

Causal Effects of Life Course Adiposity on Chronic Kidney Disease: A Mendelian Randomization Study

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Research

Keywords: Chronic kidney disease, Life course adiposity, Mendelian randomization

Posted Date: August 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-746367/v1>

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Abstract

Background Obesity is reported to be tightly correlated the development of chronic kidney disease (CKD). However, whether there exists causation is unknown, and it remains controversial about the role of obesity in CKD is protective or destructive. In this study, we try to infer the causal relationship between life course adiposity and CKD, to provide a rationale for obesity management in CKD patients.

Methods A two-sample Mendelian randomization (MR) analysis was conducted to explore the causal relationship of life course adiposity traits including 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 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 four MR methods. And other indexes including childhood BMI, body fat percentage, and waist/hip circumference also have a causal effect on the risk of CKD. The results were robust under all sensitivity analyses.

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

Introduction

Chronic kidney disease (CKD) is a global public health problem, characterized by persistent alterations in kidney structure and function(1). CKD is tightly associated with the development of end-stage renal disease (ESRD) and cardiovascular disease(2). Because 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 the higher risk of CKD. For example, longitudinal cohort studies and case-control studies indicated that higher body mass index (BMI) may contribute to an increased risk for CKD, indicating that 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 also demonstrated that increased waist-to-hip ratio (WHR) increased the risk of CKD mortality(8). Although these population-based studies reported a positive association between obesity/adiposity and CKD, conflicting evidence showed that obesity was paradoxically associated with greater survival once CKD is onset(9, 10). Nevertheless, all these observational studies are influenced by the possibility of confounding factors and/or reverse

causation. 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)(11, 12). The MR approach is widely used to identify risk factors and causal associations in human diseases. Here, we chose the single nucleotide polymorphism (SNP) data from large genome-wide association study (GWAS) on hematological traits as instrumental variables for the exposure. By MR approach, we demonstrate 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 ($P < 5.00E-8$) 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 were retained.

Instrument variables (IVs) for BMI were drawn from the published GWAS meta-analysis involving 339,224 individuals of European ancestry(13). BMI was defined as the body mass divided by the square of body height. The units of BMI are kilograms per square meter. IVs for childhood BMI were identified from 47,541 European ancestry children(14). The childhood age ranges from 2 to 10 years old. The units of childhood BMI are kilograms per square meter. IVs for body fat were obtained from a GWAS meta-analysis involving 89,297 individuals of European ancestry(15). 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. IVs for birth weight were identified from a multi-ancestry GWAS including up to 153,781 individuals(16). BW is the body weight of a baby at birth collected from obstetric records, medical registers or interviews with the mother and self-report as adults. The unit of BW is grams. For WHR, waist circumference and hip circumference measures were obtained from a GWAS on 224,459 individuals of European ancestry(17). WHR is 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 published GWAS meta-analysis of estimated glomerular filtration rate (eGFR) involving 1,046,070 individuals of European ancestry(18). CKD was defined as eGFR

< 60 ml min⁻¹ per 1.73 m². Harmonization was undertaken to rule out strand mismatches and ensure alignment of SNP effect sizes.

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

We performed a two-sample MR analysis to estimate the effect of each trait on CKD with Inverse variance weighted (IVW) method. Since IVW was not sensitive to horizontal pleiotropy of instrument SNPs, another three methods including Mendelian randomization Egger regression, Weighted mode, 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(19), (ii) evaluated the directional pleiotropy of instruments with MR-Egger regression methods, (iii) evaluated reverse causal inference with Steiger analysis(20) to check whether CKD has a causal effect on each trait, and (iv) checked heterogeneity with the Cochran Q test.

To estimate bias from sample overlap, we computed the F-statistic of each SNP to evaluate the strongness of selected instrument variables(21). We also 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) should be considered statistically significant after Bonferroni correction for each trait. A P-value between 0.007 and 0.05 implies a suggestive association. The main statistical analyses were conducted using R package TwoSampleMR(21). This study only utilized publicly available summarized results from published genome-wide association studies. 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 seven life course adiposity related traits including BMI, childhood BMI, body fat percentage, birth weight, 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 four methods, including IVW (OR: 1.214, 95% 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) (Fig. 1). The scatter and funnel plot displays symmetric pattern of effect size variation around the point estimated

(Figs. 2 and 3). And 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). It's noted that the other three 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 four MR methods, suggesting the adult BMI may have larger influence on CKD risk than childhood BMI.

We also found that 1-SD increase in body fat 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 (Fig. 1). But no association was found between birth weight and CKD risk (Fig. 1). Moreover, it's noted 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. And similar results were found in Weighted median and Weighted mode methods (Fig. 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 (ranging from 19.45 to 447), indicating absence of weakness in the selected instruments. The intercept of MR-Egger is not significantly deviated 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 suggest that no single instrumental variable can influence the estimated causal effect.

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

SE, standard error; IVW, Inverse variance weighted; Q, Cochran's Q test estimate; df, Cochran's Q test degrees of freedom.

Discussion

It's long been appreciated that obesity is a risk factor in the development of CKD through observational studies, but the causation of this association is unknown mainly due to ethical issues. Here, using a comprehensive two-sample MR analysis, we show that increased life course adiposity is causally associated with increased risk of CKD. We demonstrate that adult/childhood BMI, body fat and hip/waist circumference, but not birth weight and WHR, have a causal effect on the risk of CKD. To the best of our knowledge, this study is the first exploration that attempts to illuminate the directional causal relationship between life course obesity/adiposity and CKD, through a genetic approach based on summary statistics.

Currently, a large body of epidemiologic evidence has revealed that obesity might be a significant risk factor for CKD because of its strong link with type 2 diabetes and hypertension, the two major causes of CKD(22). Indeed, obesity-induced hypertension, hyperglycemia, hyperlipidemia, and other metabolic alternations are all potential risk factors for CKD(23). These findings are also supported by the fact that weight-loss strategies by either lifestyle intervention or bariatric surgery are associated with decreased risk of kidney failure in CKD patients(24). Thus, lower adiposity composition seems to be protective in CKD patients. However, controversial results showed that weight loss during the course of CKD was associated with a substantially higher risk for death, especially after dialysis therapy initiation(25). Therefore, it is still not clear whether adiposity composition exhibit 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 Mendelian randomization (MR) approach, we demonstrate that increased life course adiposity increases the risk of CKD.

Our findings reveal that some of the indexes of adiposity, including adult and childhood BMI, body fat percentage, 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 as that adult adiposity has a larger influence on CKD. In addition, there was weak evidence of a causal association between childhood BMI and CKD. On the other hand, we found that birth weight and waist-to-hip ratio (WHR) were not found to be causally associated with CKD in our MR study, like waist circumference and hip circumference.

There are strengths in 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 merit 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 might be another source of bias, as in all MR analyses.

Conclusions

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

Abbreviations

CKD: chronic kidney disease,

MR: Mendelian randomization,

BMI: body mass index,

BF: body fat percentage,

BW: birth weight,

WHR: waist-to-hip ratio,

GWAS: genome-wide association study,

IVs: Instrument variables,

IVW: Inverse variance weighted.

Declarations

Ethical Approval and Consent to participate

The present study was approved by the Ethics Committee of Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital (Sichuan, China).

Consent for publication

Not applicable.

Availability of data and materials

The GWAS summary statistics used to perform the analyses described in the study were obtained from publicly available published data.

Competing interests

The authors have no competing interests to declare.

Funding

This work was supported by the funding of Chinese Hospital Association Foundation (No. CHABP2016-12) and Wu Jieping Medical Foundation (No. 320.6750.16193).

Authors' contributions

(I) Conception and design: Wanchun Yang, Hongchun Chen and Yang Zou, (II) Administrative support: Yang Zou, (III) Provision of study materials or patients: Wanchun Yang, Hongchun Chen, Qiuyun Yuan, (IV) Collection and assembly of data: Wanchun Yang, Hongchun Chen, Qiuyun Yuan, (V) Data analysis and interpretation: Wanchun Yang, Hongchun Chen and Yang Zou, (VI) Manuscript writing: Yang Zou, (VII) Final approval of manuscript: All authors.

Acknowledgments

We thank the investigators who made the GWAS summary data publicly available and the participants who contributed to those studies. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Figures

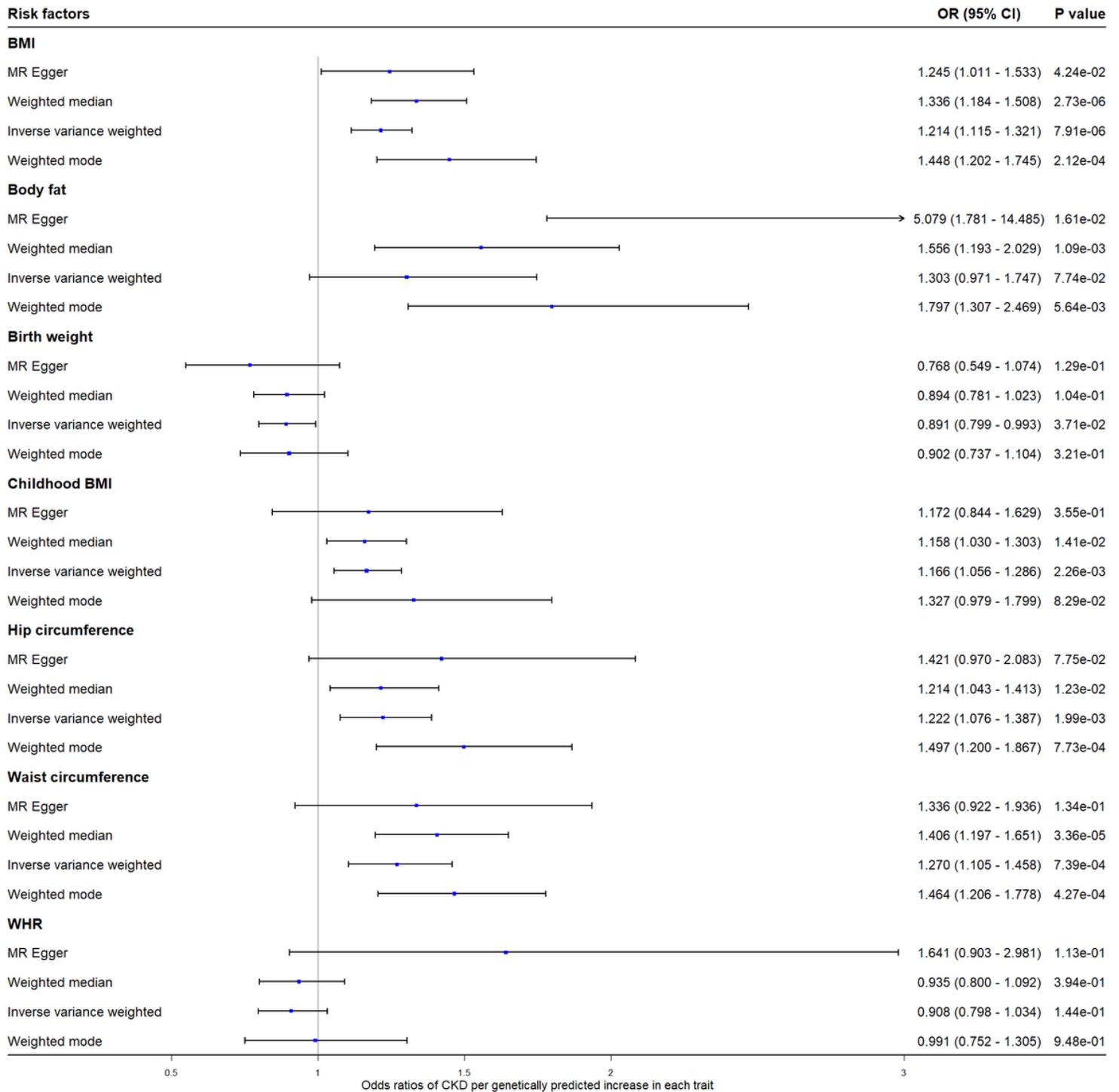


Figure 1

Mendelian randomization analysis results. Forest plot showing results from the Mendelian randomization (MR) analysis to evaluate potential causal associations between obesity traits and CKD. Estimates are per 1 standard deviation increase in the trait.

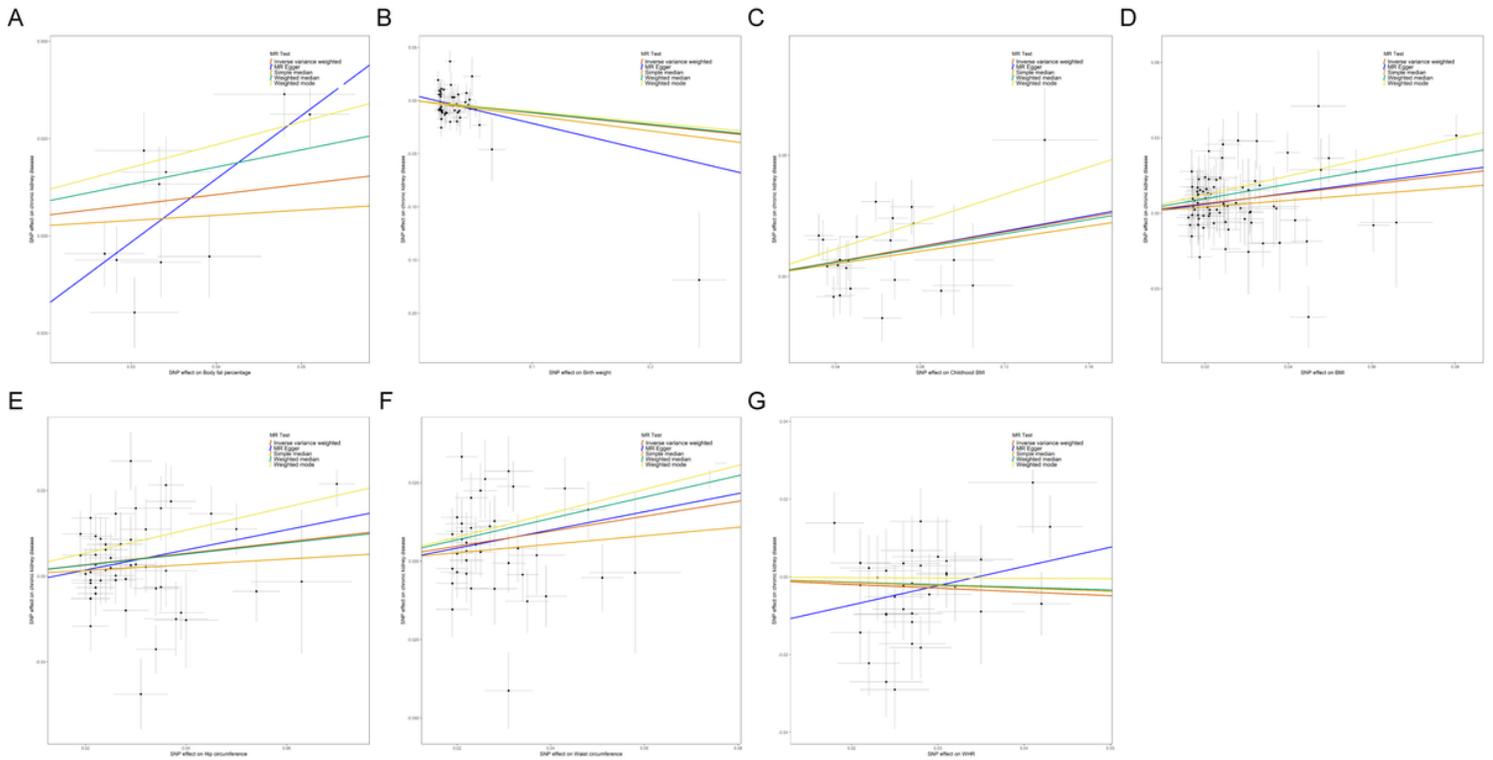


Figure 2

Scatter plot of single nucleotide polymorphism (SNP) potential effects on obesity traits versus CKD. The 95% CI for the effect size on CKD is shown as vertical lines, while the 95% CI for the effect size is shown as horizontal lines. The slope of fitted lines represents the estimated Mendelian randomization effect per method.

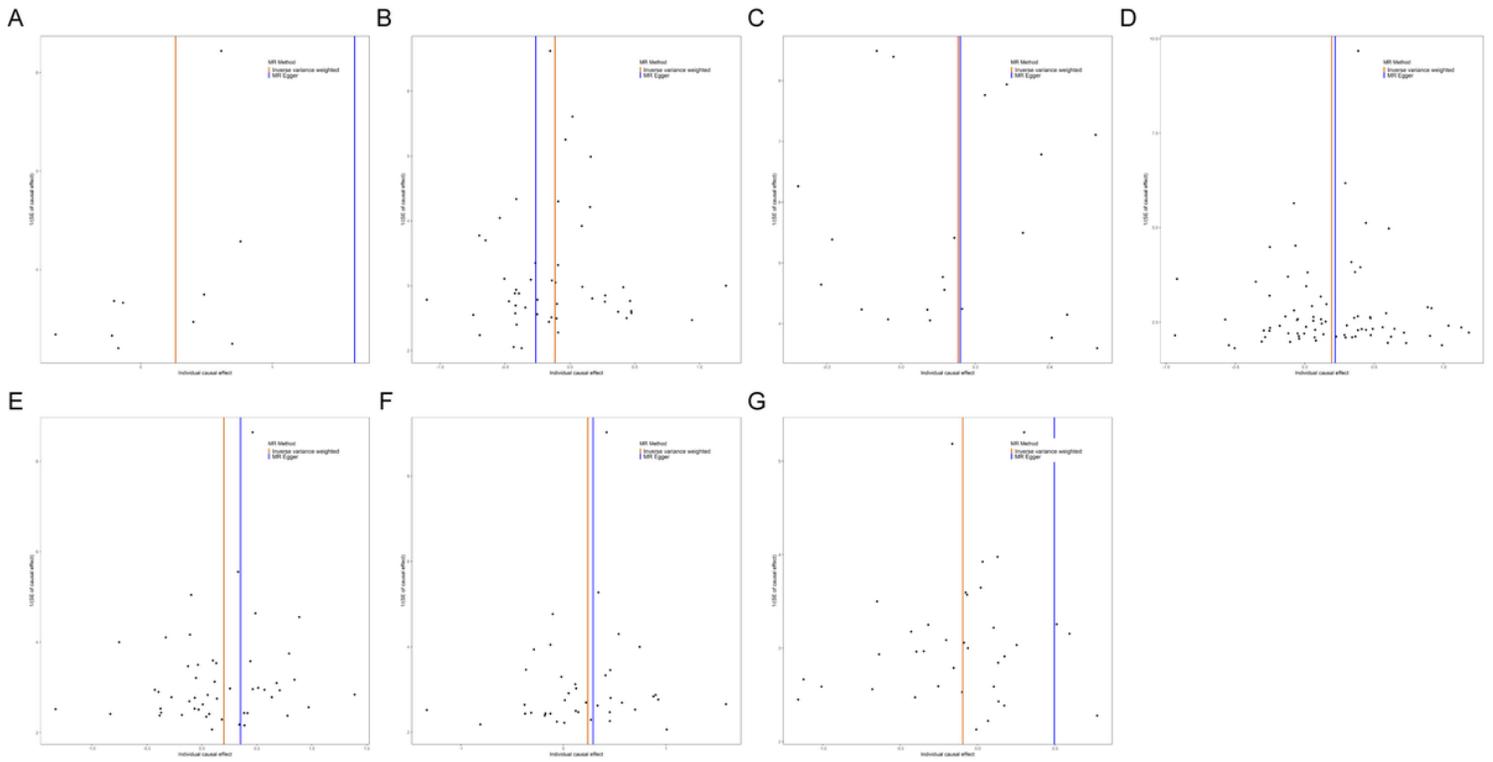


Figure 3

Funnel plot shows the estimation using the inverse of the standard error of the causal estimate with each individual SNP as a tool. The vertical line represents the estimated causal effect obtained using IVW and MR-Egger method.