Association Between Obesity and Chronic Kidney Disease: Multivariable Mendelian Randomization Analysis and Observational Data From a Bariatric Surgery Cohort

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Obesity is postulated to independently increase chronic kidney disease (CKD), even after adjusting for type 2 diabetes (T2D) and hypertension. Dysglycemia below T2D thresholds, frequently seen with obesity, also increases CKD risk. Whether obesity increases CKD independent of dysglycemia and hypertension is unknown and likely influences the optimal weight loss (WL) needed to reduce CKD. T2D remission rates plateau with 20–25% WL after bariatric surgery (BS), but further WL increases normoglycemia and normotension. We undertook bidirectional inverse variance weighted Mendelian randomization (IVWMR) to investigate potential independent causal associations between increased BMI and estimated glomerular filtration rate (eGFR) in CKD (CKD_{eGFR} (<60 mL/min/1.73 m^2) and microalbuminuria (MA). In 5,337 BS patients, we assessed whether WL influences >50% decline in eGFR (primary outcome) or CKD hospitalization (secondary outcome), using <20% WL as a comparator. IVWMR results suggest that increased BMI increases CKD_{eGFR} (b = 0.13, $P = 1.64 \times 10^{-4}$; odds ratio [OR] 1.14 [95% CI 1.07, 1.23]) and MA (b = 0.25; $P = 2.14 \times 10^{-4}$; OR 1.29 [1.13, 1.48]). After adjusting for hypertension and fasting glucose, increased BMI did not significantly increase CKD_{eGFR} (b = −0.02; $P = 0.72$; OR 0.98 [0.87, 1.1]) or MA (b = 0.19; $P = 0.08$; OR 1.21 [0.98, 1.51]). Post-BS WL significantly reduced the primary outcome with 30 to <40% WL (hazard ratio [HR] 0.53 [95% CI 0.32, 0.87]) but not 20 to <30% WL (HR 0.72 [0.44, 1.2]) and ≥40% WL (HR 0.73 [0.41, 1.30]). For CKD hospitalization, progressive reduction was seen with increased WL, which was significant for 30 to <40% WL (HR 0.37 [0.17, 0.82]) and ≥40% WL (HR 0.24 [0.07, 0.89]) but not 20 to <30% WL (HR 0.60 [0.29, 1.23]). The data suggest that obesity is likely not an independent cause of CKD. WL thresholds previously associated with normotension and normoglycemia, likely causal mediators, may reduce CKD after BS.

ARTICLE HIGHLIGHTS

- Obesity is likely not an independent contributor to chronic kidney disease (CKD).
- Obesity likely contributes to CKD via effects on glycemia and blood pressure.
- Weight loss at thresholds associated with normoglycemia and normotension may reduce CKD.

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Obesity is a risk factor for chronic kidney disease (CKD), a rising health care burden worldwide that increases morbidity and premature mortality (1,2). Observational studies suggest that obesity may increase CKD, independent of metabolic risk factors such as type 2 diabetes (T2D) and hypertension (3–11). Unlike observational data, Mendelian randomization (MR) is less prone to confounding and can be used to infer causal associations between an exposure and outcome (12). A prior MR study suggested a causal association between increased BMI and CKD but not increased waist-to-hip ratio (a phenotype more strongly associated with metabolic disease) (13). Multivariable MR studies indicate that increased BMI increases CKD, even after adjusting for hypertension and/or T2D, and has been proposed to be an independent causal factor for CKD (14,15). Dysglycemia and elevated fasting glucose (FG) in the non-T2D range have been implicated in glomerular hyperfiltration and associated with CKD in both observational and MR studies (16–19) and may potentially contribute to obesity-associated CKD. Thus, whether obesity is truly an independent causal factor for CKD after adjusting for dysglycemia and hypertension is not known but may inform future strategies to reduce/prevent CKD, including weight loss (WL)–based interventions.

Although WL can potentially reduce/prevent CKD, the optimal amount of WL needed to reduce CKD is unknown and likely depends on the underlying etiology of obesity-associated CKD. Bariatric surgery (BS) is the most efficacious WL intervention and has shown reductions in estimated glomerular filtration rate (eGFR)–based measures of CKD (CKD_{eGFR}) (20,21) in observational studies and microalbuminuria (MA) in people with T2D in a randomized control trial (22). Remission rates of T2D (defined as hemoglobin A_{1c} [HbA_{1c}] <6.5%) after BS plateau after a WL in the 20–25% range (23). WL above this threshold has been associated with an increased likelihood of normalization of glycemia (HbA_{1c} <6%) and achievement of normotension (24–26).

In this study, we undertook bidirectional MR to assess potential causal associations between BMI and CKD_{eGFR} (stage III CKD or worse defined by eGFR <60 mL/min/1.73 m^2) (27) and the presence of MA (urinary albumin-to-creatinine ratio [UACR] >25 mg/g in women or >17 mg/g in men) in people of European descent using summary statistics from the largest genome-wide association studies (GWAS). Consistent with prior studies, we found suggestive causal associations between BMI and CKD (14,15) and, therefore, undertook multivariable MR analysis to assess to what extent these potential causal associations are independent of increased FG, T2D, and hypertension. Finally, we assessed the association between WL within 1 year of BS and a 50% decline in eGFR (primary outcome) and CKD hospitalization (secondary outcome).

RESEARCH DESIGN AND METHODS

MR Studies

Cohorts

MR analyses were undertaken in participants of European ancestry using summary statistics from the largest published GWAS. The instruments for glycemic parameters include GWAS of fasting glucose undertaken in people without T2D (i.e., variation in FG in the non-T2D range), as well as GWAS in T2D case and control cohorts (28–34) (Table 1). Informed consent and institutional approval were previously obtained by the individual cohort investigators.

Primary MR Analyses

For our primary analysis, we undertook bidirectional MR with CKD_{eGFR} and MA as outcomes and BMI as exposure with subsequent multivariable MR adjusted for hypertension, T2D, and FG. $P < 0.05$ was considered significant for each analysis. The recently published Strengthening the Reporting of Observational Studies in Epidemiology using MR reporting guideline (35) has been incorporated in this article (Supplementary File 1).

Additional Analyses. We also undertook additional bidirectional MR analysis assessing the effect of BMI as exposures on UACR and eGFR creatinine and cystatin C–based eGFR measures.

MR Assumptions. First, the instrument is robustly associated with the exposure; thus, we used single nucleotide polymorphisms (SNPs) that were associated with the exposure at genome-wide significance (12). Second, there is no horizontal pleiotropy, meaning that the instrument does not influence the outcome via another pathway other than the outcome (12). Finally, the instrument is not influenced by any confounders (12). For bidirectional MR, we used inverse variance weighted (IVW) MR (IVWMR) and additional sensitivity analyses, including MR-Egger, weighted median, weighted mode, and leave-one-out analyses.

IVWMR was analyzed using meta-analysis of the individual Wald ratio for each SNP. By permitting the IVW to have a nonzero intercept, MR-Egger relaxes the assumption of no horizontal pleiotropy and returns an unbiased causal estimate, in the case of horizontal pleiotropy, provided that the horizontal pleiotropic effects are not correlated with the SNP-exposure effects (instrument strength independent of direct effect assumption) (12,36). The median effect of all SNPs in the instrument was used for analysis using weighted median MR, allowing SNPs with a greater effect on the association to be evaluated by weighting the contribution of each SNP by the inverse variance of its association with the outcome (37). Even if only 50% of the SNPs satisfy all three MR assumptions, the method is robust (37). Finally, SNPs were clustered into groups based on similarity of causal effects for weighted mode MR, with the cluster with the largest number of SNPs deriving the causal effect estimate (38).

Table 1—Cohort details

Trait	Population cohort	Mean age, years	Female, %	Sample size, *n*	Study participants, *n*	Control participants, *n*	PMID
BMI	GIANT/UK Biobank	55.5/56.9*	54.0/54.2*	681,275			30124842
WHR	GIANT/UK Biobank	55.5/56.9*	54.0/54.2*	694,649			30239722
Hypertension	UK Biobank	56.9*	54.2*	463,010	54,358	408,652	GWAS ID: ukb-b-12493[a]
T2D	DIAGRAM/GERA/ UK Biobank	54.1/63.3/56.9*	50.1/59.0/54.2*	655,666	61,714	593,952	30054458
FG	MAGIC	50.9	47.7	133,010			22885924
CKD	CKDGen	54.0	50.0	625,219	64,164	561,055	31152163
UACR	CKDGen	57.0	54.4	547,361			31511532
MA	CKDGen	57.0	53.0	54,116	54,116		26631737
eGFR creatinine	CKDGen	54.0	50.0	567,460			31152163

All participants were of European descent. MAGIC, Meta-analyses of Glucose and Insulin-Related Traits Consortium; PMID, PubMed Identifier; WHR, waist-to-hip ratio. *Study-specific characteristics were not available for all UK Biobank data and were extrapolated from data available. [a]Output from Medical Research Council Integrative Epidemiology Unit GWAS pipeline analysis using Phesant-derived variables from UK Biobank, version 2 (https://doi.org/10.5523/bris.pnoat8cxo0u52p6ynfaekeigi). DIAGRAM, Diabetes Genetics Replication and Meta-analysis; GERA, Genetic Epidemiology Research on Aging; CKDGEN, Chronic Kidney Disease Genetics; MRC-IEU, Medical Research Council Integrative Epidemiology Unit.

To assess heterogeneity, Cochran *Q* test was used, while leave-one-out analysis was conducted to assess whether any MR estimate was biased by a single SNP potentially with horizontal pleiotropic effect (12). *F* statistics were calculated manually for continuous exposures (12,39,40).

Univariable MR was conducted using the TwoSampleMR package in R (RStudio version 1.3.1073 and R version 4.0.3). Linkage disequilibrium pruning was used to select a proxy ($r^2 > 0.8$) if a SNP was not directly matched from the 1000 Genomes Project. The ggplot2 and metaphor packages in R were used to create plots.

We undertook multivariable IVWMR to assess the effect of BMI on CKD independent of hypertension, T2D, and FG (41). Our data indicate a significant correlation between the effects of BMI-associated SNPs on FG and T2D (Spearman rank correlation $\rho = 0.37$; $S = 527{,}411$; $P = 7.9 \times 10^{-7}$). The correlation remained significant after removing four SNPs that were genome-wide significant for both traits (Spearman $\rho = 0.32$; $S = 527{,}412$; $P = 2.4 \times 10^{-5}$) (Supplementary File 5). Given the potential collinearity between the traits, we undertook an analysis adjusted for each glycemic trait individually and in combination with hypertension. Multivariable MR was conducted using the TwoSampleMR, Multivariable MR, and RMultivariable MR packages in R, where the latter two packages assessed heterogeneity via Cochran *Q* test and strength of the instrument via *F* statistics (39,41). Plots were generated using plotobject in R.

Overlap Between Exposure and Outcome Cohorts

A total of 456,426 participants from the UK Biobank composed ~67% of the Genetic Investigation of Anthropometric Traits (GIANT)/UK Biobank GWAS of BMI, 69% of the Diabetes Genetics Replication and Meta-analysis (DIAGRAM)/Genetic Epidemiology Research on Aging (GERA)/UK Biobank GWAS of T2D, and 80% of the Chronic Kidney Disease Genetics (CKDGEN) GWAS of CKD.

Observation Study in a Cohort of Patients Who Underwent BS

Study Design

We conducted a retrospective cohort study using population-level health care administrative databases in Ontario, Canada. The data sources included the Ontario Bariatric Registry, which provides information on patients assessed at bariatric centers and whether they eventually had surgery. Other data sources included the Discharge Abstracts Database, which includes detailed information on all hospital admissions in Ontario; the Registered Persons Database, with demographic information on all Ontario residents; and the Ontario Laboratory Information System to which all community and most hospital-based laboratories have gradually enrolled since 2006 to contribute laboratory test results. These data sets were linked using unique encoded identifiers and analyzed at ICES. We have received institutional ethics approval for the study.

Patients

We identified all people who underwent primary BS between April 2010 and October 2016. Exclusion criteria included residence outside of Ontario, a diagnosis of CKD prior to surgery, eGFR of ≤45 mL/min/1.73 m^2 at baseline, last eGFR before index date of ≤0.6× baseline eGFR, no weight recorded at either the 6- or 12-month follow-up visit at the bariatric center, death or left Ontario in the first 12 months after surgery, and no eGFR measurements

Table 2—Univariable and multivariable MR analyses of BMI adjusted for hypertension, T2D, and FG as exposure and CKD or MA as outcome

Method	B	SE	*P*	Egger intercept	P_{Egger}	Cochran *Q*	*Q df*	P_Q	I^2	*F*	OR (95% CI)
Univariable MR analysis (exposure: BMI, 446 SNPs; outcome: CKD)											
MR-Egger	0.095	0.092	0.306	0.001	0.644	612.243	444	1.89E-07	27.480	97.437	1.099 (0.917, 1.317)
Weighted median	0.121	0.058	0.035							97.437	1.129 (1.008, 1.264)
IVW	0.134	0.036	1.64E-04			612.538	445	2.14E-07	27.351	97.437	1.143 (1.066, 1.226)
Simple mode	−0.125	0.162	0.440							97.437	0.882 (0.642, 1.213)
Weighted mode	0.078	0.098	0.427							97.437	1.081 (0.892, 1.308)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and T2D, 340 SNPs; outcome: CKD)											
IVW	0.124	0.049	0.011			575.703	380	3.31E-10	33.994	16.082	1.132 (1.028, 1.246)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and FG, 167 SNPs; outcome: CKD)											
IVW	−0.021	0.059	0.725			240.787	180	1.67E-03	25.245	12.119	0.980 (0.873, 1.099)
Univariable MR analysis (exposure: BMI, 441 SNPs; outcome: MA)											
MR-Egger	0.477	0.182	0.009	−0.004	0.190	444.000	439	0.424	1.126	97.437	1.611 (1.127, 2.303)
Weighted median	0.340	0.122	0.005							97.437	1.405 (1.104, 1.786)
IVW	0.255	0.069	2.14E-04			445.741	440	0.415	1.288	97.437	1.291 (1.128, 1.478)
Simple mode	0.446	0.324	0.170							97.437	1.562 (0.827, 2.949)
Weighted mode	0.416	0.202	0.040							97.437	1.516 (1.020, 2.255)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and T2D, 338 SNPs; outcome: MA)											
IVW	0.141	0.090	0.117			383	378.000	0.418	1.318	16.232	1.151 (0.965, 1.372)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and FG, 164 SNPs; outcome: MA)											
IVW	0.194	0.110	0.080			168	177.000	0.675	−5.382	13.524	1.214 (0.977, 1.507)

in the year prior to surgery or after surgery. The final sample size was 5,337 (Supplementary File 4).

Variables

By comparing the lower of weights recorded at the 6- and 12-month follow-up visit with the baseline weight, we calculated the percentage of WL achieved, categorized into <20%, 20 to <30%, 30 to <40%, and ≥40%. The primary outcome was a 50% reduction from baseline in eGFR. Reduction of eGFR of this magnitude is associated with an increased risk of end-stage CKD and death and has been used in clinical trials (42–44). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021 equation (45):

$$eGFR = 142*\min\left(\frac{Scr}{\kappa},1\right)^{\alpha}*\max\left(\frac{Scr}{\kappa},1\right)^{-1.200}*0.9938^{Age}*\delta,$$

where *Scr* = serum creatinine value (mg/dL), κ = 0.7 for females and 0.9 for males, α = −0.241 for females and −0.302 for males, *Age* = age of person in years at time of test, and δ = 1.012 for females and 1 for males.

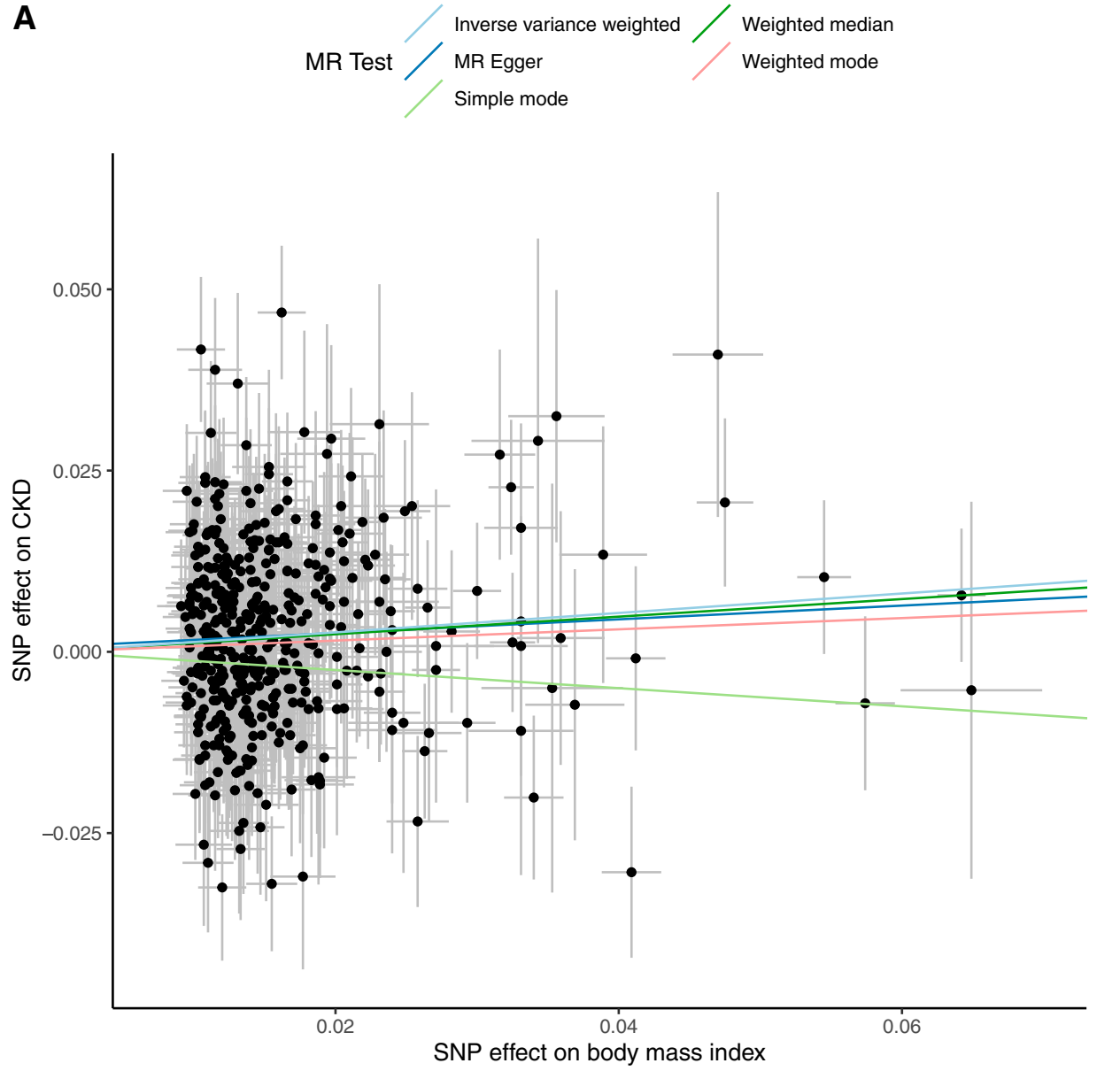

Figure 1—Univariable and multivariable MR analysis. The exposure is BMI adjusted for hypertension, T2D, and FG. The outcome is CKD (eGFR <60 mL/min/1.73 m^2) as a binary outcome. *A*: Scatter plot showing the SNPs associated with BMI against SNPs associated with CKD (vertical and horizontal gray lines around points show 95% CI for five different MR association tests. *B*: Funnel plot of the effect size against the inverse of the SE for each SNP. *C*: Multivariable MR analyses of increased BMI adjusted for covariates on CKD as the outcome.

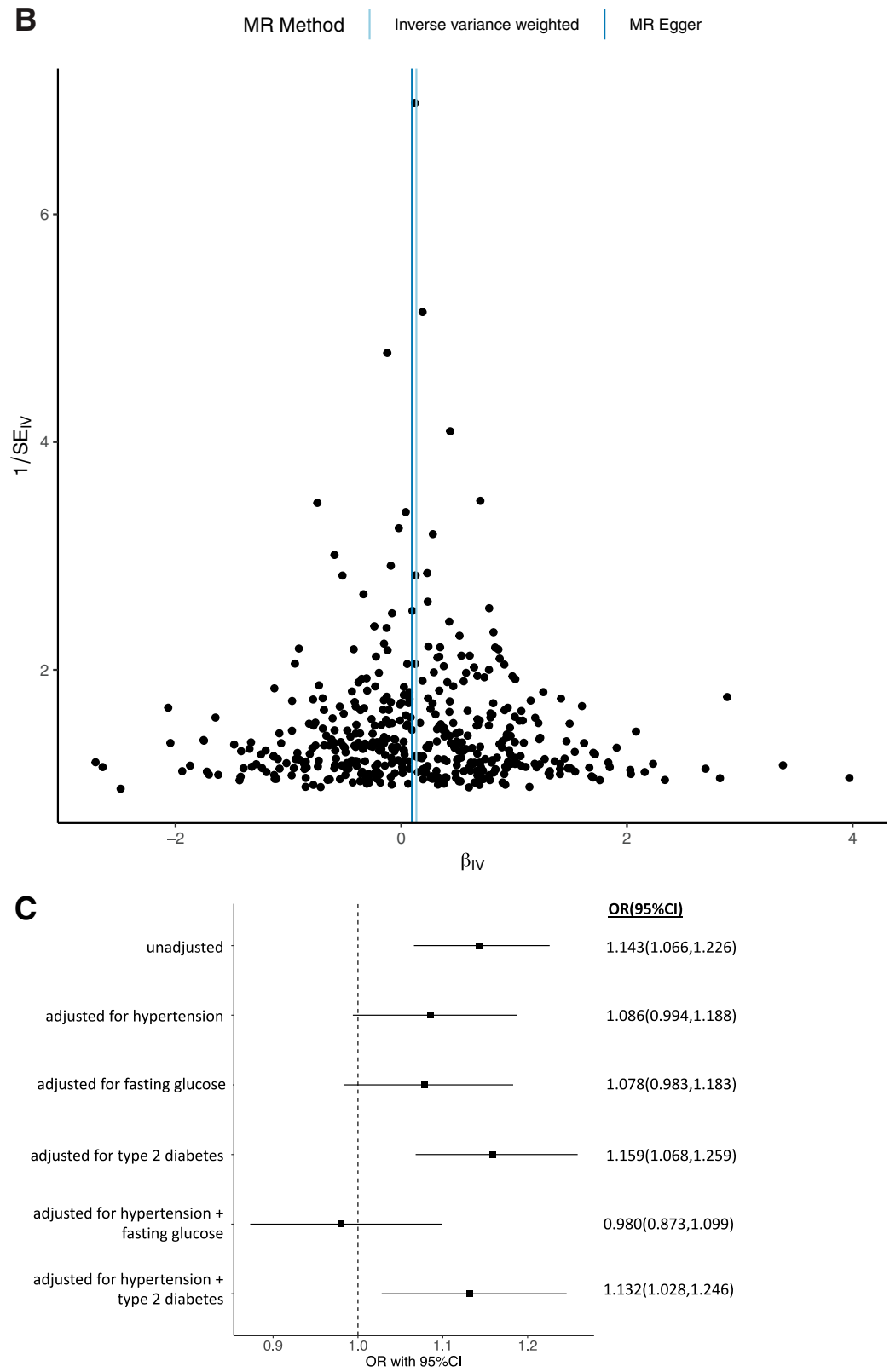

Figure 1—Continued

The secondary outcome was first hospitalization for CKD based on the following hospital diagnostic codes: ICD-9 (4030, 4031, 4039, 4040, 4041, 4049, 585,586, 5888, 5889, 2504) and ICD-10 (E102, E112, E132, E142, I12, I13, N08, N18, N19). Outcome ascertainment started 1 year after surgery and ended 31 March 2020.

Baseline characteristics ascertained for each patient included age, sex, income (defined ecologically based on neighborhood-level median household income, divided into quintiles), rurality of residence (46), and prior history of diabetes (47). In addition, the following comorbidities were ascertained from the Ontario Bariatric Registry: hypertension, dyslipidemia, and vascular disease (coronary artery disease, cerebrovascular disease, or heart failure) (48).

Statistical Analysis

Baseline characteristics of the cohort, stratified by the exposure variable, were compared using ANOVA for continuous variables and χ^2 tests for categorical variables. Multiple imputation, using five imputed data sets, was used to impute the random missing values for baseline characteristics (49): the number of missing values is included in Table 4. Cox proportional hazards models were fit for each primary and secondary outcome, adjusting for the baseline characteristics and baseline eGFR. The Cox proportional hazards model assumptions were verified with weighted Schoenfeld residuals. Modeling with restricted cubic splines (50) indicated a nonlinear relationship between WL and the primary outcome and linear relationship for the secondary outcome. We therefore assessed outcomes by WL category for the primary outcome. For the secondary outcome, we undertook analyses using WL as a continuous variable. For the primary outcome, patients were censored at the last available eGFR result in the Ontario Laboratory Information System. For the secondary outcome, patients were censored on death or the end of follow-up. We also undertook additional Fine-Gray model analyses with death as a competing risk factor for the secondary outcome (51) but not the primary outcome (as everyone included in the analyses had an eGFR measurement and were alive). Analyses were repeated among the subgroup of patients who had a history of diabetes prior to surgery.

Data and Resource Availability

All data are included in the article.

RESULTS

MR Studies

Primary Outcome

MR Analyses of BMI as Exposure and CKD (eGFR <60 mL/min/1.73 m^2) as Outcome. Consistent with previous data, MR suggested that increased BMI increases CKD (b = 0.134; $P = 1.64 \times 10^{-4}$; odds ratio [OR] 1.143 [95% CI 1.066, 1.226]), which remained significant after adjusting for T2D and hypertension (b = 0.124; $P = 0.011$; OR 1.132 [1.028, 1.246]). However, the effect was not significant after adjusting for hypertension and FG (b = −0.02; $P = 0.72$; OR 0.98 [0.87, 1.10) (Table 2, Fig. 1, and Supplementary File 2). Mediation analysis indicates hypertension mediated ∼40% and elevated glucose ∼45% of the effect of obesity and in combination, likely entirely mediated the effect of increased BMI on CKD (Fig. 1).

MR Analyses of BMI as Exposure and MA as Outcome. Univariable MR indicated that increased BMI increases MA (b = 0.255; $P = 2.14 \times 10^{-4}$; OR 1.291 [95% CI 1.128, 1.478]). This finding was not significant after adjustment for hypertension and T2D (b = 0.141; $P = 0.117$; OR 1.151 [0.965, 1.372), consistent with prior data. Mediation analysis indicated that hypertension mediates ∼11% and T2D ∼48%, with a combined estimate of ∼52% of the effect of increased BMI on MA. Similarly, multivariable MR suggested that elevated FG is a likely contributor to BMI-associated MA. The causal association between increased BMI and MA was not significant after adjustment for hypertension and FG (b = 0.19; $P = 0.08$; OR 1.21 [0.98, 1.51]) (Table 2, Fig. 2, and Supplementary File 2). In combination, hypertension and increased FG are estimated to mediate ∼20% of the effect of increased BMI on MA (Fig. 2).

Reverse MR Analyses of CKD and MA as Exposure on BMI as Outcome. We did not find evidence that CKD defined by eGFR <60 mL/min/1.73 m^2 (b = 0.009; $P = 0.495$) or presence of MA (b = 0.003; $P = 0.835$) increased BMI (Supplementary File 3).

Additional Analyses

Univariable MR indicated that increased BMI decreases UACR (b = −0.031 ± 0.011; $P = 0.004$) (Table 3). Multivariable MR after adjustment for hypertension and T2D (b = −0.071; $P = 3.9 \times 10^{-7}$) and hypertension and FG (b = −0.061; $P = 0.001$) indicated that BMI decreases UACR. Univariable MR indicated that increased BMI reduces cystatin C–based eGFR (b = −0.05; $P = 6.8 \times 10^{-16}$), which remained significant after adjustment for hypertension and T2D (−0.05; $P = 1 \times 10^{-8}$) and hypertension and FG (b = −0.03; $P = 0.03$) (Table 3). Univariable MR suggested that increased BMI did not affect creatinine-based eGFR (b = −0.0004; $P = 0.8$) (Table 3). We did not find MR evidence that creatinine- or cystatin C–based measures of eGFR or UACR impacts BMI (Supplementary File 3).

Observation Studies in Patients Undergoing BS

The total sample size was 5,337. Baseline demographic features are listed in Table 4. Older age, male sex, rural location, presence of T2D, hypertension, hyperlipidemia, and vascular disease were associated with reduced WL at 1 year after BS, as well as more frequent measurement of creatinine and a consequently shorter interval between baseline measurement and surgery. The median follow-up was 4.63 (interquartile range [IQR] 3.35–5.81) years for the primary outcome and 5.53 (IQR 4.23–6.45) years for the secondary outcome.

Primary Outcome: WL Categories and Primary Outcome of >50% Decline in eGFR

There were 172 events among 5,337 patients. In unadjusted models, WL of 20 to <30% (3.6%), 30 to <40% (2.5%), and ≥40% (3.2%) was associated with a reduction in the primary outcome compared with <20% (5.2%; P = 0.02). After adjustment for covariates, WL was associated with a reduction in the primary outcome, which was significant for the 30 to <40% group (hazard ratio [HR] 0.53 [95% CI 0.32, 0.87]) (Fig. 3) but not the 20 to <30% group (HR 0.72 [0.44, 1.2]) or the ≥40% group (HR 0.73 [0.4, 1.3]). Similar trends were seen in the subgroup of patients with diabetes (n = 2,227 [41.7%]; 20–30% group: HR 0.61 [0.36, 1.05]; 30–40% group: HR 0.4 [0.22, 0.72]; ≥40% group: HR 0.58 [0.28, 1.21]) (Fig. 3).

Secondary Outcome: WL and Hospitalization for CKD

There were 53 hospitalizations for CKD. In unadjusted models, WL of 20 to <30% (1.3%), 30 to <40% (0.7%), and ≥40% (0.4%) was associated with a reduction in the secondary outcome compared with <20% (2.6%)

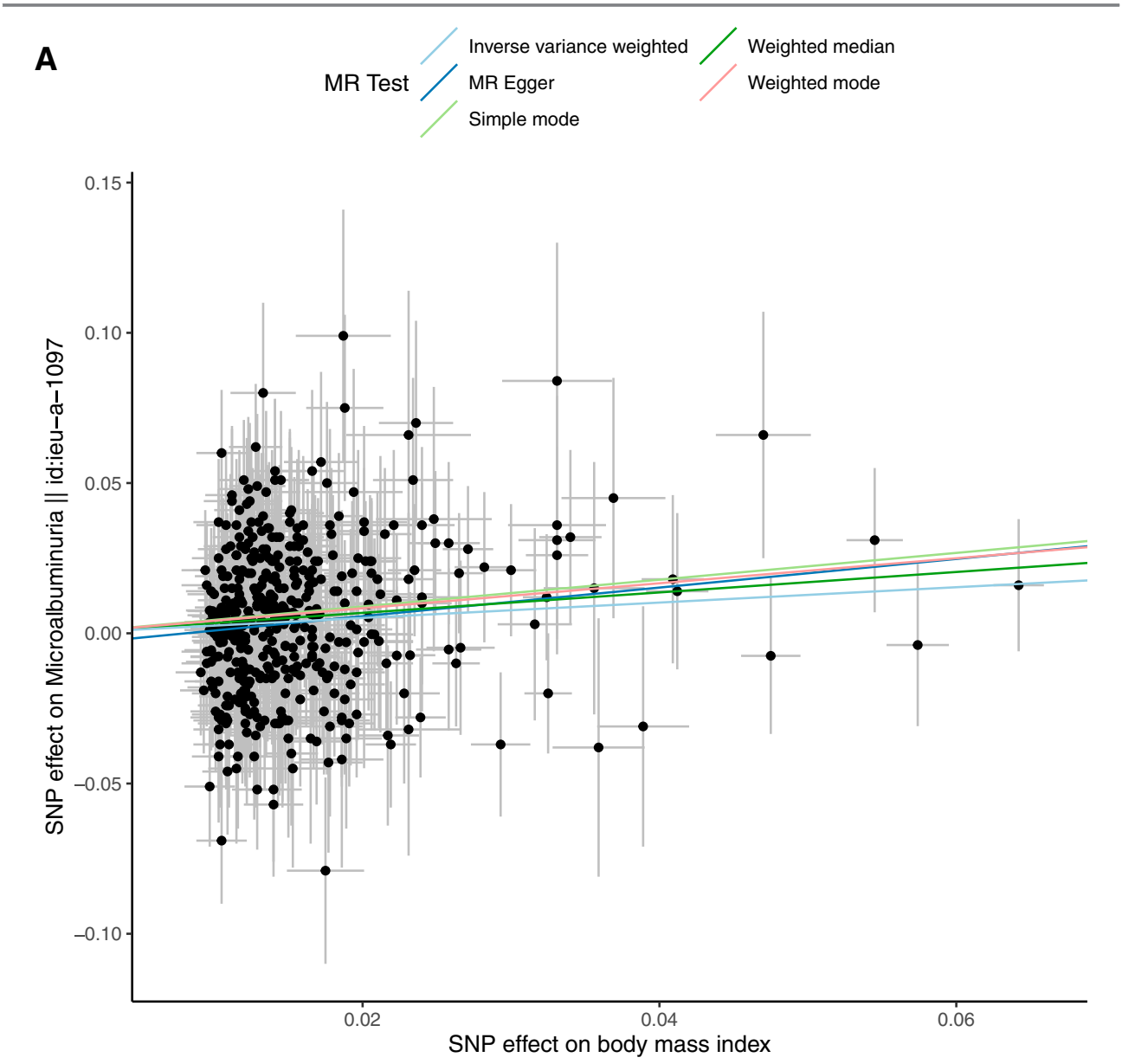

Figure 2—Univariable and multivariable MR analysis. The exposure is BMI adjusted for hypertension, T2D, and FG. The outcome is MA as a binary outcome. *A*: Scatter plot showing the SNPs associated with BMI against SNPs associated with MA (vertical and horizontal gray lines around points show 95% CI for five different MR association tests. *B*: Funnel plot of the effect size against the inverse of the SE for each SNP. *C*: Multivariable MR analyses of increased BMI adjusted for covariates on MA as the outcome.

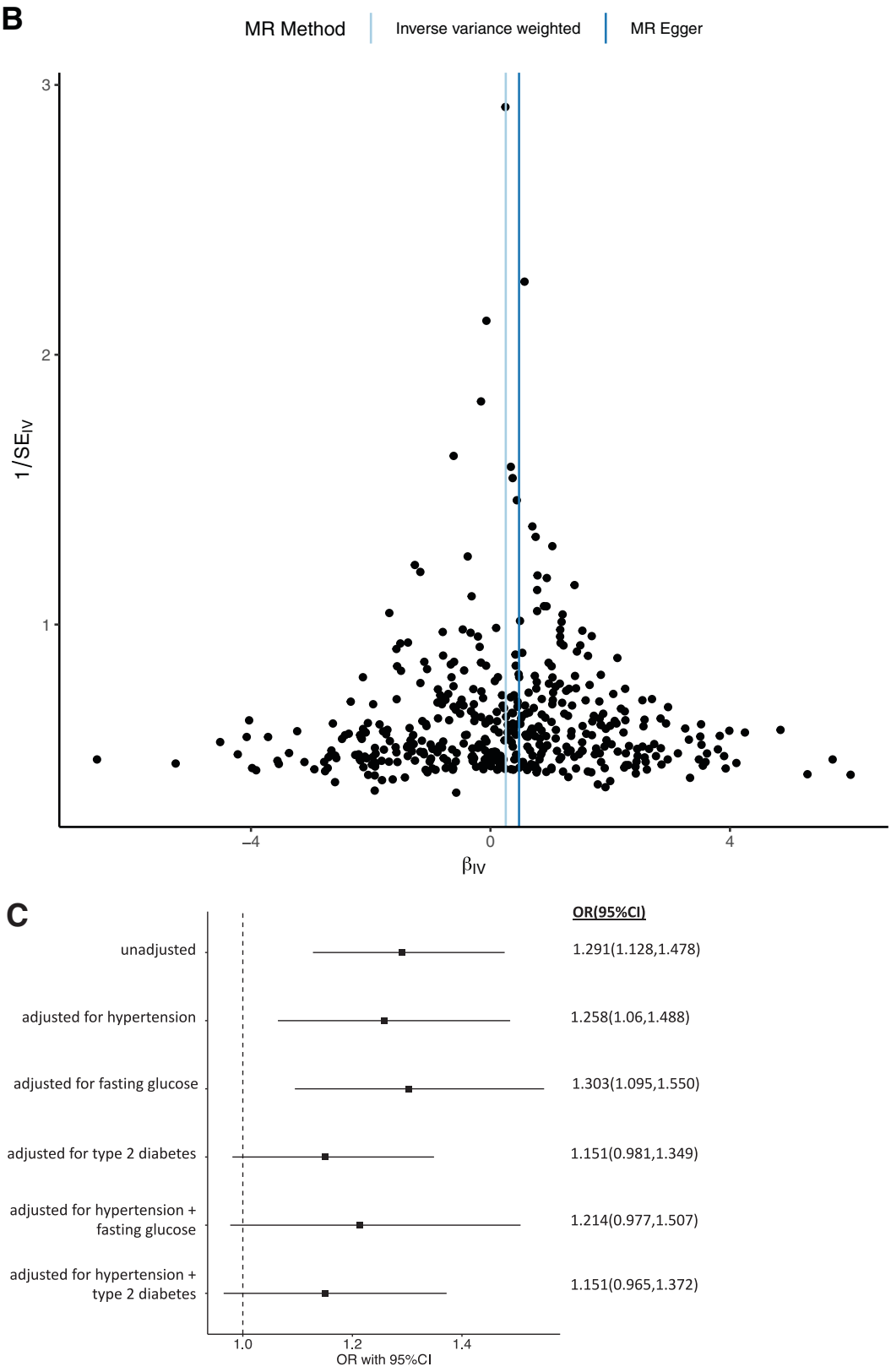

Figure 2—Continued

Table 3—Univariable and multivariable MR analyses of BMI adjusted for hypertension, T2D, and FG as exposure and UACR, eGFR defined using creatinine, and eGFR defined using cystatin C as continuous outcome

Method	B	SE	*P*	Egger intercept	P_{Egger}	Cochran *Q*	*Q df*	P_Q	I^2	*F*	OR (95% CI)
Univariable MR analysis (exposure: BMI, 446 SNPs; outcome: UACR)											
MR-Egger	0.051	0.028	0.068	−0.001	0.001	1,194.343	444	4.64E-70	62.825	97.437	1.052 (0.996, 1.111)
Weighted median	−0.027	0.012	0.029							97.437	0.973 (0.950, 0.997)
IVW	−0.031	0.011	0.004			1,221.872	445	1.23E-73	63.580	97.437	0.969 (0.949, 0.990)
Simple mode	−0.058	0.047	0.217							97.437	0.944 (0.861, 1.035)
Weighted mode	−0.038	0.032	0.236							97.437	0.962 (0.904, 1.025)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and T2D, 340 SNPs; outcome: UACR)											
IVW	−0.071	0.014	3.86E-07			969.480	380	3.53E-53	60.804	16.080	0.932 (0.907, 0.958)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and FG, 167 SNPs; outcome: UACR)											
IVW	−0.061	0.019	0.001			510.937	180	1.87E-33	64.771	12.119	0.941 (0.906, 0.976)
Univariable MR analysis (exposure: BMI, 446 SNPs; outcome: eGFR defined using creatinine)											
MR Egger	0.004	0.005	0.439	0.000	0.355	1,429.722	444	0.000	68.945	97.437	1.004 (0.994, 1.015)
Weighted median	0.004	0.002	0.102							97.437	1.004 (0.999, 1.008)
IVW	−4.24E-04	0.002	0.835			1,432.480	445	0.000	68.935	97.437	1.000 (0.996, 1.004)
Simple mode	0.008	0.008	0.345							97.437	1.008 (0.992, 1.024)
Weighted mode	0.006	0.004	0.148							97.437	1.006 (0.998, 1.015
Univariable MR analysis (exposure: BMI, 469 SNPs; outcome: eGFR defined using cystatin C)											
MR Egger	−0.05	0.018	0.0014	0.00	0.04	1,334.57	444	2.36E-4	63.48	97.437	
Weighted median	−0.06	0.01	1.09E-7							97.437	
IVW	−0.05	0.007	6.8E-16			1,384.91	445	2.41E-4	63.31	97.437	
Simple mode	−0.06	0.022	0.017							97.437	
Weighted mode	−0.06	0.016	0.0013							97.437	
Multivariable MR analysis (exposure: BMI adjusted for hypertension and T2D, 338 SNPs; outcome: eGFR defined using cystatin C)											
IVW	−0.05	0.09	1E-8			1,288.98	380	6.44E-7	61.0	16.08	0.951 (0.797, 1.13)
Multivariable MR analysis (exposure: BMI adjusted for hypertension and FG, 152 SNPs; outcome: eGFR defined using cystatin C)											
IVW	−0.03	0.12	0.014			1,093.29	6.45E-7	64.51	64.51	14.93	0.97 (0.767, 1.23)

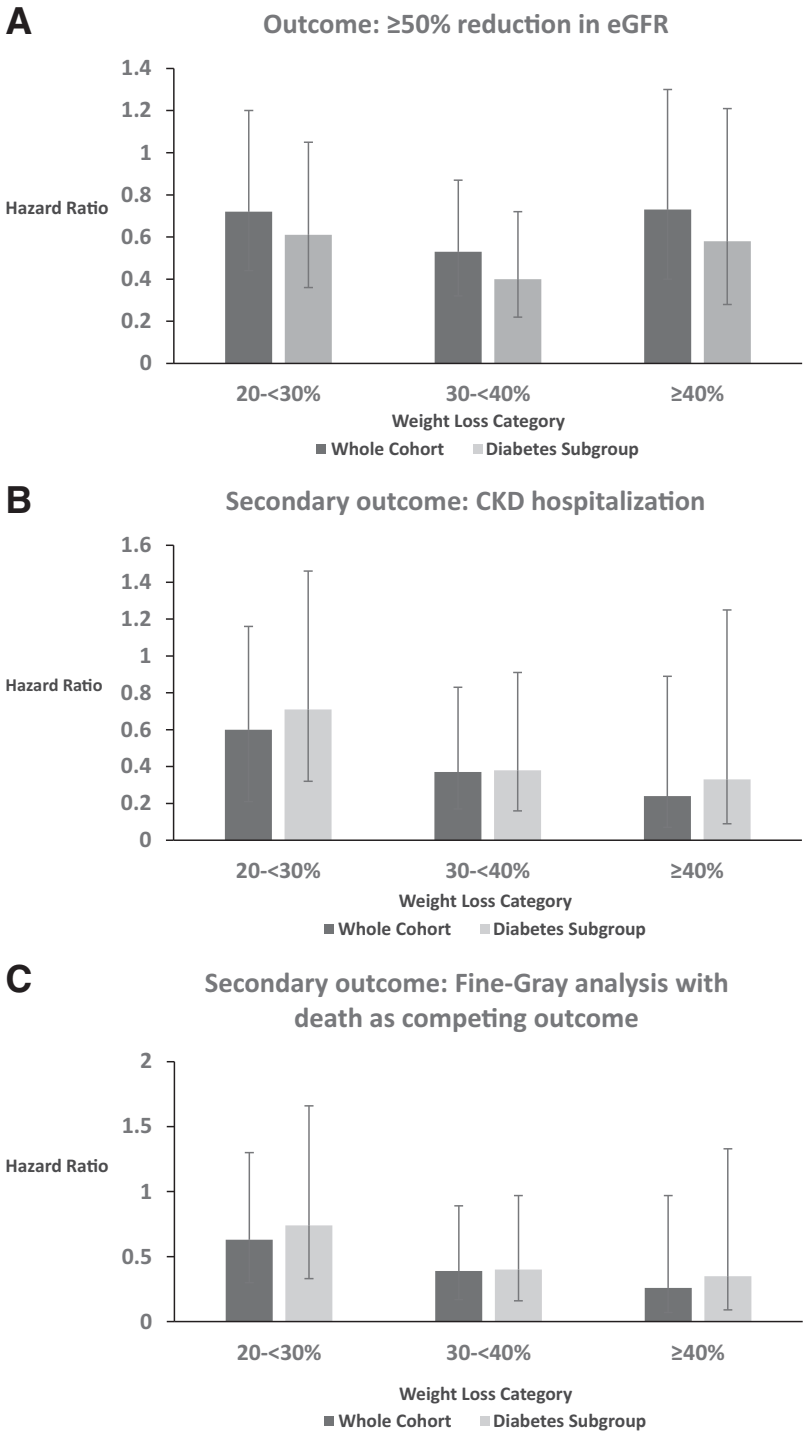

Figure 3—Outcomes after BS by WL category (20 to <30%, 30 to <40%, and ≥40%). The <20% WL group is the comparator. Each outcome is presented for the whole cohort and the subgroup with diabetes. Lines indicate 95% CIs. *A*: Primary outcome (≥50% reduction in eGFR). *B*: Secondary outcome (CKD hospitalization). *C*: Secondary outcome with Fine-Gray analysis with death as a competing outcome.

(P = 0.0005). After adjustment for covariates, compared with the <20% WL category, increased WL was associated with a progressive reduction in CKD hospitalization, which was significant for 30 to <40% (HR 0.37 [95% CI 0.17, 0.83]) and ≥40% (HR 0.24 [0.07, 0.89]) WL but not 20 to <30% WL (HR 0.60 [0.29, 1.23]). Fine-Gray analysis with death as a competing outcome yielded similar estimates (20 to <30% group: HR 0.63 [0.30, 1.3]; 30 to <40% group: HR 0.39 [0.17, 0.89]; ≥40% group: HR 0.26 [0.07, 0.97]) (Fig. 3).

Similar trends were seen in the diabetes subgroup (20 to <30% group: HR 0.71 [95% CI 0.32, 1.56]; 30 to <40% group: HR 0.38 [0.16, 0.91]; ≥40% group: HR 0.33

Table 4—Baseline characteristics according to maximum WL categories for patients undergoing BS in the observational study cohort

	Maximum WL within 1 year postsurgery, % body weight					
	<20%	20 to <30%	30 to <40%	≥40%	Missing value, *n*	*P*
Participants, *n*	426	1,894	2,184	833		
Age, years						
Mean (SD)	48.81 (9.62)	47.35 (10.28)	45.58 (10.10)	43.41 (9.66)	0	<0.0001
Median (IQR)	50 (42–56)	48 (40–55)	46 (38–53)	43 (37–50)	<0.0001	
Sex, *n* (% female)	330 (77.5)	1,531 (80.8)	1,865 (85.4)	739 (88.7)		<0.0001
Income quintile, *n* (%)						
1	101 (23.7)	428 (22.6)	509 (23.3)	184 (22.1)		0.047
2	79 (18.5)	439 (23.2)	513 (23.5)	183 (22.0)		
3	97 (22.8)	424 (22.4)	419 (19.2)	201 (24.1)		
4	76 (17.8)	346 (18.3)	435 (19.9)	158 (19.0)	14	
5	72 (16.9)	255 (13.5)	298 (13.6)	106 (12.7)		
Rural residence, *n* (%)						
No	375 (88.0)	1,640 (86.6)	1,819 (83.3)	692 (83.1)	0	0.003
Yes	51 (12.0)	254 (13.4)	365 (16.7)	141 (16.9)		
Baseline BMI, kg/m^2						
Mean (SD)	48.32 (8.21)	48.95 (8.25)	48.92 (7.57)	50.68 (7.88)	9	<0.0001
Median (IQR)	47 (42–53)	47 (43–54)	48 (43–53)	49 (45–55)	<0.0001	
Diabetes, *n* (%)						
No	193 (45.3)	969 (51.2)	1,363 (62.4)	585 (70.2)	0	<0.0001
Yes	233 (54.7)	925 (48.8)	821 (37.6)	248 (29.8)		
Hypertension, *n* (%)						
Missing data	3 (0.7)	4 (0.2)	3 (0.1)	0 (0.0)		<0.0001
No	172 (40.4)	871 (46.0)	1,125 (51.5)	478 (57.4)	10	
Yes	251 (58.9)	1,019 (53.8)	1,056 (48.4)	355 (42.6)		
Hyperlipidemia, *n* (%)						
Missing data	4 (0.9)	4 (0.2)	4 (0.2)	2 (0.2)		<0.0001
No	237 (55.6)	1,143 (60.3)	1,458 (66.8)	599 (71.9)	14	
Yes	185 (43.4)	747 (39.4)	722 (33.1)	232 (27.9)		
Vascular composite, *n* (%)						
Missing data	4 (0.9)	5 (0.3)	3 (0.1)	2 (0.2)		0.0292
No	370 (86.9)	1,716 (90.6)	1,976 (90.5)	761 (91.4)	14	
Yes	52 (12.2)	173 (9.1)	205 (9.4)	70 (8.4)		
Baseline serum creatinine, μmol/L						
Mean (SD)	68.57 (15.46)	66.06 (13.37)	65.73 (12.89)	65.53 (12.60)	0	0.0004
Median (IQR)	67 (58–76)	65 (57–74)	65 (57–72)	64 (57–72)	0.0066	
Baseline eGFR, mL/min/1.73 m^2						
Mean (SD)	98.27 (16.79)	101.36 (15.40)	102.26 (15.32)	103.15 (15.52)	0 ≥	<0.0001
Median (IQR)	101 (88–110)	104 (91–113)	105 (94–113)	106 (93–115)	<0.0001	
Days from baseline creatinine measurement to surgery						
Mean (SD)	111.30 (107.40)	118.13 (108.33)	133.76 (110.07)	146.44 (110.78)		<0.0001
Median (IQR)	64 (19–190)	79 (21–211)	115 (26–229)	143 (32–240)		<0.0001

Cox proportional hazards models were fit for each primary and secondary outcome, adjusting for the baseline characteristics and baseline eGFR. Multiple imputation was used to impute missing values. ANOVA tests were used for continuous variables, and χ^2 tests were used for categorical variables.

[0.09, 1.25]). Fine-Gray analysis with death as a competing outcome yielded similar estimates (20 to <30% group: HR 0.74 [0.33, 1.66]; 30 to <40% group: HR 0.40 [0.16, 0.97]; ≥40% group: HR 0.35 [0.09, 1.33]) (Fig. 3).

Assessment of WL as a continuous variable showed that after adjustment for covariates, each 1% increase in WL was associated with a further reduction in hospitalization for CKD (HR 0.94 [95% CI 0.91, 0.98). Fine-Gray analysis with death as a competing outcome yielded the same conclusion (HR 0.94 [0.91, 0.98]). Analysis of the patients with diabetes was similar with each 1% additional WL associated with an HR of 0.94 (0.91, 0.98). Fine-Gray analysis with death as a competing outcome yielded similar estimates in patients with diabetes (HR 0.95 [0.90, 0.99]).

DISCUSSION

Observational and MR studies have suggested that obesity may be an independent cause of CKD based on an increased risk of CKD after adjusting for T2D and hypertension (3–6,13–15). Findings from our MR analyses suggest that obesity is likely not an independent cause of CKD but, rather, the effect is mediated by hypertension and dysglycemia. Notably, elevated FG in the non-T2D range is likely a significant contributor to both eGFR-based measures of CKD and MA in people with obesity. The mediation analysis findings suggest that increased FG is likely the largest contributor to the creatinine-derived eGFR measure of CKD, while T2D is the biggest contributor to MA. Concordant with MR analysis, WL at thresholds previously associated with normoglycemia and normotension is associated with reduced CKD outcomes after BS. WL of 30 to <40% was associated with significantly reduced primary (50% decline in eGFR) and secondary CKD outcome (hospitalization for CKD), while ≥40% WL was associated with a significantly greater reduction in the secondary outcome. Prior data suggests T2D remission rates plateau with 20–25% WL, but further WL is associated with increased normoglycemia and normotension (23–26,52). The reduction in the primary outcome did not reach statistical significance with ≥40% weight loss, which likely reflects the smaller sample size for this category and hence merits some caution in interpretation. Given the nonlinear relationship between WL and the primary outcome, studies with a larger sample size will likely yield more definitive insights into the relationship between the amount of WL and reduction in eGFR. Subgroup analyses in people with T2D yielded generally similar findings for both the primary and secondary outcome. Whether achieving normoglycemia and normotension via means other than WL/BS also reduces obesity-associated CKD outcomes remains to be determined.

Our MR analyses suggests that increased BMI increases eGFR estimated by cystatin C measurement, even after adjustment for hypertension, increased FG, and/or T2D. However, previous work suggests that increased BMI, diabetes, and inflammation can underestimate eGFR based on cystatin C measurement compared with direct measures of eGFR, thus precluding definitive conclusions from these data (53). Consistent with prior data (14), we also report that increased BMI decreases UACR but with no effect on eGFR. We did not have individual-level data on participants, including medication use. Greater use of renoprotective medications in people with a higher BMI may plausibly explain these findings. Illustrating this, recent MR analyses suggest that increased BMI lowers apolipoprotein B likely because of the confounding effects of cholesterol-lowering medication, an effect not seen when analyzing people not taking statins (54).

The strengths of this study include MR analyses with the largest available GWAS in populations of European descent along with observational data from patients undergoing BS. However, this study has several limitations. We used a creatinine-based diagnosis of CKD, which is an indirect measure of renal function and can be affected by muscle mass. Similarly, cystatin C–based measures of eGFR can be underestimated with increased BMI, diabetes, and inflammation (53). The retrospective observational nature of the BS cohort with potential uncaptured confounders is a major limitation; however, these limitations are less likely with MR analyses. There was a >50% sample overlap between MR population cohorts, which can overestimate the effect size when weak instrument bias is present, although this effect is attenuated by the strength of the instruments (40). The MR analyses was undertaken in European populations and may not translate to other ethnic groups. The greater availability of genetic data from other ethnicities will enable similar analyses in these cohorts. Although we do not have data on ethnicity in our BS cohort, previous data suggests that ∼20% of patients undergoing BS are of non-European ancestry (55). Lack of individual-level data, including medications, is a limitation of our analyses. We also do not have details on the type of BS performed, MA/proteinuria, and longer-term WL.

In summary, the MR analyses suggest that obesity is likely not an independent causal factor for CKD, with its deleterious renal effects mediated by dysglycemia and hypertension. These data underscore the likely causal role of hyperglycemia below the T2D threshold to obesity-associated CKD. WL at or above thresholds known to improve/remit these cardiometabolic parameters are associated with reduced CKD outcomes after BS, and these findings await confirmation with well-powered prospective studies. Whether achieving normoglycemia and normotension in the absence of WL reduces CKD also awaits independent confirmation.

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