Causal Association Between Dietary Factors and Chronic Kidney Disease: A Mendelian Randomization Study

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Abstract

Dietary intervention is a key strategy for preventing and managing chronic kidney disease (CKD). However, evidence on specific foods' effects on CKD is limited. This study aims to clarify the impact of various foods on CKD risk. We used two-sample Mendelian randomization (TSMR) to analyze the causal relationships between the intake of 18 foods (e.g., cheese, processed meat, poultry, beef, non-oily fish) and CKD risk, as well as eGFRcr and eGFRcys levels. The inverse variance weighting (IVW) method, weighted median method, MR-Egger regression, simple mode and weighted mode were employed. Sensitivity analysis included Cochran's Q test and the Egger intercept test. Frequent alcohol intake was linked to higher CKD risk (P=0.007, 0.048). Protective factors included cheese (OR=0.71, [95%CI: 0.53, 0.94], P=0.017), tea (OR=0.66, [95%CI: 0.43, 1.00], P=0.048) and dried fruit (OR=0.78, [95%CI: 0.63, 0.98], P=0.033). Oily fish (β=0.051, [95%CI: 0.001, 0.102], p=0.046) and dried fruit (β=0.082, [95%CI: 0.016, 0.149], p=0.014) were associated with elevated eGFRcys. Salad/raw vegetables (β=0.024, [95%CI: 0.003, 0.045], p=0.028) and dried fruit (β=0.013, [95%CI: 0.001, 0.031], p=0.014) were linked to higher eGFRcr, while cereal intake (β=-0.021, [95%CI: -0.033, -0.010], p<0.001) was associated with lower eGFRcr. These findings provide insights for optimizing dietary strategies for CKD patients.

Keywords: chronic kidney disease; eGFRcr; eGFRcys; mendelian randomization analysis; diet

Abbreviations: CKD: Chronic Kidney Disease; TSMR: Two-sample Mendelian Randomization; eGFR: Estimated Glomerular Filtration Rate; Cr: Creatinine; Cys: Cystatin C; IVW: Inverse Variance Weighting; IVs: Instrumental Variables; GWAS: Genome-wide Association Study; LD: Linkage Disequilibrium; BMI: Body Mass Index; WM: Weighted-Median; OR: Odds Ratio; CI: Confidence Interval; SNP: Single Nucleotide Polymorphism; MAC: Medial Arterial Calcification;

1.Introduction

Chronic kidney disease (CKD) is a significant global public health issue, defined as kidney abnormalities that persist for more than 3 months. The prevalence of CKD is substantial, with a global median prevalence of 9.5% across 73.9% of countries [(1)]. Measuring substances present in plasma, such as creatinine (Cr) and cystatin C (Cys), to calculate the estimated glomerular filtration rate (eGFR) is the most widely used method for evaluating renal function. CKD is classified into stages based on the severity of kidney damage and function, ranging from stage 1 (mildest) to stage 5 (most severe), according to eGFR levels [(2)].

CKD is associated with higher morbidity and mortality. People with CKD frequently suffer from cardiovascular diseases, such as heart failure and may die from these issues before reaching end-stage kidney failure. Additionally, hypertension and type 2 diabetes are commonly associated with CKD. While medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and statins are commonly used in CKD management, they often come with side effects including hyperkalemia, hypotension and adverse effects on cardiovascular health and kidney function [(3; 4; 5)]. Due to the relatively lower burden of side effects, dietary modification is considered a key strategy for preventing and managing CKD [(6)].

Emerging evidence suggests that oxidative stress, a condition where the body's antioxidant defenses are overwhelmed by excess free radicals, can accelerate CKD progression and exacerbate kidney damage [(7)]. Some foods, particularly those rich in antioxidants, such as tea, cheese, oily fish and vegetarian diet rich in antioxidant compounds may help protect against CKD by reducing oxidative stress, a key factor contributing to kidney damage [(8; 9; 10; 11)]. Therefore, identifying and understanding modifiable dietary factors that protect against CKD is of great clinical and public health significance for establishing effective preventive measures.

Currently, many assessments of dietary risk or protective factors rely on animal experiments, cross-sectional studies and retrospective analyses. However, these methodologies may struggle to effectively isolate and exclude other potential confounders that could affect experimental outcomes. The UK Biobank, which contains genetic and health related

information from over 500 000 European volunteers, includes diets-related data for several aspects. Mendelian randomization (MR) analysis offers a powerful tool that uses instrumental variables and summary-level data to explore causal relationships while minimizing confounding and reverse causality biases [12]. Understanding the impact of dietary factors on eGFRcr, eGFRcys levels and CKD can help to develop dietary intervention strategies that contribute to the prevention and management of CKD. Therefore, this study employed two-sample MR to analyze the causal effects of various dietary factors on eGFRcr, eGFRcys levels and CKD. Our findings will significantly aid in the development of tailored dietary strategies for individuals with CKD.

2. Methods

The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) MR checklist (Supplementary Materials 1: Table 1) [13]. This study utilized only publicly available summary data, which had been approved for human experimentation by an ethics committee. Therefore, no additional ethical approval was necessary for this study. MR employs genetic variants to explore causal relationships within observational data [14; 15; 16]. The foundation lies in Mendelian laws of inheritance and instrumental variable (IV) estimation methods, allowing for the estimation of causal effects even when unobserved confounding factors are present. The relationships among exposure factors (dietary factors), IVs and the outcome (CKD, eGFR) are showed in Figure 1: the flowchart for this two-sample MR study and the three fundamental assumptions were considered when conducting MR analysis as follows:

1), the instrumental variables (IVs) are strongly associated with the exposure.

2), the IVs are not associated with potential confounders of the exposure, outcome association.

3), the IVs do not affect outcome independently of exposure.

2.1. Data sources

To avoid potential bias caused by sample overlap and population differences, all GWAS data are European ancestry without a known sample overlap [17].

Exposure data concerning food intake were sourced from the UK Biobank (UKB), a large-scale prospective study encompassing genetic and phenotypic information from more than 500,000 individuals aged 40 to 69 years across the United Kingdom. We included food-intake-related GWAS data covering 18 items, including cheese intake, processed meat intake, poultry intake, beef intake, non-oily fish intake, oily fish intake, pork intake, lamb/mutton intake and alcohol intake frequency, which were categorized as categorical variables, whereas bread intake, cooked vegetable intake, tea intake, fresh fruit intake, cereal intake, salad / raw vegetable intake, coffee intake, dried fruit intake and average weekly red wine intake were treated as continuous variables. Detailed information on how these variables were categorized can be found in Supplementary Materials 1: Table 2, and further specifics are available at the following link: https://biobank.ndph.ox.ac.uk/ukb/label.cgi?id=100050. The data ID are all available from the IEU open GWAS database (Table 1, https://gwas.mrcieu.ac.uk/).

The CKD outcome data were collected from the FinnGen (eleventh release including 11, 265 cases and 436, 208 controls) and CKDgen (European-ancestry including 41,395 cases and 439,303 controls) [18; 19]. (Table 1)

Because eGFRcr and eGFRcys are of great significance for the early diagnosis, disease monitoring and management of CKD, we also obtained eGFRcr and eGFRcys GWAS data from the CKDGen European-ancestry meta-analysis [19; 20]. Each study fitted sex- and age-adjusted linear regression models to log(eGFR).

2.2. Outcome Phenotype definition.

Creatinine values obtained with a Jaffé assay before 2009 were calibrated by multiplying them by 0.95. For adults over 18 years of age, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, by using the R package nephro. For individuals who were 18 years old or younger, the Schwartz formula was used. eGFRcys was estimated using the formula 76.7*(serum cystatin C) $^{-1.19}$ [21]. To manage extreme values, eGFR was winsorized at 15 and 200ml min^{-1} per 1.73 m^2. CKD was defined as an eGFR below 60 ml min^{-1} per 1.73 m^2 [18; 19].

2.3. Instrumental Variables (IV) Selection

All statistical analyses were performed using R software (version 4.4.0; https://www.r-project.org/) and the TwoSampleMR package, ensuring thorough and robust data evaluation.

Firstly, SNPs significantly associated with the exposure phenotype were identified using a selection criterion where only those with a p-value$<5\times10^{-8}$ were considered. This threshold is consistent with common practice in Mendelian randomization to reduce the risk of weak instruments. Secondly, a linkage disequilibrium (LD) threshold of $R^2 < 0.001$ and a window size greater than 10,000 kb were applied during the IV clumping procedure to minimize the possibility of selecting correlated SNPs that could undermine the validity of the instruments. The strength of association between the IVs and exposure factors was assessed using the F statistic. To mitigate bias stemming from weak IVs, our criteria included only SNPs with an F statistic >10. Detailed information regarding the data can be found in Supplementary Materials 2.

To prevent confounding from secondary phenotypes, such as body mass index (BMI), hypertension and diabetes, we further screened the selected SNPs using the LDlink tool (https://ldlink.nih.gov/?tab=ldtrait). This ensured that the SNPs influenced the outcome through the exposure of interest rather than through potential confounders.

2.4 Mendelian Randomization Analysis

The standard inverse-variance weighted (IVW) method with a random-effects model was the primary analysis approach and was used to estimate the causal relationship. This method assumes that all instrumental variables (IVs) are valid and provides high efficiency. To further validate our results, we also applied MR Egger [(22)], Weighted Median methods [(23)], Simple mode and Weighted mode [(24)] as additional analyses. MR Egger operates under the assumption that all IVs are invalid, whereas the Weighted Median method requires that at least half of the IVs are valid. Simple Mode uses the most common effect (or a simple average effect) of all instrumental variables as an estimate of the causal effect. Weighted Mode adjusts for genotype frequency differences by weighting each genotype according to its frequency or effect size. These supplementary methods help to assess the robustness of our findings.

All statistics were processed with a 95% confidence interval (CI). The causal effects of dietary factors on the risk of CKD were analyzed using odds ratios (ORs) with 95% confidence intervals (CIs). Since eGFRcys and eGFRcr levels were continuous data, the estimated effect values were assessed as β (95% CI).

2.5 Sensitivity Analysis

Cochran's Q test was employed to evaluate the heterogeneity of the analyzed results, while the Egger intercept test was utilized for the pleiotropy analysis. To address the potential influence of horizontal pleiotropy on the reliability of our findings in the MR analysis, MR-Presso with NbDistribution set to 10,000 was applied to identify and mitigate outlier SNPs. Moreover, any positive findings from the two-sample MR analyses were subjected to additional leave-one-out analyses to assess their robustness.

3. Results

After screening of IVs, the analysis incorporated a range of IVs numbering between 8 and 93, all possessing an F-statistic > 10 (10.07- 569.92; Supplementary Materials 2).

The IVW approach was selected as the primary method based on a $p < 0.05$ and the results were analyzed without horizontal pleiotropy except dried fruit intake and eGFRcr (Supplementary Materials 2: p value of pleiotropy analysis = 0.016). We determined that a more frequent alcohol intake cheese intake, tea intake and dried fruit intake were associated with the incidence of CKD. Oily fish intake and dried fruit intake were associated with eGFRcys levels. Salad / raw vegetable intake, cereal intake and dried fruit intake were associated with eGFRcr levels. The results suggesting that they are risk/protective factors for CKD (Figure 2).

3.1. Causality between Cheese intake, Alcohol intake frequency, Tea intake and CKD

A total of 56 SNPs were included in the analysis after screening. The IVW method revealed that cheese intake is associated with a reduced risk of CKD ($p = 0.017$), with an estimated odds ratio (OR) of 0.707. Supplementary analysis methods depicted in Figure 3 consistently

supported the direction of effect observed with the IVW method. The leave-one-out analysis plot in Figure 4 suggests robustness in the derived SNP analysis results.

Alcohol intake frequency was found to be associated with the risk of CKD (P = 0.007, 0.048) based on the causal inference from 85 and 81 screened SNPs derived from CKDgen and FinnGen, respectively. The estimated effect value OR of 1.163, 1.171 suggested that Alcohol intake frequency was a risk factor for CKD attacks, with a 1.163, 1.171-fold increase in the risk of CKD attacks for every 1-unit increase in Alcohol intake frequency. Figure 3 consistently supported the direction of effect observed with the IVW method in CKDgen. However, when analyzed by the complementary method (MR Egger and Weighted mode) in FinnCKD, inconsistent directions of the effect value were found (Figure 3). The leave-one-out analysis suggested the overall robustness of the analysis (Figure 4).

Tea intake was found to be associated with a reduced risk of CKD (p=0.033), with the causal inference of 34 screened SNPs derived CKDgen. The estimated effect value OR of 0.783. The leave-one-out analysis suggested the overall robustness of the analysis (Figure 4). Consistent directions of the effect were found by the complementary method (Figure 3).

3.2. Causality between Oily fish intake and eGFRcys level

After screening, a total of 55 SNPs were included in the causal analysis examining the relationship between oily fish intake and eGFRcys level. Analysis using the IVW method indicated a significant association between oily fish intake and elevated eGFRcys level (p = 0.046). The estimated effect value (β = 0.051) suggests that for every 1-unit increase in oily fish intake, eGFRcys level increases by approximately 1.053 units. The leave-one-out analysis plot in Figure 4 suggests robustness in the results derived from these 55 SNPs. The supplementary analysis method MR-egger depicted in Figure 3 showed inconsistent direction of effect observed with the IVW method.

3.3 Causality between Cereal intake, Salad / raw vegetable intake and eGFRcr level

After screening, 25 SNPs were included in the causal analysis examining the relationship between cereal intake and eGFRcr level. Analysis using the IVW method indicated a

significant association between cereal intake and decreased eGFRcr levels (p=0.028). The estimated effect values (β=-0.022) suggest that for every 1-unit increase in cereal intake, eGFRcr decreases by approximately 0.978 units. The supplementary analysis methods depicted in Figure 3 showed consistent direction of effect observed with the IVW method. The leave-one-out analysis plot in Figure 4 suggests robustness in the results derived from these 25 SNPs.

After screening, 15 SNPs were included in the causal analysis examining the relationship between Salad / raw vegetable intake and eGFRcr level. Analysis using the IVW method indicated a significant association between Salad / raw vegetable intake and elevated eGFRcr levels (p=0.028). The estimated effect values (β=0.024) suggest that for every 1-unit increase in Salad / raw vegetable intake, eGFRcr increase by approximately 1.024 units. The supplementary analysis methods depicted in Figure 3 showed consistently direction of effect observed with the IVW method. The leave-one-out analysis plot in Figure 4 suggests robustness in the results derived from these 15 SNPs.

3.4 Causality between Dried fruit intake and eGFRcr, eGFRcys level, CKD

After screening, 35 and 38 SNPs were included in the causal analysis examining the relationship between dried fruit intake and eGFRcr, eGFRcys level. Analysis using the IVW method indicated a significant association between Dried fruit intake and elevated eGFRcr, eGFRcys levels (p=0.048, 0.031). The estimated effect values (β=0.013, 0.082) suggest that for every 1-unit increase in Salad / raw vegetable intake, eGFRcr increase by approximately 1.013, 1.086 units. The leave-one-out analysis plot in Figure 4 suggests robustness in the results. However, the analysis method MR egger depicted in Figure 3 showed inconsistently direction of effect observed with the IVW method. Additionally, for eGFRcys, the directions of effect in Simple mode and Weighted mode were also inconsistent with those observed in IVW.

Dried fruit intake was found to be associated with a reduced risk of CKD (p=0.048), with the causal inference of 35 screened SNPs derived FinnCKD. The estimated effect value OR of 0.658. The leave-one-out analysis suggested the overall robustness of the analysis (Figure 4). Consistent directions of the effect value were found by the complementary methods (Figure 3).

4. Discussion

We conducted a MR investigation to examine the casual associations between dietary habits and the risk of kidney function-related indices (eGFRcr, eGFRcys) as well as CKD. This study found that a more frequent alcohol intake was associated with an increased risk of CKD, whereas cheese intake, tea intake and dried fruit intake were protective factors against the incidence of CKD (Figure 2). The present study found that oily fish intake (β= 0.051, [95%CI: (0.001,0.102)], p = 0.046) and dried fruit intake (β = 0.082, [95%CI: 0.016,0.149], p =0.014) were associated with elevated eGFRcys levels. Salad / raw vegetable intake (β = 0.024, [95%CI: 0.003,0.045], p =0.028) and dried fruit intake (β = 0.013, [95%CI: 0.001,0.031], p =0.014) were factors for elevated eGFRcr levels, while cereal intake (β = -0.021, [95%CI: -0.033, -0.010], p <0.001) was associated with decreased eGFRcr levels (Figure 4).

Currently, there is a notable lack of extensive randomized controlled trials examining the correlation between dietary intake and the incidence of CKD. Instead, the majority of existing research predominantly relies on cross-sectional and retrospective survey methods. Consistent with our findings, specific dietary patterns have been shown to reduce the risk of CKD and to elevate eGFR levels. Interestingly, the protective foods identified in our study, such as tea, cheese, dried fruits, oily fish, and vegetarian diet are rich in antioxidant compounds [8; 9; 10; 11]. These antioxidants may contribute to their protective effects by reducing oxidative stress, which is a factor in the progression of CKD. A cross-sectional survey from China showed that two dietary patterns rich in plant-derived foods (cereals, fruits and vegetables) have proven to be beneficial for kidney function [25]. One aspect that contrasts to our research results, because our results showed that increasing frequency of cereal consumption decreased eGFRcr. This may be due to the differences in the ingredients of cereal products in Europe and China, and this study was based on European samples. Potassium additives are widely distributed in processed foods and therefore pose a risk of hidden sources of potassium in CKD dietary management. According to a study analyzing the labeling of 715 products from France, Germany and Spain, the frequency of potassium additives in processed foods is notably high. The food categories that showed the greatest presence of additives were breaded products, meat derivatives, non-alcoholic beverages, ready-to-eat products and cereal derivatives [26].

Recently, an MR study reported a causal relationship between an extra cup of tea per day and a reduced risk of CKD, involving 117,165 participants with 12,385 cases from the CKDGen consortium [27]. This is consistent with our findings, which included 439,303 participants with 41,395 cases from the CKDGen consortium. Tea consumption (camellia sinensis) has been correlated with a lower incidence of chronic pathologies. The health benefits attributed to tea consumption are believed to be associated with their high content of bioactive ingredients, such as polyphenols [28]. Studies have shown that the natural polyphenol epigallocatechin-3-gallate (EGCG), found in green tea, can reduce oxidative stress and modulate epigenetic changes, thereby attenuating arsenic-induced cytotoxicity and fibrogenic changes in kidney epithelial cells [29]. Another study also demonstrated that EGCG protects against medial arterial calcification (MAC) in CKD via modulation of the JunB-dependent Ras/Raf/MEK/ERK signaling pathway [30].

Besides tea consumption, we also found other dietary habits that may have protective effects against CKD, such as cheese intake. The cheese maturation process is notable for producing bioactive peptides due to the action of enzymes produced by lactic acid bacteria. In addition to being proteins with high biological value due to their excellent amino acid profiles, peptides from some types of cheese possess functional properties such as anti-hypertensive, antioxidant and zinc-binding activities [31]. In a preclinical study, consumption of probiotic-enriched Mina's cheese (Lact. acidophilus La-05) suggested a promising cardioprotective effect and was able to downregulate superoxide dismutase (SOD) activity in a rat model of CKD [32].

Using MR analysis, we found that oily fish intake was a factor for elevated eGFRcys levels. The results analyzed by the MR Egger method showed a different direction of the effect value. Although the existence of a causal relationship cannot be concluded based on the results of the current analyses, from the perspective of genomic association. However, fish oil, rich in omega-3 fatty acids, may play a crucial role in preventing CKD. After adjusting for key confounders, habitual use of fish oil was linked to a significantly reduced risk of developing CKD, with a hazard ratio (HR) of 0.90 (95% CI, 0.87-0.95) compared to non-use in the UK Biobank [33]. Another study showed that fish oil supplementation can reduce the inflammatory

factor IL-1β in nondialysis CKD patients [34]. A cross-sectional study conducted in Japan found that higher dietary fish intake was associated with higher serum levels of n-3 polyunsaturated fatty acids (PUFAs). Participants in the higher PUFA tertiles had non-significantly higher eGFRcr and significantly higher eGFRcys. They reported that eGFRcys might be more useful than eGFRcr when investigating the relationship between eGFR and PUFA profiles, as muscle mass could be an important factor influencing the relationship between serum PUFAs and eGFR [35]. This may explain why no such association was found with eGFRcr levels.

Although our MR analysis identified some dietary risk factors associated with CKD, a more nuanced interpretation of these results is necessary. For example, cereal intake was analyzed as a risk factor for decreased eGFR levels. While cereals are generally considered healthy due to their high fiber content and essential nutrients, it is important to recognize that some processed cereals can contain high levels of potassium additives. These additives pose a hidden risk for individuals with CKD, as excessive potassium intake can exacerbate kidney dysfunction and elevate serum potassium levels. Therefore, the interpretation of this result should be limited to processed cereals that may contain higher levels of potassium additives, which could negatively impact kidney function. Similarly, while dried fruits are rich in nutrients beneficial to health and may have a positive impact on CKD patients, the potential risk of mycotoxin contamination needs to be taken seriously. To reduce health risks for CKD patients, it is important to choose dried fruit products that have undergone strict quality control and to pay attention to the origin and storage conditions of the dried fruits to minimize mycotoxin intake [36]. However, it is crucial to note that the supplement methods revealed inconsistencies in the direction of the effect. In addition, horizontal pleiotropy analysis indicated eGFRcr level may be affected by other pathways, not just the exposure factor dried fruit intake. This discrepancy calls for caution in interpreting the causality of dried fruit intake, oily fish on eGFR levels. In the CKDgen database, both the IVW and MR Egger methods consistently show a significant association between alcohol intake and CKD risk. Previous studies present that chronic ethanol consumption correlates with significantly increased renal oxidative stress [37]. However, in the FinnCKD database, although IVW indicates significance, the MR Egger and Weighted mode methods shows a different direction, possibly due to

different alcohol consumption patterns, genetic variations, environmental factors.

These results emphasize the complexity of diet-disease relationships. The protective effects of dietary factors such as tea, cheese, dried fruits and oily fish are likely due to their antioxidant properties, which help reduce renal oxidative stress. Additionally, bioactive compounds including polyphenols, bioactive peptides and omega-3 fatty acids, may provide anti-inflammatory and cytoprotective benefits, further supporting kidney health. We recommend a balanced and varied diet that includes protective foods such as cheese, dried fruits, tea, salad/raw vegetables and oily fish, as these may help support kidney function and potentially reduce the risk of CKD. On the other hand, reducing alcohol consumption and limiting cereal intake are important to lower the risk of CKD. While these dietary habits may offer protection, patients with CKD should work with dietitians to adjust these recommendations to their individual needs and ensure proper monitoring, particularly in the case of processed foods.

It is crucial to acknowledge the limitations of our study. As our MR analysis is based on large-scale GWAS data, it is subject to the constraints of its study design. Notably, our research instrument could not differentiation between processed and unprocessed forms of certain foods (e.g., cereals, dried fruits), which may have led to an oversimplification of the observed associations. Additionally, our findings are primarily based on data from European populations, limiting the generalizability of the results to other ethnic groups. Furthermore, the causal relationship identified through the MR analysis represents the impact of long-term exposure, meaning that short-term exposure may lack clinical significance. Another limitation is that, we were unable to distinguish causal effects at different time points; for example, patients with CKD may consciously adjust their eating habits after being diagnosed. Therefore, our findings may not apply to patients with early kidney disease or those who change their eating behaviors quickly after being diagnosed. Finally, while we analyzed data from two CKD databases, most dietary factors showed significance in only one of the two databases, with alcohol intake being the exception. However, it is important to note that the direction of the OR values was consistent across both databases by IVM methods, providing some reassurance about the robustness of the findings. Future studies should differentiate between processed and

unprocessed food forms and include more diverse populations, account for potential confounders such as lifestyle factors and environmental influences to improve the accuracy of dietary recommendations related to kidney health and enhance the applicability of the results across different genetic backgrounds.

5.Conclusion:

In conclusion, our study successfully identified several dietary factors associated with chronic kidney disease (CKD) risk and eGFRcr. Frequent alcohol intake was found to increase CKD risk in CKDgen consortium. Protective factors included cheese, tea and dried fruit. Additionally, salad/raw vegetable intake was linked to higher eGFRcr levels, while cereal intake was associated with lower eGFRcr levels. These findings align with existing observational studies and offer valuable insights for optimizing dietary strategies to manage CKD and improve renal function.

Author contributions statement:

Huang Ya'nan, Tang Wei designed the study. Huang Ya'nan contributed to data acquisition. Huang Ya'nan, Tang Wei and Zhao Zhenhua contributed to the data analysis and interpretation. Huang Ya'nan performed the statistical analysis, Huang Ya'nan, Tang Wei and Yang Jianfeng contributed to drafting and revising the manuscript critically for important intellectual content of the manuscript together. All authors read and approved the final manuscript. Huang Ya'nan and Tang Wei contributed to the work equally.

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Data availability: The exposure data ID are all available from the IEU open GWAS database (https://gwas.mrcieu.ac.uk/). GWAS outcome date of summary statistics for CKD, eGFRcys and eGFRcrea from the CKDGen European-ancestry meta-analysis (https://ckdgen.imbi.uni-freiburg.de/). GWAS outcome data of CKDfinn for this study available from FinnGen (https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_N14_CHRONKIDNEYDIS.gz).

Competing interests: The authors declare no competing interests.

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Table 1. Exposure and outcome phenotypic data

Phenotype		Year	Consortium	Sample size	SNPs	PMID	IEU OpenGWAS ID
Exposure							
	Cheese intake	**2018**	**UKB**	**451,486**	**9,851,867**	**--**	**ukb-b-1489**
	Processed meat intake	**2018**	**UKB**	**461,981**	**9,851,867**	**--**	**ukb-b-6324**
	Poultry intake	**2018**	**UKB**	**461,900**	**9,851,867**	**--**	**ukb-b-8006**
	Beef intake	**2018**	**UKB**	**461,053**	**9,851,867**	**--**	**ukb-b-2862**
	Non-oily fish intake	**2018**	**UKB**	**460,880**	**9,851,867**	**--**	**ukb-b-17627**
	Oily fish intake	**2018**	**UKB**	**460,443**	**9,851,867**	**--**	**ukb-b-2209**
	Pork intake	**2018**	**UKB**	**460,162**	**9,851,867**	**--**	**ukb-b-5640**
	Lamb/mutton intake	**2018**	**UKB**	**460,006**	**9,851,867**	**--**	**ukb-b-14179**
	Alcohol intake frequency	**2018**	**UKB**	**462,346**	**9,851,867**	**--**	**ukb-b-5779**
	Average weekly red wine intake	**2018**	**UKB**	**327,026**	**9,851,867**	**--**	**ukb-b-5239**
	Coffee intake	**2018**	**UKB**	**428,860**	**9,851,867**	**--**	**ukb-b-5237**
	Tea intake	**20**	**UKB**	**447,4**	**9,851,8**	**--**	**ukb-b-6066**

		18		85	67		
	Cooked vegetable intake	2018	UKB	448,651	9,851,867	--	ukb-b-8089
	Salad / raw vegetable intake	2018	UKB	435,435	9,851,867	--	ukb-b-1996
	Fresh fruit intake	2018	UKB	446,462	9,851,867	--	ukb-b-3881
	Dried fruit intake	2018	UKB	421,764	9,851,867	--	ukb-b-16576
	Bread intake	2018	UKB	452,236	9,851,867	--	ukb-b-11348
	Cereal intake	2018	UKB	441,640	9,851,867	--	ukb-b-15926
Outcome							
	eGFRcr (creatinine)	2019	CKDGen	567,460	--	31152163	--
	eGFRcys (cystatin C)	2017	CKDGen	24,061	--	28452372	--
	CKD	2019	CKDGen	41,395/439,303	--	31152163	--
	CKD	2024	FinnGen	11265/436208	21306707	--	--

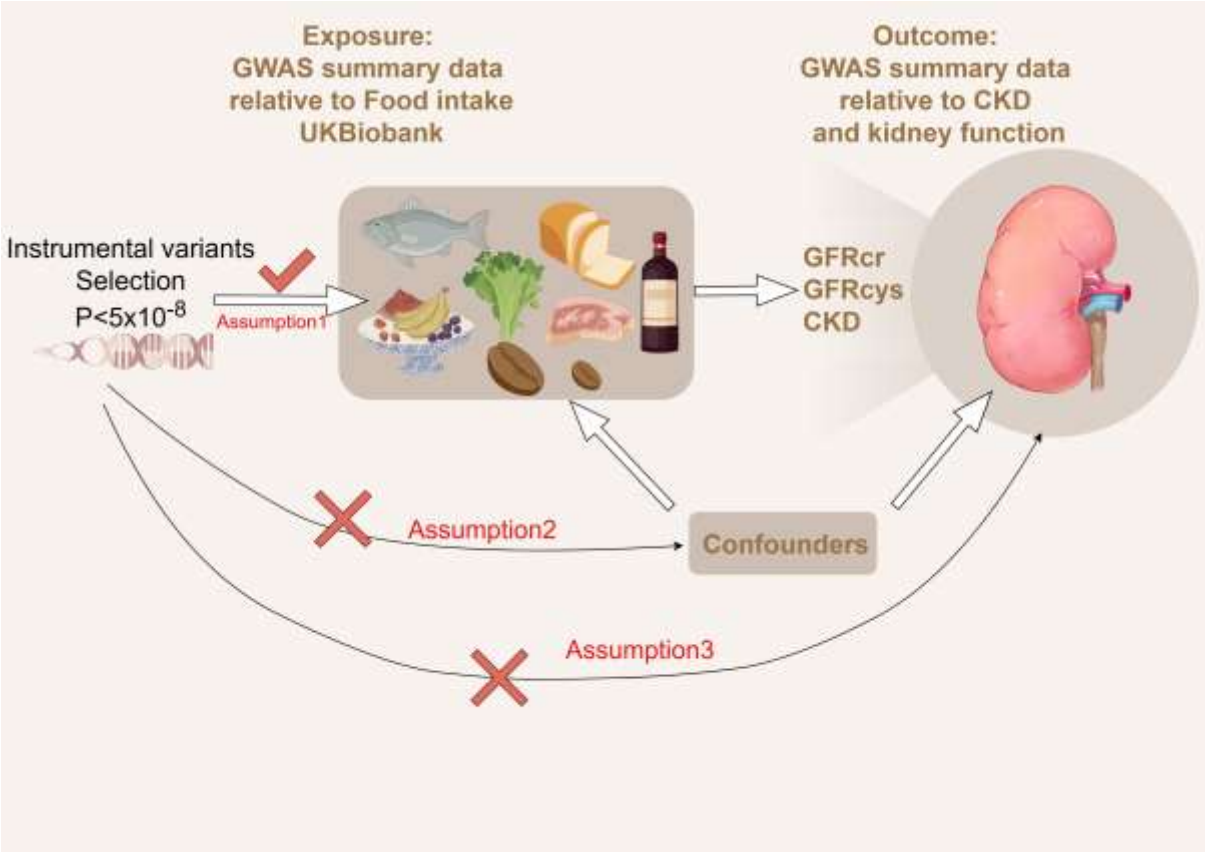
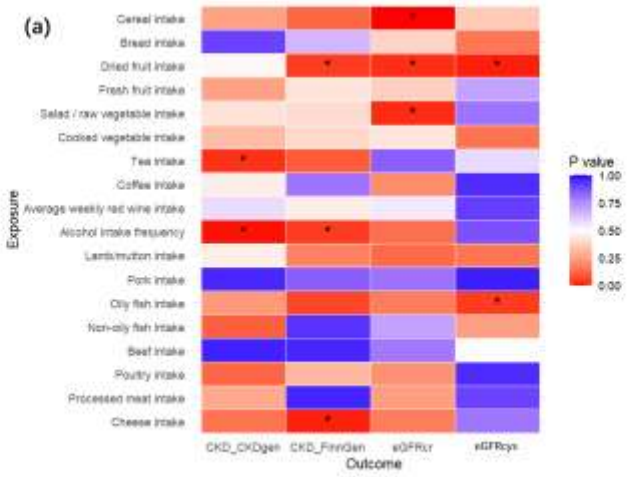


Figure 1. Flow chart for two Mendelian randomization (MR) study for dietary factors and chronic kidney disease and kidney function. And the three assumptions of MR study (created by Figdraw).



(b)

Exposure	Outcome	OR(95%CI)	P value	Cochran's Q test P value	Egger intercept test P value	MR-presso (Global Test P value)
Cheese intake	CKD/CKDgen	0.87(0.72,1.05)	0.153	0.179	0.326	0.179(no outlier)
	CKD/FinnGen	0.71(0.53,0.94)	0.017	0.098	0.883	0.101(no outlier)
Alcohol intake frequency	CKD/CKDgen	1.16(1.04,1.30)	0.007	0.181	0.892	0.191(no outlier)
	CKD/FinnGen	1.17(1.00,1.37)	0.048	0.244	0.545	0.245(no outlier)
Tea intake	CKD/CKDgen	0.78(0.63,0.98)	0.033	0.215	0.736	0.232(no outlier)
	CKD/FinnGen	0.79(0.60,1.05)	0.101	0.377	0.258	0.418(no outlier)
Dried fruit intake	CKD/CKDgen	0.91(0.69,1.92)	0.482	0.826	0.940	0.828(no outlier)
	CKD/FinnGen	0.66(0.43,1.00)	0.048	0.495	0.296	0.518(no outlier)

Exposure	Outcome	β(95%CI)	P value	Cochran's Q test P value	Egger intercept test P value	MR-presso (Global Test P value)
Oily fish intake	eGFRcr	0.005(-0.002,0.013)	0.172	0.475	0.161	0.484 (no outlier)
	eGFRcys	0.051(0.001,0.102)	0.046	0.271	0.274	0.282 (no outlier)
Cereal intake	eGFRcr	-0.021(-0.033,-0.010)	<0.001	0.488	0.115	0.516 (no outlier)
	eGFRcys	-0.070(-0.112,-0.029)	0.365	0.394	0.174	0.397 (no outlier)
Salad / raw vegetable intake	eGFRcr	0.024(0.003,0.045)	0.028	0.766	0.510	0.767 (no outlier)
	eGFRcys	0.012(-0.040,0.064)	0.604	0.342	0.123	0.316 (no outlier)
Dried fruit intake	eGFRcr	0.013(0.001,0.025)	0.031	0.159	0.016	0.158 (no outlier)
	eGFRcys	0.082(0.016,0.149)	0.014	0.517	0.462	0.512 (no outlier)

Figure 2. Risk/protective factor analysis of dietary intake based on IVW method: a: Heat map of the correlation between dietary factors and eGFRcr, eGFRcys or CKD (*, p<0.05); b: MR analysis of risk/protective factors associated with eGFRcr, eGFRcys and CKD, along with the results of sensitivity analyses.

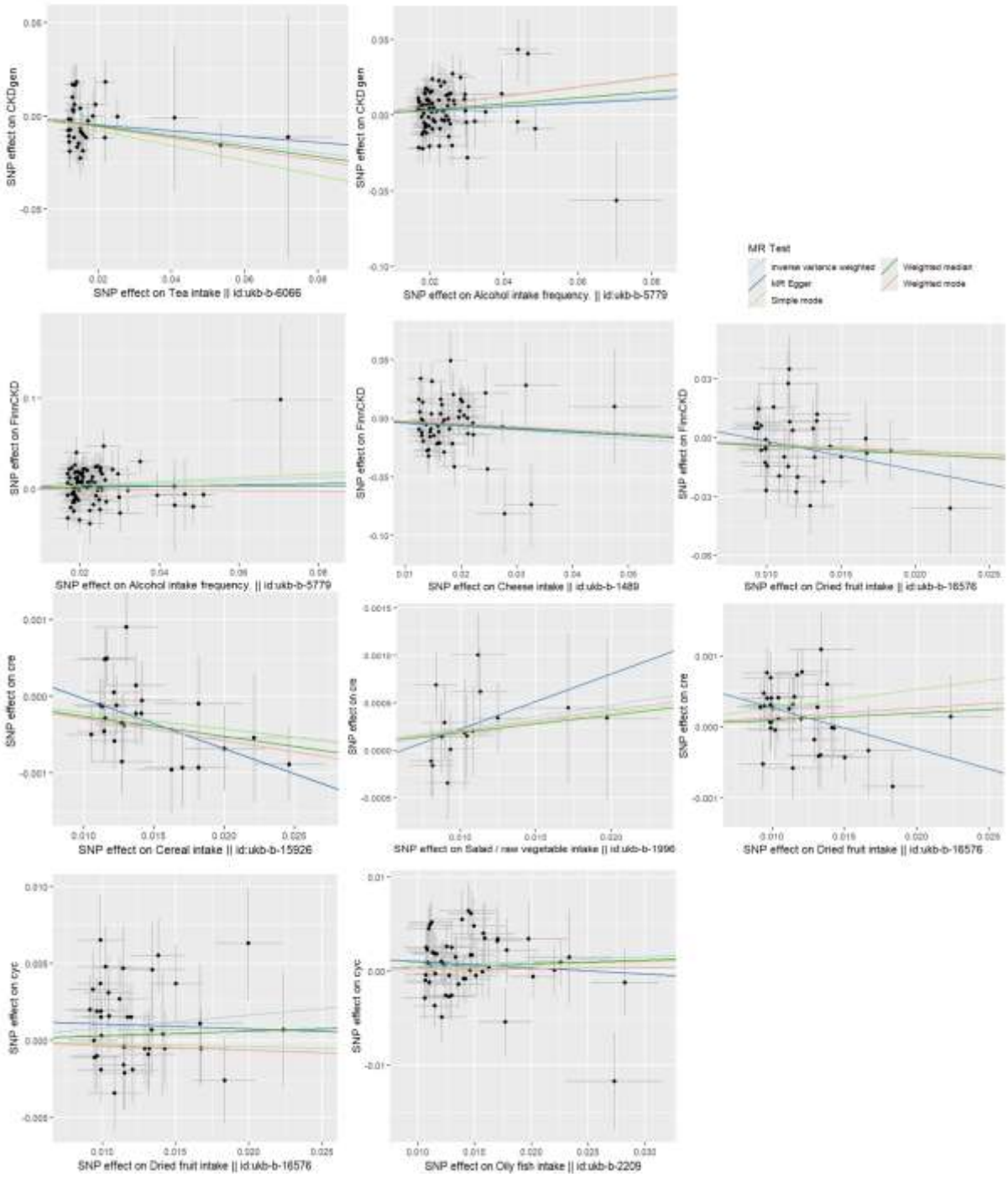


Figure 3: Scatter plots of MR analysis of dietary factors significantly associated with eGFRcr, eGFRcys or CKD (based on IVW, MR Egger, Weighted Median, Simple mode and Weighted mode)

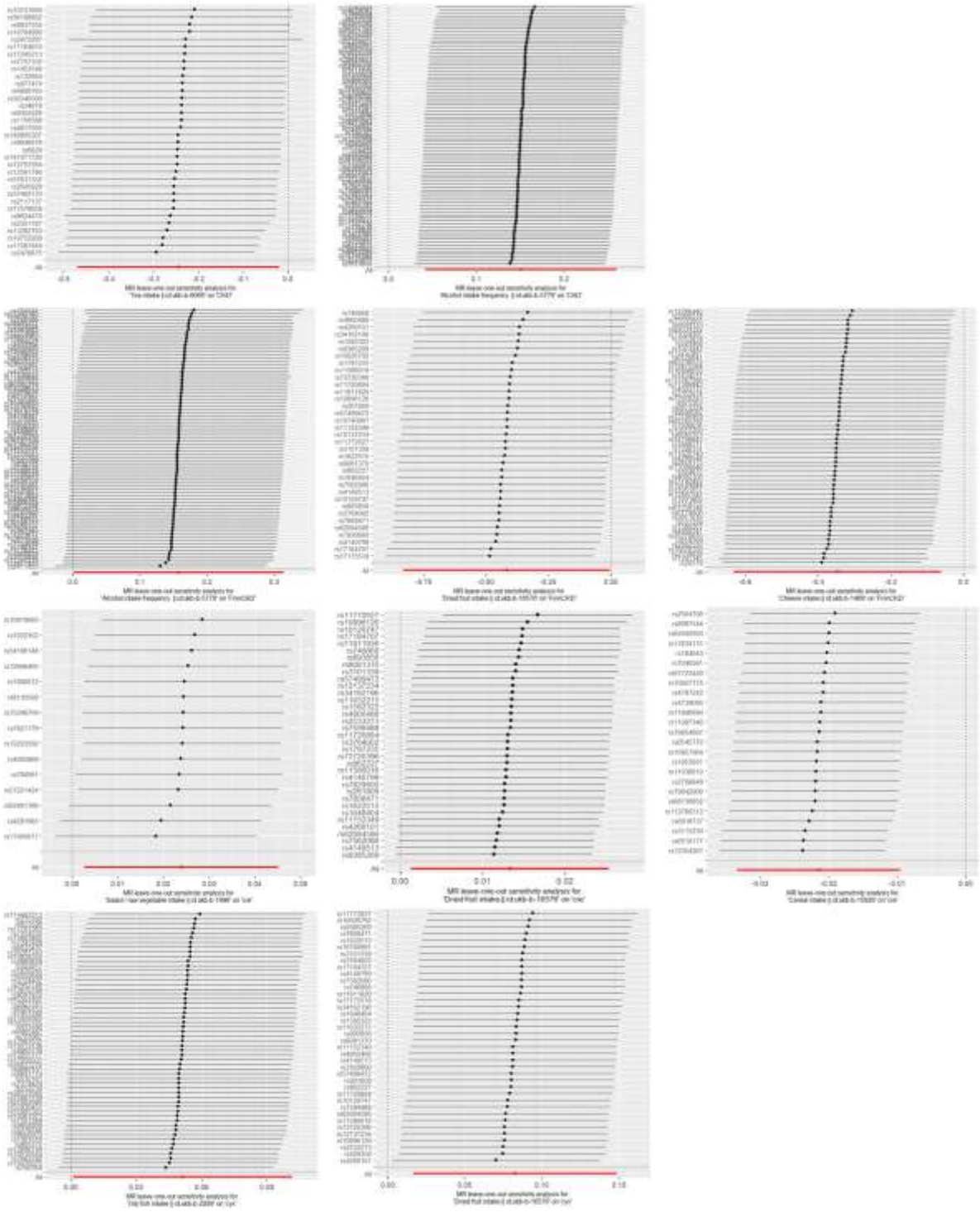


Figure 4. Leave-one-out sensitivity analysis of dietary factors significantly associated with eGFRcr, eGFRcys or CKD. (Each line represents the estimated effect value and its confidence interval after excluding a specific SNP. The "ALL" in the bottom row reflects the combined estimated effect value and confidence interval, considering all SNPs.)