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Serum Creatinine Within Its Reference Range and Erectile Dysfunction: Exploring Non-Filtration Determinants in NHANES 2001–2004

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Abstract

Erectile dysfunction (ED) is associated with renal dysfunction, but its relationship with serum creatinine is uncertain because creatinine reflects both renal filtration and creatinine generation. We examined serum creatinine and ED among men aged ≥ 20 years in NHANES 2001–2004, with secondary analyses of body composition and eGFR. Survey-weighted logistic regression was used with adjustment for demographic and clinical covariates. Across the full creatinine range (n = 3776; 1057 with ED), higher creatinine was not significantly associated with ED (OR 0.98, 95% CI 0.94–1.01 per 0.1 mg/dL; P = 0.14). A post hoc analysis restricted to creatinine 0.74–1.35 mg/dL (n = 3355; 873 with ED) showed lower odds of ED with higher creatinine (OR 0.91, 95% CI 0.84–0.99; P = 0.034). Adjustment for appendicular lean mass and fat mass attenuated this association (OR 0.94, 95% CI 0.86–1.02; P = 0.15). Higher lean mass was associated with lower odds of ED, whereas higher fat mass was associated with higher odds. In men with eGFR > 90 mL/min/1.73 m², higher eGFR was associated with greater odds of ED but was not reproduced with cystatin C-based measures. Lower creatinine within the post hoc range was associated with higher odds of ED and may reflect non-filtration determinants such as muscle mass.

Introduction

Erectile dysfunction (ED) is common in men and is associated with diabetes, hypertension, obesity and cardiovascular disease; it is also frequent in men with kidney disease [1–3]. In our previous multicentre study of men with type 2 diabetes, serum creatinine was among the factors associated with ED [4], and in a subsequent study of men with diabetes and ED, older age and higher serum creatinine were associated with the need for dual phosphodiesterase-5 inhibitor therapy [5]. These findings were hypothesis-generating and prompted the present analysis.

Serum creatinine reflects both renal filtration and creatinine generation, the latter being influenced by skeletal muscle mass, body composition, and diet [6, 7]. Consequently, a low creatinine concentration or high creatinine-based estimated glomerular filtration rate (eGFR) does not necessarily indicate higher filtration. The National Health and Nutrition Examination Survey (NHANES) 2001–2004 provides nationally representative data linking serum creatinine and erectile function with dual-energy X-ray absorptiometry (DXA)-derived lean and fat mass.

We therefore examined the association of serum creatinine with prevalent ED in men, first across the full creatinine range and then, in a post hoc analysis, within the reference range (0.74–1.35 mg/dL). We also explored creatinine-based eGFR in men with eGFR > 90 mL/min/1.73 m² and assessed whether associations changed after adjustment for DXA-derived appendicular lean mass index (ALMI) and fat mass index (FMI), with additional sensitivity analyses.

Materials and Methods

Study population

We analysed publicly available NHANES 2001–2002 and 2003–2004 data [8, 9]. NHANES is a cross-sectional, multistage probability survey of the US civilian population. We included men aged ≥ 20 years. Participants were included in each analysis according to the availability of required variables. Principal analytic populations were the full creatinine range (n = 3776), the creatinine-range population (0.74–1.35 mg/dL), the body-composition population, and the eGFR-above-90 subgroup. Detailed participant selection and missing-data procedures are provided in Supplementary Methods and Table S1.

Erectile dysfunction

ED was based on one self-reported questionnaire item [10]. Men who were “sometimes able” or “never able” to get and keep an erection adequate for intercourse were classified as having ED. A broader sensitivity definition also classified men who were “usually able” as having ED.

Serum creatinine, cystatin C, eGFR, and albuminuria

Serum creatinine was analysed continuously per 0.1 mg/dL and, for the reference-range analysis, within 0.74–1.35 mg/dL, the Mayo Clinic Laboratories male reference interval [11]. The full observed range was examined first; because this showed no clear age-adjusted linear association, we then examined the reference range using a restricted cubic spline. The restriction was post hoc and exploratory and was motivated by previous work on variation in serum creatinine within conventional reference ranges [12].

NHANES creatinine was measured using the kinetic Jaffe method, was recorded to one decimal place (six values within the interval), and published calibration data indicated that no correction was required for these survey cycles [13].

We then examined whether the association with ED was also evident among men with preserved creatinine-based eGFR (> 90 mL/min/1.73 m²). This subgroup analysis was exploratory. eGFR was calculated from serum creatinine and age, so this analysis is mathematically linked to the creatinine analysis and is not an independent confirmation or replication of it.

eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [7]. The urinary albumin-to-creatinine ratio (UACR) was calculated from a single spot urine sample; UACR ≥ 30 mg/g was considered increased albuminuria [14, 15].

Serum cystatin C had been measured in 2018–2020 in stored serum of NHANES 1999–2004 participants and was available for 4176 of the 4661 examined men [16]. For sensitivity analyses, we calculated cystatin C-based eGFR (eGFRcys) using the 2012 CKD-EPI cystatin C equation [17] and creatinine–cystatin C-based eGFR (eGFRcr-cys) using the 2021 equation [7].

Body composition

ALMI was calculated as appendicular lean soft-tissue mass divided by height² and FMI as total fat mass divided by height². DXA missing or invalid values were multiply imputed by the National Center for Health

Statistics (NCHS); we performed no imputation ourselves, and estimates were pooled across imputations [18–21].

Covariates

The primary adjustment set comprised age, race and ethnicity, survey cycle, diabetes and cardiovascular disease. An extended set additionally included smoking and hypertension. Diabetes and cardiovascular disease were based on self-report; borderline diabetes was treated as missing.

Statistical analysis

All analyses accounted for the NHANES complex sampling design using examination weights, strata, and primary sampling units. Logistic regression estimated associations with ED as odds ratios (ORs), and linear regression estimated associations of ALMI and FMI with creatinine. ALMI and FMI were entered together and reported per standard deviation (SD). Creatinine was modelled linearly and with restricted cubic splines, across the full range and within the creatinine-range population; age was modelled flexibly with a restricted cubic spline. Creatinine models were fitted before and after adding ALMI and FMI. Unadjusted, age-adjusted and fully adjusted creatinine models were compared in the creatinine-range population (Table S5). Sensitivity analyses are described in Supplementary Methods and Tables S2 and S3. A secondary analysis compared the AUC before and after adding creatinine to age, diabetes, hypertension, smoking, and waist circumference. Results are reported with 95% CIs; secondary analyses were exploratory, with no correction for multiple comparisons. Analyses were performed in R.

In the eGFR-above-90 subgroup with cystatin C, we fitted the primary eGFR model in the same participants using eGFRcr, eGFRcys, or eGFRcr-cys as the exposure and tested each for nonlinearity. Discordance was calculated as eGFRcr minus eGFRcys and as eGFRcr minus eGFRcr-cys; a positive value indicates a higher creatinine-based estimate. Associations were estimated per 10 mL/min/1.73 m^2 greater discordance using the cystatin C subsample weights [9, 16].

Results

Participant characteristics

The body-composition population comprised 3 889 men, including 1 122 with ED. Men with ED were older and more often had diabetes, cardiovascular disease, and hypertension; they had lower ALMI, higher FMI, higher crude mean creatinine, and lower eGFR (Table 1).

Serum creatinine and ED

Across the full creatinine range (n = 3776), the OR for ED per 0.1 mg/dL higher creatinine was 0.98 (95% CI 0.94–1.01), without a clear linear association (Table 2). The fitted curves showed no rise at higher values; nonlinearity was $P = 0.148$ for the primary definition and $P < 0.001$ for the broader definition, for

which odds of ED decreased to about 1.1 mg/dL and then plateaued (Fig. 1). We therefore examined the post hoc reference range. Among 3355 men with creatinine 0.74–1.35 mg/dL and complete covariates, the OR per 0.1 mg/dL higher creatinine was 0.91 (95% CI 0.84–0.99). Without adjustment it was 1.06 (95% CI 0.99–1.13), reversing after age adjustment (OR 0.89, 95% CI 0.82–0.97) and changing little with full adjustment (Table S5).

Relative to 1.0 mg/dL, the fitted spline gave higher odds of ED at 0.8 mg/dL (OR 1.51, 95% CI 1.07–2.13) and 0.9 mg/dL (OR 1.41, 95% CI 1.06–1.88) (Fig. 1, panel A). The curve also rose towards 1.3 mg/dL, but the estimate was imprecise (OR 1.32, 95% CI 0.77–2.27; 159 men, 77 with ED). The spline therefore suggested a possible U-shaped pattern, but nonlinearity was not conventionally significant for the primary definition (P = 0.091 before and P = 0.126 after ALMI/FMI adjustment).

Body composition, creatinine, and ED

In mutually adjusted models, higher ALMI was associated with higher creatinine (difference 0.026 mg/dL per SD, 95% CI 0.010–0.041) and lower odds of ED (OR 0.82, 95% CI 0.69–0.98), whereas higher FMI was associated with lower creatinine (difference − 0.033 mg/dL per SD, 95% CI − 0.046 to − 0.019) and higher odds of ED (OR 1.45, 95% CI 1.22–1.72) (Table 2, Fig. 2).

Adjustment for ALMI and FMI attenuated the association of creatinine with ED among the 3 355 men with creatinine 0.74–1.35 mg/dL: the OR per 0.1 mg/dL higher creatinine was 0.91 (95% CI 0.84–0.99) before and 0.94 (95% CI 0.86–1.02) after adjustment (Table 2, Table S2). Adjustment modestly attenuated the lower limb of the fitted curve without changing its overall shape; after adjustment, the OR relative to 1.0 mg/dL was 1.42 (95% CI 1.00–2.01) at 0.8 mg/dL and 1.35 (95% CI 1.00–1.81) at 0.9 mg/dL (Fig. 1, panels A and B).

Creatinine-based eGFR and ED

In this exploratory analysis of 2 151 men with eGFR > 90 mL/min/1.73 m², 367 had ED. After flexible age adjustment, each 10 mL/min/1.73 m² higher eGFR was associated with higher odds of ED (OR 1.54, 95% CI 1.30–1.83; P < 0.001); there was no evidence of nonlinearity (P = 0.874) (Fig. 3). Very high eGFR was concentrated in younger men: 345 of 356 men with eGFR > 120 mL/min/1.73 m² were aged 20–39 years (Table S3).

Sensitivity analyses

In sensitivity analyses, the linear creatinine estimate retained the same direction but its 95% CI included 1.0 with age as a linear term, the extended adjustment set, and measured DXA data (Table S2). Among 2135 men with UACR data, the eGFR association remained after excluding 159 men with UACR ≥ 30 mg/g (OR 1.53, 95% CI 1.25–1.87) and after adjustment for log-transformed UACR (OR 1.48, 95% CI 1.25–1.75). In the secondary prediction analysis, the AUC was 0.859 without and 0.860 with creatinine (difference 0.001, 95% CI − 0.001 to 0.002).

Cystatin C-based eGFR

Cystatin C had been measured in 2038 of the 2151 men with eGFR > 90 mL/min/1.73 m², of whom 353 had ED. In these same men, each 10 mL/min/1.73 m² higher eGFRcr was again associated with higher odds of ED (OR 1.54, 95% CI 1.29–1.83; P < 0.001), with no evidence of nonlinearity (P = 0.933) (Table S4, Figure S1).

The associations of eGFRcys and eGFRcr-cys with ED showed evidence of nonlinearity (P = 0.018 for eGFRcys and P = 0.008 for eGFRcr-cys). Relative to the median, the odds of ED for eGFRcys were higher at the 5th percentile (OR 2.01, 95% CI 1.27–3.19) but not clearly different at the 95th (OR 1.32, 95% CI 0.87–2.01); for eGFRcr-cys they were higher at both the 5th (OR 1.55, 95% CI 1.03–2.36) and the 95th percentile (OR 1.89, 95% CI 1.22–2.93).

The eGFRcr estimate was almost unchanged after adjustment for ALMI and FMI (OR 1.52 before and 1.50 after). Greater positive discordance was associated with higher odds of ED. Per 10 mL/min/1.73 m² greater discordance, the OR was 1.33 (95% CI 1.17–1.51) for eGFRcr minus eGFRcys and 1.55 (95% CI 1.25–1.91) for eGFRcr minus eGFRcr-cys (Table S4).

Discussion

After adjustment for age, lower serum creatinine within the reference range was associated with higher odds of ED. The fitted spline suggested a possible U-shaped pattern; however, the evidence for nonlinearity was inconclusive in the primary analysis. In exploratory analyses, the modest attenuation after adjustment for body composition and the discordance between eGFR estimates suggest that non-filtration determinants of serum creatinine may contribute to the association, although the underlying mechanism remains uncertain and the cross-sectional design precludes causal conclusions.

We began by examining serum creatinine across its full observed range, where there was no clear linear association with ED (Table 2) and the fitted curves showed no rise at higher creatinine values (Fig. 1, panels C and D). Previous work has related high-normal serum creatinine to cardiovascular risk [12], providing a rationale for examining variation within the reference range without assuming that the association would be similar for ED. We therefore restricted the spline analysis, post hoc, to 0.74–1.35 mg/dL.

Within this range, the inverse association was modest: the CI included 1.0 after body-composition adjustment and in several sensitivity analyses. Without adjustment, the association was in the opposite direction (OR 1.06, 95% CI 0.99–1.13) and reversed after age adjustment (Table S5), so the inverse association depends on age adjustment. Our earlier observation of higher creatinine with the need for dual PDE5 inhibitor therapy [5] was in the opposite direction. Odds of ED were higher at 0.8 and 0.9 mg/dL than at 1.0 mg/dL; the rise towards 1.3 mg/dL was imprecise and absent in the full-range curves. The spline suggested a possible U-shaped pattern, but nonlinearity was not conventionally significant for

the primary definition (P = 0.091). We therefore interpret the findings primarily as a modest, age-adjusted association between lower serum creatinine and higher odds of ED.

J- or U-shaped relationships of creatinine have been reported for mortality, functional limitation and cardiovascular outcomes, including heart failure [22–24]. Our data provided clearer support for higher odds of ED at lower than at higher creatinine. This is not evidence that creatinine directly affects erectile function.

Higher ALMI was associated with higher serum creatinine and lower odds of ED, whereas higher FMI was associated with lower creatinine and higher odds of ED. This pattern is consistent with studies linking lower muscle mass or sarcopenia with ED, including prospective evidence that decreased muscle mass was associated with incident severe ED [25, 26, 29]. Serum creatinine is also strongly influenced by muscle mass. In the PREVEND cohort, lower muscle mass was associated with substantial divergence between creatinine- and cystatin-C-based estimates of GFR, and longitudinal muscle loss led to increasing discordance [27]. A subsequent PREVEND study replicated the positive association between serum creatinine and muscle mass in NHANES, whereas cystatin C showed little association with muscle mass [28]. In our analysis, adjustment for ALMI and FMI attenuated the creatinine association (OR 0.91 to 0.94 per 0.1 mg/dL) and modestly attenuated the lower limb of the spline. These findings are consistent with, but do not establish, a role for muscle mass as a non-filtration determinant of creatinine and a potential link between lower creatinine and ED.

Because serum creatinine reflects both filtration and non-filtration determinants, we examined creatinine-based eGFR among men with eGFR > 90 mL/min/1.73 m². Higher eGFR was associated with higher odds of ED (OR 1.54 per 10 mL/min/1.73 m²). Previous studies have linked impaired renal function or lower eGFR with ED, particularly in cardiovascular disease or CKD [30–32]. Our finding concerns the upper range of calculated eGFR. At a given age, higher creatinine-based eGFR corresponds mathematically to lower serum creatinine, so it is not an independent confirmation of the creatinine association.

Cystatin C is less dependent on skeletal muscle mass than creatinine, but it is not a direct measure of GFR and has its own non-GFR determinants, including diabetes and inflammation [17, 33]. In the same men, the positive linear association with eGFRcr was not reproduced with eGFRcys. Greater positive discordance was associated with higher odds of ED, although discordance is calculated from eGFRcr and is therefore not independent of the creatinine-based association. These findings are compatible with a contribution of non-filtration determinants of creatinine, but discordance does not directly measure creatinine generation, muscle mass, muscle function, or true GFR.

Huang et al. also analysed NHANES 2001–2004 and reported associations between renal health measures and ED using eGFR, CKD classification and UACR [34]. Because the same survey cycles were used, that study is not an independent replication of our findings.

Previous studies have consistently linked CKD or reduced renal function with a high burden of ED, particularly in men with cardiovascular or renal disease [30–32]. A recent NHANES analysis reported associations between eGFR, CKD classification and ED, but used the same 2001–2004 cycles and therefore is not an independent replication [34]. A case-control study found only a borderline difference in serum creatinine between men with and without ED, but substantially higher BUN and BUN/creatinine ratios in men with ED [35]. Together with our findings, these studies suggest that creatinine, filtration estimates and urea-related biomarkers may reflect overlapping but distinct determinants of erectile function. Prediction models incorporating age, diabetes, smoking, hypertension and cardiovascular disease have shown moderate-to-good discrimination, including an XGBoost model using the same NHANES cycles [36, 37].

Strengths include the nationally representative sample, DXA-measured body composition, and comparison of three eGFR estimates in the same men. Limitations include the self-reported ED measure and potential selection bias from missing responses; absence of measured GFR, creatinine generation and muscle function; indirect measurement of muscle by DXA; and the non-prespecified cystatin C analysis. The creatinine interval was chosen post hoc and creatinine was recorded to one decimal place, limiting assessment of curve shape. Cystatin C was measured in stored serum [38], and assay standardization could not be fully verified. Residual confounding by factors such as testosterone, physical activity, medications and psychological factors cannot be excluded. The NHANES 2001–2004 population may not represent contemporary populations.

In conclusion, after age adjustment, lower serum creatinine within the reference range was associated with higher odds of ED. The spline suggested a possible U-shaped pattern, but evidence for nonlinearity was inconclusive in the primary analysis. Body-composition adjustment partly attenuated the creatinine association, and the creatinine-based eGFR association was not reproduced with cystatin C-based eGFR. These findings suggest that non-filtration determinants, particularly muscle mass, may contribute, but the mechanism remains uncertain. Creatinine did not meaningfully improve ED discrimination beyond routine variables. The cross-sectional design and absence of measured GFR prevent causal or mechanistic conclusions; prospective studies with repeated measures of creatinine, cystatin C, muscle mass and erectile function, and ideally measured GFR, are needed.

Declarations

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Ethical approval

The NHANES 1999–2004 protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (Protocol #98 – 12) [39]. Signed informed consent was obtained from all

participants [40]. The present analysis used only de-identified, publicly available data.

Competing interests

No conflict of interest related to this topic

Author contributions

Both authors contributed equally to the development, analysis, interpretation, and writing of the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Data availability

All data are publicly available from the National Center for Health Statistics (https://wwwn.cdc.gov/nchs/nhanes/).

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Figures

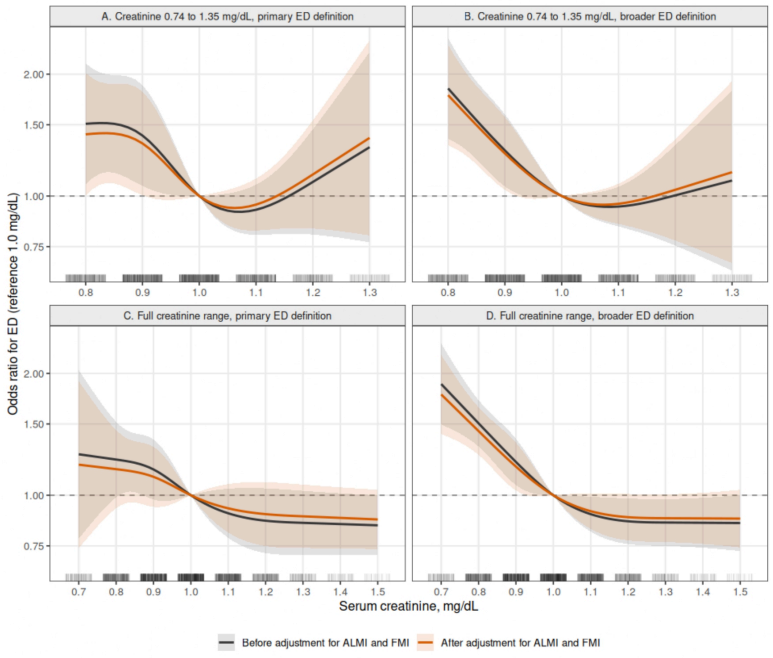


Figure 1

Adjusted associations of serum creatinine with prevalent erectile dysfunction (ED), with 1.0 mg/dL as the reference. Panels A and B show men with creatinine from 0.74 to 1.35 mg/dL (n = 3 355), an interval that was chosen post hoc. Panels C and D show the full creatinine range (n = 3 776), drawn from the 2nd to the 98th percentile. Panels A and C use the primary ED definition; panels B and D use the broader definition, which was a sensitivity analysis. Curves are restricted cubic splines before (dark grey) and after (orange)

adjustment for ALMI and FMI, with the primary adjustment set and flexible age adjustment. Shaded areas are 95% confidence intervals. Creatinine was recorded to one decimal place, and the bottom marks show the participants at each recorded value. Within the interval, the numbers of men (men with ED by the primary definition) were 512 (136) at 0.8, 818 (186) at 0.9, 905 (228) at 1.0, 618 (142) at 1.1, 343 (104) at 1.2, and 159 (77) at 1.3 mg/dL. P values of the tests for nonlinearity, before and after adjustment for ALMI and FMI: panel A, 0.091 and 0.126; panel B, 0.054 and 0.057; panel C, 0.148 and 0.437; panel D, <0.001 and <0.001. ***In panel D, the significant nonlinearity reflects decreasing odds of ED up to about 1.1 mg/dL followed by a plateau at higher creatinine values, not a rise.*** *With age as a linear term, the values were 0.068 and 0.099 for panel A and 0.020 and 0.022 for panel B. No panel shows clear evidence of higher odds of ED at higher creatinine values. ALMI, appendicular lean mass index; FMI, fat mass index.*

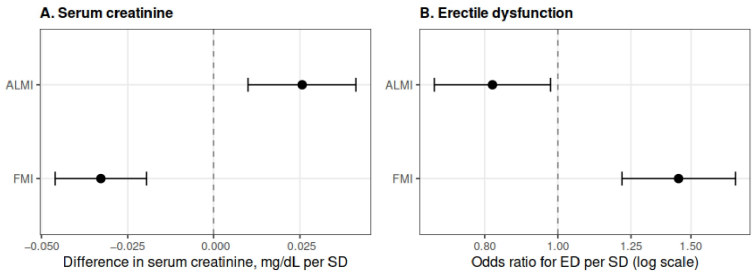


Figure 2

Associations of appendicular lean mass index (ALMI) and fat mass index (FMI) with serum creatinine (A) and with erectile dysfunction (ED) (B). ALMI and FMI were included in the same model, with the primary adjustment set and flexible age adjustment. Estimates are reported per survey-weighted standard deviation (SD). In panel A, one SD corresponded to 1.34 kg/m² for ALMI and 3.17 kg/m² for FMI (n = 4 152). In panel

B, one SD corresponded to 1.35 kg/m² for ALMI and 3.21 kg/m² for FMI (n = 3 923). Bars are 95% confidence intervals

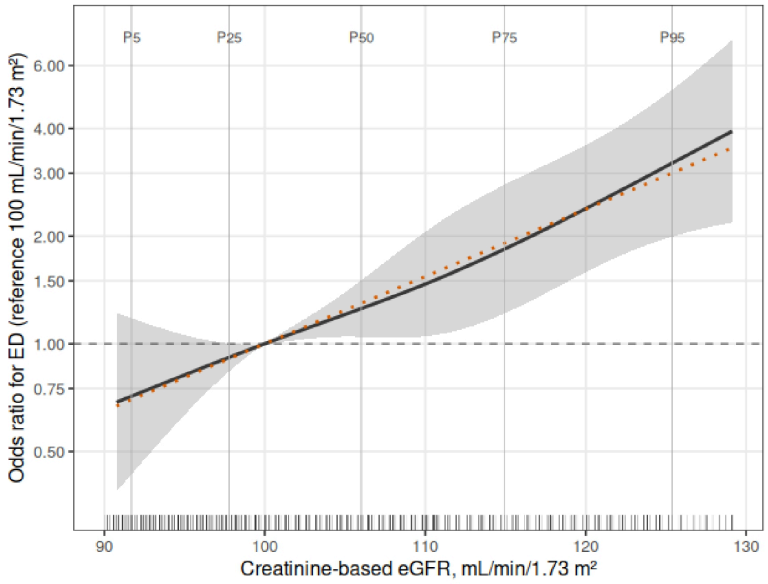


Figure 3

Adjusted association of creatinine-based estimated glomerular filtration rate (eGFR) with prevalent erectile dysfunction (ED) among men with eGFR above 90 mL/min/1.73 m², using 100 mL/min/1.73 m² as the

reference. Both curves use flexible age adjustment. The solid curve allows a nonlinear association with eGFR, whereas the dotted line shows the linear estimate from Table 2. The shaded area is the 95% confidence interval. Bottom marks show participants, and vertical lines show the survey-weighted 5th, 25th, 50th, 75th, and 95th percentiles. The curves cover the 2nd to 98th percentile. Very high eGFR occurred mainly in younger men: 345 of 356 men with eGFR above 120 mL/min/1.73 m² were aged 20 to 39 years. The curves for serum creatinine are shown in Figure 1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.docx
- Table1.docx
- SupplementFINALV31clean.docx