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CLINICAL STUDY

Dietary habits and risk of diabetic kidney disease: a two-sample and multivariate Mendelian randomization study

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ABSTRACT

Objective: We explored the causal relationship between certain dietary habits and the risk of developing diabetic kidney disease (DKD) using two-sample Mendelian randomization and multivariate Mendelian randomization.

Research design and methods: This study is based on pooled data from a genome-wide association study (GWAS) of 83 dietary habits in a European population. We performed a two-sample Mendelian randomization analysis using GAWS data on diabetic nephropathy in a European population. Validation was then performed against positive results ($p < 0.05$) in different GAWS data on diabetic nephropathy of European origin. Finally, multivariate Mendelian randomization analyses were performed on dietary habits with positive results ($p < 0.05$) in both datasets and GWAS data on postprandial glucose in the European population.

Results: This study showed causal relationships between 18 dietary habits and the risk of developing DKD. After validation, causal relationships were found between the risk of DKD and two dietary habits: abstaining from sugar consumption (OR 2.86; 95%CI 1.35, 6.08; $p = 0.006$) and consuming whole grain/multigrain bread (OR 0.53; 95%CI 0.32, 0.89; $p = 0.016$). Correcting for the effect of postprandial glucose, the multivariate MR results showed that never eating sugar increased the risk of developing DKD (OR 0.08; 95%CI 0.018, 0.36; $p = 0.001$), whereas eating whole grain/multigrain bread did not reduce the risk of developing DKD (OR 1.37; 95%CI 0.55, 3.41; $p = 0.50$).

Conclusions: Our MR results suggest a causal relationship between never eating sugar and an increased risk of developing DKD. Therefore, people with diabetes need a reasonable range of sugar intake.

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Dietary habits; diabetic kidney disease; sugar intake; Mendelian randomization; genome-wide association studies; causal relationship

1. Introduction

Diabetic kidney disease (DKD) is a common microvascular complication in patients with diabetes and is comorbid in about 40% of diabetic patients [1]. Without a doubt, the presence of DKD complicates the management of diabetes, and many hypoglycemic agents are not permitted due to decreased renal function. At the same time, DKD accelerates cardiovascular events [2] and severely shortens patient life expectancy [3]. Therefore, DKD has become a significant public health problem that cannot be ignored.

The treatment strategy for DKD has shifted from intensive metabolic control to strong multifactorial infarction (MI) [4]. MI consists mainly of metabolic control and lifestyle interventions [1]. The impact of lifestyle interventions on DKD has been noted by Gao et al. [5], who found that Life's Essential 8 scale scores were inversely associated with kidney damage in DKD. A Mendelian randomization study [6] showed that short sleep duration increases the risk of developing chronic kidney disease. A previous study [7] demonstrated that a vegetarian diet reduces the risk of kidney disease in patients with hyperuricemia. Unhealthy eating habits are recognized as a significant risk factor for disease or death [8]. Therefore, changing dietary habits is an essential initiative in lifestyle interventions.

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The Look AHEAD randomized clinical trial [9] showed that dietary changes can reduce the incidence of DKD in diabetic patients. Sulaiman et al. [10] also concluded that dietary intervention is essential in delaying the onset and progression of DKD and is no longer a supplementary measure. These studies have demonstrated that changing patients' poor dietary habits is an important primary preventive measure.

Suckling et al. [11] conducted a meta-analysis of salt intake and showed that limiting daily salt intake to 2 g reduced the incidence of DKD in diabetic patients. Fotheringham et al. [12] found that eating foods high in Advanced Glycation End Products (AGEs) may increase the risk of kidney disease. However, no studies specify what dietary habits increase the risk of DKD in people with diabetes, and no causal relationship between dietary habits and the risk of developing DKD can be proven. So, we conducted this Mendelian randomization study for 83 different diets.

Mendelian randomization is a typical means of exploring causality in epidemiology. As an alternative approach, Mendelian randomization uses genes as instrumental variables (IVs) to infer whether exposure factors contribute to the occurrence of outcome factors [13]. Because genes are randomly assigned to offspring at conception, Mendelian randomization can mimic the setup of a randomized control and avoid the effects of confounders or the reverse of the ending factor [14]. We conducted this study using pooled data from genome-wide association studies to comprehensively report the causal relationship between dietary habits and the risk of developing DKD. This study helps to further explore the value of dietary habits in preventing the development of DKD.

2. Materials and methods

Our Mendelian randomization study report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE-MR) [15]. The data used in this study were publicly available and did not have human participants, so it did not require institutional review board approval or patient-informed consent.

2.1. Study design

We used a two-sample and multivariate MR approach to explore the causal relationship between dietary habits and the risk of developing DKD. Single nucleotide polymorphisms (SNPs) were defined as IVs. All analyses were performed in R 4.3.1 with the packages 'TwoSampleMR' (version: 0.5.7), 'MR-PRESSO' (version: 1.0), and 'Cause' (version: 1.2). The MR analyses were guided by the following three assumptions [16]:

1. The instrumental variables were strongly correlated with the exposure factors;
2. The instrumental variables were independent of observed or unobserved confounders;
3. The instrumental variables influenced the results only through the exposure.

The three assumptions can be found in Figure 1.

2.2. Data sources

We downloaded GWAS data for 83 dietary habits from the official website of the Type 2 Diabetes Knowledge Portal (http://www.kp4cd.org/dataset_downloads/t2d) provided by Cole et al. [17] This is the current pooled genetic association data on eating habits for European ancestry. GWAS summary data for DKD was obtained from the FinnGen consortium [18] (https://r9.finngen.fi/). The R9 release (May 2023) of the FinnGen consortium data was used, which contains 4,111 cases and 308,539 controls. We used the GWAS data on diabetic kidney disease summarized by Zuydam et al. [19] to validate the previous MR analysis results. The official IEU open GWAS project website (https://gwas.mrcieu.ac.uk/) provides GWAS data on blood glucose two hours after a glucose tolerance test. This can replace the blood sugar level after eating. All of the above data are from European pedigrees. Specific information on related GWAS can be found in Table 1.

2.3. Instrumental variable selection

To ensure the accuracy and authenticity of the findings of this paper, the following criteria were used to determine the instrumental variables [20,21]:

1. SNPs were associated with dietary habits at suggestive levels on a genome-wide scale ($p < 5 \times 10^{-6}$).
2. There is no cascading imbalance between SNPs ($r^2 <$ 0.001 and clump distance > 10,000 kb).
3. SNPs can only influence outcome factors (DKD) through exposure factors (Dietary factors). We used

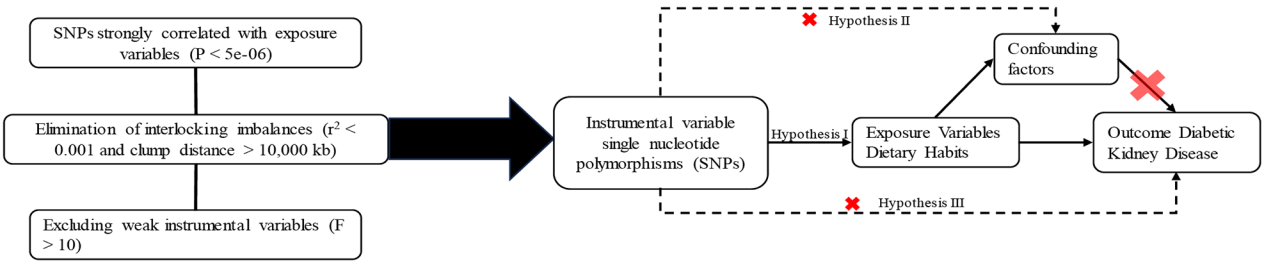

Figure 1. Three hypotheses for two-sample MR.

the PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/) to assess whether SNPs are associated with other risk factors for DKD, such as blood pressure and lipid levels [22].
4. Weak instrumental variable bias was excluded [23] (F > 10).
5. Removal of palindromic SNP.

The F-value formula is shown in Figure 2. β represents the association effect of Effect Allele, and SE represents the standard error of β.

2.4. MR analysis

This study used dietary habits as the exposure variable and DKD as the outcome variable, and causal association analyses were performed using two-sample Mendelian Randomization.

Table 1. The characteristics of GWAS studies.

Variant		Sample size	Consortium	Web Source
Exposing Variables	Dietary Habits	NA	Type 2 Diabetes Knowledge Portal	https://www.kp4cd.org/dataset_downloads/t2d
Ending Variables	Diabetic kidney disease	312,650	FinnGen R9	https://r9.finngen.fi/
		40,340	GWAS Catalog	https://www.ebi.ac.uk/gwas/studies/GCST005881
Confounding variable	Postprandial glucose	45,854	GWAS Catalog	https://www.ebi.ac.uk/gwas/studies/GCST000569

NA: Not Available.

$$F = \beta^2 expodure / SE^2 exposure$$

Figure 2. F-value formula.

Five methods, Inverse variance weighted, MR Egger, Weighted median, Simple mode, and Weighted mode, were selected for MR analysis. Among them, Inverse variance weighted was used as the main result, and the rest of the methods were used as supplementary evidence. IVW provides the most accurate results in the absence of pleiotropy present [24]. Odds Ratio (OR) and Confidence Interval (CI) were used to assess the relative risk of developing DKD due to dietary habits. $p < 0.05$ was considered nominally significant [25]. After Bonferroni correction, $p < 0.0006$ (0.05/83/1) was considered statistically significant [26]. For positive results, further two-sample and multivariate Mendelian Randomization validation was performed. The study process design diagram can be found in Figure 3.

2.5. Sensitivity

We used Cochran's Q test to assess the heterogeneity among SNPs [27]. All MR analyses were conducted under a random effects model. We used three methods to evaluate pleiotropy:

1. We used the MR-Egger intercept as an indicator for evaluating directional pleiotropy [28]. Causal Analysis Using Summary Effect Estimates (CAUSE) [29] was used to reassess the robustness of positive results in the presence of horizontal pleiotropy.
2. We performed a sensitivity analysis of the results using the 'leave-one-out' method to determine the degree of influence of individual SNPs on causality;
3. Potential pleiotropy and outliers were assessed using MR pleiotropy residual sum and outlier (MR-PRESSO), Global test was used to detect the presence of horizontal pleiotropy and outliers in the instrumental variables, and Distortion test was used to detect whether the results before and after the removal of outliers were significantly different [30]. If outliers existed, the MR analysis was repeated after eliminating these outliers.

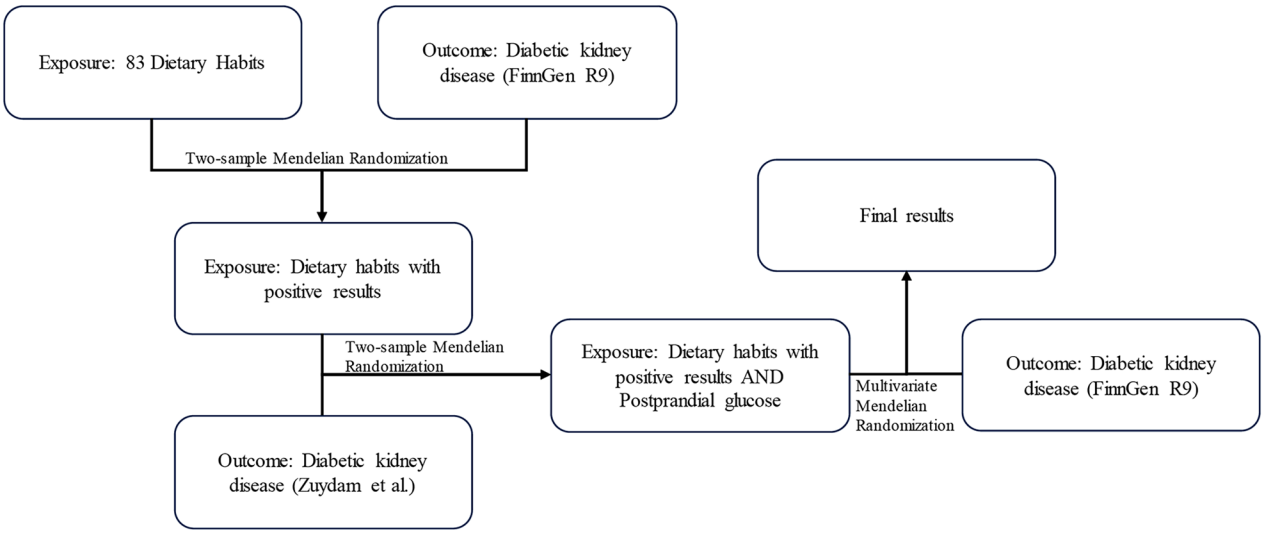

Figure 3. Study design flowchart.

3. Results

Instrumental variables and F-values for all 83 dietary habits can be found in the Supplementary Material.

We found suggestive causal relationships between the intake of sugar, vegetables, fresh fruits, tea, coffee, hot beverages, alcohol and the intake of different types of milk, cream, bread, and cereal with the risk of developing DKD. We did not find a significant causal association between dietary factors and the development of DKD. All positive results can be found in Figure 4.

In the validation set, we re-analyzed the previous positive results by MR. The results showed that never eating sugar increased the risk of developing DKD compared to an unrestricted diet (OR 2.86; 95%CI 1.35, 6.08; $p = 0.006$) while eating whole wheat or mixed grain bread decreased the risk of developing DKD compared to eating white and brown bread (OR 0.53; 95%CI 0.32, 0.89; $p = 0.016$). Related results can be found in Figure 5.

In multivariate Mendelian randomization, we found that after correcting for the effect of postprandial glucose, never eating sugar compared to an unrestricted diet increased the

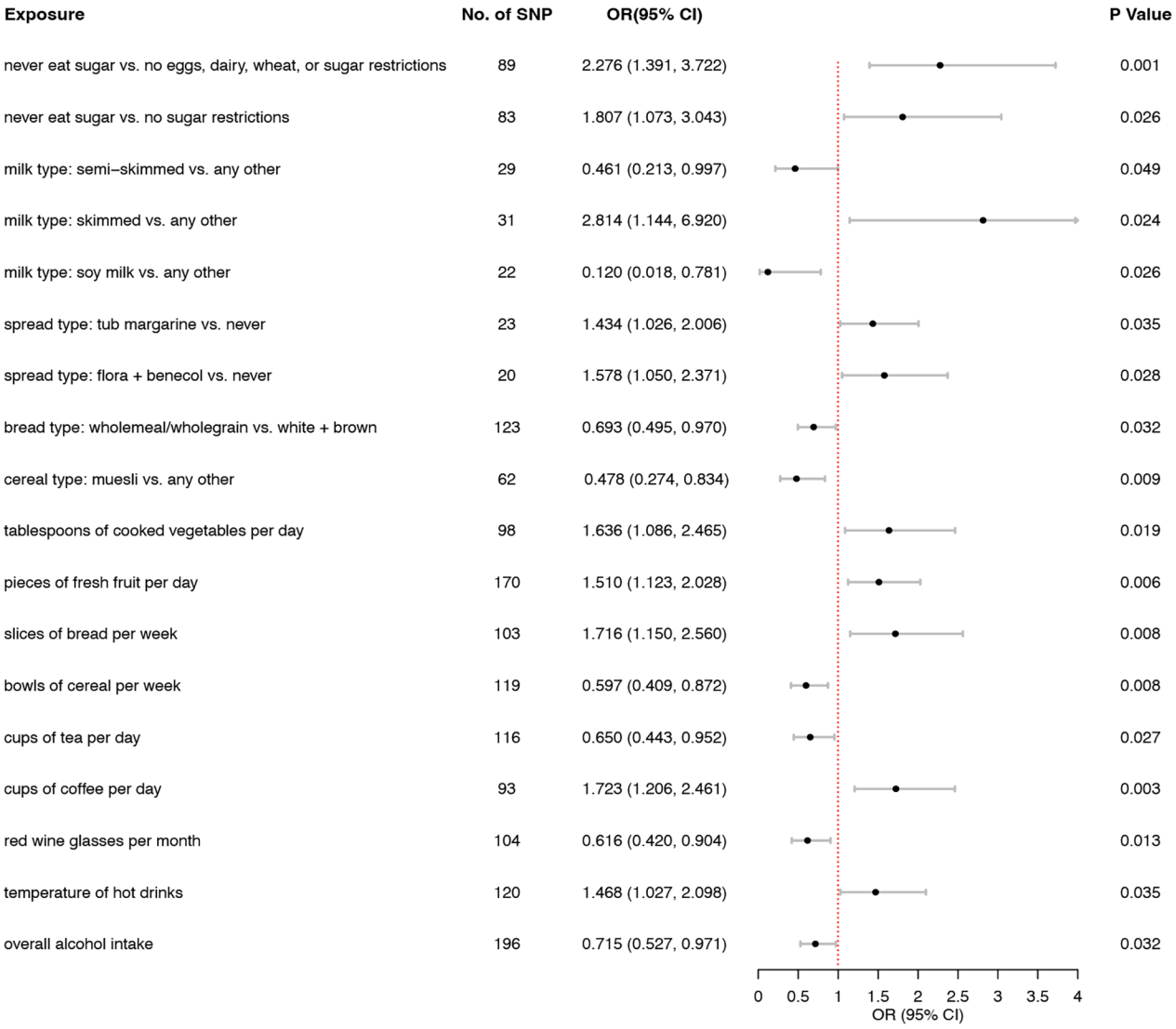

Figure 4. Causal relationships of dietary habits and diabetic kindney disease in the European population (Cole et al.).

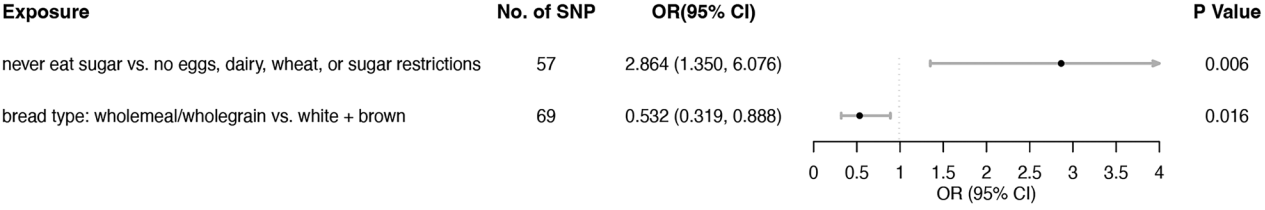

Figure 5. Causal relationships of dietary habits and diabetic kindney disease in the European population (Zuydam et al.).

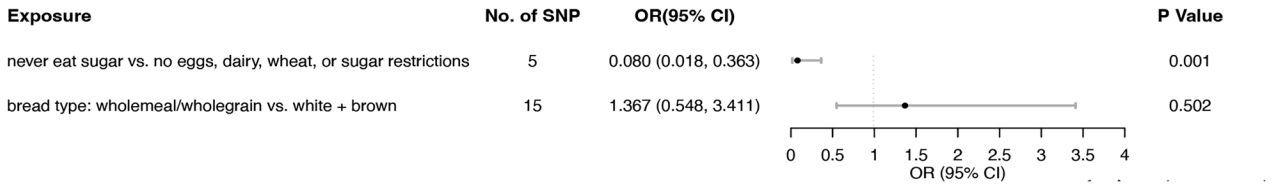

Figure 6. Causal relationships of dietary habits and diabetic kindney disease in the European population (MVMR).

risk of DKD onset (OR 0.08; 95%CI 0.018, 0.36; $p=0.001$); eating whole grain/mixed grain bread compared to eating white and brown bread did not reduce the risk of DKD onset (OR 1.37; 95%CI 0.55, 3.41; $p=0.50$). Related results can be found in Figure 6.

The results of the specific sensitivity analyses can all be found in the Supplementary Materials. Of particular note, we found a suggestive causal association between weekly intake of red wine and the development of DKD. However, the results of the sensitivity analyses showed horizontal pleiotropy in the results of this MR analysis. Therefore, we reran the MR analysis in the presence of pleiotropy. The results showed no statistically significant causal relationship between them ($p=0.66$). The results of the analysis can be found in the Supplementary Materials. None of the results were multivariate, except for the effects on weekly intake of red wine and the risk of developing DKD. Heterogeneity was not seen in others.

4. Discussion

As one of the most common microvascular complications of diabetes, the incidence of DKD is increasing worldwide [31]. However, due to the lack of effective treatment, DKD is currently the leading cause of end-stage renal disease [32]. A great deal of money and socio-medical resources are being used to address the consequences of this problem. Therefore, the prevention and early detection of DKD is a challenge that currently plagues clinicians and researchers.

Our initial explorations identified a suggestive causal relationship between 18 dietary habits and the risk of developing DKD. However, after the Bonferroni correction, we found no significant causal relationship. We argue that Mendelian randomization is designed to screen for substantial or potential causality rather than simply ignoring potential cause by setting a threshold for significance [33]. P value is not the only basis for explaining robustness [34]. Since 83 dietary habits were included in our MR study, Bonferroni corrections will likely produce false-negative results [35]. Therefore, we consider MR analysis with $p<0.05$ in the exploratory and validation datasets a significant positive result.

After replacing the database of outcome variables, dietary habits associated with previously positive outcomes were re-analyzed for MR using a two-sample Mendelian Randomization analysis. We hope this will improve the robustness of causality. Hyperglycemia, hypertension, and hyperlipidemia are now commonly recognized risk factors of DKD [36], so we excluded SNPs related to blood pressure and lipids when screening IVs. Even after drinking pure water, we all know that eating can lead to blood sugar fluctuations [37]. To avoid these dietary habits from damaging glomerular and interstitial glomeruli through the elevation of blood glucose after eating, which mediates the activation of downstream pathways by epigenetic effects [38,39], including DNA methylation, we chose the 2-h glucose profile in the glucose tolerance test as the GWAS data for postprandial blood glucose. A multivariate Mendelian Randomization was used to determine whether dietary habits directly affect the development of DKD after adjusting for the effect of postprandial glucose [40].

We found that people who never eat sugar have a higher risk of DKD than those who don't limit their eggs, dairy, wheat, or sugar intake. This is an exciting result. Because we all know that elevated serum glucose levels are one of the risk factors for developing DKD, our study shows that completely restricting sugar intake increases the risk of DKD instead. We hypothesize this is related to the hypoglycemic response in people with diabetes. The UK Prospective Diabetes Study (UKPDS) [41] confirmed that intensive glycemic control reduces the incidence of microvascular complications of diabetes and decreases mortality from cardiovascular events. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) [42] showed that intensive glycemic control lowers the risk of hypoglycemia, increasing the risk of cardiovascular and all-cause mortality in people with diabetes. The UKPDS trial recruited all patients with new-onset diabetes, whereas the ACCORD trial recruited diabetic patients with cardiovascular risk, which may account for this difference. This suggests that hypoglycemia can have potentially adverse cardiovascular effects, and renal vasculature is no exception. It has been suggested that hypoglycemia induces an inflammatory response that leads to dysfunction of nitric oxide-mediated endothelial stretch [43], resulting in altered intraglomerular hemodynamics and damage to the glomerular filtration membrane [10]. At the same time, the onset of hypoglycemia is followed by sympathetic activation and massive secretion of catecholamines, which prompts renal vasoconstriction, increases intraglomerular pressure, and affects hemodynamics within the renal vasculature. Chow et al. [44] found that these inflammatory responses with hemodynamic changes tend to persist for weeks.

Second, ingesting glucose is the quickest and most convenient way for humans to obtain energy. Glucose intake is insufficient, and the energy required for cellular metabolism can be obtained by conversion by gluconeogenesis. At this point, both fat and protein can be converted to glucose. But this conversion is undoubtedly a waste of energy. More fat or protein intake is required to convert to normal glucose requirements. However, too much fat or protein intake can

lead to new problems, such as the unending debate about ketogenic diets [45]. Even though fruits are rich in sugar, a diet rich in fruits, vegetables, fish, grains, whole grains, fiber, and polyunsaturated fatty acids but low in saturated fatty acids is currently considered a healthy diet for people with chronic kidney disease [46]. This is because dietary fiber and other known or unknown nutrients are consumed when sugar is finished, which may slow down the rapid digestion and absorption of sugar [47].

We found that the current guidelines emphasize salt intake but not sugar intake. It is now well established that a diet high in sugar is a risk factor for developing DKD [22]. Ideally, a strictly sugar-restricted diet should reduce the risk of developing DKD. However, this is the exact opposite of what our MR study found. Animal experiments or clinical randomized controlled trials have not confirmed this causal relationship. We have made a reasonable speculation that strict sugar restriction increases the risk of developing DKD, and more studies are needed to ensure this. In addition to renal microcirculatory lesions, other microvascular complications due to diabetes, such as retinal microangiopathy and peripheral nerve microangiopathy, should be analyzed by MR as outcome factors.

It is worth mentioning that we performed a reverse analysis of the causal relationship between dietary habits and the risk of developing DKD. However, we did not find statistically significant results. This suggests that the causal relationship between dietary habits and the risk of developing DKD is unidirectional. Considering that the clinical significance of the effect of dietary habits on the development of DKD is much lower than the effect of dietary habits on the risk of developing DKD, we stopped exploring this reverse causality in depth.

Indeed, our study has some things that could be improved. First, dietary habits were not derived from a questionnaire for people with diabetes and may have influenced the study results. Second, we did not use a strict Bonferroni correction to confirm the robustness of the causality. Finally, due to missing GWAS data, we used only the two-hour postprandial glycemic profile as the post-feeding glycemic change. Postprandial glucose data from more time points in the future should be included in MR analyses to improve the reliability of causality.

5. Conclusion

We confirmed the causal relationship between the increased risk of developing DKD from not eating sugar by two-sample and multivariate Mendelian randomization. For people with diabetes, sugar intake should be limited to a reasonable amount.

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Author contributions

ZQ designed the study. ZQ and JY wrote the manuscript. ZQ, JY, WH, YQ collected, analyzed, and interpreted the data. JY critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

Disclosure statement

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of this study.

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Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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