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Supplementary File 1.

STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies[1]

Item No.	Section	Checklist item	Page No.	Relevant text from manuscript
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study		Pg. 1: Title " Association between obesity and chronic kidney disease: multivariable Mendelian randomization analysis and observational data from a bariatric surgery cohort "
	INTRODUCTION			Pg. 4-5: Obesity is a risk factor for chronic kidney disease (CKD), a rising health care burden worldwide which increases morbidity and premature mortality.
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question		Pg. 4-5: Here we undertook bidirectional MR to assess potential causal associations between BMI and CKDeGFR (stage III CKD or worse defined by glomerular filtration rate <60 ml/min1.73m2) (26) and presence of microalbuminuria defined by urinary albumin-to-creatinine ratio, UACR, >25 or >17 mg/g in women and men respectively) in people of European descent using summary statistics from largest genome wide association studies (GWAS). Consistent with prior studies, we found suggestive causal associations between BMI and CKD and therefore we undertook multivariable MR analysis to assess to what extent these potential causal associations are independent of increased fasting glucose, T2D and hypertension. Finally, we assessed the association between weight loss within 1-year of bariatric surgery and a 50% decline in eGFR (primary outcome) and CKD hospitalization (secondary outcome).
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any).		Pg. 2: We undertook bidirectional inverse variance weighted MR (IVMR) to investigate potential independent causal associations between increased BMI and CKDeGFR (estimated glomerular filtration rate, eGFR < 60 ml/min1.73m2) and microalbuminuria (MA). In 5337 BS patients, we assessed whether >50% decline in eGFR (primary outcome) or CKD hospitalization (secondary outcome) is influenced by the amount of WL, compared to <20% WL.
	METHODS			
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:		
	a)	Setting: Describe the study design and the underlying population, if possible.		Pg. 6: MR analyses were undertaken in participants of European ancestry using summary statistics from the largest published genome wide association study (GWAS) (Table 1).
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis		Pg. 6: MR analyses were undertaken in participants of European ancestry using summary statistics from the largest published genome wide association study (GWAS) (Table 1). Informed consent and institutional approval were previously obtained by the individual cohort investigators.
	c)	Describe measurement, quality control and selection of genetic variants		Pg. 6: Genetic variants that were significant at p-value threshold of 5x10-8 in meta-GWAS were used in the instrument; effect size and standard error was also calculated from these meta-GWAS.

		d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	Pg. 6-7: Univariable MR was conducted using the "TwoSampleMR" package in R (R studio® v1.3.1073 and R® v4.0.3), while multivariable MR was conducted using both the "TwoSampleMR", "Multivariable MR" and "RMultivariable MR" packages in R (R studio® v1.3.1073 and R® v4.0.3).
		e)	Provide details of ethics committee approval and participant informed consent, if relevant	Pg. 6: Informed consent and institutional approval were previously obtained by the individual cohort investigators.
5	**Assumptions**		Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	Pg. 7: The first assumption is that the instrument is associated with the exposure, therefore we used SNPs that were associated with the exposure at genome-wide significance. Second that the instrument does not influence the outcome via another pathway other than the outcome (horizontal pleiotropy). Third, there are no confounders associated with the instrument.
6	**Statistical methods: main analysis**		Describe statistical methods and statistics used	
		a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	Pg. 6-7: MR using GWAS data Pg. 10-11: Observational data
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	Pg. 6-7: Genetic variants were weighted based on effect size in prior meta-GWAS.
		c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	Pg. 6-7: Univariable MR using an inverse variance weighted (IVW) approach, i.e. meta-analysis of the individual Wald ratio for each SNP was conducted to assess potential causality between traits.
		d)	Explain how missing data were addressed	Pg. 7: If the SNP was not matched directly, LD pruning was used to select a proxy (r2>0.8).
		e)	If applicable, indicate how multiple testing was addressed	Pg. 6-7
7	**Assessment of assumptions**		Describe any methods or prior knowledge used to assess the assumptions or justify their validity	Pg. 3: Observational studies suggest that obesity may increase CKD, independent of metabolic risk factors such as type 2 diabetes (T2D) and hypertension.
8	**Sensitivity analyses and additional analyses**		Describe any sensitivity analyses or additional analyses performed	Pg. 7: Sensitivity analyses included MR Egger, weighted median and weighted mode as well as tests of heterogeneity (Cochrane's Q test), F-statistics and leave-one-out analyses.
9	**Software and preregistration**			
		a)	Name statistical software and package(s), including version and settings used	Pg. 6-7: Univariable MR was conducted using the "TwoSampleMR" package in R (R studio® v1.3.1073 and R® v4.0.3), while multivariable MR was conducted using both the "TwoSampleMR", "Multivariable MR"

				and “RMultivariable MR” packages in R (R studio® v1.3.1073 and R® v4.0.3).
		b)	State whether the study protocol and details were pre-registered (as well as when and where)	The study was not pre-registered.
	RESULTS			
10	**Descriptive data**			
		a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Cohort details in Table 1.
		b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Cohort details in Table 1.
		c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	Cohort details in Table 1; PMID to original GWAS studies are provided.
		d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples	Cohort details in Table 1.
			ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	Pg. 8: 456,426 participants from the UK Biobank composed approximately 67% of the GIANT/UK Biobank GWAS of BMI, 69% of the DIAGRAM/GERA/UK Biobank GWAS of T2D and 80% of the CKDGEN GWAS of CKD
11	**Main results**			
		a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Pg. 11-13: Associations were reported as exposure increases or reduces the outcome.
		b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	Pg. 11-13: MR estimates were provided as beta +/- standard error with p-value for continuous variables. For binary variables, odds ratio was also provided.
		c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
		d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	Scatter, funnel, forest and leave-one-out plots were provided for significant associations (see figures and supplementary files).
12	**Assessment of assumptions**			
		a)	Report the assessment of the validity of the assumptions	MR-Egger intercept with p-value was reported as a measure of horizontal pleiotropy for all significant associations (see tables and supplementary files).

		b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	Cochrane's Q statistic, F statistic and I2 values were provided for significant associations (see tables and supplementary files).
13	**Sensitivity analyses and additional analyses**		
		a) Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	MR-Egger, weighted-median and weighted-mode analyses were also conducted (see tables and supplementary files).
		b) Report results from other sensitivity analyses or additional analyses	Visualization of the scatter and funnel plots, and leave-one-out analyses were also completed (see tables and supplementary files).
		c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	Pg. 6: We undertook additional bidirectional MR analysis assessing the effect of BMI as exposures on urinary albumin creatinine ratio and eGFR creatinine (eGFRcrea) and cystatin C based eGFR (eGFRCyst) measures.
		d) When relevant, report and compare with estimates from non-MR analyses	Not applicable.
		e) Consider additional plots to visualize results (e.g., leave-one-out analyses)	See supplementary files.
	DISCUSSION		Pg. 14-17
14	**Key results**	Summarize key results with reference to study objectives	Our MR analyses suggest that obesity may not be an independent cause of CKD, but rather these effects are likely mediated by hypertension and dyglycemia. Further, weight loss of 30-<40% was associated with significantly reduced primary and secondary CKD outcomes after bariatric surgery while ≥40% weight loss was associated with significantly greater reduction in the secondary outcome.
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	Pg. 16: The study has were several limitations. We used creatinine-based diagnosis of CKD, which is an indirect measure of renal function. Similarly, cystatin C based measures of eGFR can be under-estimated with increased BMI, diabetes and inflammation. The retrospective observational nature of the bariatric surgery cohort with potential uncaptured confounders is a major limitation, however these limitations are less likely with MR analyses. There is >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. The MR analyses was undertaken in European populations and may not translate to other ethnic groups.
16	**Interpretation**		

		a) Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies.	Pg. 16: The MR analyses suggests obesity may not be an independent causal factor for CKD. Established metabolic risk factors including dysglycemia, T2D and hypertension are likely mediators of obesity associated CKD. This data also underscores the potential causal role of hyperglycemia below the T2D threshold to obesity associated CKD. Weight loss at or above thresholds known to improve/remit these cardiometabolic parameters are associated with reduced CKD outcomes after bariatric surgery: these findings await confirmation with well powered prospective studies.
		b) Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	In the introduction and discussion, we have discussed potential mechanisms including potential effects mediated by horizontal pleiotropy by analyses of individual SNPs in the instrument, as well as the evidence from prior studies.
		c) Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	Not applicable.
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	Pg. 16: The MR analyses was undertaken in European populations and may not translate to other ethnic groups.
	OTHER INFORMATION		
18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	Pg. 18: SD is funded by CIHR, Heart & Stroke Foundation of Canada, Diabetes Canada and Banting & Best Diabetes Centre (DH Gales Family Charitable Foundation New Investigator Award and a Reuben & Helene Dennis Scholar in Diabetes Research).
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	All data used in this study is public access. PMID/GWAS id for cohorts are provided in Table 1. TwoSampleMR R code is also publicly available.
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	No conflicts of interests.

1. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.

Supplemental File 2

Table with individual SNP Data and Leave-One-Out Data — BMI as an exposure on CKD, urinary albumin creatinine ratio (UACR), microalbuminuria and eGFRcrea

Link to file:
https://www.dropbox.com/scl/fi/dwhl44cdfrr3akqdsnzo5/SF2_FP_LOO_Export_Exp_BMI.xlsx?dl=0&rlkey=69yp2yvidlz63935d15vszrfl

Supplementary file 3. Reverse MR analysis of CKDegfr, UACR, MA and eGFRcrea on BMI.

Method	B	Standard Error	p	Egger-Intercept	p_{Egger}	Cochrane's Q	Q df	p_Q	I^2	F
Exposure: Chronic Kidney Disease, Outcome: Body Mass Index										
MR Egger	-0.013	0.067	0.847	0.002	0.737	53.403	12	3.49E-07	77.529	*
Weighted median	0.011	0.011	0.341							*
Inverse variance weighted	0.009	0.014	0.495			53.929	13	6.22E-07	75.894	*
Simple mode	0.020	0.022	0.373							*
Weighted mode	0.018	0.018	0.336							*
Exposure: Urinary Albumin Creatinine Ratio, Outcome: Body Mass Index										
MR Egger	-0.051	0.391	0.897	0.000	0.952	91.787	36	2.59E-122	60.779	8.520
Weighted median	-0.148	0.048	0.002							8.520
Inverse variance weighted	-0.074	0.087	0.394			691.858	37	1.11E-121	94.652	8.520
Simple mode	-0.309	0.132	0.024							8.520
Weighted mode	-0.188	0.126	0.145							8.520
Exposure: Microalbuminuria, Outcome: Body Mass Index										
MR Egger	Insufficient number of SNPs for analysis									
Weighted median	Insufficient number of SNPs for analysis									
Inverse variance weighted	0.003	0.012	0.835							
Simple mode	Insufficient number of SNPs for analysis									
Weighted mode	Insufficient number of SNPs for analysis									
Exposure: eGFR Creatinine , Outcome: Body Mass Index										
MR Egger	-0.542	0.469	0.250	0.001	0.376	1659.865	133	9.39E-262	91.987	97.16297
Weighted median	-0.095	0.099	0.336							97.16297
Inverse variance weighted	-0.157	0.179	0.379			1669.716	134	3.57E-263	91.975	97.16297
Simple mode	0.015	0.188	0.937							97.16297

Weighted mode	-0.023	0.124	0.852							97.16297

*****Variance of trait not provided for CKD GWAS which is required for manual F-Statistic calculation.

Supplemental File 4 – Cohort Creation

Numbers of individuals included and excluded at each step of cohort creation		
Cohort Creation Steps	**Included**	**Excluded**
All records	11765	
Exclude invalid ikn	11410	355
Exclude invalid bdate and missing sex	11410	0
Death before index date	11388	22
Non-ON resident at index	11353	35
Ineligible for OHIP at index	11297	56
Exclude non-primary surgeries	10994	303
Exclude missing both M6 and Y1 weights	8072	2922
Exclude prior CKD history	7882	190
Exclude baseline eGFR <= 45 or if the last eGFR before index is <= 0.6 * eGFR at baseline	7864	18
Exclude no eGFR during follow-up	7623	241
Exclude no eGFR at baseline	Final N=5337	2286

Supplementary File 5 – Beta of BMI on fasting glucose (Y Axis) vs. Beta of BMI on Type 2 Diabetes (X Axis)