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Allometric body shape indices, type 2 diabetes and kidney function: A two-sample Mendelian randomization study

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Abstract

Aim: To examine the association between body mass index (BMI)-independent allometric body shape indices and kidney function.

Materials and methods: We performed a two-sample Mendelian randomization (MR) analysis, using summary statistics from UK Biobank, CKDGen and DIAGRAM. BMI-independent allometric body shape indices were: A Body Shape Index (ABSI), Waist-Hip Index (WHI) and Hip Index (HI). Kidney function outcomes were: urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate and blood urea nitrogen. Furthermore, we investigated type 2 diabetes (T2D) as a potential mediator on the pathway to albuminuria. The main analysis was inverse variance-weighted random-effects MR in participants of European ancestry. We also performed several sensitivity MR analyses.

Results: A 1-standard deviation (SD) increase in genetically predicted ABSI and WHI levels was associated with higher UACR ($\beta = 0.039$ [95% confidence interval: 0.016, 0.063] log [UACR], $P = 0.001$ for ABSI, and $\beta = 0.028$ [0.012, 0.044] log [UACR], $P = 6 \times 10^{-4}$ for WHI) in women, but not in men. Meanwhile, a 1-SD increase in genetically predicted HI was associated with lower UACR in women ($\beta = -0.021$ [−0.041, 0.000] log [UACR], $P = 0.05$) and in men ($\beta = -0.026$ [−0.058, 0.005] log [UACR], $P = 0.10$). Corresponding estimates in individuals with diabetes were substantially augmented. Risk of T2D increased for genetically high ABSI and WHI in women ($P < 6 \times 10^{-19}$) only, but decreased for genetically high HI in both sexes ($P < 9 \times 10^{-3}$). No other associations were observed.

Conclusions: Genetically high HI was associated with decreased risk of albuminuria, mediated through decreased T2D risk in both sexes. Opposite associations applied to genetically high ABSI and WHI in women only.

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KEYWORDS
albuminuria, blood urea nitrogen, diabetes mellitus, type 2, glomerular filtration rate, kidney function tests, Mendelian randomization analysis, obesity, renal insufficiency, chronic

1 | INTRODUCTION

Chronic kidney disease (CKD) is characterized by albuminuria and reduced glomerular filtration rate (GFR).[1] The global prevalence of CKD is approximately 10% in the general population,[2] and up to 40% in individuals with diabetes.[3] Obesity is a risk factor for CKD, partly mediated through type 2 diabetes (T2D).[4-6] Defining obesity is traditionally based on the body measurements (anthropometrics) of height, weight, waist circumference (WC), and hip circumference (HC). Specifically, the most common definition of obesity is based on body mass index (BMI), representing weight adjusted for height. In order to also utilize information offered by the other anthropometrics on fat amount and distribution, WC and waist-hip ratio (WHR) are commonly used to complement BMI. However, they are highly correlated to BMI and to each other. To overcome this, the independent allometric body shape indices: the A Body Shape Index (ABSI), Waist-Hip Index (WHI) and Hip Index (HI) have been developed.[7-9] These indices better complement BMI by being independent of weight but enable different fat and muscle distributions within the same weight class to be differentiated. Allometry is defined as the scaling relationships between different dimensions of an organism.[10] Thus, ABSI, WHI and HI can be seen as allometric counterparts of the respective anthropometrics: WC, WHR and HC (see Methods for calculations). In observational studies, higher ABSI, in particular, is associated with T2D,[11,12] albuminuria,[13,14] and lower estimated GFR (eGFR),[15] but whether these associations are confounded or causal and mediated through T2D is unknown.

Mendelian randomization (MR) can be used to examine whether allometric body shape indices (ABSI, WHI and HI) are causally associated with kidney function (eg, albuminuria and eGFR) and whether this association is mediated through T2D. The MR method assesses the direction and magnitude of the effects of genetically predicted life-long exposures, such as allometric body shape indices, on outcomes such as kidney function. The MR method overcomes reverse causation[16] because genotypes are established at conception (Mendel's law of segregation) and confounding because potential confounders are evenly distributed across genotype (Mendel's law of independent assortment). We recently used this method to show that genetically high BMI was associated with impaired kidney function, driven by adverse obesity (high BMI and high WHR, ie, abdominal obesity) and, for albuminuria, additionally by T2D.[17]

In the present two-sample MR study, using summary statistics from UK Biobank, CKDGen Consortium and DIAGRAM, we examined the association between genetically predicted (BMI-independent) allometric body shape indices (ABSI, WHI and HI) and kidney function (related to albuminuria, eGFR and blood urea nitrogen [BUN]). Furthermore, we investigated T2D as a potential mediator on the pathway to albuminuria. Importantly, we conducted sex-stratified MR analyses, due to sexual dimorphism for genetically predicted allometric body shape indices (see Methods for details).

2 | MATERIALS AND METHODS

Mendelian randomization uses genetic variants (typically single-nucleotide polymorphisms [SNPs]) associated with life-long exposure of interest as instrumental variables to infer causality with the outcome of interest. We employed a two-sample MR approach that leverages the publicly available summary statistics (β-coefficients and standard errors [SEs]) on SNP-exposure and SNP-outcome associations from two different genome-wide association studies (GWASs). First, the top independent SNPs robustly associated with the exposure of interest (eg, ABSI) are identified (from a GWAS on the exposure of interest), and the SNP-exposure summary statistics are extracted. Second, the SNP-outcome summary statistics for the identified SNPs are extracted from a GWAS on the outcome of interest (eg, albuminuria). Third, SNP-exposure and SNP-outcome summary statistics are harmonized (aligned to the effect allele associated with increased level of exposure). MR analyses can then be performed to assess the direction and magnitude of the effect of genetically predicted exposure on outcome (eg, causal effect of ABSI on albuminuria).

The three core assumptions for exposure SNPs are: (i) must be strongly associated with the exposure; (ii) must not be associated with confounders of the exposure-outcome relationship, and (iii) must not be associated with outcome through any other pathway than the exposure.

2.1 | Identification of allometric body shape indices SNPs

We identified a single GWAS on the allometric body shape indices ABSI, WHI and HI performed on UK Biobank data comprising 219 872 women and 186 825 men of European ancestry (Table S1).[9]

The allometric counterparts of waist and hip circumference, ABSI and HI, were calculated using published formulas derived for participants in the National Health and Nutrition Examination Survey (NHANES)[7,8] as:

$$\text{ABSI} = \text{waist circumference (m)} * \text{weight (kg)}^{-\frac{2}{3}} * \text{height (m)}^{\frac{5}{6}}$$

and

$$\text{HI} = \text{HC (cm)} * \left(\frac{\text{weight (kg)}}{73\,\text{kg}}\right)^{-0.482} * \left(\frac{\text{height (cm)}}{166\,\text{cm}}\right)^{0.310}$$

To investigate the allometric counterpart of WHR, the authors of the allometric body shape indices GWAS created a novel index, following the same general formula, and determined WHI as:

$$\text{WHI} = \text{WHR} * (\text{weight (kg)} * \text{height (cm)})^{-1/4}$$

The general formula is:

$$\text{Index} = \text{measure} * \text{weight}^{-\beta} * \text{height}^{-\gamma}$$

The index represents the measure (eg, WC or HC) divided by the expected value for the measure given weight and height. The familiar formula for BMI is obtained when $\beta = 0$ and $\gamma = 2$, that is, weight is expected to be proportional to height-squared as derived by Adolphe Quetelet in 1832, and known as BMI since 1972.[18] Importantly, all three allometric shape indices were calibrated for UK Biobank participants.

As genetic associations were sexually dimorphic, that is, they had estimates that differed substantially between the sexes (30% for ABSI and 10% for HI), this GWAS was performed on women and men separately, with fewer SNPs identified in men compared to women. However, as only sex-combined, but not sex-stratified summary statistics were publicly available for kidney function outcomes, we only included allometric body shape indices SNPs that showed some, but no substantial sexual dimorphism (SexDiff = 0, Table S9).[9] Furthermore, we only included top independent SNPs (see Methods section) and those with SNP-exposure association at GWAS significance level ($P < 5 \times 10^{-8}$). Using the above-mentioned criteria, we identified 223 and 56 SNPs for ABSI, 369 and 98 SNPs for WHI, and 193 and 76 SNPs for HI in women and men of European ancestry, respectively (Table S2).

2.2 | Kidney function outcomes

We examined kidney function outcomes related to albuminuria, eGFR and BUN. The main analyses were performed in participants of European ancestry in order to reduce the risk of population stratification. Thus, the main kidney function outcomes were: urinary albumin-to-creatinine ratio (UACR; in overall population as well as individuals with and without diabetes), microalbuminuria, eGFR (in overall population as well as individuals with and without diabetes), CKD and BUN (Table S1).[19-23]

UACR was calculated as the ratio of urinary albumin (in mg) and urinary creatinine (in g), where urinary albumin values below the detection limit of the used assays were set to the lower limit of detection. Microalbuminuria was defined in the respective GWASs as either UACR above 25 mg/g in women and 17 mg/g in men[21] for cases and the remaining individuals as controls, or UACR > 30 mg/g for cases and UACR < 10 mg/g for controls in both sexes.[20] eGFR based on serum creatinine ($\text{eGFR}_{\text{crea}}$) was calculated by the presently recommended CKD Epidemiology Collaboration (CKD-EPI) formula for creatinine.[24] CKD was defined as $\text{eGFR}_{\text{crea}} < 60$ mL/min/1.73 m^2. BUN measurements were converted from mmol/L to mg/dL (multiplied by 2.8), prior to natural log transformation.[19] However, in order to substantially increase power, that is, sample sizes (for UACR in individuals with diabetes, microalbuminuria and BUN), and in order to investigate kidney function outcomes (eGFR based on serum cystatin C [$\text{eGFR}_{\text{cysC}}$], and measures of eGFR decline) where summary statistics were not publicly available in participants of European ancestry separately, we performed additional analyses in transethnic, but predominantly (up to 97%) European, populations.[19,20,25,26] Thus, although referred to as transethnic, these analyses should be considered and interpreted as European. Furthermore, in a post hoc analysis, in order to include sex-stratified albuminuria-related kidney function, we also examined microalbumin in (spot) urine in Europeans. These additional kidney function outcomes are described in the Appendix S1.

2.3 | Additional analyses related to T2D

First, in order to investigate whether the potential causal effects of allometric body shape indices on albuminuria were mediated by T2D, we performed additional analyses restricted to allometric body shape SNPs that were also nominally significantly associated with increased risk of T2D.[27]

Second, we used a two-step MR (for estimating mediation analysis with MR)[28] to further explore a potential mediating role of T2D on the pathway to albuminuria. Specifically, we examined the potential causal association between: (i) allometric body shape indices and T2D risk, and (ii) T2D and albuminuria risk. The latter served as a positive control, as a previous MR study using UK Biobank and CKDgen showed that genetic predisposition to T2D was associated with increased UACR.[29]

Third, we performed a bidirectional MR analysis to examine whether T2D causes UACR, or vice versa. For this purpose, using the same criteria for SNP identification described above, we identified 246 SNPs for T2D from the DIAGRAM Consortium[27] and 61 SNPs for UACR from the CKDGen Consortium.[20]

Importantly, as summary statistics for allometric body shape indices were publicly available for top SNPs only, and not for the entire GWAS, we were unable to perform bidirectional or multivariable MR (accounting for T2D) analyses for these.[30]

2.4 | Data access

We downloaded sex-stratified summary statistics on top independent SNPs on ABSI, WHI and HI from UK Biobank from Table S9 in a recent GWAS on these traits.[9]

The GWAS summary statistics on T2D (sex-combined and sex-stratified) provided by the DIAGRAM Consortium were downloaded from: http://diagram-consortium.org/downloads.html.[27]

The CKDGen Consortium provided the sex-combined GWAS summary statics on kidney function measures. These were accessed at: http://ckdgen.imbi.uni-freiburg.de/,[19-21,23,25] and through the OpenGWAS project provided by the MRC Integrative Epidemiology Unit at the University of Bristol at: https://gwas.mrcieu.ac.uk.[31]

Sex-stratified summary statistics on microalbumin in (spot) urine from the UK Biobank were provided by Neale Lab (http://www.nealelab.is/uk-biobank/).

Summary statistics necessary for analyses include β-coefficient and its SE, and the effect allele, the other allele, and effect allele frequency of each SNP-trait association.

2.5 | Ethics

All of the above-mentioned GWASs have collected relevant ethical approvals.

2.6 | Statistical analysis

Analyses were performed in R version 4.0.4 using Two Sample MR[32,33] version 0.5.6, MRPRESSO[34] version 1.0, and MR[35] version 0.6.0 packages. The latter was only used for calculating I^2_{GX}.

The R code used in this study is publicly available at: https://github.com/AlisaDK/ABSI_kidney.

Traditionally, a P value < 0.05 is taken to indicate statistical significance. However, since a P value above a chosen threshold is not proof of lack of an association,[36] we performed an overall evaluation of each result, even with a $P \geq 0.05$, individually by considering the effect size, SE, biological plausibility and consistency across the examined exposures, outcomes and MR analyses. For this reason we did not correct for multiple comparisons.

We only included top independent exposure SNPs, by excluding SNPs in linkage disequilibrium within a 10-Mb window and R^2 cut-off at 0.01. All SNPs had sufficient strength ($F > 10$) to be used as genetic instruments, calculated as: $F = \beta^2_{exposure}/SE^2_{exposure}$.

Summary statistics for these exposure SNPs were then extracted from outcome GWASs. Not all of the exposure SNPs were available in all outcome GWASs, so number of SNPs varies for different MR analyses. Only the single oldest GWAS[21] had many SNPs missing, which is why we used proxies instead of the missing SNPs for this GWAS only. We accessed this GWAS through the OpenGWAS project (ieu-a-110, ieu-a-1101 and ieu-a-1097),[31] as proxy query through this resource is supported and automatized by the TwoSampleMR R package.

Data harmonization between the SNP-exposure and SNP-outcome summary statistics was performed by aligning the effect estimates to the effect allele of each SNP, defined as the allele associated with increased level of the relevant exposure. Inconsistent and palindromic SNPs with effect allele frequencies close to 50% were excluded.

Individual causal estimates, calculated as Wald ratios of the SNP-outcome and SNP-exposure association for each SNP, were meta-analysed into an overall causal estimate for each exposure and outcome combination.[37] The main MR analysis was the inverse variance weighting (IVW) meta-analysis. Specifically, we used multiplicative random-effects rather than fixed-effects IVW meta-analysis because it accounts for the heterogeneity (assessed as Cochran's Q and corresponding I^2) of the individual causal estimates.[38] However, both IVW methods assume that all SNPs are valid genetic instruments with no measurement error (NOME) in the SNP-exposure association. We therefore performed sensitivity MR analyses with other assumptions regarding SNP validity and pleiotropy: MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), weighted median (WM) and MR-Egger regression analyses.

MR-PRESSO is a simulation-based approach that minimizes horizontal pleiotropy by excluding outlier SNPs with greatest heterogeneity contributions.[34] While WM requires that at least 50% of the weight contributed by genetic variants comes from valid genetic instruments,[39] MR-Egger provides robust estimates even in cases of substantial pleiotropy.[40] We tested the directional pleiotropy by MR-Egger intercept test, and quantified the violation of the NOME assumption by the I^2_{GX}.[40]

Directionality of potential causal associations was examined by MR Steiger (true/false), and additional MR analyses were performed after Steiger filtering. While Steiger filtering excludes SNPs that explain more of the variation in outcomes than the exposures, MR Steiger uses all SNPs to assess whether the causal direction examined is true (if all the SNPs combined explain more variance in the exposure than the outcome) or false (if all the SNPs combined explain more variance in the outcome than the exposure).

3 | RESULTS

3.1 | Albuminuria and T2D

In the population of European ancestry, a 1-standard deviation (SD) increase in genetically predicted ABSI and WHI levels was associated with higher UACR ($\beta = 0.039$ [0.016, 0.063] log[UACR], $P = 0.001$ for ABSI, and $\beta = 0.028$ [0.012, 0.044] log[UACR], $P = 6 \times 10^{-4}$ for WHI) in women, but not in men (Figure 1, Tables S3 and S4). Meanwhile, a 1-SD increase in genetically higher HI was associated with lower UACR in women ($\beta = -0.021$ [−0.041, 0.000] log[UACR], $P = 0.05$) as well as in men ($\beta = -0.026$ [−0.058, 0.005] log[UACR], $P = 0.10$, Figure 1, Tables S3 and S4). Corresponding estimates restricted to individuals with diabetes were substantially augmented (Figures 1 and 2, and Tables S3 and S4).

Overall, these findings were in agreement with estimates for microalbuminuria, and for sensitivity MR analyses, although some of

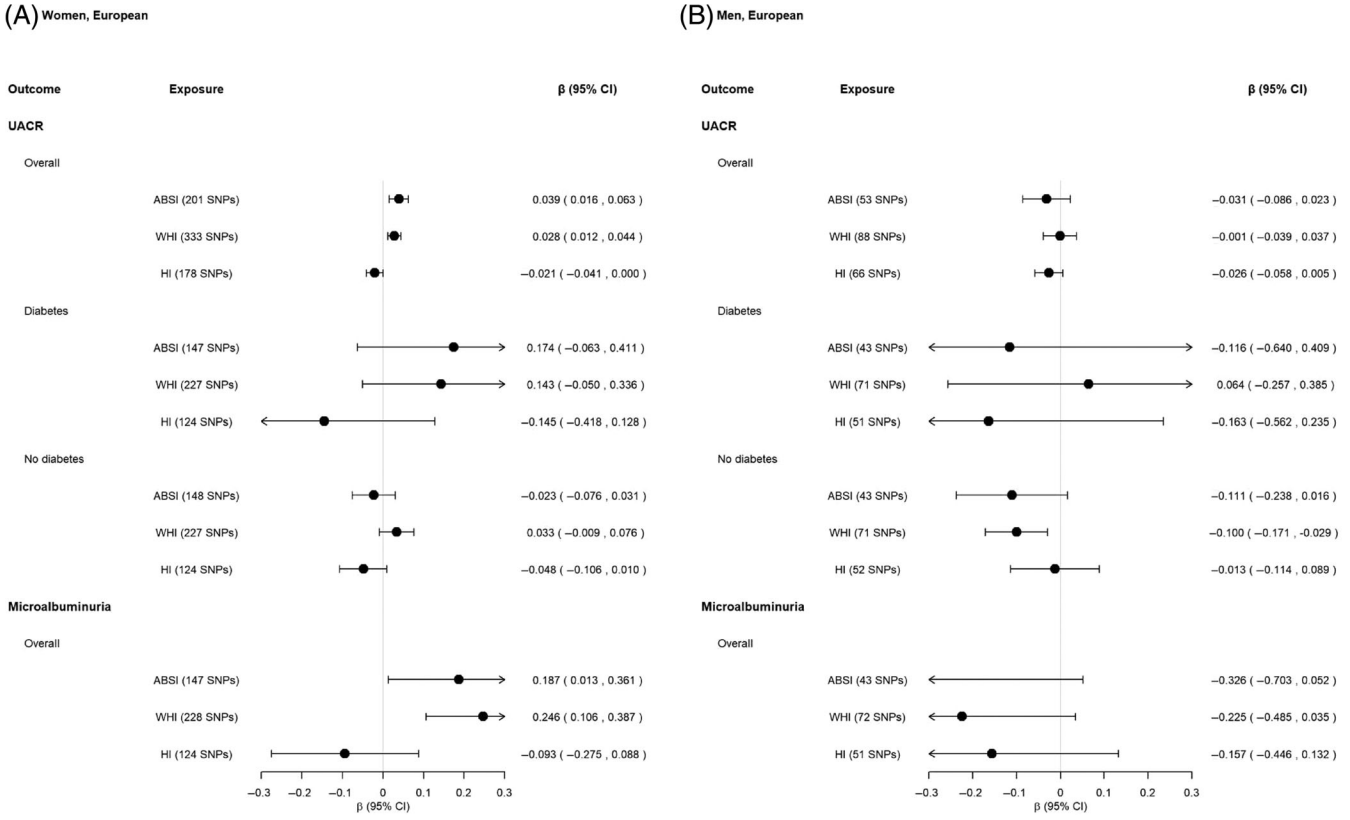

FIGURE 1 Causal effects of allometric body shape indices on albuminuria in (A) women and (B) men of European ancestry. Estimates (β-coefficients and 95% confidence intervals [CIs]) are from the inverse variance-weighted random-effects Mendelian randomization (MR) analysis, and expressed in log units per standard deviation increase in the relevant exposure. For each exposure, the number of single-nucleotide polymorphisms (SNPs) included in the analysis is shown in parenthesis. Allometric body shape indices (A Body Shape Index [ABSI], waist-hip index [WHI], and hip index [HI] in up to 219 872 women and 186 825 men of European ancestry from the UK Biobank) are sex-stratified, as sex-combined summary statistics were not publicly available. In contrast, albuminuria-related kidney function outcomes are sex-combined, as sex-stratified summary statistics were not publicly available. The outcomes were urinary albumin-creatinine ratio (UACR), available in the overall population (CKDGen and UK Biobank combined: $N_{overall} = 547\,361$) as well as stratified by diabetes status (CKDGen: $N_{Diabetes} = 5825$, $N_{No\ diabetes} = 46\,061$) and genetic predisposition to microalbuminuria (CKDGen: $N_{cases} = 5996$, $N_{controls} = 48\,140$). Sensitivity MR analyses are shown in Tables S2 and S3

the estimates had 95% confidence intervals (CIs) that included 0 (Figures 1 and 2, and Tables S3–S6).

Further support for these findings is illustrated in Figure 3 and Tables S5 to S8. Compared to using the full set of allometric body shape indices SNPs, restricting these SNPs to those nominally associated with increased risk of T2D yielded similar UACR for ABSI (0.033 vs. 0.039) and WHI (0.035 vs. 0.028) and flipped the UACR decrease to increase in HI (0.130 vs. −0.021, with overlapping 95% CIs) in women (Figures 1A and 3). Overall, these findings were in agreement with estimates for microalbuminuria in women (Figures 1A and 3). Indeed, while genetically high HI was associated with decreased risk of albuminuria, T2D-related genetically high HI was associated with increased risk in women. We did not perform corresponding analyses in men because there were substantially fewer SNPs for allometric body shape indices in men compared to women.

Figure 4, the two-step MR analysis, shows that genetically high ABSI and WHI were associated with increased risk of T2D in women ($P < 6 \times 10^{-19}$), but not in men ($P > 0.55$), and that genetic predisposition to T2D was associated with increased albuminuria in sex-combined analysis (Tables S9 and S10).

Collectively, this suggests that the causal effect of high ABSI and WHI on increased risk of albuminuria is (at least partly) mediated through increased risk of T2D in women, but not in men.

Meanwhile, genetically high HI was associated with decreased risk of T2D in women ($P = 9 \times 10^{-18}$) as well as in men ($P = 9 \times 10^{-3}$; Figure 4, Tables S9 and S10). Overall, this was in agreement with the association between genetically high HI and decreased risk of albuminuria (Figures 1 and 2) in all populations and in both sexes, although some of the estimates had CIs that included 0 (Figures 1, 2, S1 and S2; Tables S3–S6).

Collectively, this suggests that the causal effect of high HI on decreased risk of albuminuria is (partly) mediated through decreased risk of T2D in women as well as in men.

Finally, the directionality of this association was supported by Steiger filtering and MR Steiger, as well as the bidirectional MR,

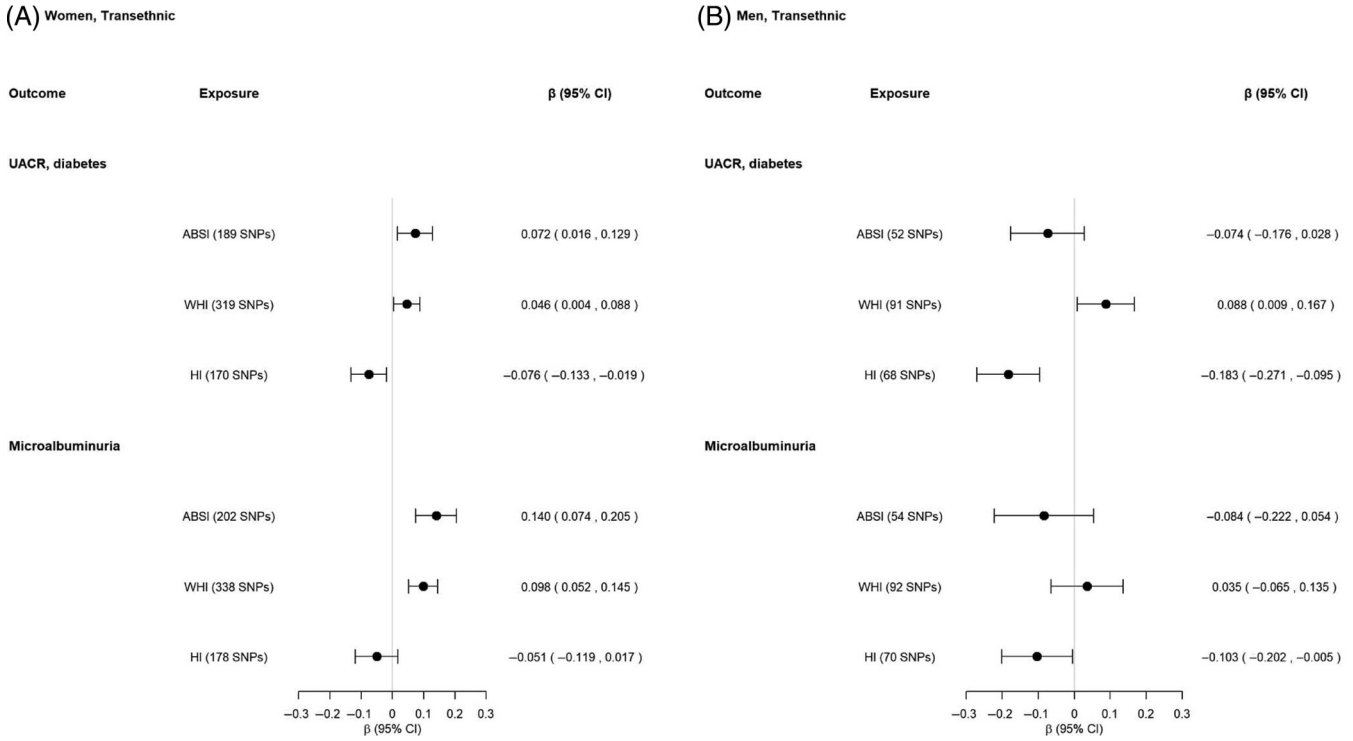

FIGURE 2 Causal effects of allometric body shape indices on albuminuria in (A) women and (B) men of transethnic ancestry. Estimates (β-coefficients and 95% confidence intervals [CIs]) are from the inverse variance-weighted random-effects Mendelian randomization (MR) analysis, and expressed in log units per standard deviation increase in the relevant exposure. For each exposure, the number of single-nucleotide polymorphisms (SNPs) included in the analysis is shown in parenthesis. Allometric body shape indices (A Body Shape Index [ABSI], waist-hip index [WHI], and hip index [HI] in up to 219 872 women and 186 825 men of European ancestry from the UK Biobank) are sex-stratified, as neither sex-combined nor transethnic population summary statistics were publicly available. In contrast, albuminuria-related kidney function outcomes are sex-combined, as sex-stratified summary statistics were not publicly available. The outcomes for transethnic (>95% European ancestry) population were urinary albumin-creatinine ratio in individuals with diabetes (UACR, diabetes, CKDGen and UK Biobank combined: N = 51 541) and genetic predisposition to microalbuminuria (CKDGen and UK Biobank: N_{cases} = 51 861, $N_{controls}$ = 297 093). Sensitivity MR analyses are shown in Tables S3 and S4

indicating that T2D was more likely a cause of increased UACR than vice versa (Tables S9–S11).

3.2 | Kidney function related to eGFR and BUN

Genetically high ABSI, WHI and HI were not associated with kidney function outcomes related to eGFR and BUN (Figures S1 and S2; Tables S3 and S4).

4 | DISCUSSION

The association between obesity and kidney function has huge clinical and societal implications since global prevalences of both obesity and kidney disease are increasingly high. Meanwhile obesity is potentially preventable and reversible. However, obesity is traditionally studied as high BMI and/or WHR, whereas alternative allometric body shape indices remain understudied. Indeed, this is the first MR study examining whether the link between allometric body shape indices and kidney function is causal, and whether it is mediated through T2D. Using summary statistics from the largest publicly available GWASs, we found evidence that high HI is causally associated with decreased risk of albuminuria, mediated through decreased T2D risk in both sexes, whereas high ABSI and WHI have the opposite effects in women only. Thus, this study showed that an adverse body shape associated with abdominal obesity independent from body size was causally associated with increased albuminuria, a marker of structural kidney damage, and mediated through T2D.

Previous MR studies using traditional anthropometric measures have found that abdominal obesity measured as BMI-adjusted WHR rather than high BMI alone is associated with albuminuria and driven by T2D as an important mediator.[4-6,17,29] In a recent MR study, we showed that genetically high BMI was associated with impaired kidney function, driven by adverse obesity (high BMI and high WHR) and for albuminuria additionally by T2D.[17] Two recent studies that combined conventional epidemiological and MR methods found that high BMI and WHR were associated with impaired kidney function, partly

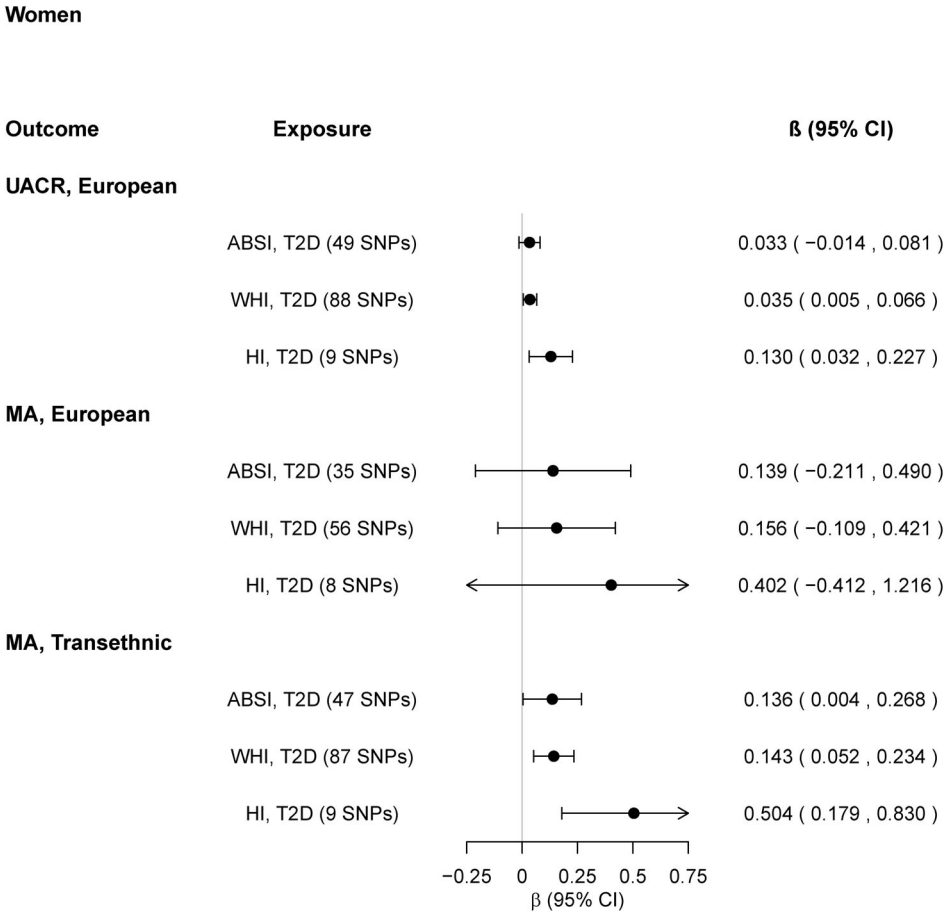

FIGURE 3 Causal effects of type 2 diabetes (T2D)-related allometric body shape indices on albuminuria in women. Estimates (β-coefficients and 95% confidence intervals [CIs]) are from the inverse variance-weighted random-effects Mendelian randomization (MR) analysis, and expressed in log units per standard deviation increase in the relevant exposure. For each exposure, the number of single-nucleotide polymorphisms (SNPs) included in the analysis is shown in parenthesis. The analyses were restricted to SNPs nominally associated with increased risk of T2D (see Methods). Allometric body shape indices indices (A Body Shape Index [ABSI], waist-hip index [WHI], and hip index [HI] in up to 219 872 women and 186 825 men of European ancestry from the UK Biobank) are for European women only, as neither sex-combined nor transethnic summary statistics were publicly available. In contrast, albuminuria-related kidney function outcomes are sex-combined, as sex-stratified summary statistics were not publicly available. The outcomes were urinary albumin-creatinine ratio (UACR, $N_{European} = 547\,361$) and genetic predisposition to microalbuminuria (CKDGen: $N_{European} = 54\,116$, and CKDGen, UK Biobank combined: $N_{Transethnic} = 348\,954$). Sensitivity MR analyses are shown in Tables S7 and S8

mediated through diabetes (and high blood pressure).[4,6] Another MR study showed that genetically high BMI as well as genetic predisposition to T2D were associated with increased risk of CKD.[5] Furthermore, yet another MR study found that genetically high BMI-adjusted WHR was causally associated with increased albuminuria, while 'favourable adiposity' (defined as genetically higher body fat but with low cardiometabolic risk) was associated with decreased albuminuria.[29] However, in contrast, a conventional epidemiological study of >400 000 individuals from the UK Biobank, found that (measured) high BMI and WHR were (mutually) independently associated with increased UACR levels.[41]

In contrast to previous reports on BMI (and WHR),[4-6,17] we did not find causal associations between allometric body shape indices and eGFR (or BUN). A possible explanation for the discrepancy may be the differences in body size bias: larger in BMI (and highly correlated WHR) than in ABSI and HI. Thus, ABSI and HI may be superior to BMI (and WHR) as markers of adverse body shape, that is, abdominal obesity, independent from body size. Furthermore, a cross-sectional study in 7053 South Koreans aged ≥60 years showed that high ABSI was associated with lower eGFR, and a higher correlation between ABSI and eGFR than between BMI and eGFR.[15] This may be explained by ethnicity-related heterogeneity in the Korean study, residual confounding and/or chance findings.

Observationally high ABSI was associated with T2D in cross-sectional studies of 2536 Qatari residents.[11] In two prospective studies of 687 Chinese individuals, ABSI was associated with increased risk of developing T2D, whereas HI was not.[12,42] Furthermore, a recent GWAS on visceral adipose tissue using the UK Biobank (European) cohort showed visceral fat to be a causal risk factor for T2D, with causal estimates being substantially larger in women than

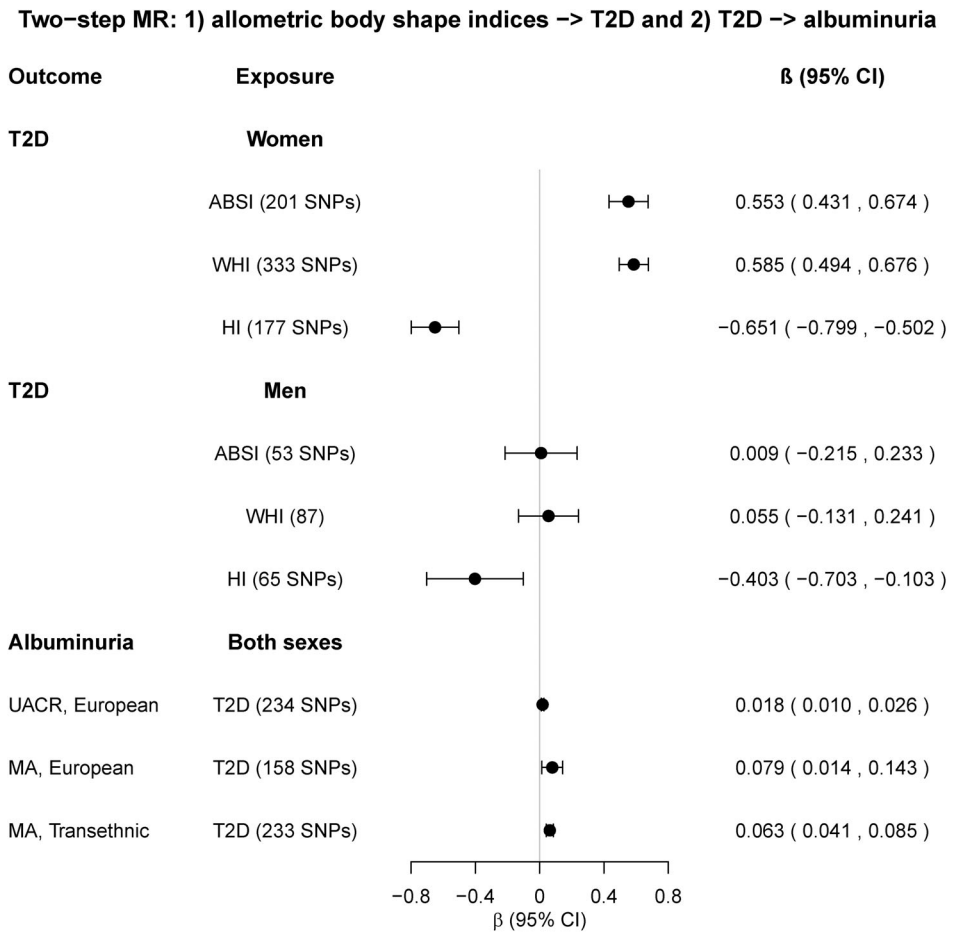

FIGURE 4 Two-step Mendelian randomization (MR) analysis: Causal effects of allometric body shape indices on type 2 diabetes (T2D), and of T2D on albuminuria. Estimates (β-coefficients and 95% confidence intervals [CIs]) are from the inverse variance-weighted random-effects MR analysis, and expressed in log units per standard deviation increase in the relevant exposure or genetic predisposition to T2D. For each exposure, the number of single-nucleotide polymorphisms (SNPs) included in the analysis is shown in parenthesis. Allometric body shape indices indices (A Body Shape Index [ABSI], waist-hip index [WHI], and hip index [HI] in up to 219 872 women and 186 825 men of European ancestry from the UK Biobank) are for women of European ancestry only, as neither sex-combined nor transethnic summary statistics were publicly available. In contrast, albuminuria-related kidney function outcomes are sex-combined, as sex-stratified summary statistics were not publicly available. The outcomes were (a) T2D (DIAGRAM Consortium and UK Biobank combined: $N_{European\ women} = 464\ 389$, $N_{European\ men} = 425\ 613$, $N_{European\ both} = 898\ 130$) and (b) urinary albumin-creatinine ratio (UACR, $N_{European} = 547\ 361$) and genetic predisposition to microalbuminuria (CKDGen: $N_{European} = 54\ 116$, and CKDGen, UK Biobank combined: $N_{Transethnic} = 348\ 954$). Sensitivity MR analyses are shown in Tables S9 and S10

in men (odds ratio 7.34 vs. 2.50).[43] This is largely in agreement with our findings that genetically high ABSI and WHI were associated with increased risk of T2D in women, but not in men, whereas genetically high HI was associated with decreased risk of T2D in women and men.

The present study showed internal consistency of the mediating role of T2D on the pathway from abdominal obesity to albuminuria across results. This was illustrated by (i) higher UACR estimates in individuals with diabetes compared to the overall population, (ii) similar UACR estimates in analyses restricted to T2D-concordant SNPs, (iii) findings from the two-step MR analysis, and (iv) that T2D was more likely a cause of increased UACR than vice versa. The latter also served as a positive control to confirm that genetic predisposition to T2D was associated with increased UACR.[29] There was also consistency in the direction of the results from the continuous UACR measure and the binary microalbuminuria outcome. Our study was unlikely to suffer from weak instrument bias since we only included SNPs with sufficient instrument strength ($F > 10$) associated with their respective outcomes at GWAS significance level ($P < 5 \times 10^{-8}$) and excluded SNPs in linkage disequilibrium.

A potential limitation of this study is that it assumes linear associations between allometric body shape indices and kidney function outcomes. As only summary statistics, but not individual level data are publicly available, we could not assess non-linearity in detail. However, it is worth noting that ABSI, unlike BMI, showed a linear association with age and mortality.[7,8] Thus, we have no knowledge of a potentially nonlinear association between allometric body shape indices and UACR, eGFR and BUN.

Sex differences in kidney function are complex and have not yet been addressed in clinical practice.[44] Genetic variants (and

corresponding summary statistics) for ABSI, WHI and HI were sex-stratified, as sex-combined summary statistics were not publicly available. Of note, we only excluded the very few SNPs that were substantially sexually dimorphic, thus not removing sexual dimorphism altogether. On the other hand, only sex-combined summary statistics were publicly available for kidney function outcomes. A likely explanation for the association of HI with albuminuria in both sexes, but of ABSI and WHI with albuminuria only in women, can be found in sexual dimorphism. Indeed, HI SNPs showed substantially less sexual dimorphism than ABSI (and WHI) SNPs. Furthermore, overall heritability of allometric body shape indices was lower in men, illustrated by an up to fourfold higher number of SNPs in women. The finding for ABSI and WHI only in women also contradicts the evidence that oestrogen has a kidney-protective effect.[44] Further studies should pursue the underlying pathophysiological mechanisms for the sex differences in body shape heritability and associations between shape indices and kidney function.

In conclusion, our findings suggest that individuals with allometrically defined abdominal obesity are at increased risk of T2D and consequently albuminuria. These findings extend the previous associations with BMI, where low HI and high ABSI and WHI represent body shapes conducive to abdominal obesity independent of body size. The lack of an adverse effect of high ABSI (and WHI) on albuminuria in men as opposed to women is unexplained and deserves further evaluation. This study underscores the utility of separate dual consideration of the waist and hip allometric indices ABSI and HI, as compared to a one-dimensional ratio such as WHI.

AUTHOR CONTRIBUTIONS

Conceptualization: Alisa D. Kjaergaard, Jesse Krakauer, Nir Krakauer, Christina Ellervik. Formal analysis: Alisa D. Kjaergaard. Investigation: Alisa D. Kjaergaard. Data curation: Alisa D. Kjaergaard. Resources (CKDGen Consortium): Alexander Teumer, Thomas W. Winkler. Writing—original draft preparation: Alisa D. Kjaergaard, Christina Ellervik. Writing—review and editing: Alisa D. Kjaergaard, Jesse Krakauer, Nir Krakauer, Alexander Teumer, Thomas W.Winkler, Christina Ellervik. Visualization: Alisa D. Kjaergaard. Supervision: Christina Ellervik. Alisa D. Kjaergaard is the guarantor of this work.

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CONFLICTS OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets analyzed for this study are publicly available and accessed as described in the Data Access under the Methods section. Furthermore, the R code used in this study will upon publication be made publicly available at: https://github.com/AlisaDK/ABSI_kidney."

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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