It has been suggested that estrogen may exert direct effects on renal structure and function through various mechanisms that contribute to maintaining renal health and regulating GFR [45,46]. First, estrogen is known to have vasodilatory effects on renal blood vessels, mediated in part through increased production of nitric oxide (NO), a potent vasodilator that improves renal perfusion and reduces systemic and renal vascular resistance [47,48]. Reduced levels of estrogen during menopause could lead to diminished NO availability, resulting in increased renal vascular resistance and impaired renal perfusion, potentially contributing to a decline in GFR [49]. Additionally, estrogen has anti-inflammatory properties that protect renal tissue from damage. It modulates the immune response by inhibiting the release of pro-inflammatory cytokines and promoting the production of anti-inflammatory mediators [50]. This effect reduces systemic and renal inflammation, which is critical for preserving renal function [51]. With the reduction of estrogen during menopause, an increase in inflammatory processes may occur, leading to tissue damage and fibrosis within the kidney, ultimately contributing to GFR decline [52]. Furthermore, estrogen has antioxidative effects that help mitigate oxidative stress—a condition characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses. Estrogen upregulates the expression of key antioxidant enzymes, including superoxide dismutase (SOD) and catalase [53–55], which play a protective role in safeguarding renal cells from oxidative damage. Furthermore, estrogen attenuates the post-injury increase in NADPH oxidase activity, a key enzyme in the production of ROS such as superoxide anion, one of the primary ROS generated in renal tissue, thereby further reducing oxidative stress in the

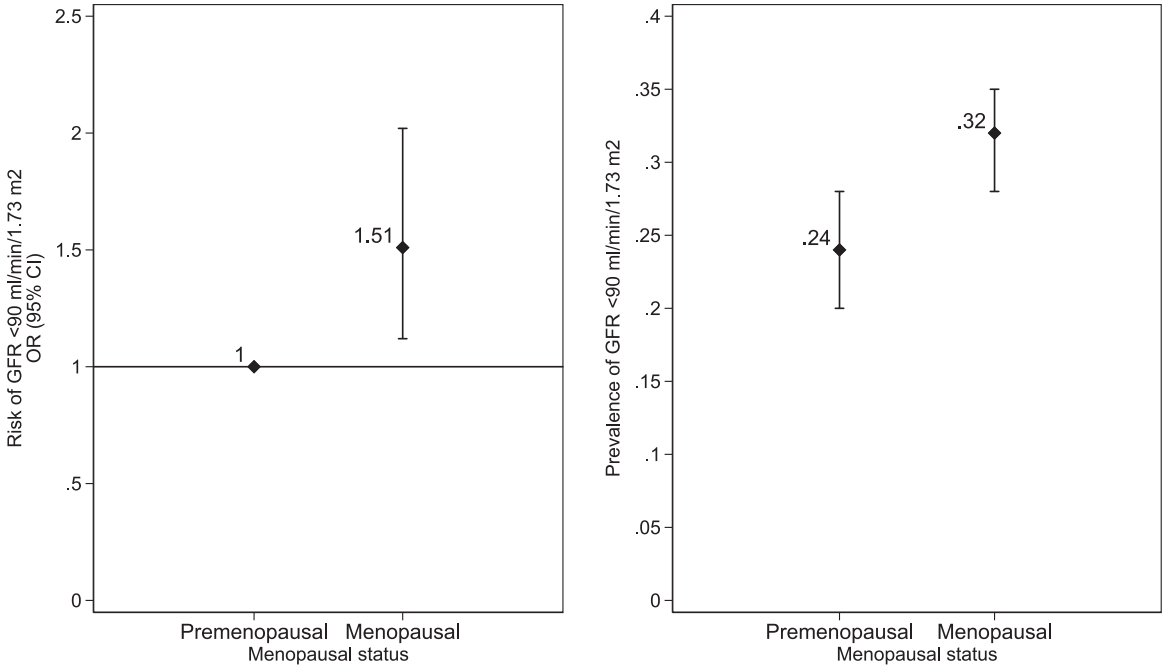

Fig. 3. Association of menopausal status with the risk of GFR <90 ml/min/1.73m^2. Values are OR and 95 % confidence intervals obtained from a multivariable linear regression models adjusted for age, FFMI, FMI, waist circumference, triglycerides, HDL, glucose, systolic and diastolic blood pressure, number of pregnancies and use of oral contraceptives and hormone replacement therapy (A) and marginal probabilities of reduced GFR obtained from the multivariable logistic model (B).

kidneys [56,57]. Menopause-induced estrogen reduction may increase ROS accumulation within renal tissue, promoting cellular damage, vascular dysfunction, and fibrosis, all of which can negatively impact GFR [53,58]. The effects of progesterone on kidney function are also determinant. Kidney tissues have also progesterone receptors, mainly located in distal tubule [59], where progesterone has a well-established fluid retentive effect by stimulating sodium reabsorption [60], mimicking aldosterone effects. While the effects of estrogen deficiency on health are well-studied, the impact of progesterone deficiency, particularly on kidney function and physiology, is less documented. Specifically, studies on the impact of progesterone deficiency during menopause on renal function are scarce, undoubtedly further research is required to fully understand this relationship.

Our study has some limitations. First, its cross-sectional design does not allow for the establishment of a causal or temporal relationship between the postmenopausal period and the decline in GFR. A longitudinal study would be necessary to confirm whether menopause directly contributes to renal function decline over time. Despite this limitation, our findings provide valuable insights into the association between menopause and GFR in a large cohort. Future studies with a longitudinal design are needed to further elucidate this relationship. Second, we did not account for the time elapsed since menopause onset. Given that prolonged estrogen deprivation may exacerbate vascular and renal decline, this factor could have influenced our results. Future studies should explore whether the duration of menopause affects the observed association between menopausal status and GFR. Third, body composition was assessed through skinfold measurements, which, while not considered the gold standard, still provide an estimate of fat-free mass and fat mass. However, in routine clinical practice, gold standard methods are often impractical due to high costs, time requirements, and the need for highly specialized personnel. Skinfold measurement, by contrast, is quicker and easier to perform. Additionally, at our center, the intra- and inter-operator coefficient of variation is very low. Fourth, GFR was estimated using a predictive formula rather than a direct measurement. However, we used the CKD-EPI equation, which is validated and recommended by KDIGO guidelines for assessing kidney function. Fifth, we did not measure albumin, which is another indicator of renal function. Sixth, the subjects included in the study were volunteers who had chosen to start a dietary program aimed at weight loss or maintenance, which limits the generalizability of our findings. Finally, as with any observational study, the potential for residual confounding cannot be completely ruled out.

Our study also presents several strengths. First, the large sample size enabled us to obtain highly precise estimates, as evidenced by the narrow confidence intervals. Second, this is one of the few studies to explore the effects of menopause on GFR while considering both body composition and metabolic profile. This thorough approach allowed us to identify the independent effects of menopause.

5. Conclusion

In conclusion, the results of this study suggest that menopause represents an independent risk factor for GFR decline, beyond the effects related to body composition and metabolic risk factors. These findings underscore the importance of monitoring renal function in postmenopausal women and the need to further investigate the role of estrogen in renal health protection.

Contributors

Alessandro Leone contributed to study concept and design, to data collection, and interpreting the data, composed the statistical dataset, performed the analyses, and wrote and revised the manuscript.

Francesca Menichetti contributed to data collection and wrote the manuscript.

Federica Sileo contributed to data collection and revised the manuscript.

Silvia Gallosti contributed to data collection.

Ramona De Amicis contributed to data collection.

Andrea Foppiani contributed to data collection.

Simona Bertoli contributed to study concept and design and to data collection.

Alberto Battezzati contributed to study concept and design, to data collection, and interpreting the data, and revised the manuscript.

All authors reviewed and approved the final version and no other person made a substantial contribution to the paper.

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Ethical approval

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).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Data sharing and collaboration

There are no linked research data sets for this paper. The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2025.108595.

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