Clinical Kidney Journal

*Clinical Kidney Journal*, 2025, vol. 18, no. 5, sfaf116

https://doi.org/10.1093/ckj/sfaf116
Advance Access Publication Date: 25 April 2025
Original Article



ORIGINAL ARTICLE

# Causal effects of obesity on estimated glomerular filtration rate: a Mendelian randomization and image data analysis study

Patrik Ene [1], Maria K. Svensson [1,2], Robin Strand [3], Joel Kullberg [4], Håkan Ahlström [4], Anders Larsson [5] and Lars Lind [6]

[1]Department of Medical Sciences Renal Medicine, Uppsala University Hospital, Uppsala University, [2]Uppsala Clinical Research Centre, Uppsala, [3]Department of Information Technology, Uppsala University, [4]Department of Radiology, Uppsala University Hospital, Uppsala University, [5]Department of Clinical Chemistry, Uppsala University Hospital, Uppsala University and [6]Department of Medical Sciences, Uppsala University Hospital, Uppsala University, all from Sweden

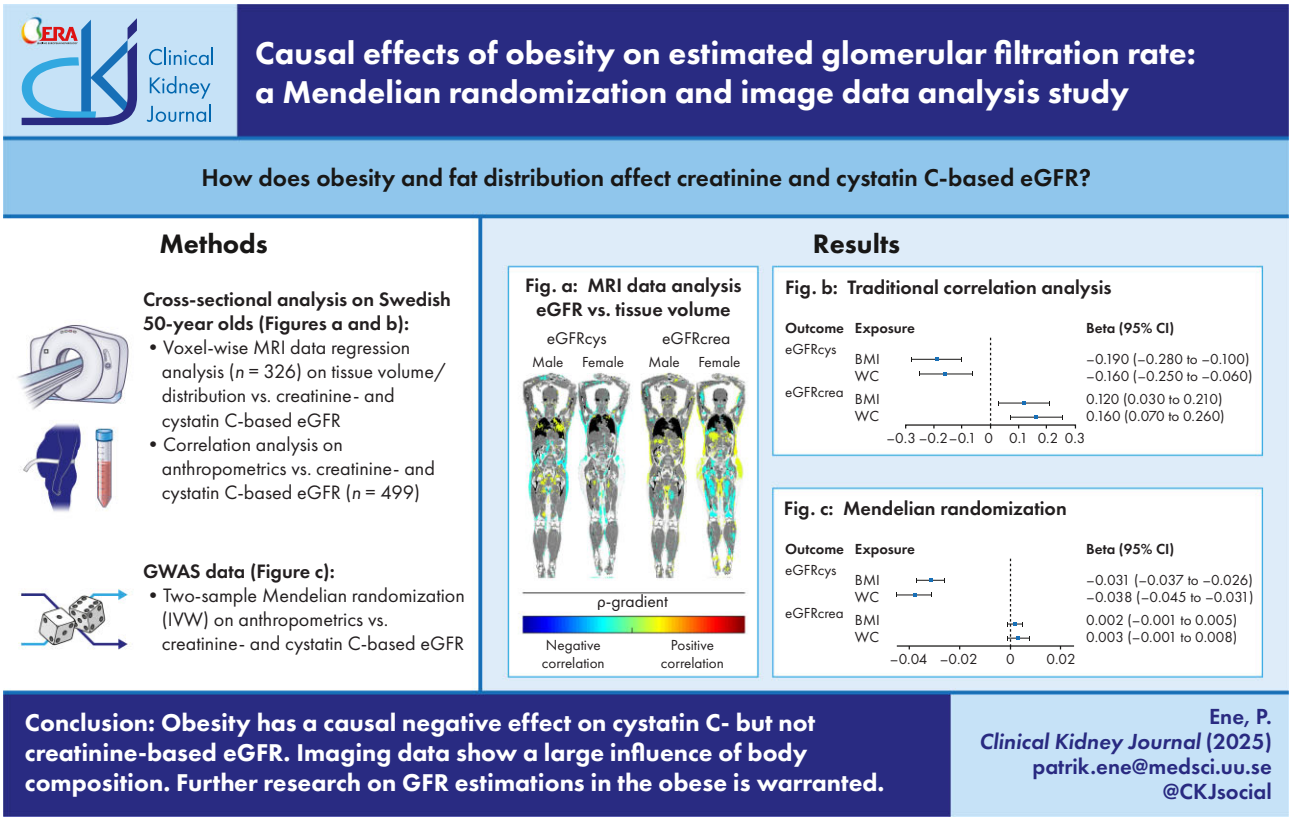
Correspondence to: Patrik Ene; E-mail: patrik.ene@medsci.uu.se

## ABSTRACT

**Background.** Obesity has been associated with onset and progression of chronic kidney disease (CKD) but causal relationship remains uncertain. This study investigated how obesity causally affects estimated glomerular filtration rate.
**Methods.** Cross-sectional and magnetic resonance imaging (MRI) data analyses were performed within the Prospective Investigation of Obesity, Energy, and Metabolism (POEM) study (502 participants, all aged 50 years). Additionally Mendelian randomization was performed using published summary data. Outcomes were creatinine- and cystatin C-based eGFR. Body mass index (BMI) and waist circumference (WC) were used as exposure variables in the cross-sectional and Mendelian randomization analyses. In the imaging data analyses, eGFR was regressed non-parametrically on tissue volume for each 3D voxel and visualized as a correlation "Imiomics" map.
**Results.** Negative correlations were shown between cystatin C-based eGFR and BMI [beta = −0.190 (95% CI: −0.280 to −0.100)] and WC [beta = −0.160 (95% CI: −0.250 to −0.060)] in an adjusted model. In contrast, a positive association was found for creatinine-based eGFR [BMI beta = 1.20 (95% CI: 0.030 to 0.210) and WC beta = 0.160 (95% CI: 0.070 to 0.260)]. Similar patterns were found using MRI analysis (Imiomics map). Mendelian randomization implied a negative causal effect of obesity-related measures on cystatin C-based eGFR [BMI beta = −0.031 (95% CI: −0.037 to −0.026) and WC beta = −0.038 (95% CI: −0.045 to −0.031)], but no statistically significant effect was found for creatinine-based eGFR.
**Conclusion.** This study suggests a causal negative effect of obesity on cystatin C-based, but not creatinine-based eGFR. These findings warrant further research regarding estimations of kidney function when assessing obesity and CKD.

*Received: 17.9.2024; Editorial decision: 11.3.2025*

## GRAPHICAL ABSTRACT




**Keywords:** body composition, estimated glomerular filtration rate, magnetic resonance imaging, Mendelian randomization, obesity

## KEY LEARNING POINTS

**What was known:**

- There is strong evidence of an association between obesity and risk of developing chronic kidney disease.
- Both of the most commonly used endogenous biomarkers for estimating glomerular filtration rate (creatinine and cystatin C) are affected by body composition.

**This study adds:**

- Using imaging and Mendelian randomization techniques this study suggests a causal negative effect of obesity on kidney function (eGFR).
- The other main finding is the congruent results showing that fat distribution and body composition profoundly affect estimations of GFR differently depending on the use of creatinine or cystatin C.

**Potential impact:**

- This warrant further research on enhancing methods for assessing kidney function in especially obese subjects.

## INTRODUCTION

Obesity is a growing worldwide epidemic, with 43% of adults being overweight in 2022 [1]. This is mirrored by an increase in hypertension, diabetes, and chronic kidney disease (CKD) [2]. Previous observational studies show a significant association between a high body mass index (BMI) and the development of CKD, defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 $m^2$ [3, 4].

Mendelian randomization is a method by which a set of single nucleotide polymorphisms (SNPs) is used as a genetic instrument mirroring the lifelong exposure of a trait. The instrument can be tested against any defined outcome. Mendelian randomization can be viewed as a way to minimize

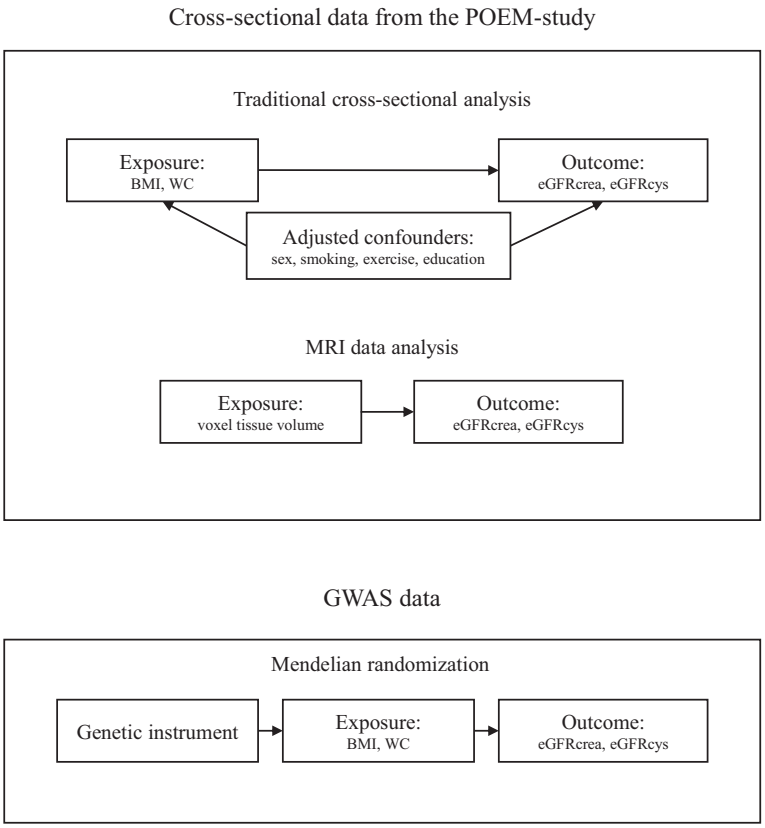



**Figure 1:** Schematic outline of the main methods used in the study.

confounding and reverse causation in a way traditional observational study methodology cannot, since the genome with its genetic variations is inherited at birth [5].

Recent Mendelian randomization studies have shown inferred causal associations between a number of anthropometric-related measures and different markers of kidney function [6–9]. There is still a need for validation of these findings since the hypothesized inferred causal negative effect of obesity on eGFR is not congruently shown across the spectrum of analyses. This could partly because eGFR could be estimated either using creatinine or cystatin C, or a combination of both these endogenous biomarkers.

None of the commonly used equations for the calculations of eGFR are developed specifically in obese individuals and both serum creatinine and cystatin C are known to be affected by body composition. Muscle mass and protein intake are considerably correlated to serum creatinine, while adipose tissue is a significant determinant of cystatin C level [10–12]. Compared to measured GFR, creatinine-based models tend to overestimate, while the use of cystatin C on average underestimates eGFR in obese individuals [13, 14]. Another potential factor could be that the commonly used adjustment of GFR by body surface area complicates the evaluation of renal function in obesity [15].

Techniques using magnetic resonance imaging (MRI) can be used for yielding rigorous body composition information, one method being so-called “Imiomics” [16]. Viewing the body as a container of >2 million three-dimensional image elements (voxels), studied individually, with Imiomics it is possible to gain detailed and visualized information regarding tissue volume and distribution without explicit segmentations or characterizations of regions of interest. Clinical parameters, such as for example kidney function, can be regressed on tissue volume for each of these 3D voxels with results visualized as a correlation Imiomics map. This is an automatic method and has previously been evaluated in a proof-of-principle study [17], and in several medical applications [18].

The aim of this study was therefore to evaluate how obesity causally affects kidney function (eGFR), derived from either creatinine or cystatin C to gain a deeper understanding of the issue of inferred causal associations between obesity, body composition and CKD. This was investigated using three methodological approaches: (i) cross-sectional observational regression analyses and (ii) whole-body MRI data analysis of body composition (correlation Imiomics map), and (iii) two-sample Mendelian randomization using already published summary data. The hypothesis tested was that obesity causes a decrease in estimated kidney function (eGFR), but that the method used to calculate eGFR could influence the relationship between obesity and kidney function.

## MATERIALS AND METHODS

### Study design and data sources

The study was conducted using two main data sources; the Prospective Investigation of Obesity, Energy, and Metabolism (POEM) study [19] and already published Genome-Wide Association Study (GWAS) summary data [20–22]. The study design is schematically outlined in Fig. 1.

### Cross-sectional data and imaging analyses

The sample for these analyses consisted of cross-sectional data obtained from the POEM study, which included 502 randomly invited 50-year-old individuals in Uppsala, Sweden. Data were collected between October 2010 and November 2016. A random subsample of 167 women and 159 men participated in an MRI substudy that was performed during a separate visit within 1 month of the main study visit. Three female participants had corrupted cystatin C analyses and were excluded.

Height, weight, BMI, and waist circumference (WC) measurements as well as blood sampling in all subjects were made by the same nurse. WC was measured at the umbilical level. Blood samples were collected during the main study visit. Both creatinine and cystatin levels were analyzed at the Department of Clinical Chemistry at Uppsala University Hospital. Creatinine and cystatin C was analyzed on Architect 8000 or 16 000 chemistry analyzers (Abbott Laboratories, Abbott Park, IL, USA). The creatinine reagent (8L24) was an isotope dilution mass spectrometry calibrated enzymatic reagent. The cystatin C reagent (1101) was a particle enhanced turbidimetric reagent from Gentian (Moss, Norway). The method was calibrated against the international reference material ERM-DA471/IFCC. Estimated GFR was calculated using the CKD-EPI equations without the ethnicity factor [23] for creatinine and cystatin C, respectively.

Linear regression analysis was applied to evaluate the relationships between BMI, WC, and eGFR calculated by creatinine or cystatin C, $eGFR_{crea}$, and $eGFR_{cys}$, respectively. Sex, education level, exercise habits, and current smoking status were used as confounders in the models (age same in all subjects).

In the subsequent MRI analysis, correlations between quantified MRI data and eGFR were examined. Using the Imiomics technique ~2 million 3D elements were created. The voxel size was fixed, meaning that each voxel could be assigned a numerical value for tissue volume in comparison to the number of corresponding voxels in a reference body. That way, up to 2 million continuous variables were created with assigned positions in a coordinate system. To summarize, individual regional tissue volumes were computed as continuous variables.

In the concomitant statistical analysis, these relative measures were defined as exposure variables while $eGFR_{crea}$ and $eGFR_{cys}$ were used as outcome variables. Non-parametric (Spearman's rank coefficient) correlation analyses between the voxel-wise imaging parameters (local volume) and subject-wise eGFR were computed, and the results were stratified by sex. The statistical estimates were visualized by color-coded correlation Imiomic maps. For additional details on the Imiomics technique, we refer to the work by Strand *et al.* [16] and Lind *et al.* [17].

### Mendelian randomization

A two-sample Mendelian randomization analysis was performed using GWAS data on participants of predominantly European descent for traits related to obesity and kidney function. Exposure variables used were from meta-analyses of BMI [19] and WC [20] from the GIANT consortium with total sample sizes of 339 224 and 224 459 individuals, respectively. As outcome variables, GWAS data on $eGFR_{crea}$ and $eGFR_{cys}$ from the CKDgen consortium [21] was used, with total sample sizes of 1 201 909 and 460 826 individuals, respectively.

To be able to infer causality between the exposure and outcome in Mendelian randomization, traditionally three key assumptions must be met: (i) the relevance assumption: the genetic variant should be associated with the exposure; (iii) the independence assumption: the genetic variant should not be associated with a confounder, and (iii) the exclusion restriction assumption: there should not be another pathway in which the instrument affects the outcome. The relevance assumption was believed to be upheld because of the large sample size and strict pruning of the SNPs. Since genes are inherited at birth, it can also be presumed that the SNPs were present before the outcome strengthening the case of causal relation. The independence and exclusion restriction assumptions were both countered by using the more conservative calculation methods MR-Egger and weighted median as sensitivity analyses. Additionally, all instrument SNPs used in the analyses were examined through the genetic database PhenoScanner [24, 25] to reduce the risk of confounding.

The genetic instruments for exposures WC and BMI were created from respective GWAS [19, 20] in three steps:

(i) SNPs with a correlation $P$ value $<5 \times 10^{-8}$ were selected.
(ii) Independency was evaluated using the clump command in the R package MRbase with pruning $R^2$ cut-off 0.001.
(iii) Remaining SNPs were examined through PhenoScanner. SNPs were excluded if associations with an alternative pathway or confounder was stronger than the association to the exposure. Pre-specified variables for this step were hypertension, inflammation, diabetes, cardiovascular disease, diet, socioeconomic status, exercise, and smoking. For BMI, rs11126666 and rs17747324 were excluded because of strong associations with hypertension and diabetes, respectively. For WC, rs7903146 was excluded being heavily associated with diabetes.

The inverse variance weighted (IVW) method was used as the main method and assumes that most genetic variants are valid instrument variables. As secondary analyses, the results were then challenged by using MR-Egger, an estimation method that is robust to pleiotropy but lacks in power. As an additional sensitivity analysis weighted median was included, being more conservative compared to IVW, while having the advantage of being more consistent in dealing with instruments containing a mixture of valid and invalid instrument variables. The Mendelian randomization analyses were performed in STATA16 using the 'mrrobust' package.

## RESULTS

### Cross-sectional data and imaging analyses

Study population characteristics for these analyses are outlined in Table 1. In the POEM study population 42% were overweight (BMI 25–29.9) and 18% were obese (BMI > 29.9). Using traditional regression analysis with a model adjusting for education level, exercise habits, current smoking status and sex on the POEM data negative correlations between $eGFR_{cys}$ and both BMI [beta = −0.190 (95% CI: −0.280 to −0.100)] and WC [beta = −0.160 (95% CI: −0.250 to −0.060)] were shown. In contrast, positive associations were found for $eGFR_{crea}$ and both BMI [beta = 0.120 (95% CI: 0.030 to 0.210)] and WC [beta = 0.160 (95% CI: 0.070 to 0.260)] as shown in Fig. 2.

This pattern was also seen in the MRI Imiomics substudy. Both visceral and subcutaneous adipose tissue volumes were negatively correlated with $eGFR_{cys}$, but positively correlated with $eGFR_{crea}$. A similar pattern was found in both men and women. In compartments typical of large muscle mass, there was an association between tissue volume and lower $eGFR_{crea}$ for women, but no associations with $eGFR_{crea}$ for men or $eGFR_{cys}$ for either

**Table 1: POEM study population characteristics.**

| Variable | Cross-sectional ($n = 499$) | MRI data subgroup ($n = 326$) |
|---|---|---|
| Sex (F/M) *n*, % | 246 F/253 M | 167 F/159 M |
| BMI kg/m$^2$ | 26.4 ± 4.3 | 26.4 ± 4.1 |
| WC cm | 92.7 ± 10.8 | 92.0 ± 10.8 |
| eGFR$_{cys}$ (ml/min/1.73 m$^2$) | 114.3 ± 15.4 | 114.7 ± 14.1 |
| eGFR$_{crea}$ (ml/min/1.73 m$^2$) | 96.0 ± 11.9 | 95.8 ± 11.8 |

Continuous variables expressed as mean values *n* ± SD.

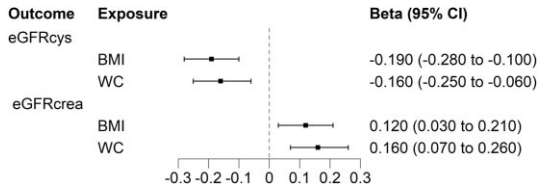



**Figure 2:** Results of traditional cross-sectional observations from the POEM study. Associations between anthropometric measurements and estimated glomerular filtration rate (eGFR). Outcomes were cystatin- and creatinine-based estimated glomerular filtration rates (eGFR$_{cys}$ and eGFR$_{crea}$) adjusted for education level, exercise habits, current smoking status, and sex.

sex. Visual presentations of the voxel-wise regression analyses are shown in Fig. 3.

### Mendelian randomization

The main results of the Mendelian randomization are shown in Fig. 4 and the genetic instruments for BMI ($n = 72$) and WC ($n = 40$) are presented in Supplementary Data, Tables S1 to S4. Mendelian randomization implied a negative causal effect of obesity-related measures on eGFR$_{cys}$, with statistically significant estimates for both BMI [beta = −0.031 (95% CI: −0.037 to −0.026)] and WC [beta = −0.038 (95% CI: −0.045 to −0.031)]. The IVW showed a numerically small, but not significant, positive correlation between both BMI and WC on eGFR$_{crea}$ [beta = 0.002 (95% CI: −0.001, 0.005) and 0.003 (−0.001, 0.008)]. The sensitivity analyses predominantly supported these findings with the weighted median showing corresponding significances and effect sizes. MR-Egger intercept did not significantly deviate from zero implying absence of bias due to pleiotropy. MR-Egger showed similar slope estimates except a smaller negative estimate size for the effect of BMI on eGFR$_{cys}$ [beta =−0.003 (95% CI: −0.040, 0.034)]. The sensitivity analyses are shown in detail in Table 2. A scatter plot of genetic associations using MR-Egger (Figure S1) and an MR-Egger funnel plot (Figure S2) are provided in the supplementary data.

## DISCUSSION

The aim of this study was to evaluate whether obesity causally affects kidney function defined as estimated glomerular filtration rate (eGFR). It was, however, clear from both the observational and Mendelian randomization analyses that the results were different depending on whether creatinine or cystatin C were used to estimate GFR.

First, a negative correlation was found between cystatin C-based eGFR and the obesity-related measures of BMI and WC in cross-sectional data from the POEM study. By contrast, a positive association was found for creatinine-based eGFR.

Second, as the unique feature of the POEM data analyses, correlation Imiomics maps were created to visualize and aid in the interpretation of the findings. This MRI data analysis accentuates the differences between GFR estimations using creatinine and cystatin C, with positive associations between volumes of both subcutaneous and visceral fat and eGFR based on creatinine and negative associations between these volumes and eGFR based on cystatin C. The correlation map over eGFR$_{crea}$ vs. tissue volume was of extra interest showing complete opposite correlations for large muscle groups and subcutaneous fat, illustrating that for a specific individual, the ratio between body fat and muscle mass could induce errors in GFR estimations.

Third, Mendelian randomization analyses implied negative causal effects on eGFR$_{cys}$ by genetically predicted BMI or WC. Regarding BMI, the MR-Egger sensitivity analysis supports the direction of correlation, but the difference in effect size should be a caveat since pleiotropy cannot be ruled out. Mendelian randomization calculations based on creatinine resulted in a non-significant trend toward a positive correlation for both BMI and WC that was replicated in sensitivity analysis with both MR-Egger and weighted median. The Mendelian randomization results are both in line with the findings from the POEM study analyses and with previous work using overlapping GWAS data [9], implying that the method is robust.

The general tendencies of an inconsistency between GFR estimation methods in the obese are in line with previous evidence of creatinine-based formulas overestimating and cystatin C-based formulas underestimating GFR [15]. Previous studies have found several non-GFR determinants that could interfere with measurement and explain these inconsistencies. For example, inflammation, obesity, smoking, and thyroid disorders have been shown to affect cystatin C-levels while protein intake, physical activity, and muscle mass are known factors affecting creatinine [26]. All of this should additionally be viewed from the perspective of adaptive kidney physiology in obese individuals with the development of hyperfiltration and later on hyperfiltration-induced kidney injury. Studies measuring GFR rather than using estimations have repeatedly shown higher than expected filtration rates (hyperfiltration) in obese individuals, which were normalized following bariatric surgery [27]. These individuals are believed to have emerging pathological processes but with a compensatory hyperfiltration leading to underestimation of early kidney pathology [28]. Hyperfiltration in obesity is customarily in a way compensated for by the indexation for body surface area which helps staging kidney failure, but deviates from reflecting actual filtration and thereby obscuring the interpretation.

One limitation of this study was not having access to measured GFR, but exclusively using estimations which increases the risk of systematic misclassification. The consequence of not having access to measured GFR is also a lack of a reference method and it is therefore no possible to state which of the

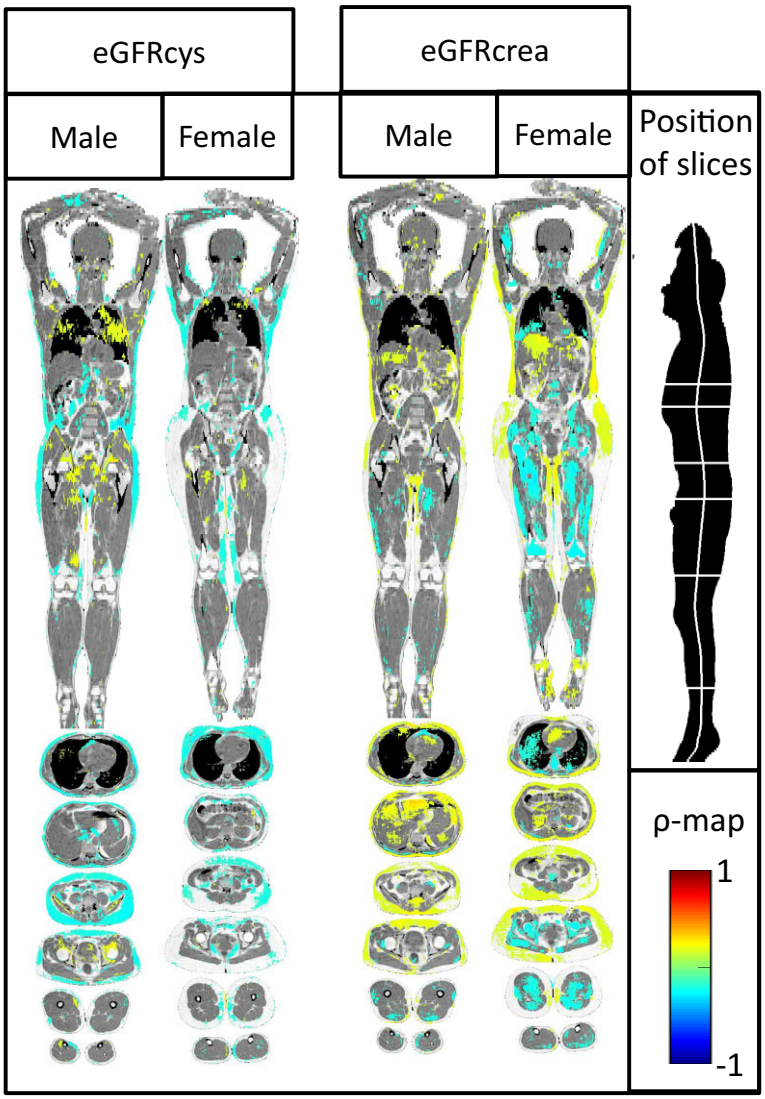



**Figure 3:** Voxel-wise visualization of local tissue volume correlations with both cystatin C-based and creatinine-based estimated glomerular filtration rates ($eGFR_{cys}$ and $eGFR_{crea}$). Results are shown stratified by sex and eGFR. A gradient of warmer colors represent an increasing positive correlation with red meaning the highest degree of association. Negative correlations are shown as a gradient of cooler colors with blue being the highest level of correlation.

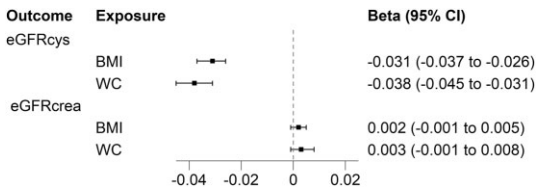



**Figure 4:** Results of Mendelian randomization analysis using GWAS data. Exposure variables were summarized data on BMI and WC. Outcomes were cystatin- and creatinine-based estimated glomerular filtration rates ($eGFR_{cys}$ and $eGFR_{crea}$).

methods to estimate kidney function that is closest to a measured GFR. Another important aspect is that only cross-sectional data were used. Even if Mendelian randomization partly counters issues on causal direction, this study is not able to propose statements on long-term implications for kidney and overall health in the study populations. Since only genetic summary statistics and no individual level data was used the strength of associations between the exposure phenotypes and the genetic instruments could not be estimated. The automated Imiomics technique, as of now, only gives the researcher data on the voxel level. The technique does not define muscle mass, different types of fat, or other tissues, and therefore these cannot be quantified. Limitations regarding the generalizability include study sample age and ethnicity. The GWAS used has a deficit of younger participants and the POEM study was performed on individuals being exclusively 50 years old, and being of European descent. The POEM study population was also generally healthy with normal or even high eGFR values, limiting the possibilities to draw conclusions on the effect of obesity on CKD.

It would be of major interest to develop better methods to evaluate kidney strain and damage in obese populations rather

**Table 2: Mendelian randomization sensitivity analysis.**

| Outcome | Exposure | Test | Estimate (95% CI) | *P* value |
|---|---|---|---|---|
| $eGFR_{cys}$ | BMI | MR-Egger intercept | −0.00068 (−0.0016, 0.00018) | .12 |
| | | MR-Egger slope | −0.003 (−0.040, 0.034) | .89 |
| | | Weighted median | −0.029 (−0.038, −0.021) | <.001 |
| | WC | MR-Egger intercept | −0.00059 (−0.0025, 0.0014) | .56 |
| | | MR-Egger slope | −0.013 (−0.097, 0.070) | .76 |
| | | Weighted median | −0.035 (−0.048, −0.022) | <.001 |
| $eGFR_{crea}$ | BMI | MR-Egger intercept | −0.000047 (−0.00076, 0.00067) | .90 |
| | | MR-Egger slope | 0.004 (−0.027, 0.034) | .81 |
| | | Weighted median | 0.002 (−0–003, 0.008) | .43 |
| | WC | MR-Egger intercept | −0.0011 (−0.0025, 0.00024) | .11 |
| | | MR-Egger slope | 0.050 (−0–008, 0.107) | .09 |
| | | Weighted median | 0.003 (−0.004, 0.010) | .40 |

than exclusively focusing on glomerular filtration rates. Suggestions for future research efforts would be to use existing GFR estimation formulas combining both cystatin C and creatinine to balance systematic errors from metabolic effects. The use of longitudinal data could additionally strengthen statements of causality. In addition, modernization of body surface area calculation might be warranted since the Du Bois equation is based on a few individuals who have a body composition that is nowhere near that of modern populations [29].

In conclusion, this study suggests a causal relation between obesity and eGFR based on cystatin C, but not when GFR is estimated using creatinine. This discrepancy is further highlighted by analyses of imaging data of fat tissue. These findings warrant further research on the impact of using the endogenous biomarkers creatinine and cystatin C to estimate renal function when assessing the link between obesity and CKD.

## SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

## ACKNOWLEDGEMENTS

We thank all participants in the study. We are grateful for the skilled work by Kerstin Marttala at the Uppsala University Hospital for her help in making this study possible (POEM study).

## FUNDING

The Uppsala University Hospital ALF grants and establishment funding (M.K.S.), the CUWX foundation and The Swedish Kidney Foundation, Swedish National Strategic Research Initiative EXODIAB (Excellence of Diabetes Research in Sweden), and the Family Ernfors Foundation, Heart-Lung Foundation (no. 20220129).

## AUTHORS' CONTRIBUTIONS

P.E., M.K.S., and L.L. developed the concept of the study. P.E., R.S., J.K., H.A., A.L., and L.L. performed all data curation. P.E. and L.L. were responsible for and performed the statistical analyses. P.E., M.K.S., R.S., J.K., H.A., A.L., and L.L. participated in data interpretation. P.E. drafted the original manuscript, with critical intellectual input from M.K.S., R.S., J.K., H.A., A.L., and L.L.

## CONFLICT OF INTEREST STATEMENT

None of the authors have direct conflicts of interest to declare in relation to this work. R.S. and J.K. have an issued patent for the image data analysis used in this study: "Whole Body Image Registration Method and Method for Analyzing Images Thereof, P1318PC00." H.A. and J.K. are co-founders and employees of Antaros Medical AB. Antaros Medical AB did not fund the study and did not have any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## DATA AVAILABILITY STATEMENT

The data will be shared on reasonable request to the corresponding author. Major parts of the data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study according to Swedish law.

## REFERENCES

1. Phelps NH, Singleton RK, Zhou B. Worldwide trends in the burden of underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million school-aged children, adolescents and adults. *Lancet* 2024;**6736**:1–24.
2. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;**377**:13–27. https://doi.org/10.1056/NEJMoa1614362
3. Chang AR, Grams ME, Ballew SH *et al*. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ* 2019;**364**;k5301. https://doi.org/10.1136/bmj.k5301
4. Garofalo C, Borrelli S, Minutolo R *et al*. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. *Kidney Int* 2017;**91**:1224–35. https://doi.org/10.1016/j.kint.2016.12.013
5. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA* 2017;**318**:1925–6. https://doi.org/10.1001/jama.2017.17219
6. Zhu P, Herrington WG, Haynes R *et al*. Conventional and genetic evidence on the association between adiposity and CKD. *J Am Soc Nephrol* 2021;**32**:127–37. https://doi.org/10.1681/ASN.2020050679
7. Zheng J, Zhang Y, Rasheed H *et al*. Trans-ethnic mendelian-randomization study reveals causal relationships between

cardiometabolic factors and chronic kidney disease. *Int J Epidemiol* 2021;**50**:1995–2010. https://doi.org/10.1093/ije/dyab203
8. Ye C, Kong L, Zhao Z *et al*. Causal associations of obesity with chronic kidney disease and arterial stiffness: a mendelian randomization study. *J Clin Endocrinol Metab* 2021;**107**:e825–e35. https://doi.org/10.1210/clinem/dgab633
9. Kjaergaard AD, Teumer A, Witte DR *et al*. Obesity and kidney function: a two-sample mendelian randomization study. *Clin Chem* 2022;**68**:461–72. https://doi.org/10.1093/clinchem/hvab249
10. Chew-Harris JSC, Florkowski CM, George PM *et al*. The relative effects of fat versus muscle mass on cystatin C and estimates of renal function in healthy young men. *Ann Clin Biochem* 2013;**50**:39–46. https://doi.org/10.1258/acb.2012.011241
11. Muntner P, Winston J, Uribarri J *et al*. Overweight, obesity, and elevated serum cystatin C levels in adults in the United States. *Am J Med* 2008;**121**:341–8. https://doi.org/10.1016/j.amjmed.2008.01.003
12. Cala A, Ahmed MS, Menon VB *et al*. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 2008;**3**:348–54.
13. Friedman AN, Moe S, Fadel WF *et al*. Predicting the glomerular filtration rate in bariatric surgery patients. *Am J Nephrol* 2014;**39**:8–15. https://doi.org/10.1159/000357231
14. Chang AR, George J, Levey AS *et al*. Performance of glomerular filtration rate estimating equations before and after bariatric surgery. *Kidney Med* 2020;**2**:10–13. https://doi.org/10.1016/j.xkme.2020.08.008
15. López-Martínez M, Luis-Lima S, Morales E *et al*. The estimation of GFR and the adjustment for BSA in overweight and obesity: a dreadful combination of two errors. *Int J Obes* 2020;**44**:1129–40. https://doi.org/10.1038/s41366-019-0476-z
16. Strand R, Malmberg F, Johansson L *et al*. A concept for holistic whole body MRI data analysis, Imiomics. *PLoS ONE* 2017;**12**:e0169966. https://doi.org/10.1371/journal.pone.0169966
17. Lind L, Kullberg J, Ahlström H *et al*. Proof of principle study of a detailed whole-body image analysis technique, "Imiomics", regarding adipose and lean tissue distribution. *Sci Rep* 2019;**9**:7388. https://doi.org/10.1038/s41598-019-43690-w
18. Strand R, Ekström S, Breznik E *et al*. Recent advances in large scale whole body MRI image analysis: Imiomics. In: *Proceedings of the 5th International Conference on Sustainable Information Engineering and Technology* 2020;10–15
19. Lind L. Population-based cardiovascular cohort studies in Uppsala. *Ups J Med Sci* 2019;**124**:16–20. https://doi.org/10.1080/03009734.2018.1515282
20. Locke AE, Kahali B, Berndt SI *et al*. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;**518**:197–206. https://doi.org/10.1038/nature14177
21. Shungin D, Winkler T, Croteau-Chonka DC *et al*. New genetic loci link adipose and insulin biology to body fat distribution. *Nature* 2015;**518**:187–96. https://doi.org/10.1038/nature14132
22. Stanzick KJ, Li Y, Schlosser P *et al*. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat Commun* 2021;**12**:4350.
23. Inker LA, Eneanya ND, Coresh J *et al*. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953
24. Staley JR, Blackshaw J, Kamat MA *et al*. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics* 2016;**32**:3207–9. https://doi.org/10.1093/bioinformatics/btw373
25. Kamat MA, Blackshaw JA, Young R *et al*. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics* 2019;**35**:4851–3. https://doi.org/10.1093/bioinformatics/btz469
26. Fu EL, Levey AS, Coresh J *et al*. Accuracy of GFR estimating equations in patients with discordances between creatinine and cystatin C-based estimations. *J Am Soc Nephrol* 2023;**34**:1241–51. https://doi.org/10.1681/ASN.0000000000000128
27. Chang AR, Grams ME, Navaneethan SD. Bariatric surgery and kidney-related outcomes. *Kidney Int Rep* 2017;**2**:261–70. https://doi.org/10.1016/j.ekir.2017.01.010
28. Palatini P. Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant* 2012;**27**:1708–14. https://doi.org/10.1093/ndt/gfs037
29. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;**17**:863–71. https://doi.org/10.1001/archinte.1916.00080130010002

*Received: 17.9.2024; Editorial decision: 11.3.2025*