Original Article

Causal effects of life course adiposity on chronic kidney disease: a Mendelian randomization study

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Background: Obesity is reported as closely correlated with the development of chronic kidney disease (CKD); however, whether causation exists is unknown, and controversy remains about whether the role of obesity is protective or destructive in CKD. In this study, we attempted to infer the causal relationship between life course adiposity and CKD, to provide a rationale for obesity management in CKD patients.

Methods: A 2-sample Mendelian randomization (MR) analysis was conducted to explore the causal relationship of life course adiposity traits including body mass index (BMI), childhood BMI, body fat percentage (BF%), birth weight (BW), waist circumference, hip circumference, and waist-to-hip ratio (WHR) to CKD. Significant single nucleotide polymorphisms from genome-wide association study on human adiposity traits were utilized as exposure instruments, and summary statistics of CKD as the outcome. The causal relationship was evaluated by inverse variance weighted, MR Egger regression and weighted median methods, and further verified by extensive sensitivity analyses.

Results: Genetically determined one standard deviation increase in adult BMI was associated with higher risk of CKD in all 4 MR methods. Other indexes including childhood BMI, body fat percentage, and waist/hip circumference were also shown to have a causal effect on the risk of CKD. The results were robust under all sensitivity analyses.

Conclusions: There exists a causal effect of life course adiposity on the risk of CKD. A genetic predisposition to higher adult BMI may increase the risk of CKD.

Keywords: Chronic kidney disease (CKD); life course adiposity; Mendelian randomization (MR)

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Introduction

Chronic kidney disease (CKD) is a global public health problem, characterized by persistent alterations in kidney structure and function (1). It is closely associated with the development of end-stage renal disease (ESRD) and cardiovascular disease (2). As CKD arises from many heterogeneous disease pathways, the underlying mechanism for CKD is complex and probably multifactorial (3). Current evidence implicates a plethora of risk factors involved in the predisposition and development of CKD, including obesity (4,5).

Obesity is a widely recognized risk factor that contributes to the development of CKD (6). Compelling observational

studies have provided extensive evidence for the correlative relationship between obesity and CKD, suggesting that obesity is associated with a higher risk of CKD. For example, longitudinal cohort studies and case-control studies have indicated that higher body mass index (BMI) may contribute to an increased risk for CKD, and early life adiposity, such as birth weight (BW) and childhood BMI, might be a long-term modifiable factor for the onset of CKD (7). Studies have also demonstrated that increased waist-to-hip ratio (WHR) increase the risk of CKD mortality (8). Although these population-based studies have reported a positive association between obesity/adiposity and CKD, conflicting evidence has shown that obesity was paradoxically associated with greater survival following the onset of CKD (9,10). Nevertheless, these observational studies might be influenced by the possibility of selection bias, information bias, confounding factors and reverse causation(11). Two pervious studies investigated the causal association between CKD and obesity traits including BMI and WHR from a genetic perspective (12,13), but no systematic analysis has been conducted to investigate the life course adiposity and CKD. Therefore, whether life course obesity/adiposity, taken as a whole, has a causal effect on the risk of CKD remains largely unknown.

To evaluate the causal relationship between life course adiposity and CKD, we employed the Mendelian randomization (MR) approach, a genetic epidemiological method to explore the causal relationship between exposures (risk factors) and outcomes (diseases) (14,15). The MR approach is widely used to identify risk factors and causal associations in human diseases. It could overcome the limitation of unmeasured confounding from observational studies, and infer causation (16). Here, we chose the single nucleotide polymorphism (SNP) data from a large genome-wide association study (GWAS) on adiposity traits as instrumental variables for the exposure. Using the MR approach, we demonstrated that several indexes of life course adiposity, particularly adult BMI, were causally associated with the increased risk of CKD.

Methods

Datasets

We conducted MR analysis for seven life course adiposity traits including BMI, childhood BMI, body fat percentage (BF%), birth weight (BW), waist circumference, hip circumference, and waist-to-hip ratio (WHR) based on summarized association results from published genome-wide association studies (GWAS) with the most recent publication dates and the largest sample sizes. Genetic variants which passed generally accepted genome-wide significance threshold (P<5E−08) were utilized as instrument variants, so that the relevance assumption of MR was satisfied. Instrument variables were clumped based on 1000 Genomes Project linkage disequilibrium (LD) structure and independent SNPs (R^2<0.001 with any other SNP within 10 Mb) with the most significant P value retained.

Instrument variables (IVs) for BMI were drawn from the published GWAS meta-analysis involving 339,224 individuals of European ancestry (17). The BMI was defined as the body mass divided by the square of body height, and the units of BMI were kilograms per square meter. The IVs for childhood BMI were identified from 47,541 children of European ancestry (18). The childhood age ranged from 2 to 10 years old, and the units of childhood BMI were kilograms per square meter. The IVs for body fat were obtained from a GWAS meta-analysis involving 89,297 individuals of European ancestry (19). The BF% was defined as the total fat mass divided by the total body mass, multiplied by 100, and was measured either with bioimpedance analysis or dual energy X-ray absorptiometry. The IVs for birth weight were identified from a multi-ancestry GWAS including up to 153,781 individuals (20). The BW was recorded as the body weight of a baby at birth collected from obstetric records, medical registers, or interviews with the mother and self-report as adults, with the unit of BW in grams. For WHR, waist circumference and hip circumference measures were obtained from a GWAS on 224,459 individuals of European ancestry (21). The WHR was recorded as the dimensionless ratio of the circumference of the waist to that of the hips measured with a portable stadiometer.

Summary statistics of CKD were drawn from a published GWAS meta-analysis of estimated glomerular filtration rate (eGFR) involving 1,046,070 individuals of European ancestry (22). CKD was defined as eGFR <60 mL/min per 1.73 m^2. Harmonization was undertaken to rule out strand mismatches and ensure alignment of SNP effect sizes.

Statistical analysis

We hypothesized that each trait as risk factor could causally increase the risk of CKD, and the following assumptions were satisfied in the MR analysis: the genetic variants used as instrumental variables were associated with the risk

factor; the genetic variants were not associated with any confounders; and genetic variants were associated with CKD through the risk factor only.

We performed a 2-sample MR analysis to estimate the effect of each trait on CKD with the inverse variance weighted (IVW) method. Since IVW was not sensitive to horizontal pleiotropy of instrument SNPs, another 3 methods including MR Egger regression, weighted mode, and weighted median were conducted as a supplement. In addition, extensive complementary sensitivity analyses were performed to evaluate potential violations of the model assumptions in MR analysis. We (I) conducted Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis to explore presence of outliers that could bias the results (23), (II) evaluated the directional pleiotropy of instruments with MR-Egger regression methods, (III) evaluated reverse causal inference with Steiger analysis (24) to check whether CKD has a causal effect on each trait, and (IV) checked heterogeneity with the Cochran Q test.

We also computed the F-statistic of each SNP to evaluate the strength of selected instrument variables (25). We performed a leave-one-out analysis with the inverse variance weighted method to check whether the overall estimate was driven by single SNP. A P value below 0.008 (0.05/7) was considered statistically significant after Bonferroni correction for each trait. A P value between 0.007 and 0.05 implied a suggestive association. The main statistical analyses were conducted using R package TwoSampleMR (25). This study only utilized publicly available summarized results from published GWASs. No individual-level data were involved.

Results

To explore the causal relationship of life course obesity/adiposity traits on the risk of CKD, we enrolled 7 life course adiposity-related traits including BMI, childhood BMI, BF%, BW, waist circumference, hip circumference and waist-to-hip ratio (WHR) for the analysis of association with CKD using four MR methods.

Results of MR analysis showed that each one standard deviation (1-SD) increase in BMI was associated with higher risk of CKD consistently in 4 methods, including IVW [odds ratio (OR): 1.214, 95% confidence interval (CI): 1.115–1.321, P=7.9E–06), MR Egger (OR: 1.245, 95% CI: 1.011–1.533, P=4.2E–02), weighted mode (OR: 1.448, 95% CI: 1.202–1.745, P=2.1E–04), and weighted median (OR: 1.336, 95% CI: 1.184–1.508, P=2.7E–06) (*Figure 1*). The scatter and funnel plot display symmetric pattern of effect size variation around the point estimated (*Figures 2,3*). A 1-SD increase in childhood BMI was also associated with higher risk of CKD at nominal significant level in IVW method (OR: 1.166, 95% CI: 1.056–1.286, P=2.3E–03). Notably, the other 3 methods did not show significant association after the Bonferroni correction, but the effect of direction trended the same. Interestingly, the effect of childhood BMI was lower than that of adult BMI consistently in the 4 MR methods, suggesting that adult BMI may have larger influence on CKD risk than childhood BMI.

We also found that 1-SD increase in BF% was associated with higher CKD risk in weighted median method (OR: 1.556, 95% CI: 1.193–2.029, P=1.1E–03) and weighted mode method (OR: 1.797, 95% CI: 1.307–2.469, P=5.64E–03), and MR Egger method showed suggestive association (*Figure 1*). No association was found between BW and CKD risk (*Figure 1*). Moreover, a suggestive positive association between waist circumference (OR: 1.270, 95% CI: 1.105–1.458, P=7.4E–04), hip circumference (OR: 1.222, 95% CI: 1.076–1.387, P=1.99E–03) and CKD risk was detected. Similar results were found in weighted median and weighted mode methods (*Figure 1*). However, no significant association was observed between WHR and CKD risk.

Finally, we performed extensive sensitivity analysis to validate the causal association between each trait and CKD. No heterogeneity of effects was detected using Cochran's Q test (*Table 1*). The F statistics of all the instrument variables were above 10 (range, 19.45 to 447), indicating absence of weakness in the selected instruments. The intercept of MR-Egger did not significantly deviate from zero, suggesting no apparent horizontal pleiotropy (*Table 1*). Directionality examination by Steiger analysis did not suggest violation of the causality either. The MR-PRESSO analysis detected potential instrumental outliers at the nominal significance level of 0.05, but removing the outlier did not lead to a substantial change of the causal effect. The leave-one-out results suggested that no single instrumental variable could influence the estimated causal effect.

Discussion

Through observational studies, it has long been appreciated that obesity is a risk factor in the development of CKD; however, mainly due to ethical issues, the causation of this association is unknown. Here, using a comprehensive 2-sample MR analysis, we have shown that increased life

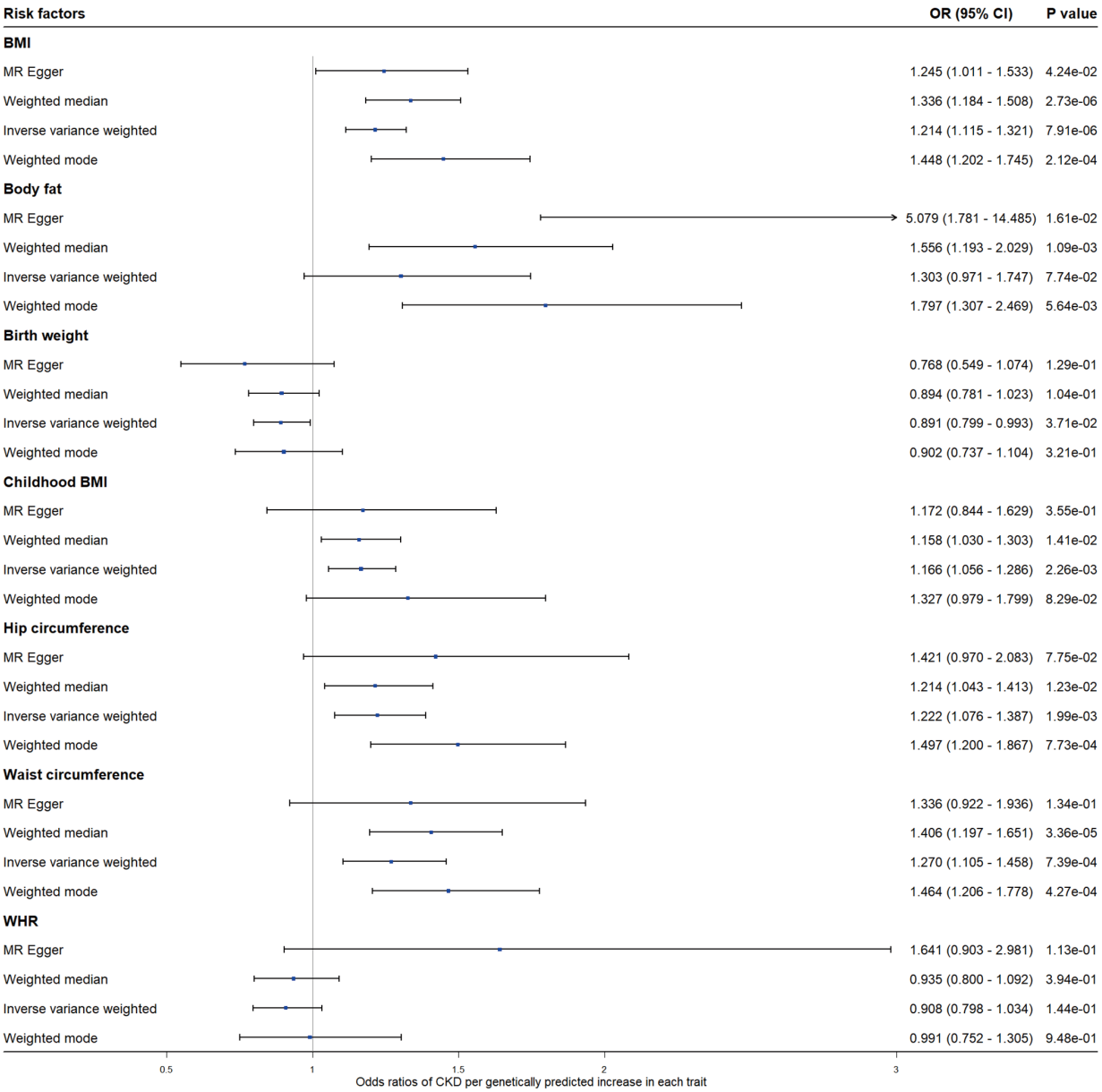

Figure 1 Results of MR analysis. Forest plot showing the potential causal associations between obesity traits and CKD. MR, Mendelian randomization; CKD, chronic kidney disease; BMI, body mass index; WHR, waist-to-hip ratio.

course adiposity is causally associated with increased risk of CKD. We demonstrate that adult/childhood BMI, body fat and hip/waist circumference, but not BW and WHR, have a causal effect on the risk of CKD. To the best of our knowledge, this study was the first systematic exploration attempting to illuminate the directional causal relationship between life course obesity/adiposity and CKD, through a genetic approach based on summary statistics from GWAS.

Currently, a large body of epidemiologic evidence has revealed that obesity might be a significant risk factor for CKD due to its strong link with the 2 major causes of CKD, type 2 diabetes and hypertension (26). Indeed, obesity-induced hypertension, hyperglycemia, hyperlipidemia, and other metabolic alternations are all potential risk factors for CKD (27). These findings are also supported by the fact that weight-loss strategies by either lifestyle intervention

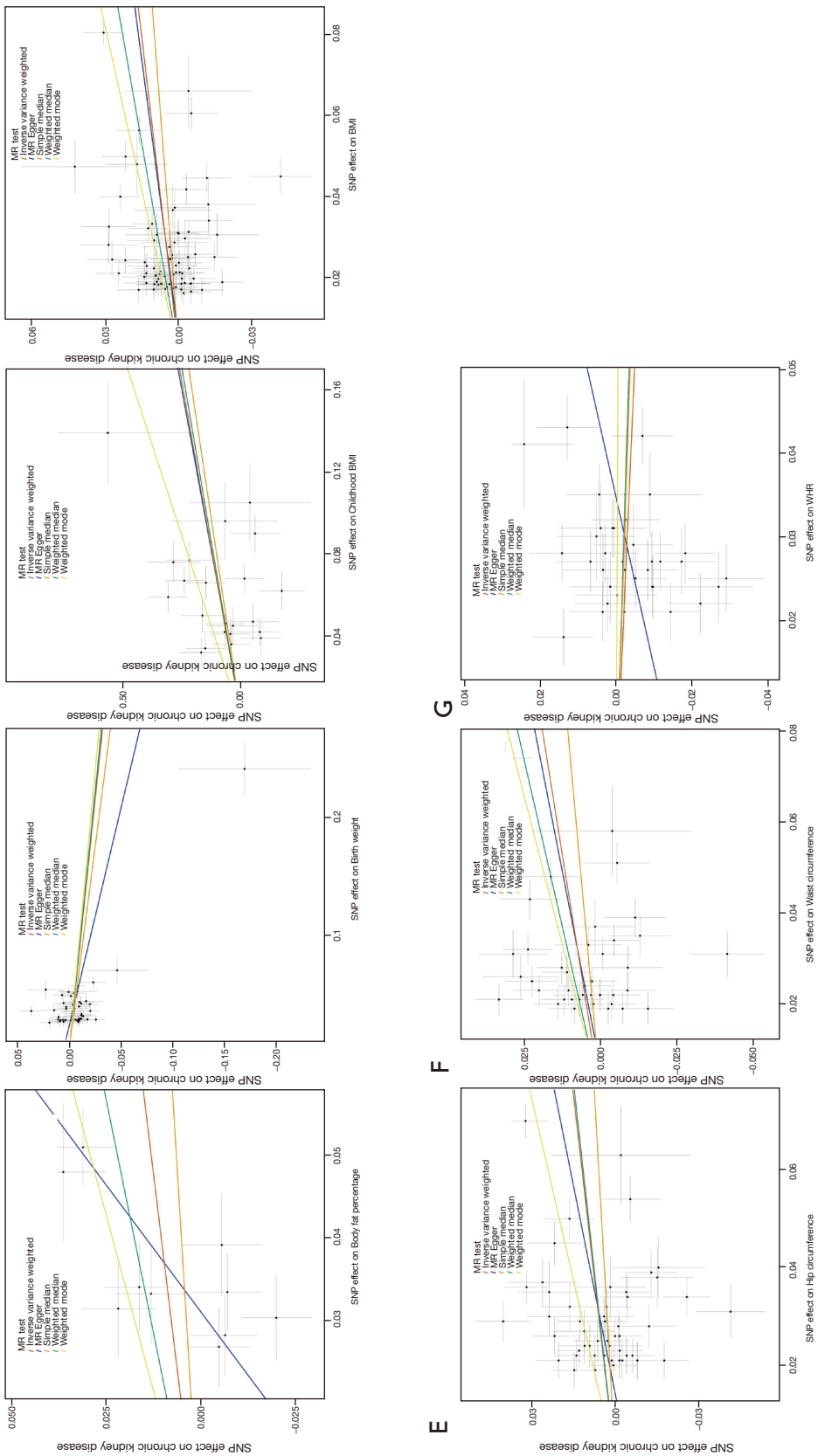

Figure 2 Scatter plots visualizing the associations of individual SNPs on CKD versus life course adiposity traits including (A) body fat percentage, (B) birth weight, (C) childhood BMI, (D) BMI, (E) hip circumference, (F) waist circumference, (G) WHR. The slope of fitted lines represents the estimated MR effect per method. SNP, single nucleotide polymorphism; CKD, chronic kidney disease; MR, Mendelian randomization; BMI, body mass index; WHR, waist-to-hip ratio.

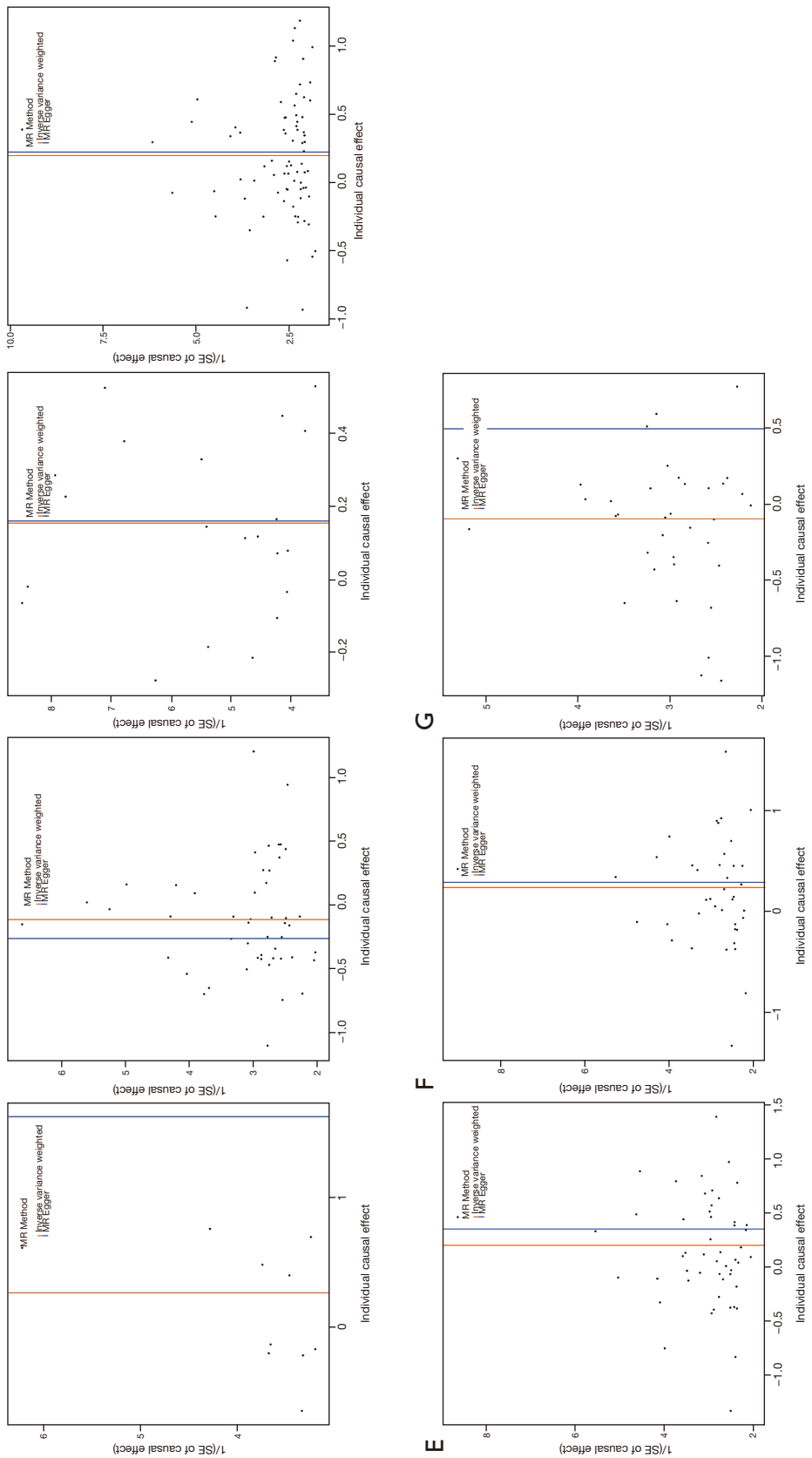

Figure 3 Funnel plot visualizing the causal estimate of each individual SNP between CKD and life course adiposity traits including (A) body fat percentage, (B) birth weight, (C) childhood BMI, (D) BMI, (E) hip circumference, (F) waist circumference, (G) WHR. The vertical line represents the estimated causal effect obtained using IVW and MR-Egger method. SNP, single nucleotide polymorphism; CKD, chronic kidney disease; MR, Mendelian randomization; BMI, body mass index; WHR, waist-to-hip ratio; IVW, inverse variance weighted.

Table 1 Heterogeneity and horizontal pleiotropy analyses results

Trait	Heterogeneity			Horizontal pleiotropy		
	IVW Q	IVW Q df	IVW P value	Egger intercept	SE	P value
BMI	104.8	77	0.019	–7.70E–04	2.95E–03	0.79
BF	30.9	9	3.06E–04	–4.20E–02	1.80E–02	0.05
birth weight	71.5	44	0.005	6.60E–03	5.53E–03	0.24
childhood BMI	40.0	21	0.007	–3.45E–04	9.41E–03	0.97
Hip circumference	118.6	50	1.69E–07	–4.87E–03	5.92E–03	0.41
Waist circumference	85.2	39	2.71E–05	–1.64E–03	5.61E–03	0.77
WHR	54.4	35	0.019	–1.71E–02	8.61E–03	0.06

BMI, body mass index; BF, body fat; WHR, waist to hip ratio; SE, standard error; IVW, inverse variance weighted; Q, Cochran's Q test estimate; df, Cochran's Q test degrees of freedom.

or bariatric surgery are associated with decreased risk of kidney failure in CKD patients (28). Thus, lower adiposity composition seems to be protective in CKD patients. However, controversial results have shown that weight loss during the course of CKD is associated with a substantially higher risk of death, especially after the initiation of dialysis therapy (29). Therefore, it is still not clear whether adiposity composition exerts a protective or destructive role in CKD development. Moreover, these observational studies could be influenced by the possibility of confounding factors. In this study, using genetic variants as proxies for each trait by MR approach, we demonstrated that increased life course adiposity increases the risk of CKD.

Our findings revealed that some of the indexes of adiposity, including adult and childhood BMI, BF%, and waist/hip circumference, have a causal effect on the risk of CKD. Particularly, the adult BMI has a larger influence than other factors in our MR study. This might be interpreted that adult adiposity has a larger influence on CKD. In addition, there was weak evidence of a causal association between childhood BMI and CKD. Conversely, we found that birth weight and WHR were not causally associated with CKD in our MR study. Compared with BMI, waist and hip circumference were better estimates of body fat, especially the internal fat deposits. In the current study, higher waist and hip circumference was associated with higher risk of CKD, suggesting fat distributions in these locations might affect the function of the kidney. Further explorations were necessary to better understand whether body fat from other parts of the body might influence the risk of CKD. In a similar manner, another study investigated the association between CKD and adiposity measured by BMI and WHR using summary statistics from different GWAS (13). In this study, the author identified causal association between both WHR and BMI with CKD. However, in our study no significant association between WHR and CKD was identified. Therefore, we screened the literature for other evidence about the association between WHR and CKD. The conclusion was not consistent in previous observational studies either (8,30,31). Therefore, further studies were warranted to elucidate the association between WHR and CKD.

Pathologically, although how adiposity could increase risk of CKD was still not well understood, chronic inflammation caused by obesity might be possible implication. Previous functional exploration demonstrated that mice fed a high-fat diets for 12 weeks developed kidney injury with increased inflammatory cytokine expression which resembled the characteristics of CKD (32). Meanwhile, caloric restriction was suggested to decrease incidence of kidney diseases (33). The effect might be related to reduction in cellular damage induced by reactive oxygen (34). In addition, studies have demonstrated alterations in the gut microbiota in obese people, and the metabolic syndrome and obese phenotypes can be induced in lean mice following the transfer of microbiota from obese mice (35). The alterations in microbiota might contribute to the leakage of inflammatory factors from the gut, disrupt intestinal homeostasis and amplify inflammation in CKD patients (36). Therefore, how inflammatory cytokines and energy reduction were involved in the function of the kidney were worth further exploration, to better understand the association between adiposity and CKD.

There are strengths to our study, including the

evaluation of life course adiposity on CKD, and the use of data from large GWASs of adiposity. Our design technique tried to minimize confounding bias with several MR methods and extensive sensitivity analysis. However, some limitations are worthy of consideration. We chose genetic variants for the exposure from a large sample size study, but weak instrument bias cannot be fully ruled out. Moreover, population stratification and potential sample overlap may be other sources of bias, as in all MR analyses.

Conclusions

In conclusion, based on our 2-sample MR analysis, we demonstrated the causal association of life course adiposity, particularly adult BMI, on the increased risk of CKD. Our work expands current understandings of the relationship between obesity and CKD, and provides the rationale for obesity management to reduce the risk of CKD.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2528). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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