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Original Article

Dietary patterns, physical activity, and risk of urinary tract diseases: a two sample Mendelian randomization analysis

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Abstract: Background: Previous studies have found associations between dietary habits, physical activity (PA) and a variety of renal/urinary disorders. However, only a few studies have used Mendelian randomisation analyses to explore the causal relationship between dietary habits, physical activity and a range of renal/urinary diseases. Methods: The exposure and outcome datasets were sourced from the BioBank, FinnGen, and the NHGRI-EBI databases. The exposure dataset comprised of 20 dietary patterns and 4 PA modalities, while the outcome dataset included 19 renal/urological disorders. The primary methods employed for MR analyses were inverse variance weighted. Heterogeneity and multiplicity analyses were conducted to ensure the validity of the results. Results: In terms of dietary habits, studies have found that consumption of soya-based sweets reduces the risk of chronic kidney disease (CKD). Consumption of fresh fruits prevented benign adrenal tumours and immunoglobulin A nephropathy (IgA-N). Consumption of paneer helps to reduce the risk of developing type 2 diabetes (T2D) nephropathy and immunoglobulin A nephropathy (IgA-N). In addition, consumption of nuts is a protective factor against type 2 diabetic nephropathy. Consumption of nuts, lean fish and fatty fish reduces the incidence of acute tubulointerstitial nephritis (ATIN). Among various forms of physical activity, recreational hiking was inversely associated with IgA-N nephritis and T2D nephritis. Other physical activities, including swimming, cycling, fitness and bowling, also reduced the risk of developing IgA-N. In contrast, leisure screen time (LST) was considered a risk factor. Conclusion: This study suggests that a sensible diet and increased leisure time walking may prevent chronic kidney diseases such as chronic renal insufficiency, chronic renal failure, type 2 kidney disease and IgA nephropathy. This study deepens the understanding of the association between diet, physical activity and renal/urinary abnormalities and provides practical recommendations for reducing the risk of developing these diseases.

Keywords: Diets, physical activity (PA), renal/urological diseases, Mendelian randomization (MR)

Introduction

The urinary system comprises important organs such as the kidneys, ureters, bladder, prostate, and urethra and is one of the eight major systems of the human body. This system is susceptible to various diseases, including chronic kidney disease (CKD), renal failure, glomerular diseases, tubular diseases, IgA nephropathy, hypertension/diabetes-related nephropathy, stones, cysts, and tumors. Kidney disease is particularly common, seriously affecting patients' quality of life and carrying a poor prognosis [1, 2]. In recent years, the incidence of urinary tract diseases has steadily increased [3]. Current research is primarily focused on the prevention and treatment of specific urinary tract diseases, with the aim of improving patient survival rates and quality of life. Significant prospective studies and animal experiments have shown a significant association between dietary factors, physical activity, and the etiology, progression, and prevention of urinary tract diseases [4-6].

The nutrients mentioned above include proteins, fats, fibre and carbohydrates. For example, while a high intake of animal protein can

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increase renal blood flow and glomerular filtration rate in people with normal kidney function, an excess of animal protein can accelerate nephropathy in people with a reduced number of nephrons [7, 8]. Moreover, a high-protein diet is associated with increased urinary albumin excretion in adults at risk for various kidney diseases [9]. Research on the impact of dietary fats (particularly fried foods and animal fats) on kidney health is limited, although they have been shown to be associated with mortality in patients with chronic kidney disease [10]. A prospective study found that carbohydrate consumption is positively associated with mortality in patients with chronic kidney disease, with high sugar consumption linked to an increased risk of death. Conversely, non-sugar carbohydrates have been shown to reduce the risk of death [11]. These findings highlight the importance of assessing nutritional risk factors in the prevention and management of urinary tract diseases. Appropriate dietary interventions play a crucial role in reducing the risks associated with kidney and urinary diseases [12].

Strong evidence indicates that insufficient physical activity increases the risk of many adverse health conditions, including coronary heart disease and type 2 diabetes, and may potentially shorten lifespan [13-15]. Therefore, the numerous benefits of physical activity are considered essential for the health and well-being of the general population. An individual's level of physical activity has a significant impact on the risk of developing disease, particularly diseases of the renal and urinary system [16, 17]. The number of clinical studies on the benefits of physical activity for patients with diseases of the renal and urinary system is increasing every year [18]. However, the choice of type and intensity of physical exercise is influenced by socioeconomic status, cultural education, lifestyle and personal fitness as well as intrinsic biological factors (e.g. age, sex hormones, epigenetics and genetics) [19]. Current research does not sufficiently focus on the genetic-level effects of physical activity on kidney and urinary tract diseases. Establishing direct cause-and-effect relationships would further emphasise the importance of physical activity.

The primary objective of clinical management and disease-process research is to guarantee a good quality of life for patients suffering from kidney and urinary tract disorders. This specifically includes maintaining a balanced diet and engaging in regular exercise [4, 5]. Currently, there is a lack of systematic research on Mendelian randomisation (MR) analyses investigating the effects of diet and physical activity on kidney and urinary tract diseases. A sceptical perspective on the causal relationships between various dietary patterns, exercise regimens, and different kidney and urinary tract diseases is also widely prevalent. In recent years, the importance of MR as an analytical method in observational epidemiological research has grown. This method uses data from genome-wide association studies (GWAS) using data collected from these studies reduces the effects of confounding, which is used to identify potential associations between risk and outcomes [20]. Additionally, it can also unravel causal inferences for confounding factors in complex diseases [21, 22]. This study utilizes MR analysis to assess the causal relationships among 20 dietary patterns, 4 physical activity patterns, and 19 kidney and urinary tract diseases. Our aim is to comprehensively elucidate the relationships between diet, physical activity, and these conditions.

Methods

Data availability, and sources

In this study, all data used were publicly available. Informed consent was obtained from all participants in the original studies. The main exposure in this study was the intake of different types of diets, which included Soya dessert intake (n=64,947), Fresh fruit intake (n=446,462), Dried fruit intake (n=421,764), Cheese intake (n=451,486), Non-oily fish intake (n=460,880), Oily fish intake (n=460,443), Pork intake (n=460,162), Salad/raw vegetable intake (n=435,435), Alcohol intake frequency (n=462,346), Milk intake (n=64,943), Yogurt intake (n=64,949), Herbal tea intake (n=64,949), Shellfish intake (n=64,949), Lobster/crab intake (n=64,949), Beef intake (n=461,053), Lamb/mutton intake (n=460,006), Whole-wheat cereal intake (n=64,949), White pasta intake (n=64,949), Pancake intake (n=64,949), Dark chocolate intake (n=64,945). These data were extracted from the IEU database (https://gwas.mrcieu.ac.uk/), using the method of genome-wide association studies

(GWAS). The data collected by the UK Biobank were self-reported by participants based on individual consumption frequency, for example, zero times per week, once per week, two to four times per week, five to six times per week. Additionally, we also included modes of PA as exposures, which were Walking for pleasure (not as a means of transport) (n=460,376), Other exercises (e.g.: swimming, cycling, keep fit, bowling) (n=460,376), Strenuous sports (n=460,376), and Leisure screen time (LST) (n=526,725) in the past four weeks. The first three were from the Biobank database (https://www.nealelab.is/uk-biobank), while LST was selected from the NHGRI-EBI Catalog of human genome-wide association studies (https://www.ebi.ac.uk/gwas/home).

For the outcomes, we selected 19 urological diseases, which included CKD (n=2872), Chronic renal failure (n=176,462), Benign neoplasm: Adrenal gland (n=218,792), Type 2 diabetes (T2D) with renal complications (n=184,481), IgA-N (n=477,784), Acute tubulointerstitial nephritis (ATIN) (n=212,244), Acute renal failure (n=215,224), Chronic tubulointerstitial nephritis (n=201,648), Acute glomerulonephritis (n=475,529), Chronic glomerulonephritis (n=475,821), Malignant neoplasm of kidney, except renal pelvis (n=174,977), Cystitis (n=455,615), Bladder cancer (n=373,295), Diabetic nephropathy (more controls excluded) (n=184,987), Type 1 diabetes with renal complications (n=184,148), Hypertensive Renal Disease (n=163,305), Gout due to impairment of renal function (n=215,308), Nephrotic syndrome (n=215,099) and Kidney stone, ureter stone or bladder stone (n=484,598). These outcomes were extracted from the Biobank database (https://www.nealelab.is/uk-biobank), the FinnGen Consortium database (https://www.finngen.fi/en), and The NHGRI-EBI Catalog of human genome-wide association studies (https://www.ebi.ac.uk/gwas/home), with data filtered by the IDC-10 system to validate diagnoses. All participants in this study were of European descent. **Tables 1** and **2** provide details and characteristics of the GWAS investigation results.

Instrumental variable selection

To satisfy the three main assumptions required for the validity of causal estimates in MR studies, genetic instrumental variables (GIVs) were selected. First, the GIV must be strongly associated with the exposure. Second, the GIV should not be associated with potential confounders of the above dietary patterns, PA modes, and 19 urological diseases. Lastly, the GIV should affect the occurrence of urological diseases only through its influence on the above dietary patterns and PA modes, without any horizontal pleiotropy [22, 23]. To ensure a strong correlation between each instrumental variable (IV) and the exposure, we considered each IV to be significantly associated with the exposure ($P < 5*10^{-8}$). However, Soya Dessert Intake had very limited SNPs in this condition, so for this exposure of Soya Dessert Intake, we adjusted the condition to $P < 5*10^{-6}$. To eliminate linkage disequilibrium between each SNP, we set the distance to 10000 kb and the LD r2 < 0.001 [24]. The SNPs for exposure and outcome should be concordant, and palindromic and non-concordant alleles should be removed [25]. To assess the possibility of bias due to weak instruments, we used an F-test to determine the strength of the initial stage regression relationship between the allele score and the exposure. We calculated the F-value for each SNP ($F=\beta^2_{exposure}/SE^2_{exposure}$) and excluded SNPs with F values < 10 [26]. Ultimately, in the positive results for dietary patterns, we identified 30 lead SNPs for Soya dessert intake, 54 lead SNPs for Fresh fruit intake, 43 lead SNPs for Dried fruit intake, 64 lead SNPs for Cheese intake, 11 lead SNPs for Non-oily fish intake, and 63 lead SNPs for Oily fish intake at the genome-wide significance level (Supplementary Tables 3-8); in the positive habits of PA modes, we identified 20 lead SNPs for Walking for pleasure (not as a means of transport), 14 lead SNPs for Other exercises (e.g.: swimming, cycling, keep fit, bowling), and 115 lead SNPs for LST at the genome-wide significance level (Supplementary Tables 9-11). The assumptions and design of the MR study are illustrated in **Figure 1**.

Statistical analyses

In this study, all two-sample MR data analyses were conducted using the R software (version 4.2.1, 2022-06-23) with the TwoSampleMR package [27, 28]. The principal method of MR employed to ascertain the combined estimates of many instrumental SNPs was the inverse

Table 1. Detailed information on relevant exposure data

Exposure	GWAS ID	Consortium	Sample Size	Number of SNPs
Diets				
Soya dessert intake	ukb-b-998	MRC-IEU	64,947	9,851,867
Fresh fruit intake	ukb-b-3881	MRC-IEU	446,462	9,851,867
Dried fruit intake	ukb-b-16576	MRC-IEU	421,764	9,851,867
Cheese intake	ukb-b-1489	MRC-IEU	451,486	9,851,867
Non-oily fish intake	ukb-b-17627	MRC-IEU	460,880	9,851,867
Oily fish intake	ukb-b-2209	MRC-IEU	460,443	9,851,867
Pork intake	ukb-b-5640	MRC-IEU	460,162	9,851,867
Salad/raw vegetable intake	ukb-b-1996	MRC-IEU	435,435	9,851,867
Alcohol intake frequency	ukb-b-5779	MRC-IEU	462,346	9,851,867
Milk intake	ukb-b-2966	MRC-IEU	64,943	9,851,867
Yogurt intake	ukb-b-7753	MRC-IEU	64,949	9,851,867
Herbal tea intake	ukb-b-13344	MRC-IEU	64,949	9,851,867
Shellfish intake	ukb-b-143	MRC-IEU	64,939	9,851,867
Lobster/crab intake	ukb-b-14746	MRC-IEU	64,938	9,851,867
Beef intake	ukb-b-2862	MRC-IEU	461,053	9,851,867
Lamb/mutton intake	ukb-b-14179	MRC-IEU	460,006	9,851,867
Whole-wheat cereal intake	ukb-b-2375	MRC-IEU	64,949	9,851,867
White pasta intake	ukb-b-2512	MRC-IEU	64,949	9,851,867
Pancake intake	ukb-b-6500	MRC-IEU	64,949	9,851,867
Dark chocolate intake	ukb-b-16139	MRC-IEU	64,945	9,851,867
Physical Activity (PA)				
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport)	ukb-b-7337	MRC-IEU	460,376	9,851,867
Types of physical activity in last 4 weeks: Strenuous sports	ukb-b-7663	MRC-IEU	460,376	9,851,867
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling)	ukb-b-8764	MRC-IEU	460,376	9,851,867
Leisure screen time	GCST90104339	-	526,725	-

variance weighted (IVW) approach [29]. Assuming that all selected IVs are independent of the confounders of the association between the risk factor and the outcome and that IVs are related to the outcome only through their association with the risk factor, the IVW method has the highest statistical power to produce the most accurate results [30]. For each individual SNP_n, its effect on exposure k is β_{kn} with standard error σ_{kn}, while its effect on the outcome l is β_{ln} with standard error σ_{ln}. The causal effect can be expressed by the Wald ratio β_{ln}/β_{xn} and its standard error is σ_{ln}/β_{xn}. Subsequently, we can employ meta-analysis to derive a comprehensive causal estimator $\tilde{\beta}_{IVW} = \frac{\sum_n k_l \sigma_{in}^{-2}}{\sum_n k^2 \sigma_{in}^{-2}}$ with standard error $\tilde{\sigma}_{IVW} = \sqrt{\frac{1}{\sum_n k^2 \sigma_{in}^{-2}}}$ [30]. The remaining four MR models - MR Egger regression, weighted median estimator, simple and weighted mode-based estimator - were calculated using complementary techniques to guarantee the stability and reliability of the results [31-33]. Statistical significance was established at $P < 0.05$, and all data were provided as odds ratios (ORs) with 95% confidence intervals (95% CIs). The heterogeneity of the causal effects was also evaluated using the Cochrane's Q test; a $P < 0.05$ result reveals heterogeneity, which permits the selection of a random-effects IVW, while a $P > 0.05$ result recommends the selection of a fixed-effects IVW. Using the MR-PRESSO (MR Pleiotropy-Resistant Estimation and Sensitivity methodology), results with horizontal pleiotropy were corrected, outlier SNPs and missing data for effects β and standard errors were identified [34]. The strength of horizontal pleiotropy was represented by the MR-Egger regression's intercept value, where $P > 0.05$ denoted the absence of

Table 2. Detailed information on relevant outcome data

Outcome	GWAS ID	n-Case	n-Control	Number of SNPs
Chronic kidney disease	ebi-a-GCST008026	1,533	1,339	17,624,171
Chronic renal failure	ebi-a-GCST90018602	2,117	174,345	12,454,326
Benign neoplasm: Adrenal gland	finn-b-CD2_BENIGN_ADRENAL	725	218,067	16,380,466
Type 2 diabetes with renal complications	finn-b-E4_DM2REN	1,296	183,185	16,380,337
IgA nephropathy	ebi-a-GCST90018866	15,587	462,197	24,182,646
Acute tubulointerstitial nephritis	finn-b-N14_PYELONEPHR	11,216	201,028	16,380,447
Acute renal failure	finn-b-N14_ACUTERENFAIL	2,383	212,841	16,380,456
Chronic tubulointerstitial nephritis	finn-b-N14_CHRONTUBULOINTNEPHRITIS	620	201,028	16,380,412
Acute glomerulonephritis	ebi-a-GCST90018788	274	475,255	24,199,179
Chronic glomerulonephritis	ebi-a-GCST90018820	566	475,255	24,199,034
Malignant neoplasm of kidney, except renal pelvis	finn-b-C3_KIDNEY_NOTRENALPELVIS_EXALLC	971	174,006	16,380,308
Cystitis	ebi-a-GCST90018831	4,921	450,694	24,187,785
Bladder cancer	ieu-b-4874	1,279	372,016	9,904,926
Diabetic nephropathy (more controls excluded)	finn-b-DM_NEPHROPATHY_EXMORE	3,283	181,704	16,380,336
Type 1 diabetes with renal complications	finn-b-E4_DM1REN	963	183,185	16,380,334
Hypertensive Renal Disease	finn-b-I9_HYPTENSRD	468	162,837	16,380,163
Gout due to impairment of renal function	finn-b-GOUT_KIDNEY	92	215,216	16,380,463
Nephrotic syndrome	finn-b-N14_NEPHROTICSYND	480	214,619	16,380,437
Kidney stone, ureter stone or bladder stone	ebi-a-GCST90038631	3,725	480,873	9,587,836

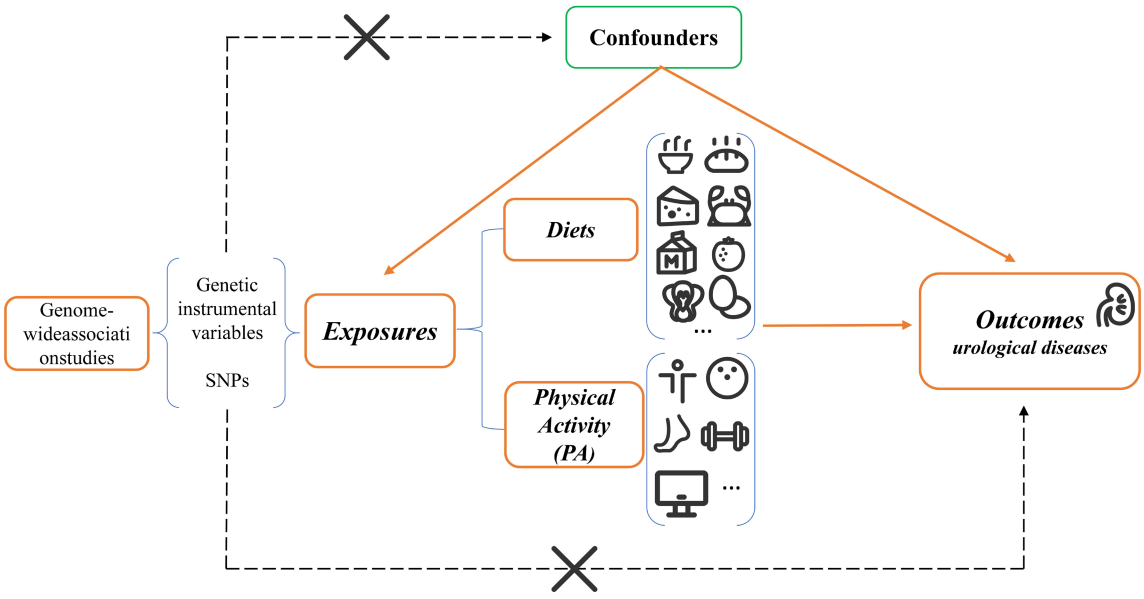

Figure 1. Flowchart of MR analysis in this study. SNP, single nucleotide polymorphism.

horizontal pleiotropy [31, 34] (Supplementary Tables 1, 2). A "leave-one-out" sensitivity analysis was carried out to ascertain whether a particular SNP was the source of heterogeneity [35]. To characterize the experimental results, we used forest plots (Supplementary Figure 1) and funnel plots (Supplementary Figure 2), focusing on exposures and outcomes with correlations. In addition, we tested the stability of the data and found that the mean of all SNPs was greater than zero or less than zero (Supplementary Figure 3).

Table 3. Summary of positive results in this study

Exposure	Outcome	Method	OR	*P*-value
Diets				
Soya dessert intake	Chronic kidney disease	IVW	0.081052	0.002973
Fresh fruit intake	Benign neoplasm: Adrenal gland	IVW	0.064870	0.002239
	IgA nephropathy	IVW	0.514422	0.02286
Dried fruit intake	Type 2 diabetes with renal complications	IVW	0.200961	0.024643
	Acute tubulointerstitial nephritis	IVW	0.534311	0.006398
Cheese intake	Type 2 diabetes with renal complications	IVW	0.307933	0.005237
	IgA nephropathy	IVW	0.667432	0.000283
Non-oily fish intake	Acute tubulointerstitial nephritis	IVW	0.395759	0.045399
Oily fish intake	Acute tubulointerstitial nephritis	IVW	0.636475	0.003806
Physical Activity (PA)				
Walking for pleasure	IgA nephropathy	IVW	0.239853	0.002761
	Type 2 diabetes with renal complications	IVW	0.010686	0.013577
	Chronic renal failure	IVW	0.006320	0.005440
Other exercises (eg: swimming, cycling, keep fit, bowling)	IgA nephropathy	IVW	0.272975	0.015494
Leisure screen time	IgA nephropathy	IVW	1.194293	0.000272

Results

The impact of dietary patterns on renal and urological diseases

In our analysis of 20 self-reported dietary exposure patterns, we identified several significant causal relationships (**Table 3**). An intake of soya dessert was found to be associated with CKD (IVW: OR=0.0811, 95% CI: 0.0154-0.4254, P=0.0030) (**Figure 2A**). Similarly, a correlation was observed between the intake of fresh fruit and Benign Neoplasm of the Adrenal Gland (IVW: OR=0.0649, 95% CI: 0.0112-0.3748, P=0.0022) (**Figure 2B**). In the context of T2D with renal complications, our study results indicated that both dried fruit intake (IVW: OR=0.2010, 95% CI: 0.0496-0.8147, P=0.0246) and cheese intake (IVW: OR=0.3079, 95% CI: 0.1347-0.7040, P=0.0052) were associated with the condition. Due to the heterogeneity and horizontal pleiotropy between dried fruit intake and T2D with renal complications, we employed a random-effects model of IVW. We found that the P-value remained unchanged and that horizontal pleiotropy was eliminated after correction with MR-PRESSO (**Figure 3**). Interestingly, cheese intake (IVW: OR=0.6674, 95% CI: 0.5365-0.8303, P=0.0003) was also strongly associated with IgA-N, as was fresh fruit intake (IVW: OR=0.5144, 95% CI: 0.2902-0.9120, P=0.0229) (**Figure 4**). We further discovered that dried fruit intake (IVW: OR=0.5343, 95% CI: 0.3405-0.8384, P=0.0064), non-oily fish intake (IVW: OR=0.3958, 95% CI: 0.1596-0.9812, P=0.0454), and oily fish intake (IVW: OR=0.6365, 95% CI: 0.4687-0.8643, P=0.0038) were all strongly associated with ATIN (**Figure 5**). However, in our study, we found no statistically significant associations between the intake of pork, salad/raw vegetables, alcohol, milk, yogurt, herbal tea, shellfish, lobster/crab, beef, lamb/mutton, whole-wheat cereal, white pasta, pancakes, and dark chocolate and any of the 19 urologic diseases included in the study.

The impact of PA on renal and urological diseases

Our MR analysis revealed that different types of PA have varying effects on renal and urological diseases (**Table 3**). Specifically, engaging in walking for pleasure was found to be associated with a decreased risk of IgA-N (IVW: OR=0.2399, 95% CI: 0.0942-0.6109, P=0.0028), T2D with renal complications (IVW: OR=0.0107, 95% CI: 0.0003-0.3927, P=0.0136), and chronic renal failure (IVW: OR=0.0063, 95% CI: 0.0002-0.2226, P=0.0054). Additionally, other physical activities such as swimming, cycling, keep fit, and bowling (IVW: OR=0.2730, 95% CI: 0.0954-0.7811, P=0.0155) and LST (IVW: OR=1.1943, 95% CI: 1.0854-1.3141, P=0.0003) were also found to have a strong association with IgA-N (**Figure 6**). In terms of other urological conditions (including CKD, benign neoplasm of the adrenal gland, ATIN, acute renal failure, chronic tubulointerstitial nephritis, acute glomerulonephritis, chronic glomerulonephritis,

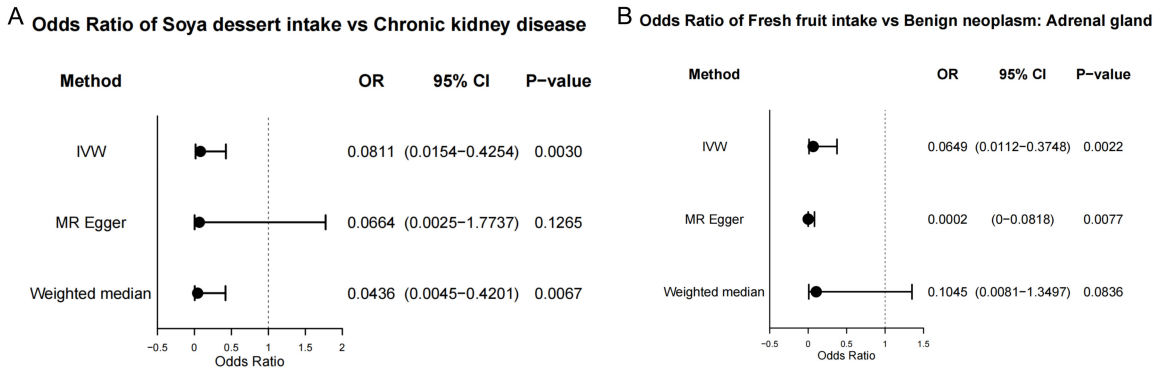

Figure 2. Mendelian randomization estimated the causal effects of Soya dessert intake on Chronic kidney disease (A), fresh fruit intake on benign neoplasm (B).

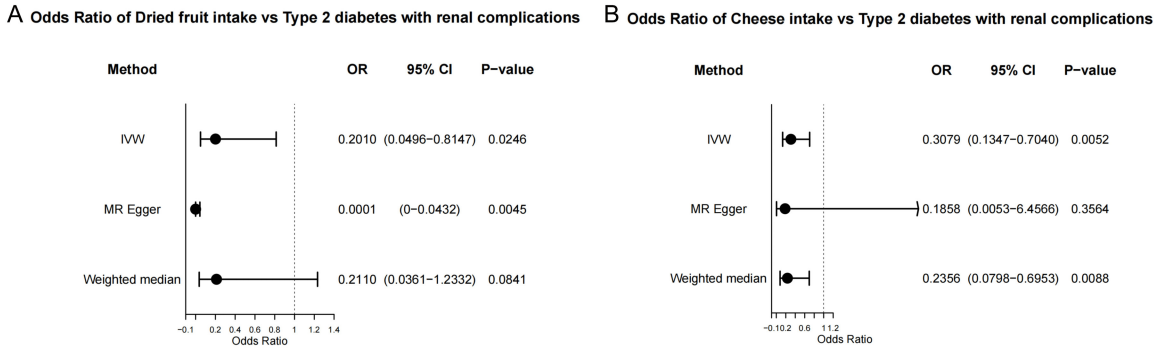

Figure 3. Mendelian randomization estimated the causal effects of Dried fruit intake (A) and Cheese intake (B) on Type 2 diabetes with renal complications.

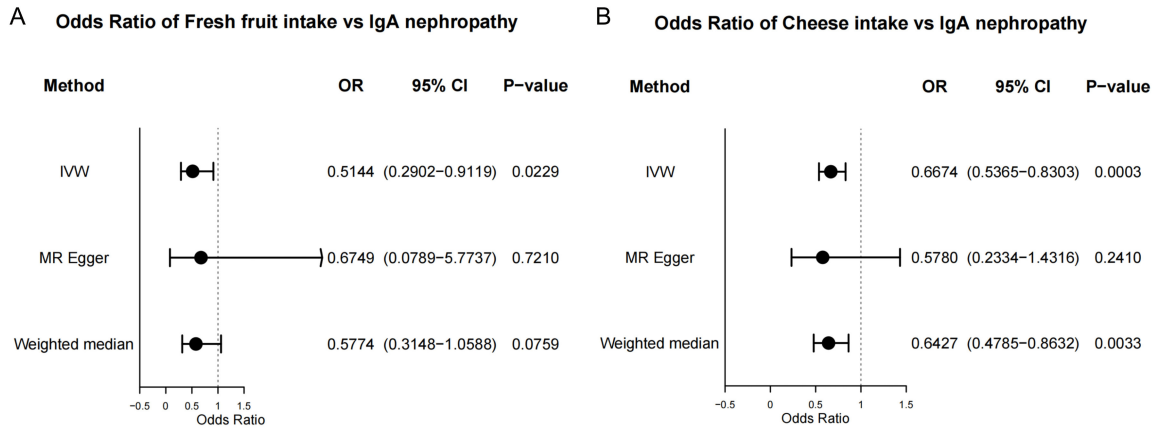

Figure 4. Mendelian randomization estimated the causal effects of Fresh fruit intake (A) and Cheese intake (B) on IgA nephropathy.

malignant neoplasm of the kidney (except renal pelvis), cystitis, bladder cancer, diabetic nephropathy, type 1 diabetes with renal complications, hypertensive renal disease, gout due to impairment of renal function, nephrotic syndrome, kidney stones, ureter stones, or bladder stones), there were no statistically significant association with the choice of PA modality.

Discussion

Western diets are characterized by higher intakes of meat, fats, and processed foods,

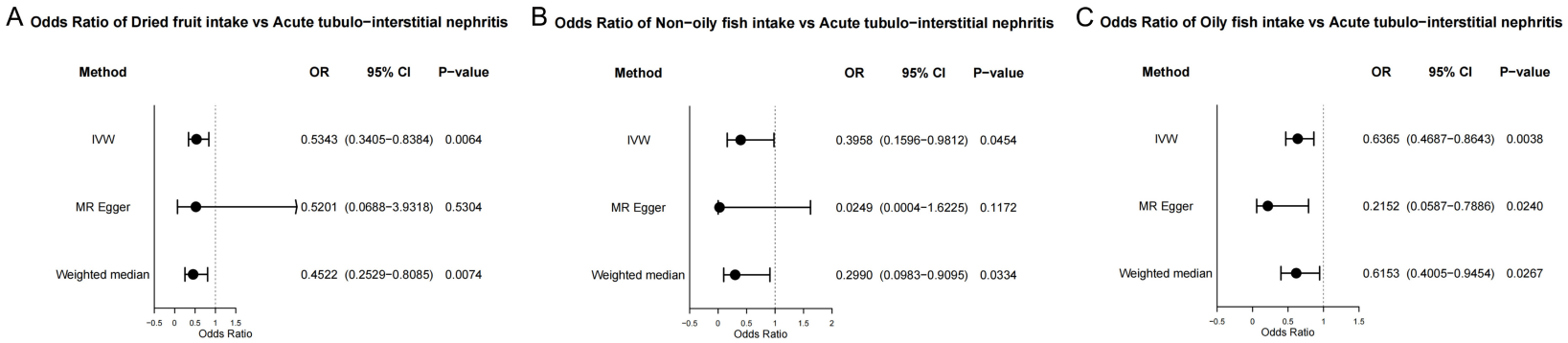

Figure 5. Mendelian randomization estimated the causal effects of Dried fruit intake (A), Non-oily fish intake (B) and Oily fish intake (C) on Acute tubulo-interstitial nephritis.

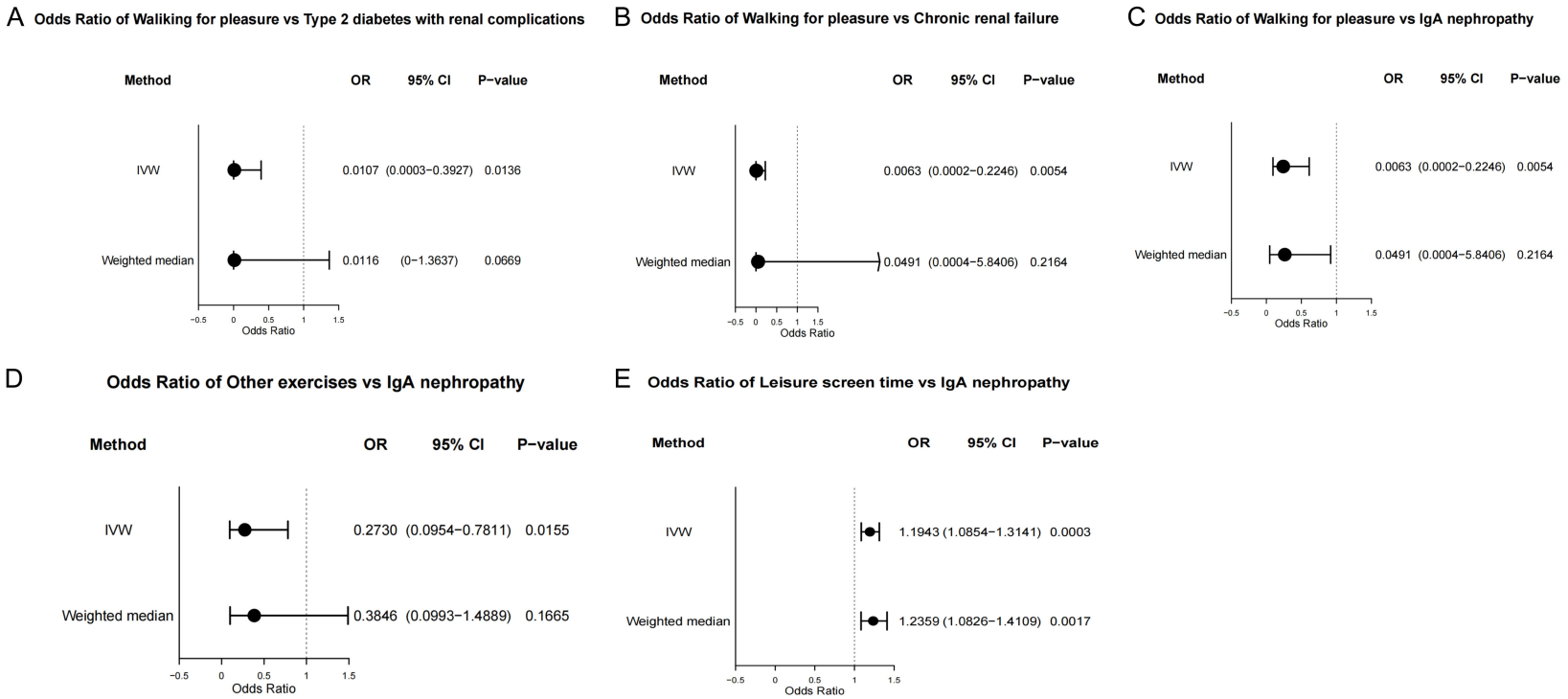

Figure 6. Mendelian randomization estimated the causal effects of Walking for pleasure on Type 2 diabetes with renal complications (A), chronic renal failure (B), IgA nephropathy (C), and other exercises (e.g. swimming, cycling, keep fit, bowling) on IgA nephropathy (D), and Leisure screen time on IgA nephropathy (E).

coupled with relatively lower consumption of fruit and vegetables. This dietary pattern may constitute one of the contributing factors to kidney damage, though the precise mechanisms remain unclear to date [36]. Moreover, as a global health issue affecting Western nations, physical inactivity plays a significant role in the rising incidence of non-communicable diseases, including kidney disease and urinary system disorders [37]. This study, conducted on a European population, established a causal relationship between specific food intake and certain kidney and urinary tract diseases. For example, consumption of soya-based desserts reduced the risk of chronic kidney disease, while fresh fruit intake had a protective effect against benign tumors/adrenal disease and IgA nephropathy. Cheese consumption not only reduces the risk of diabetic nephropathy in type 2 diabetics but also reduces the risk of IgA nephropathy. In addition, studies have confirmed the consumption of nuts as a protective factor against diabetic nephropathy in patients with type 2 diabetes. For acute kidney injury (AKI), consumption of nuts, lean fish, and oily fish reduced its incidence. The study also confirmed a causal relationship between specific physical activities and certain kidney and urinary tract diseases. Slow walking was negatively associated with IgA nephropathy, diabetic nephropathy, and chronic renal failure. Other activities, such as swimming, cycling, gym training, bowling, etc., similarly reduced the risk of IgA nephropathy, while low-intensity physical activity was a risk factor for IgA nephropathy.

Soya dessert intake and CKD

CKD is a condition characterized by the gradual loss of kidney function. The Kidney Disease Outcomes Quality Initiative updated its clinical practice guidelines for CKD nutrition in 2020, recommending a low protein diet to reduce the risk of kidney diseases [38, 39]. A plant-dominant low-protein diet has been widely proposed as an alternative dietary therapy for CKD patients [40]. Soy protein, as a typical representative of plant protein, contains over 20 unique amino acids, exhibiting renal protective effects [41, 42]. A recent prospective clinical study also suggests that soy protein, as part of a low-protein diet, is potentially protective for CKD patients [43]. Our study examined the impact of 20 types of diets on chronic kidney disease (CKD) at the genetic level and found that only soy-based foods had a causal link to CKD. The fact that frequent consumption of soy-based desserts reduces the risk of CKD corroborates the findings of previous studies. However, further evidence is needed to confirm the efficacy, safety and feasibility of this diet for CKD patients worldwide.

Cheese Intake and T2D nephropathy, IgA-N

In the global context of diabetes, type 2 diabetes represents the most prevalent form of the condition [44]. A prospective study reported that a healthy dietary quality score was associated with a reduced risk of T2D nephropathy [45]. IgA-N is the most common form of human glomerulonephritis. Sallustio and others have revealed that IgA-N has multiple susceptibility loci closely related to various environmental, dietary, and behavioral factors [46]. Omega-3 polyunsaturated fatty acids (n-3 PUFA), recognized as essential fatty acids, have been clinically and experimentally proven to have a significant impact on the prevention and treatment of diabetic nephropathy [47-49]. Furthermore, n-3 PUFA has been demonstrated to be beneficial in the treatment of IgA-N, with case-control studies indicating a negative correlation between dietary n-3 PUFA and the risk of IgA-N [50]. Cheese, a common dairy product, contains a relatively high concentration of n-3 PUFA [51]. Our MR analysis results reveal a causal relationship between cheese intake and T2D with renal complications and IgA-N. High cheese intake appears to offer protection against these diseases. We have genetically demonstrated the potential preventive and therapeutic effects of n-3 PUFA on T2D nephropathy and IgA-N.

Dried fruit intake and T2D nephropathy, IgA-N

Consumption of dried fruits has been suggested as a strategy to meet fruit recommendations and improve dietary quality [52]. However, research on the health benefits of dried fruit consumption on the renal and urinary system has been limited. Our study addresses this research gap. Our MR analysis reveals that dried fruit intake offers protection against T2D nephropathy, with the frequency of intake correlating positively with statistical significance. This promising causal association encourages further research into the role of dried fruits in

renal and urological diseases. In previous studies, dietary fiber has been implicated in the prevention and treatment ofT2D nephropathy [53, 54], while a high-protein diet has been linked to an accelerated progression of the same condition [55]. Dietary interventions for IgA-N are limited, but some research suggests that gluten-rich foods can trigger mucosal immune responses and exacerbate IgA-N [56]. However, in our MR study, we found no statistically significant evidence of a positive or negative association between a diet rich in fibre, carbohydrates or protein and type 2 diabetic nephropathy or IgA-N. However, our research highlights the impact of dietary components on T2D nephropathy and IgA-N, aiding greater precision and personalised treatment in nephrology.

Fresh fruit intake and benign adrenal tumors, IgA-N

The kidneys play an essential role in maintaining acid-base balance at the metabolic level [57]. To achieve this balance, the kidneys must be replenished with carbonate, which serves to buffer acids from food. The synthesis of new bicarbonate requires non-volatile acids, which are neutralised by alkaline substances produced during the metabolism of organic anions such as citrate and fruit malate [57, 58]. There is evidence that increased fruit consumption can reduce kidney damage and slow the decline in kidney function [59, 60]. Consistent with our findings on fresh fruit consumption, increased consumption reduces the risk of benign adrenal tumours and IgA-N. However, our MR analysis found no statistically significant association between fresh fruit consumption and kidney stones (urolithiasis), contradicting the findings of Lin et al [61]. This discrepancy may be attributed to differences in the outcome databases used or the LD clumping method employed during statistical analysis. Despite this, our research may inform the development of personalized nutritional advice in the future, particularly for individuals with benign adrenal tumors and IgA-N.

Dried fruit intake, non-oily fish intake, oily fish intake, and ATIN

ATIN is an immune-mediated disease that affects the tubulointerstitial region of the kidney. Studies on the relationship between dietary patterns and ATIN are relatively scarce. Our research has first identified a negative causal relationship between dried fruit intake, non-oily fish intake, and oily fish intake with ATIN, suggesting that a high intake of these foods is beneficial in reducing the risk of ATIN. Based on our results, the relationship with non-oily fish intake is weakly positive, while the relationship with oily fish intake is strongly positive. Therefore, we believe that oily fish intake is more crucial in the prevention of ATIN. Oily fish is a rich source of energy, protein, essential amino acids, lipids, vitamins, minerals, and it plays a beneficial role in promoting health and preventing many diseases [62]. Consumption of oily fish is important at different stages of human life, from conception to old age. When assessing the prevention or treatment of ATIN in populations, dietary patterns, especially the consumption of oily fish, can be considered, as dietary habits strongly influence the occurrence of ATIN. Therefore, it is recommended that all patients adjust their dietary habits according to their own situation to prevent the onset or progression of the disease.

Physical activity and T2D nephropathy, IgA-N, chronic renal failure

The global rise in non-communicable diseases can be significantly attributed to a lack of PA [37, 63]. Mitigating or eliminating this unhealthy behavior could substantially enhance health outcomes. A case-control study found that encouraging physical activity in patients with IgA-N may reduce the risk of progression to end-stage renal disease [64]. According to our research, activities such as recreational walking, swimming, cycling, fitness exercises and bowling may have protective effects in IgA-N. Conversely, prolonged sedentary time (PST) is a risk factor for IgA-N, suggesting that prolonged inactivity may be detrimental to IgA inhibition. This conclusion adds to our understanding of the epidemiological relationship between personal physical activity (PA) and IgA-N and offers new perspectives for studying the pathogenesis of IgA-N.

Chronic kidney failure is a serious medical condition that has significant socio-economic impacts worldwide [65]. Renal transplantation and hemodialysis are important methods for maintaining the survival of patients. PA has been reported as an important nursing intervention to improve physical function in hemodi-

alysis patients [66]. A meta-analysis indicates that exercise can ameliorate blood pressure conditions in patients with renal failure and significantly decrease their oxygen uptake [67]. Among the four PA exposures we examined, our results align, with walking for pleasure showing a negative correlation with the risk of chronic renal failure. Walking can enhance immune and inflammatory responses, augmenting certain aspects of immune function and exerting anti-inflammatory effects [68]. A previous retrospective study concluded that walking or running can lower the mortality rate of kidney disease in diabetic patients [69]. Among the 19 outcomes used in this research, in addition to IgA-N and chronic renal failure, walking for pleasure was also negatively correlated with the incidence of T2D nephropathy, indicating that it can prevent T2D nephropathy.

Conclusion

In conclusion, we used MR analysis to examine the causal relationships among 20 dietary habits, 4 patterns of physical activity (PA), and 19 kidney/urinary tract diseases. We found that CRF, type 2 nephropathy, and IgA common conditions such as CRF, type 2 nephropathy, and IgA-N have significant causal associations with dietary habits and PA patterns. These findings suggest that adopting specific dietary and physical activity patterns may influence certain kidney and urinary tract diseases. By actively modifying dietary habits and increasing the frequency of walking, the incidence of certain urinary tract disorders can be reduced. As dietary and physical activity choices are relatively simple to incorporate into daily education and medical management, our research provides significant evidence to support the primary prevention of related kidney diseases. Furthermore, a better understanding of the pathogenesis and the identification of new potential therapeutic targets can improve the precision and personalisation of nephrological treatments. A better understanding of the pathogenesis and the identification of new potential therapeutic targets can improve the precision and personalisation of nephrological treatments.

However, our study has some potential limitations that warrant mention. Firstly, our study primarily focused on Europeans, yet diseases like IgA-N, one of the most common primary glomerulonephritis globally, are particularly prevalent in Asia [64]. Taking into account the genetic variation among different castes and regions, further studies on the various populations are necessary. If SNPs from non-European populations can be collected through GWAS methods in the future, the sample size could be expanded to further validate the findings, leading to more robust conclusions. Secondly, the causal relationships identified by MR analysis reflect the impact of long-term exposure to related factors. Thus, short-term exposure may not have clinical significance. Furthermore, the mechanisms between exposure and outcomes could be extremely complex, necessitating further exploration.

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Disclosure of conflict of interest

None.

Abbreviations

PA, Physical Activity; CKD, Chronic Kidney Disease; MR, Mendelian Randomization; GWAS, Genome-wide Association Studies; LST, Leisure Screen Time; T2D, Type 2 Diabetic; IgA-N, Immunoglobulin A Nephropathy; ATIN, Acute Tubulointerstitial Nephritis; GIVs, Genetic Instrumental Variables; IV, Instrumental Variable; IVW, Inverse Variance Weighted; ORs, Odds Ratios; 95% CIs, 95% Confidence Intervals; n-3 PUFA, Omega-3 polyunsaturated fatty acids.

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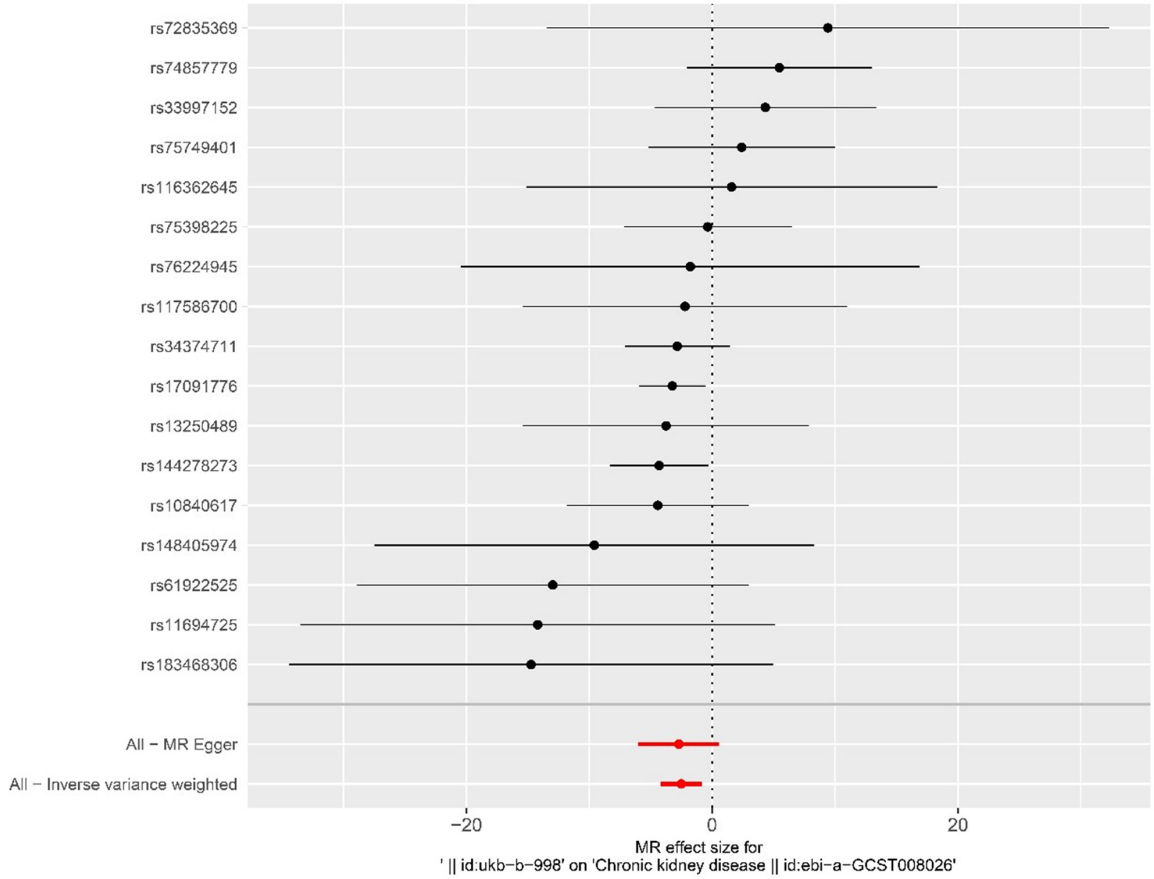
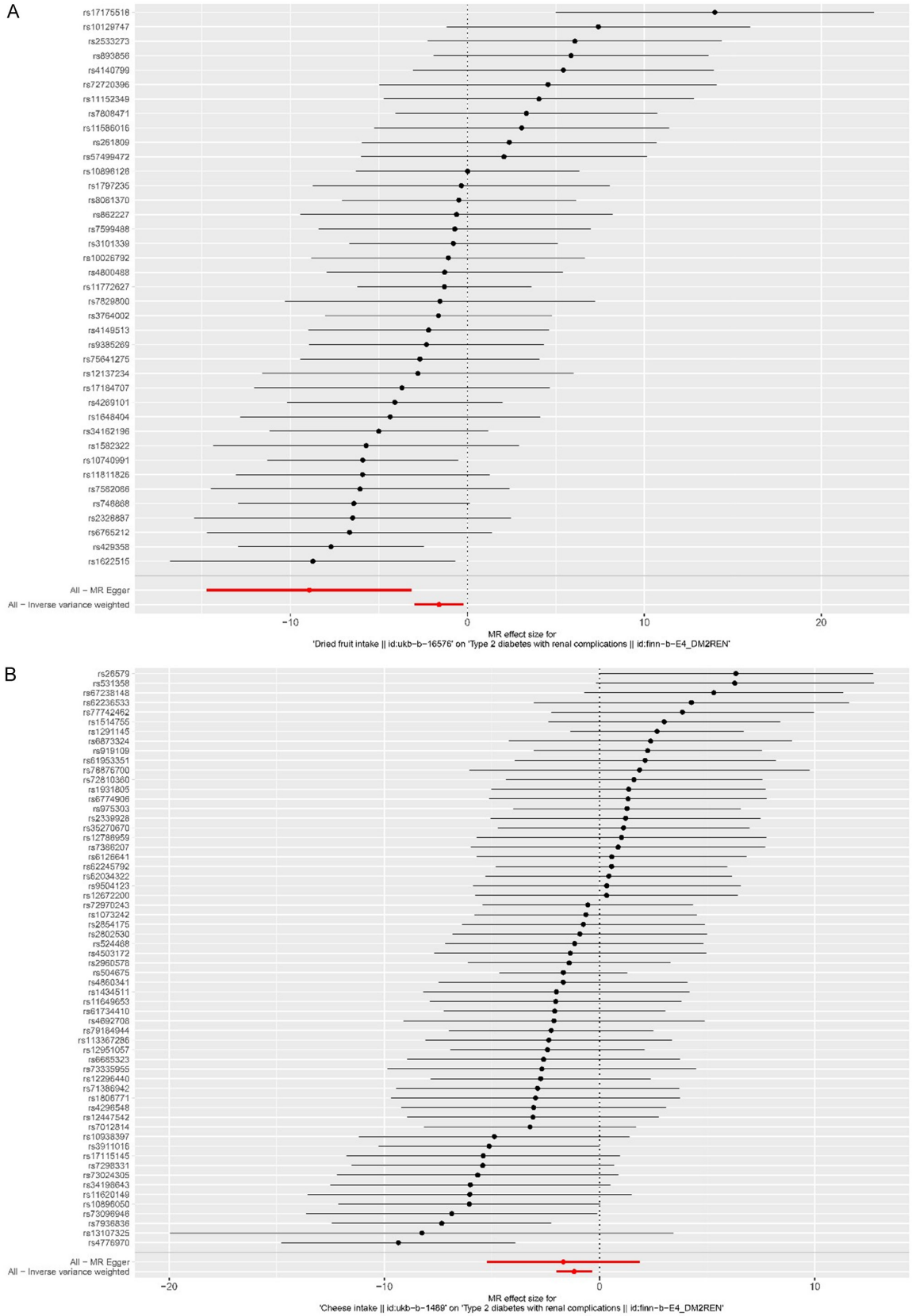


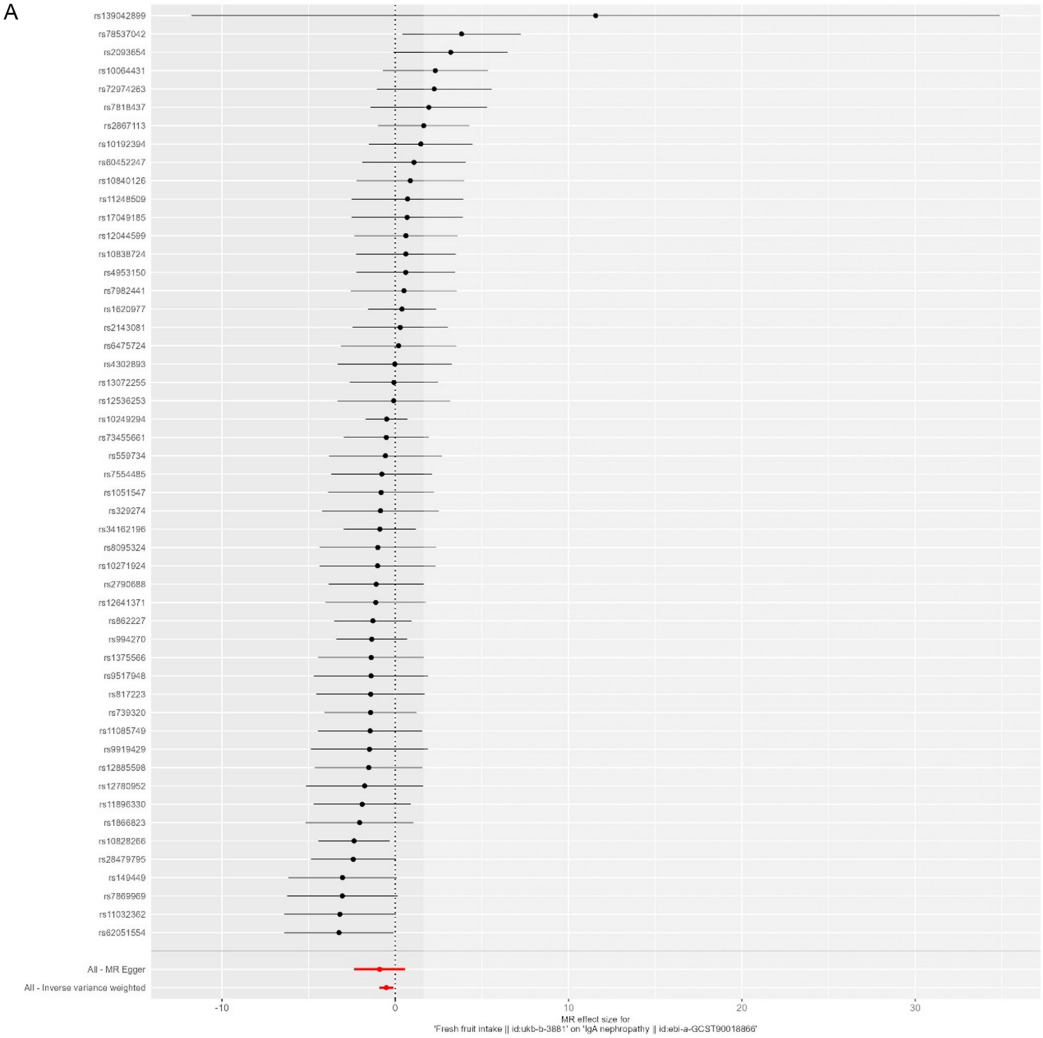
Supplementary Figure 1-1. Forest plot for Mendelian randomization (MR) analyses of the causal relationship between Soya Dessert Intake and Chronic Kidney Disease (CKD).

Supplementary Figure 1-2. Forest plot for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake and Benign neoplasm: Adrenal gland.



Supplementary Figure 1-3. Forest plots for Mendelian randomization (MR) analyses of the causal relationship between Dried Fruit Intake (A), Cheese Intake (B) and Type 2 diabetes with renal complication.

A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rs149449
rs7869969
rs11032362
rs62051554
All - MR Egger
All - Inverse variance weighted
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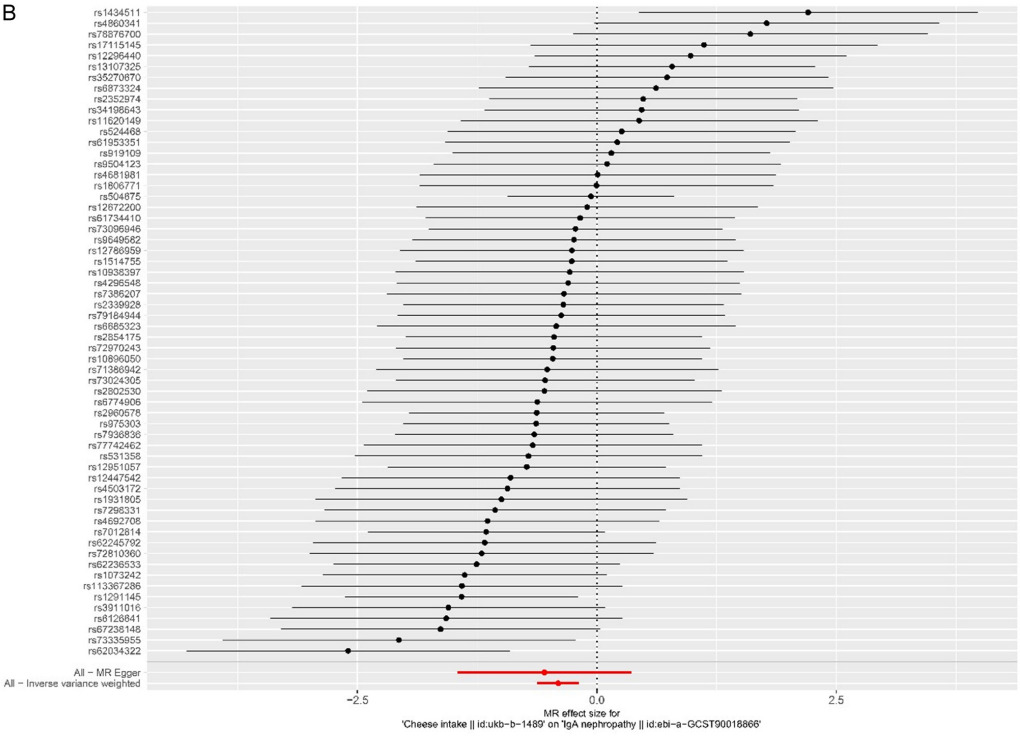
MR effect size for
'Fresh fruit intake || id:ukb-b-3881' on 'IgA nephropathy || id:ebi-a-GCST90018866'

B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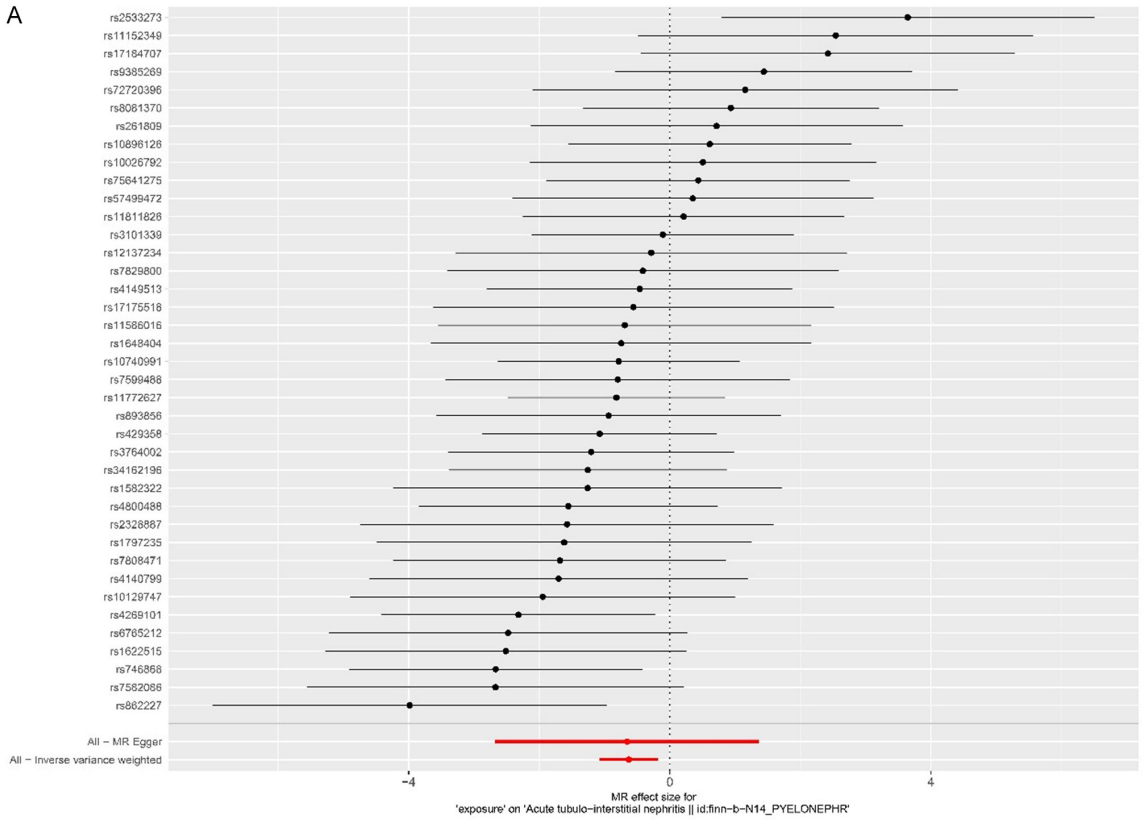
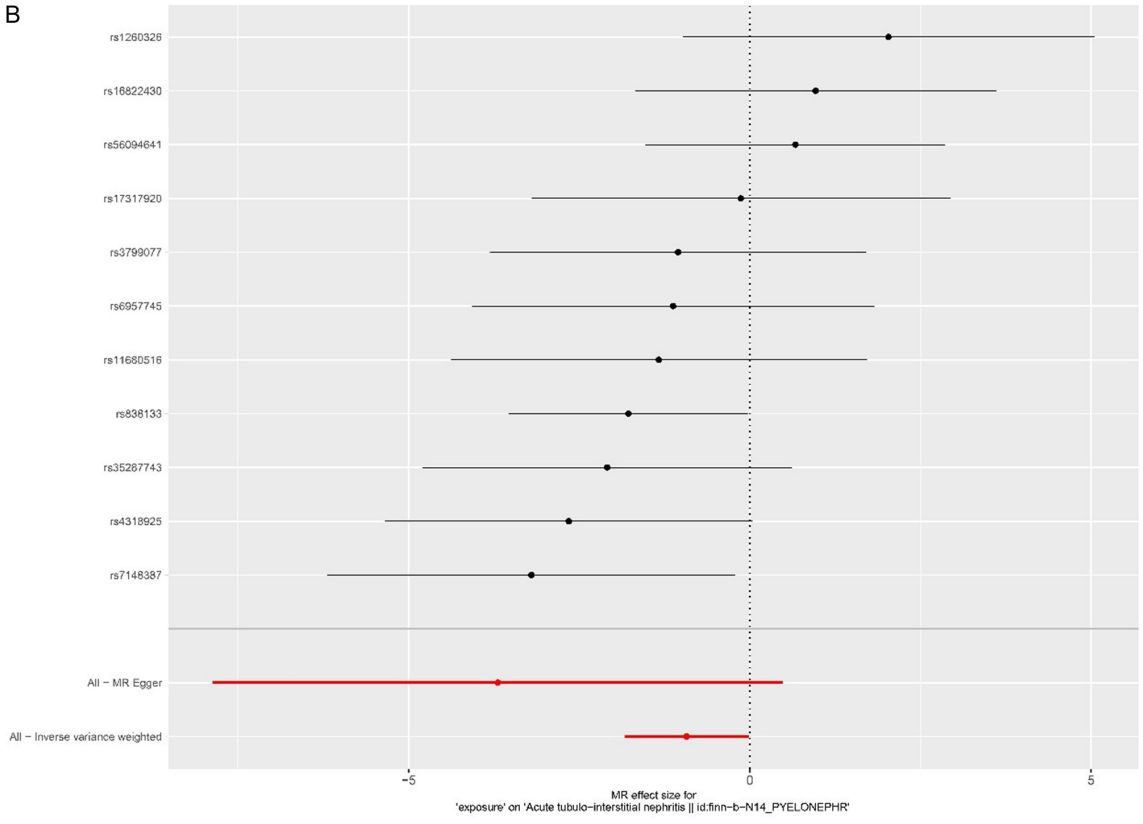
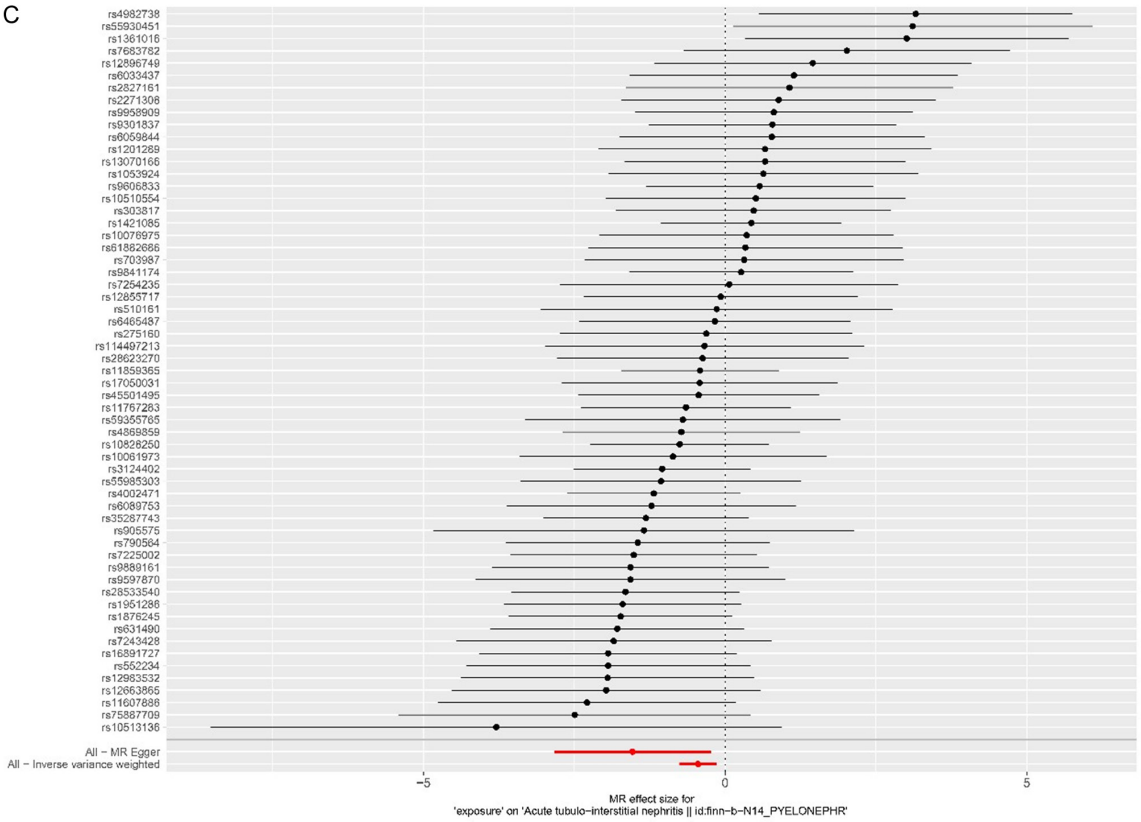
rs1073242
rs113367286
rs1291145
rs3911016
rs8126841
rs67238148
rs73335955
rs62034322
All – MR Egger
All – Inverse variance weighted
−2.5
0.0
2.5
MR effect size for
'Cheese intake || id:ukb−b−1489' on 'IgA nephropathy || id:ebi−a−GCST90018866'

Supplementary Figure 1-4. Forest plots for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake (A), Cheese Intake (B) and Immunoglobulin A Nephropathy (IgA-N).



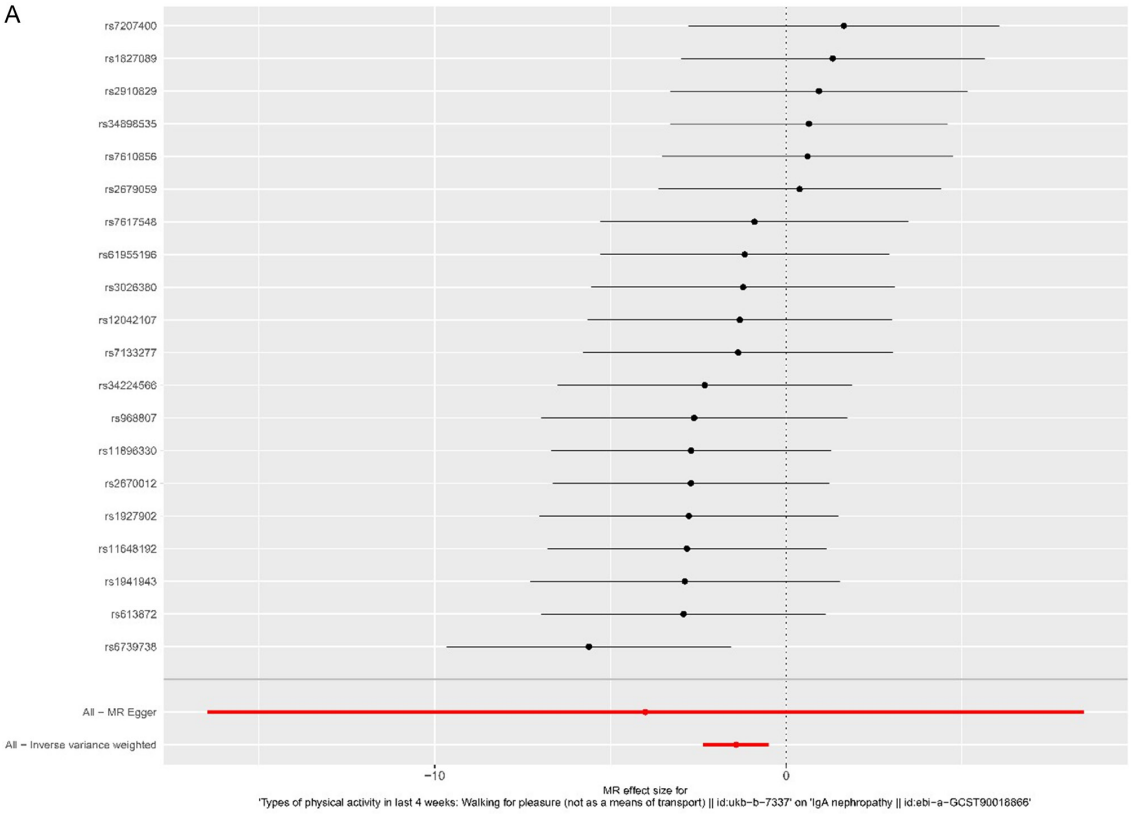


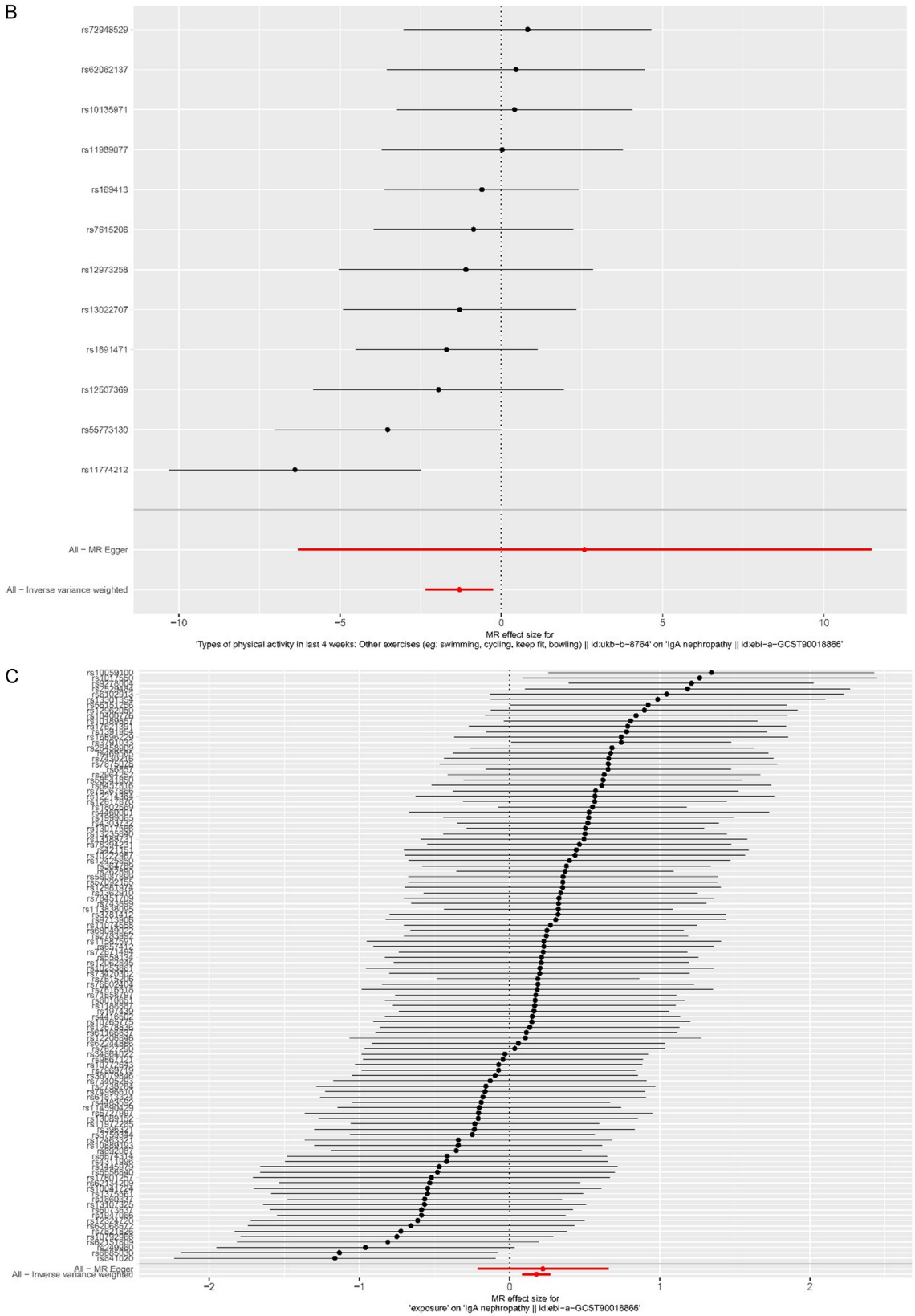
C



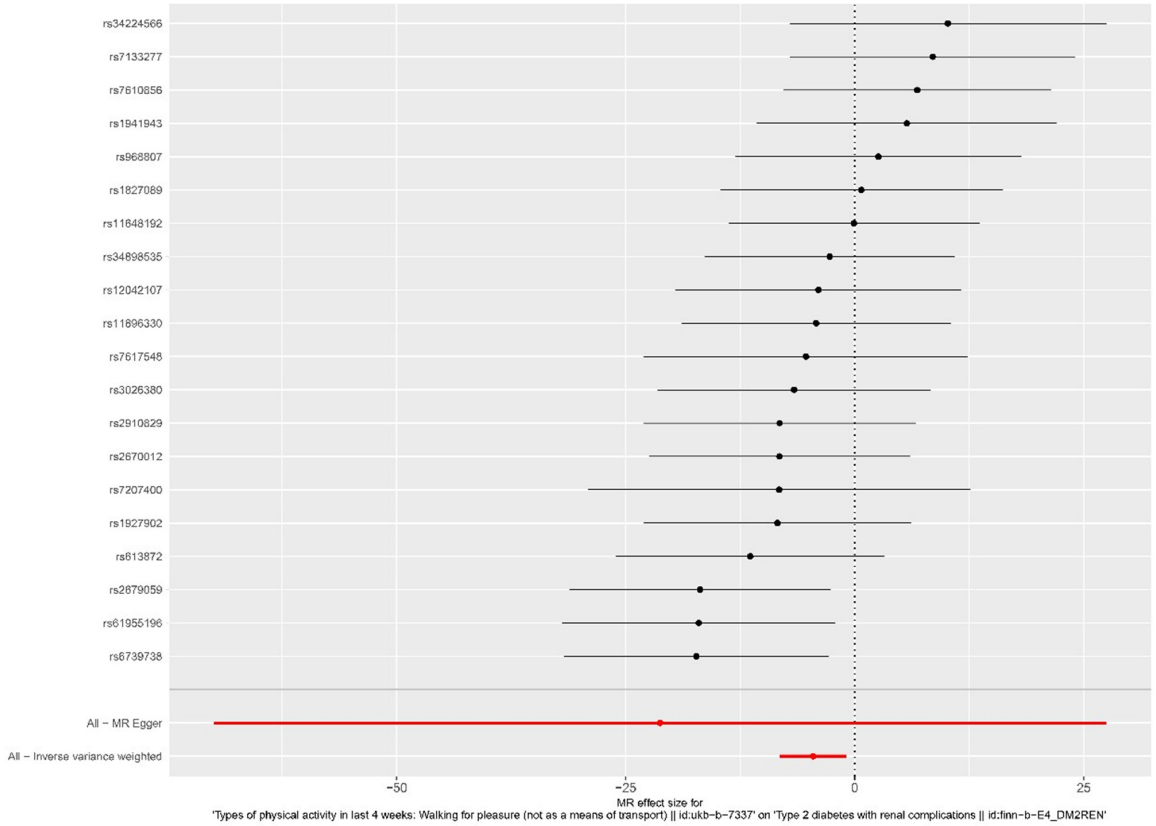
Supplementary Figure 1-5. Forest plots for Mendelian randomization (MR) analyses of the causal relationship between Dried fruit intake (A), Non-oily fish intake (B), Oily fish intake (C) and Acute tubulointerstitial nephritis (ATIN).

A

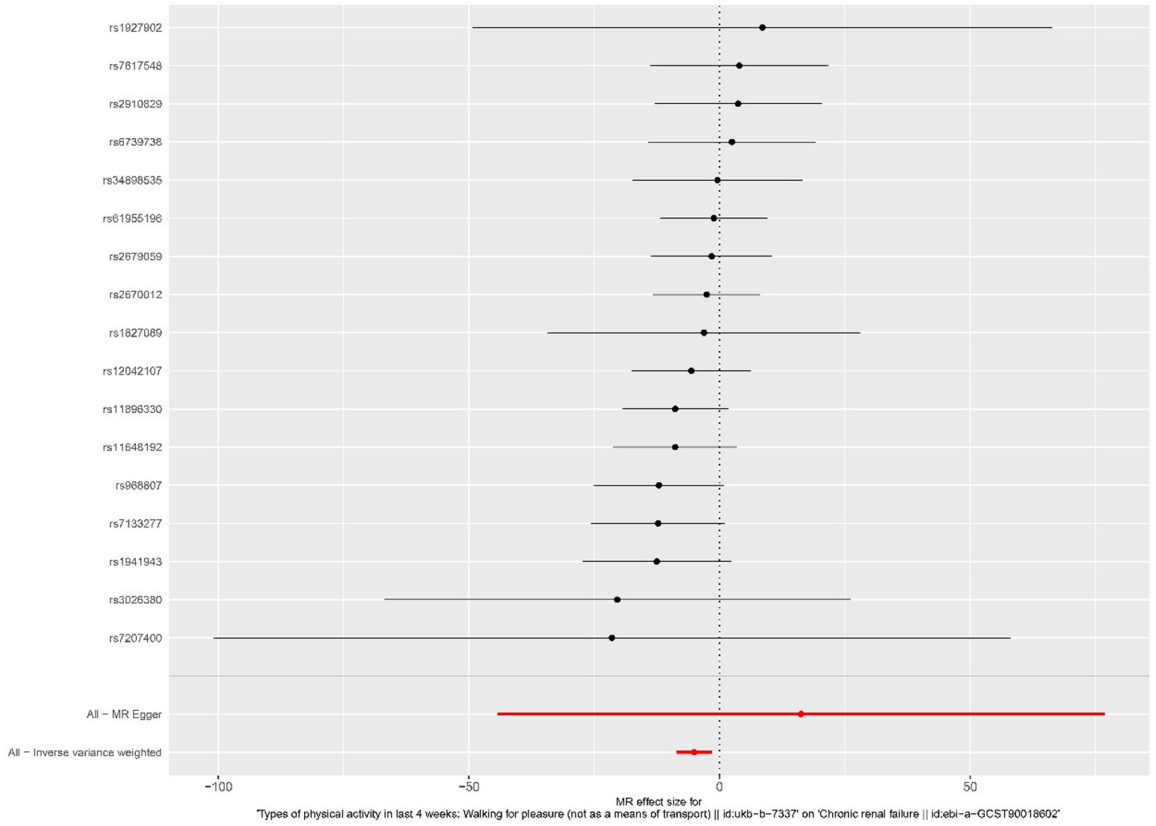




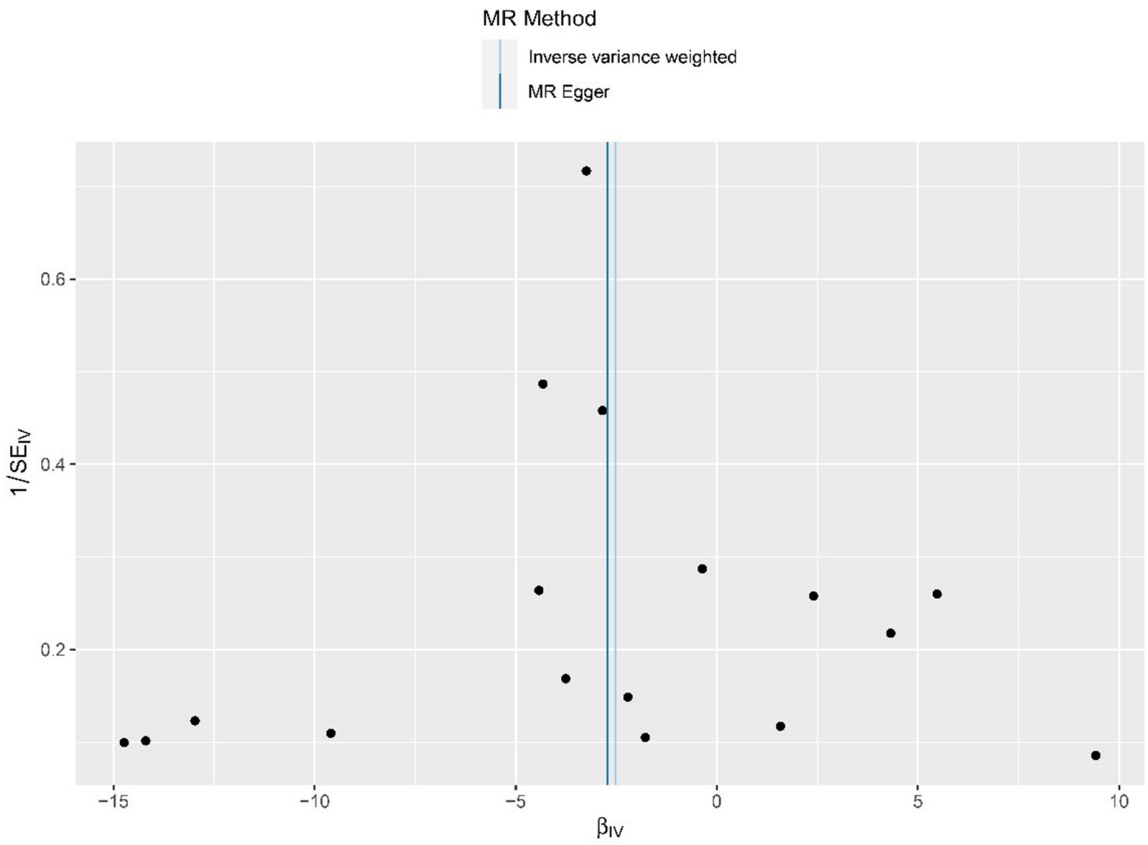
Supplementary Figure 1-6. Forest plots for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure, Other Exercises, Leisure Screen Time and Immunoglobulin A Nephropathy (IgA-N).



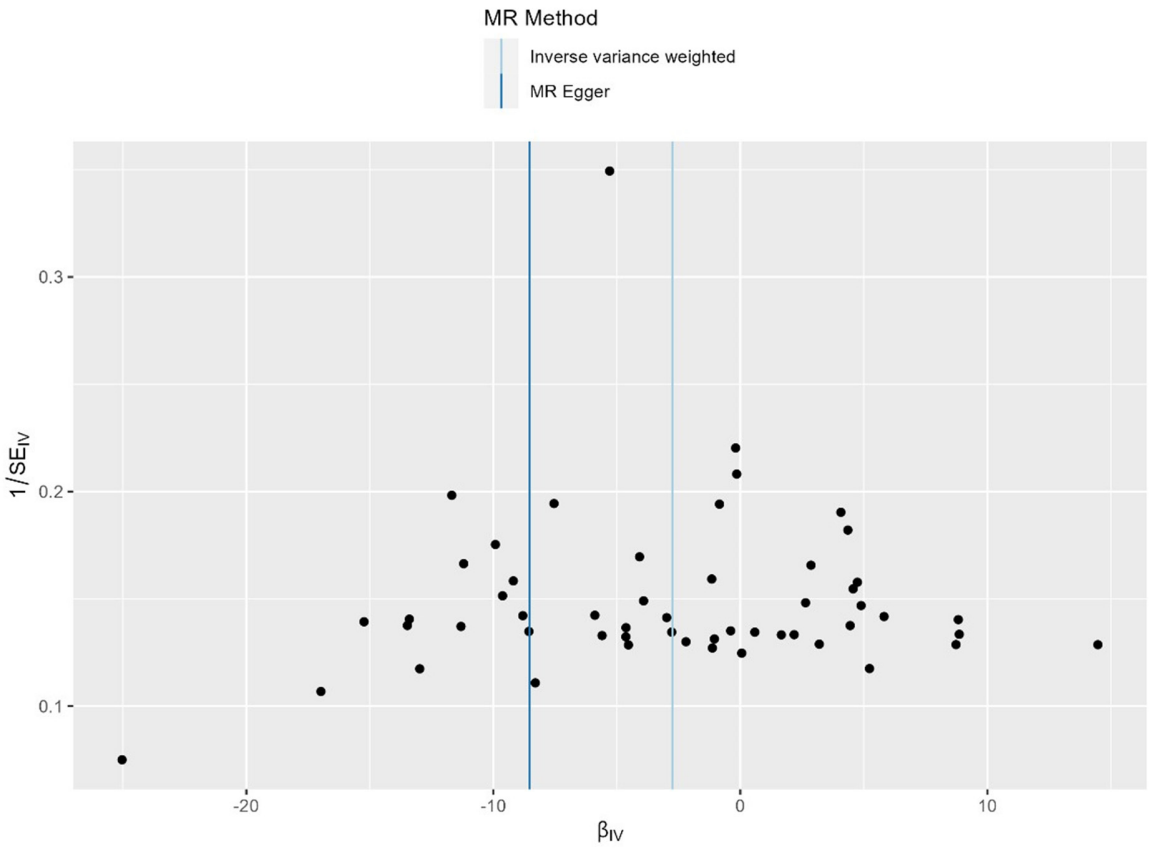
Supplementary Figure 1-7. Forest plot for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure and Type 2 Diabetes with renal complications.



Supplementary Figure 1-8. Forest plot for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure and Chronic Renal Failure.

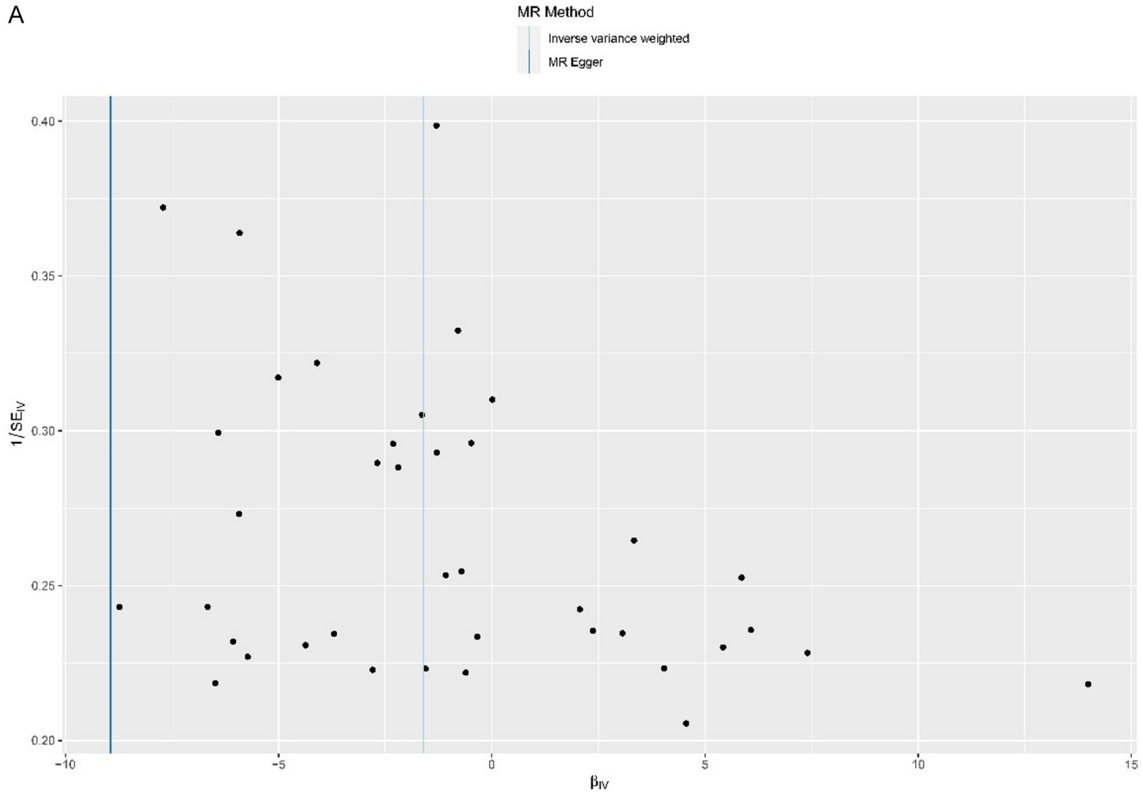


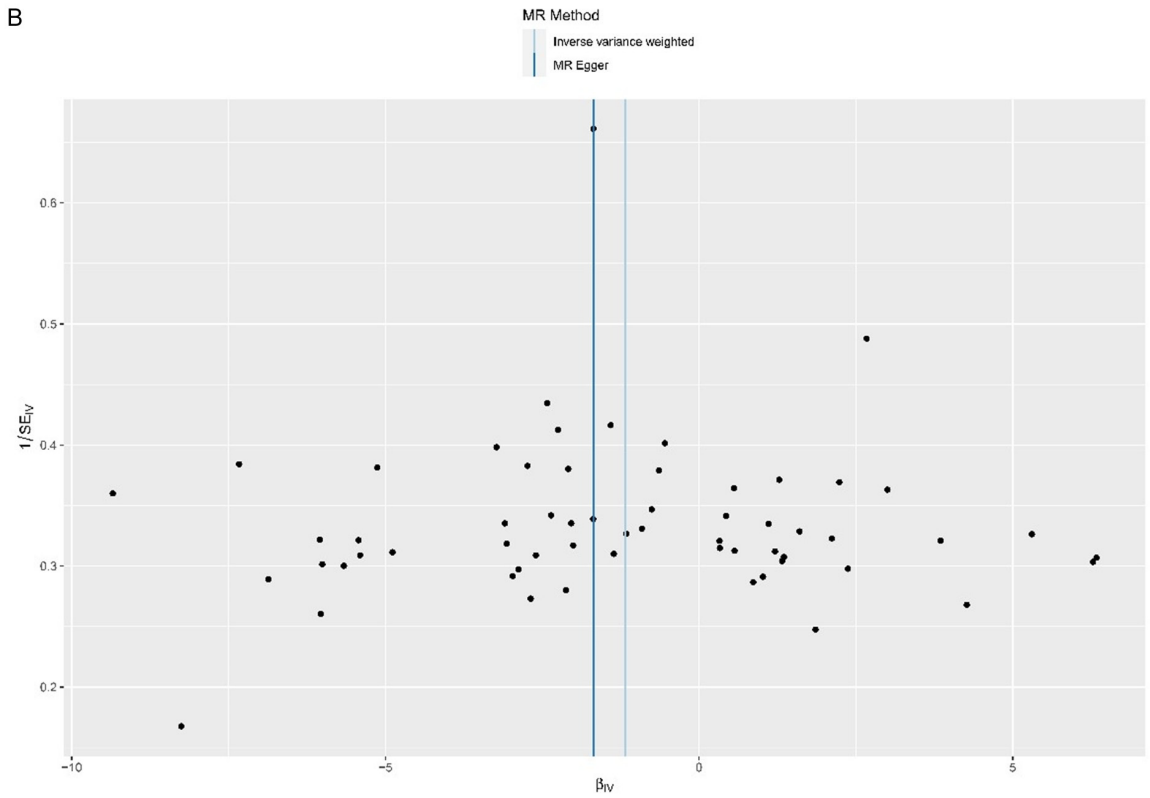
Supplementary Figure 2-1. Funnel plot for Mendelian randomization (MR) analyses of the causal relationship between Soya Dessert Intake and Chronic Kidney Disease (CKD).



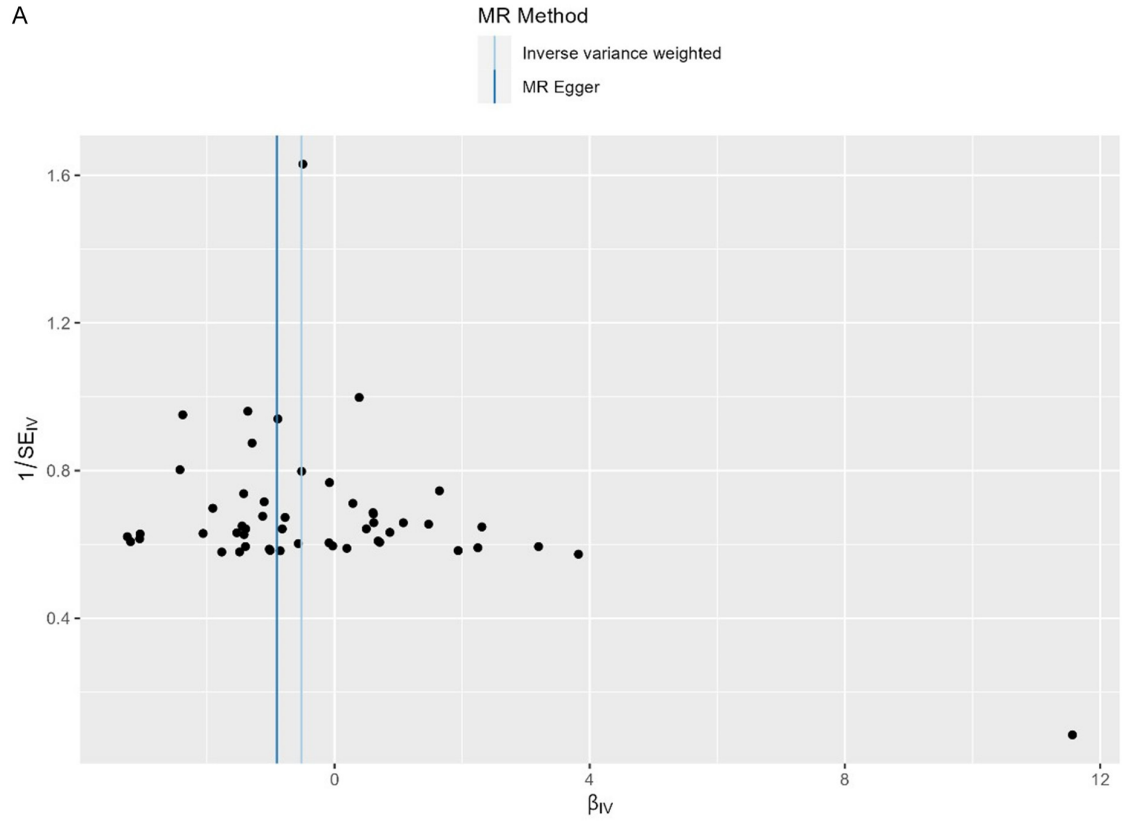
Supplementary Figure 2-2. Funnel plot for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake and Benign neoplasm: Adrenal gland.

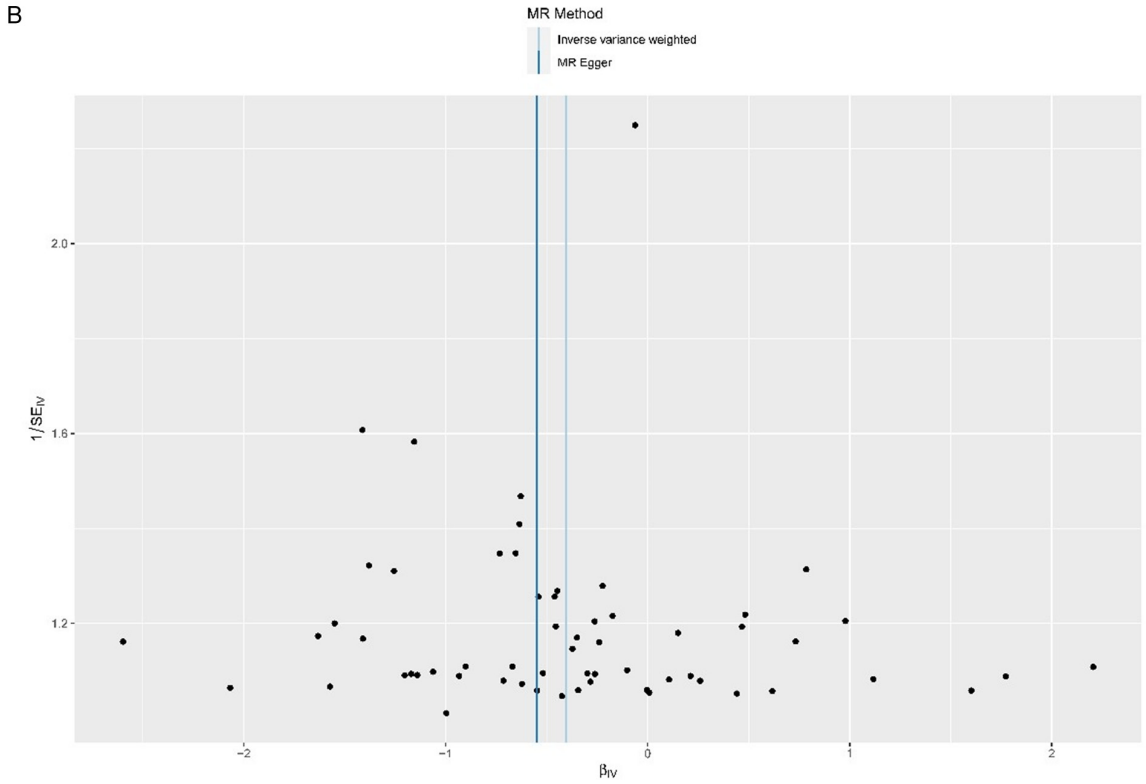
A



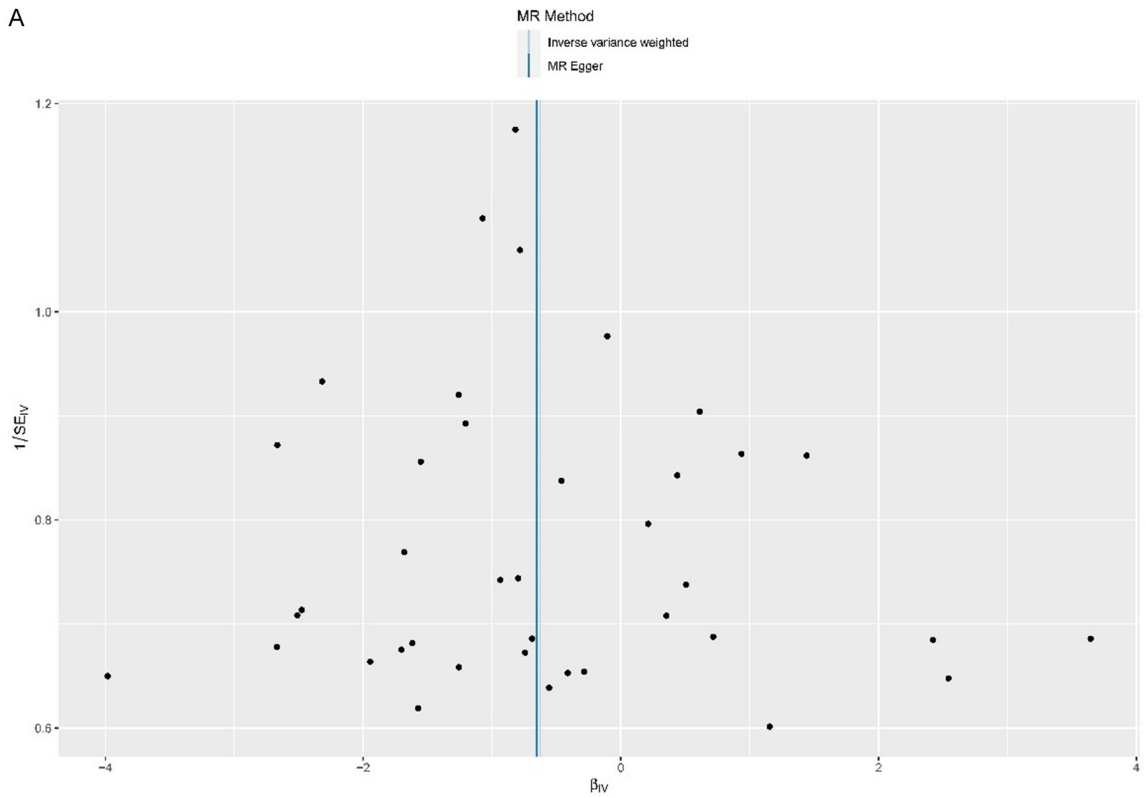


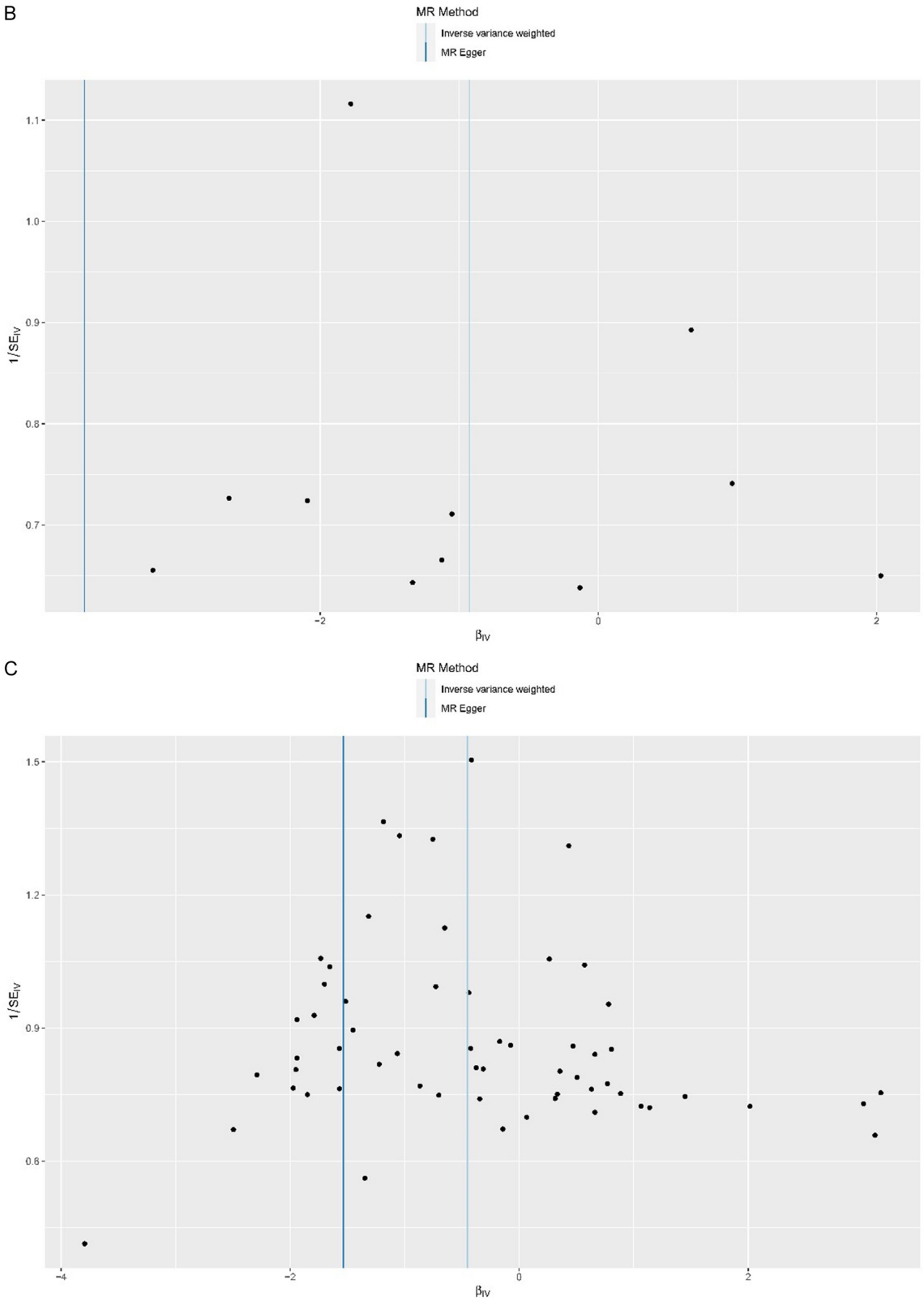
Supplementary Figure 2-3. Funnel plots for Mendelian randomization (MR) analyses of the causal relationship between Dried Fruit Intake (A), Cheese Intake (B) and Type 2 diabetes with renal complication.



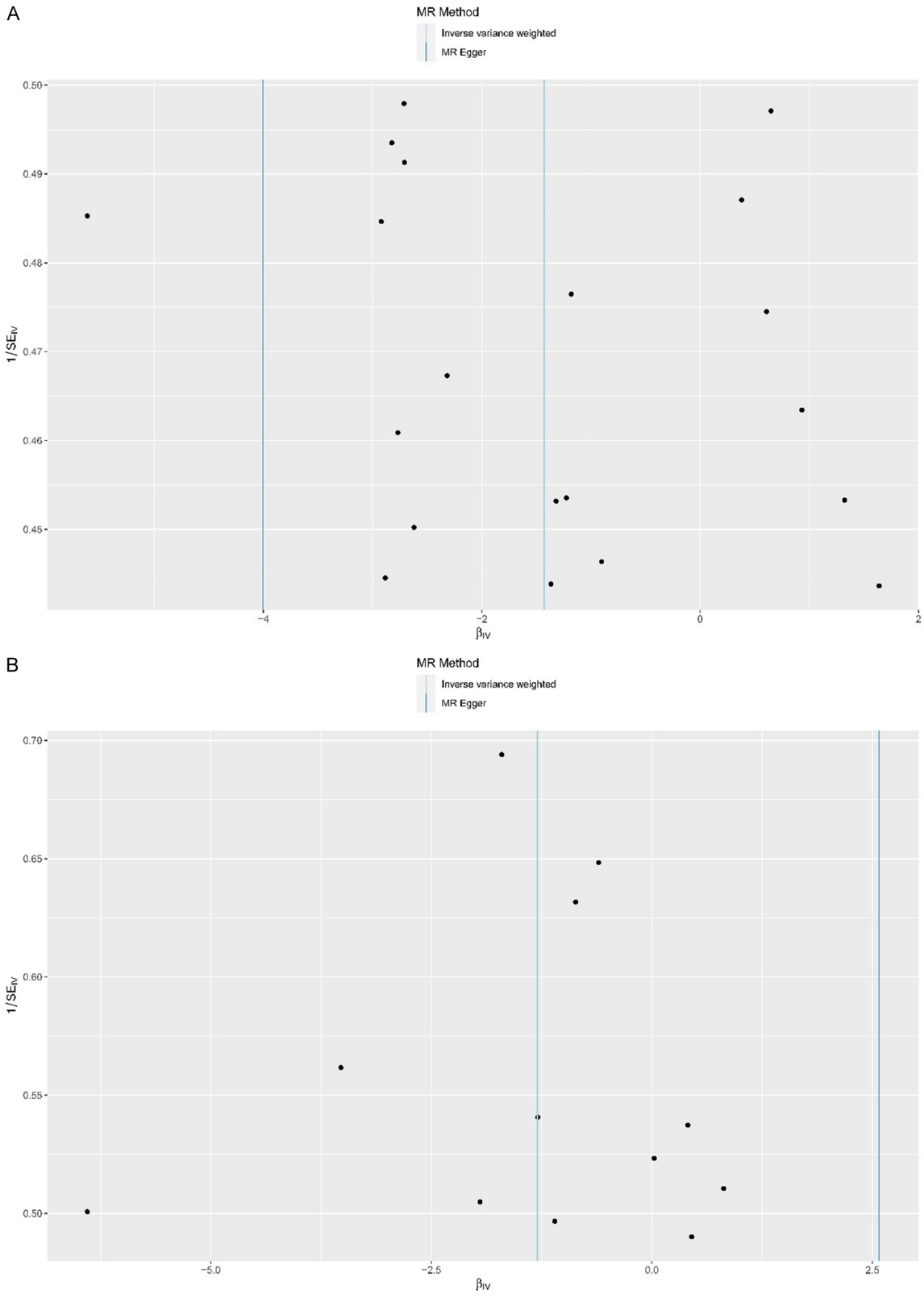


Supplementary Figure 2-4. Funnel plots for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake (A), Cheese Intake (B) and Immunoglobulin A Nephropathy (IgA-N).

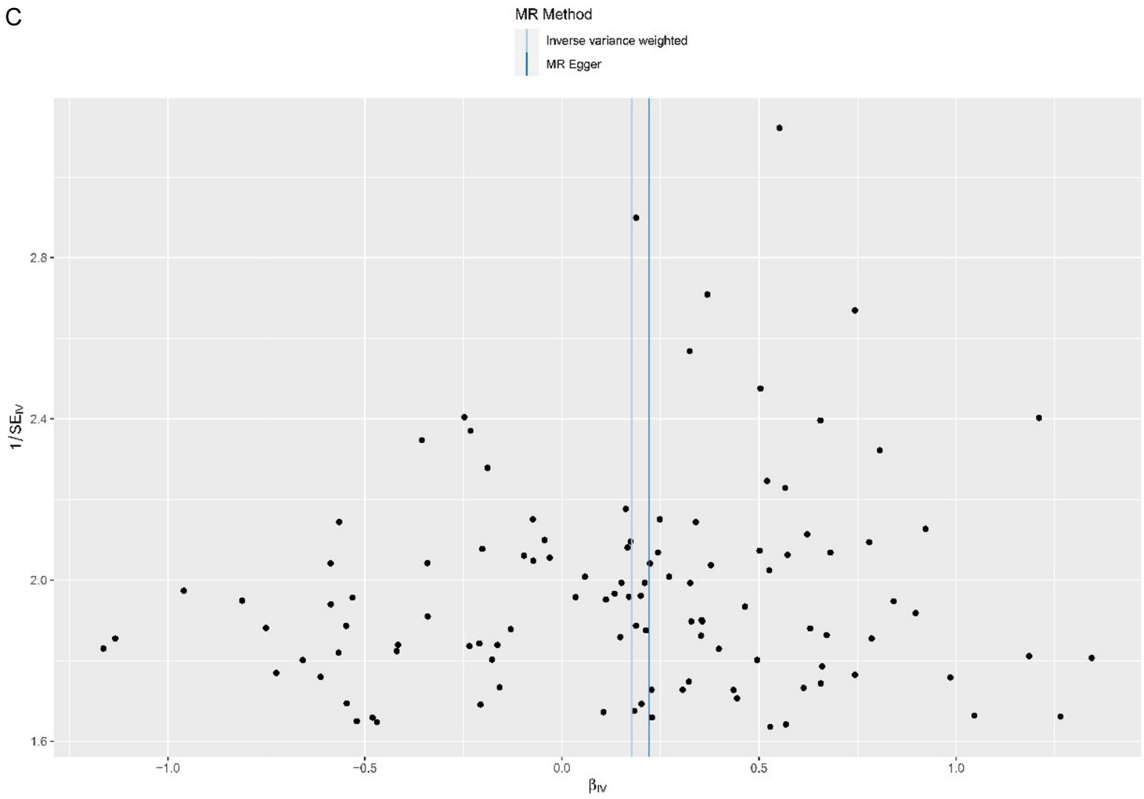




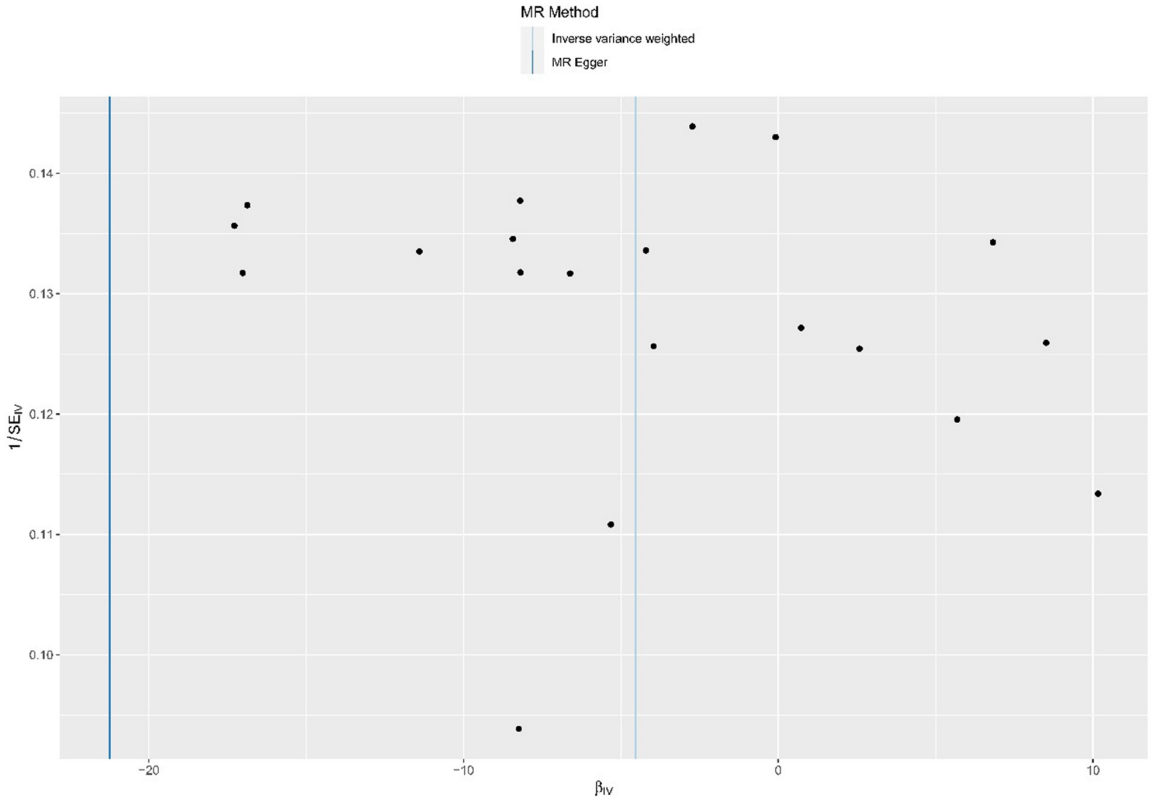
Supplementary Figure 2-5. Funnel plots for Mendelian randomization (MR) analyses of the causal relationship between Dried fruit intake (A), Non-oily fish intake (B), Oily fish intake (C) and Acute tubulointerstitial nephritis (ATIN).


A
MR Method
Inverse variance weighted
MR Egger
0.50
0.49
0.48
0.47
0.46
0.45
1/SE_IV
−4
−2
0
2
β_IV
B
MR Method
Inverse variance weighted
MR Egger
0.70
0.65
0.60
0.55
0.50
1/SE_IV
−5.0
−2.5
0.0
2.5
β_IV

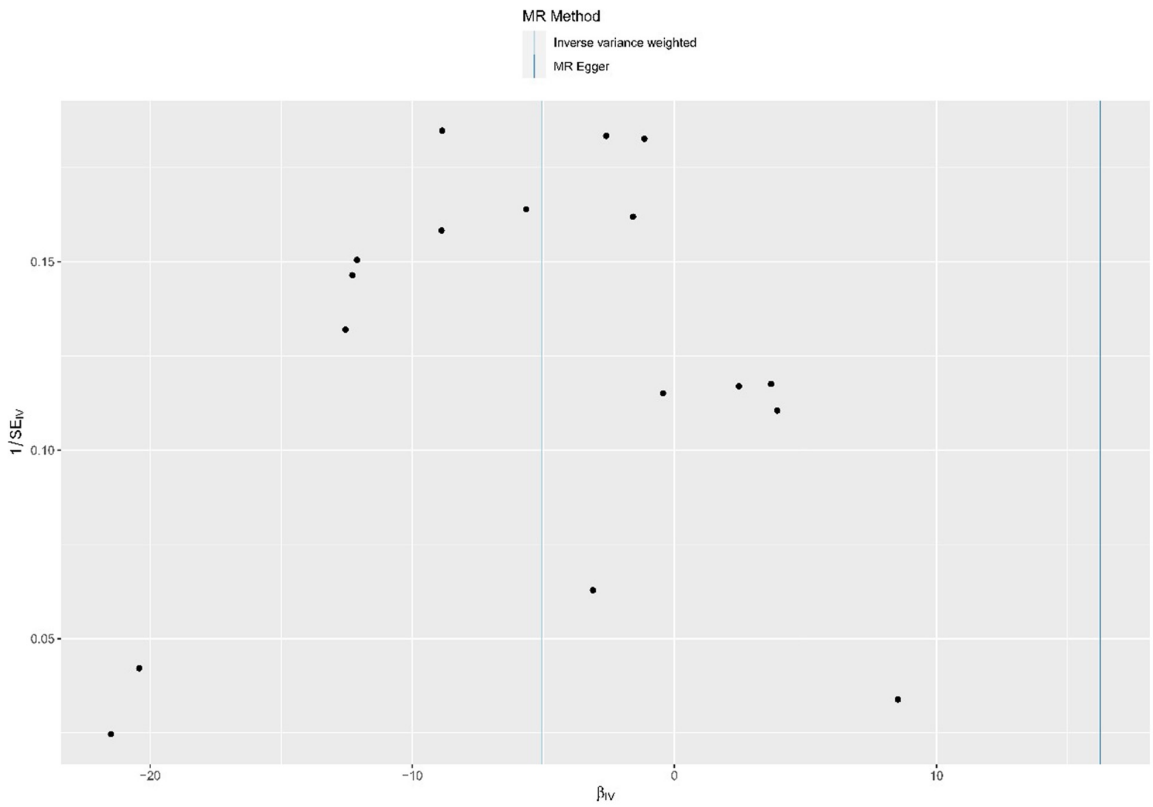
C



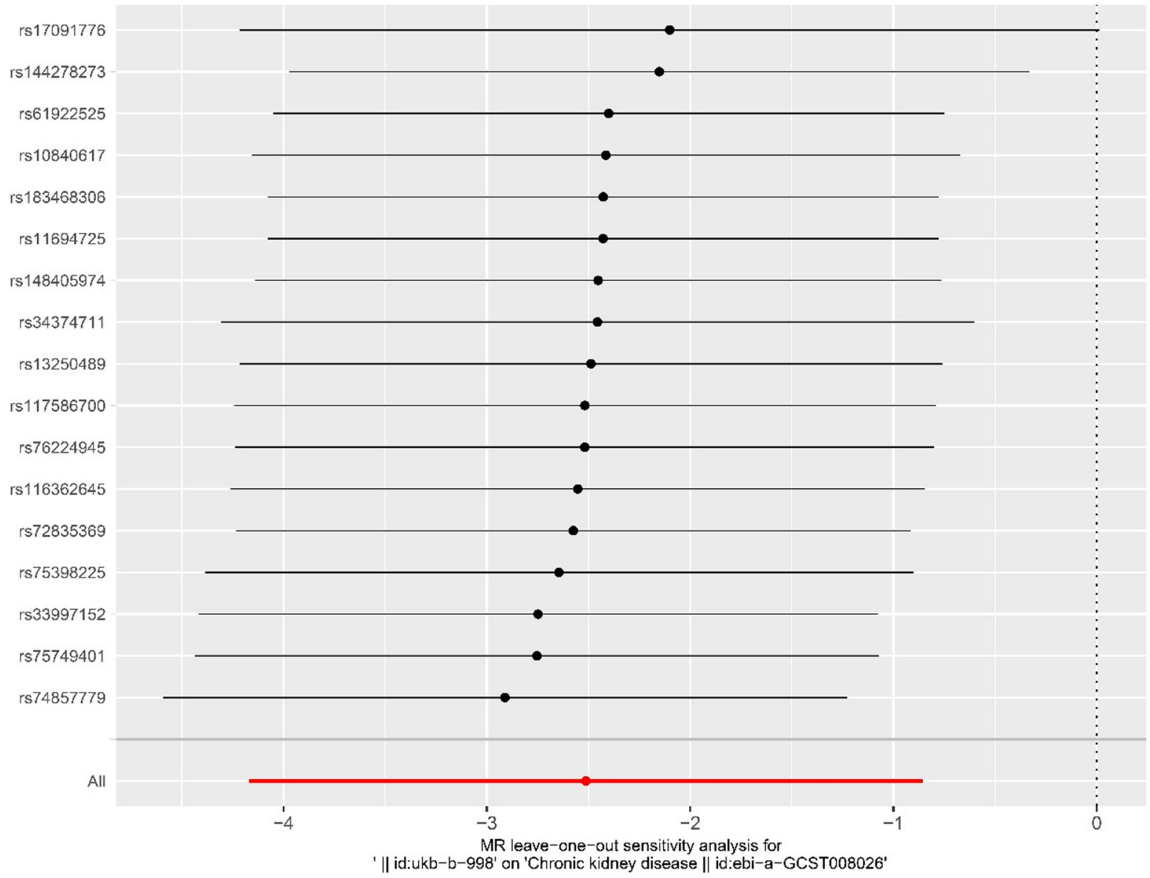
Supplementary Figure 2-6. Funnel plots for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure, Other Exercises, Leisure Screen Time and Immunoglobulin A Nephropathy (IgA-N).



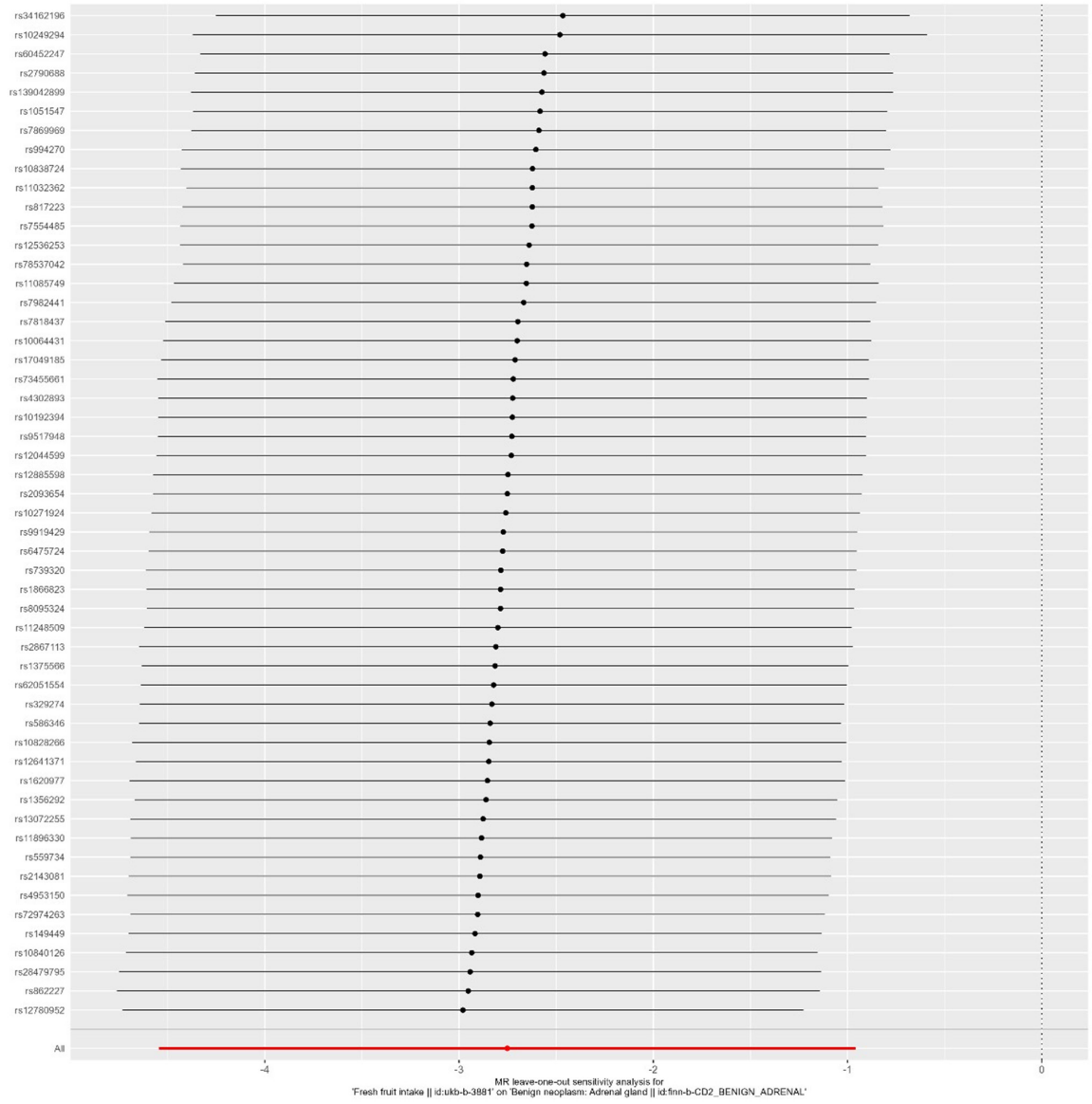
Supplementary Figure 2-7. Funnel plot for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure and Type 2 Diabetes with renal complications.



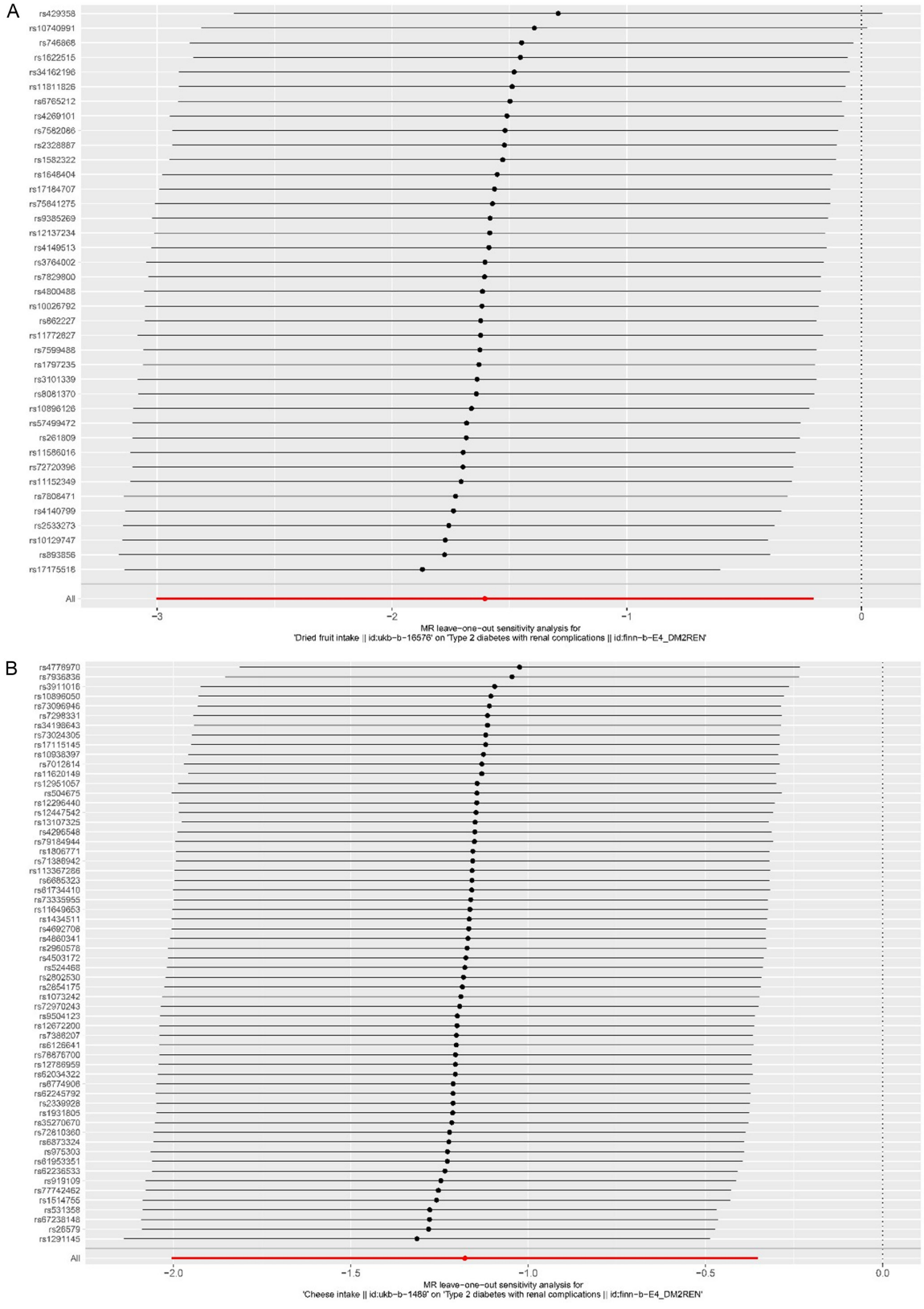
Supplementary Figure 2-8. Funnel plot for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure and Chronic Renal Failure.



Supplementary Figure 3-1. Leave-one-out sensitivity test plot for Mendelian randomization (MR) analyses of the causal relationship between Soya Dessert Intake and Chronic Kidney Disease (CKD).

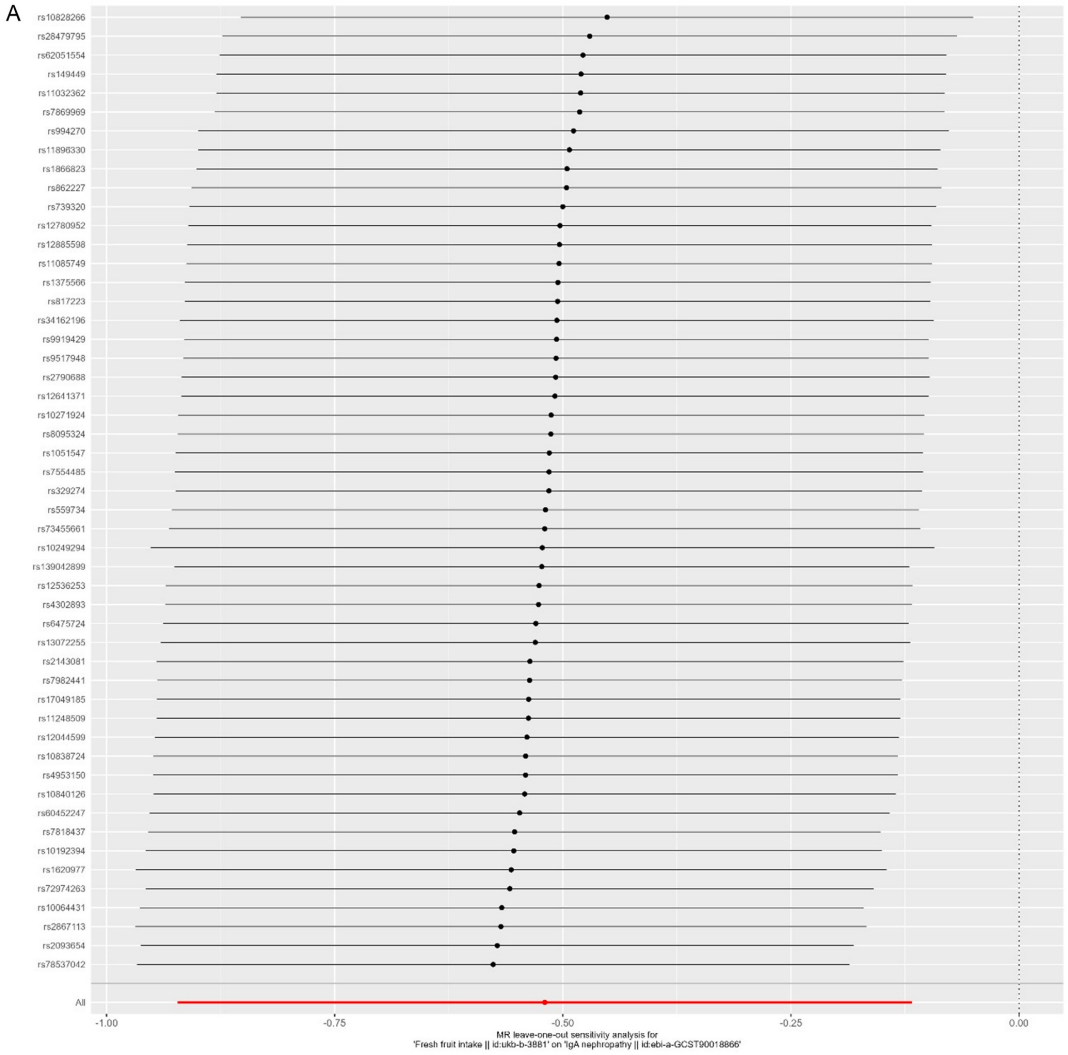


Supplementary Figure 3-2. Leave-one-out sensitivity test plot for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake and Benign neoplasm: Adrenal gland.



Supplementary Figure 3-3. Leave-one-out sensitivity test plots for Mendelian randomization (MR) analyses of the causal relationship between Dried Fruit Intake (A), Cheese Intake (B) and Type 2 diabetes with renal complication.

A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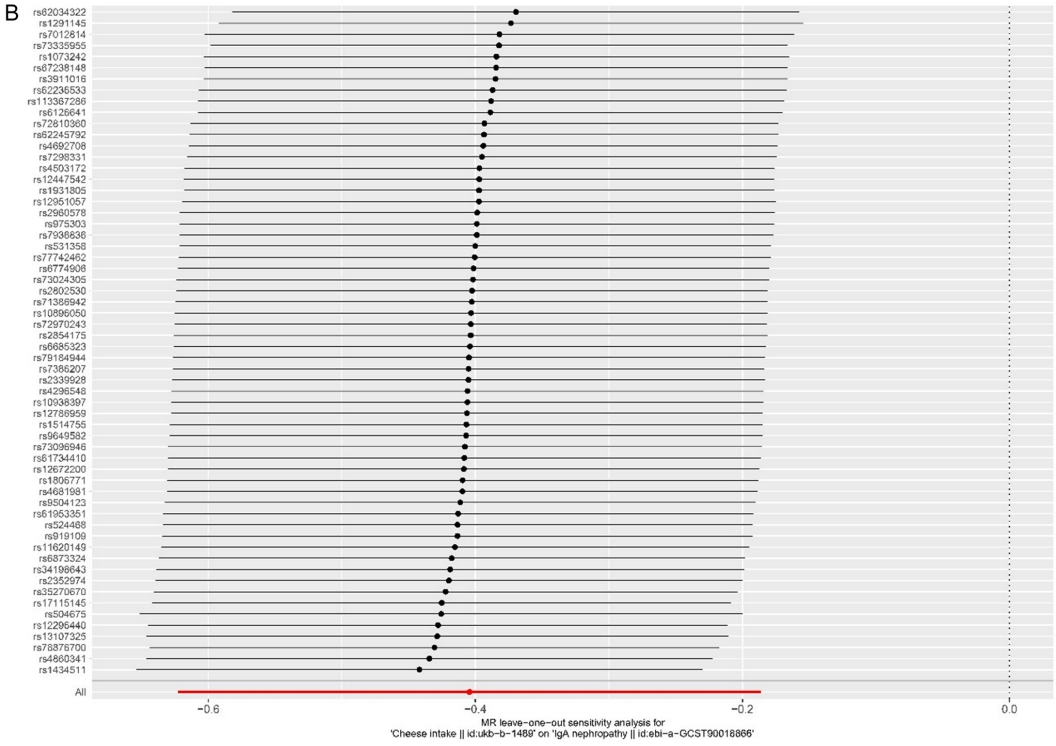
rs2093654
rs78537042
All
-1.00
-0.75
-0.50
-0.25
0.00
MR leave-one-out sensitivity analysis for
'Fresh fruit intake || id:ukb-b-3881' on 'IgA nephropathy || id:ebi-a-GCST90018866'

B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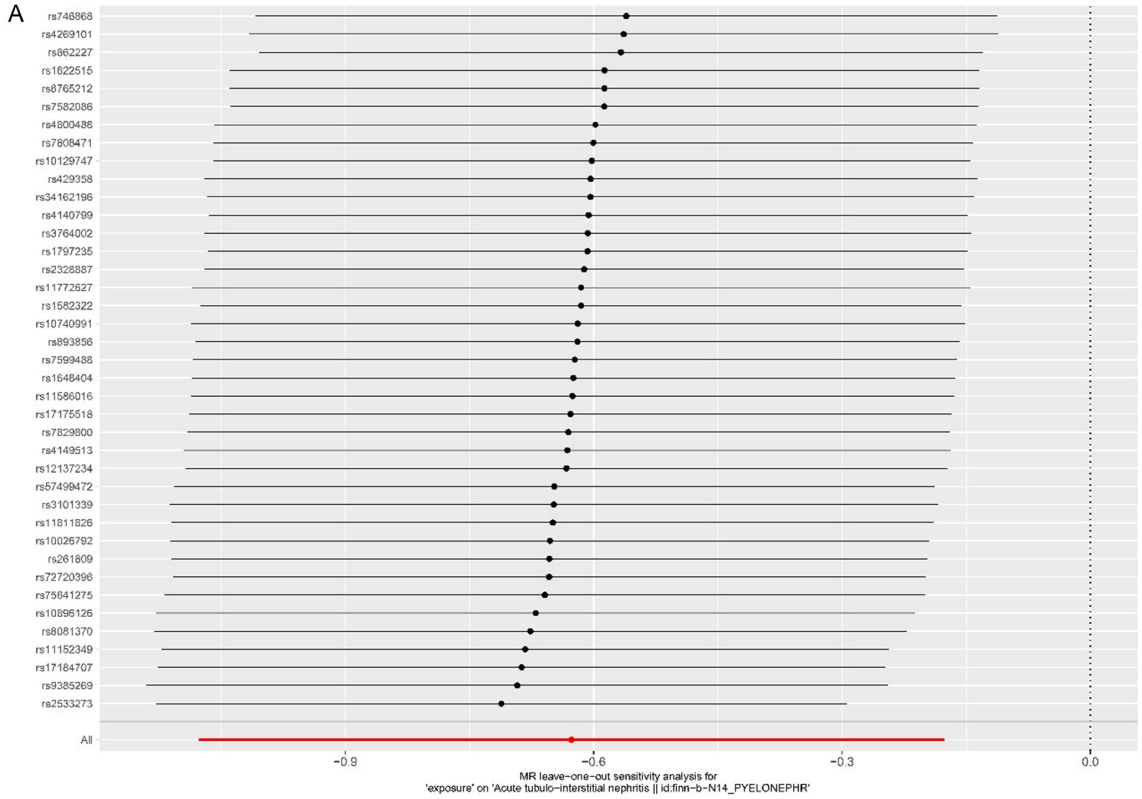
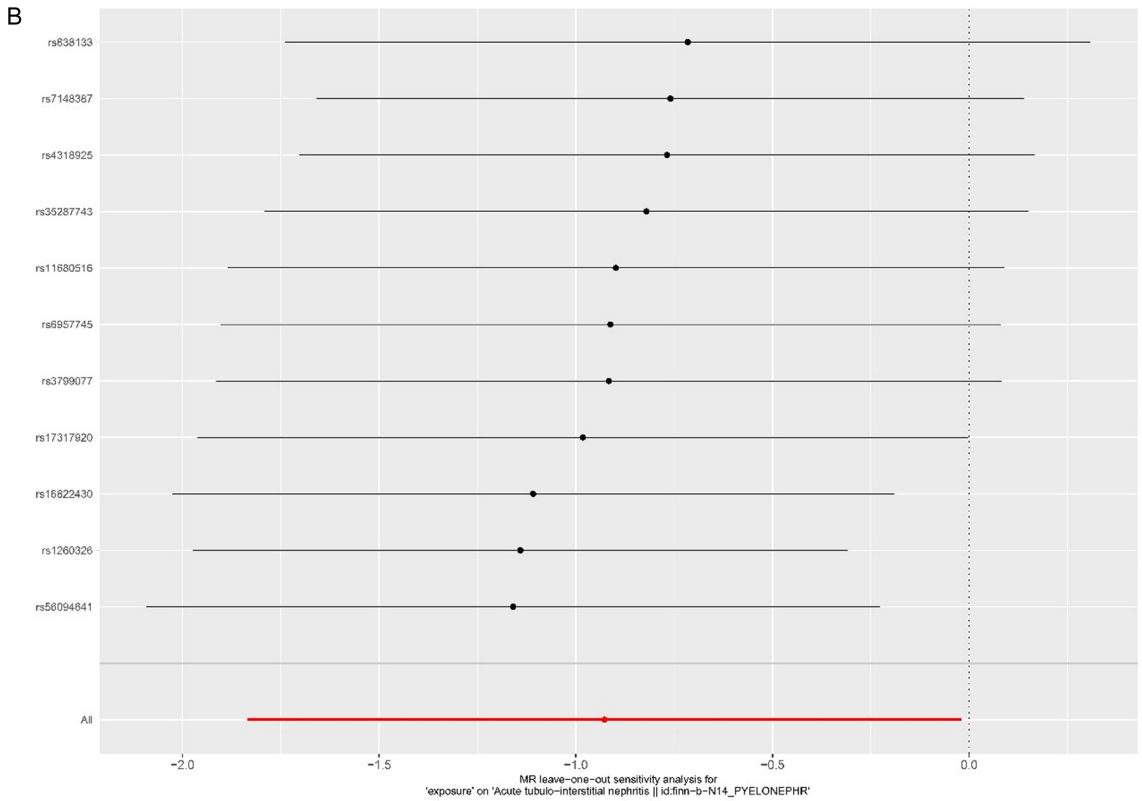
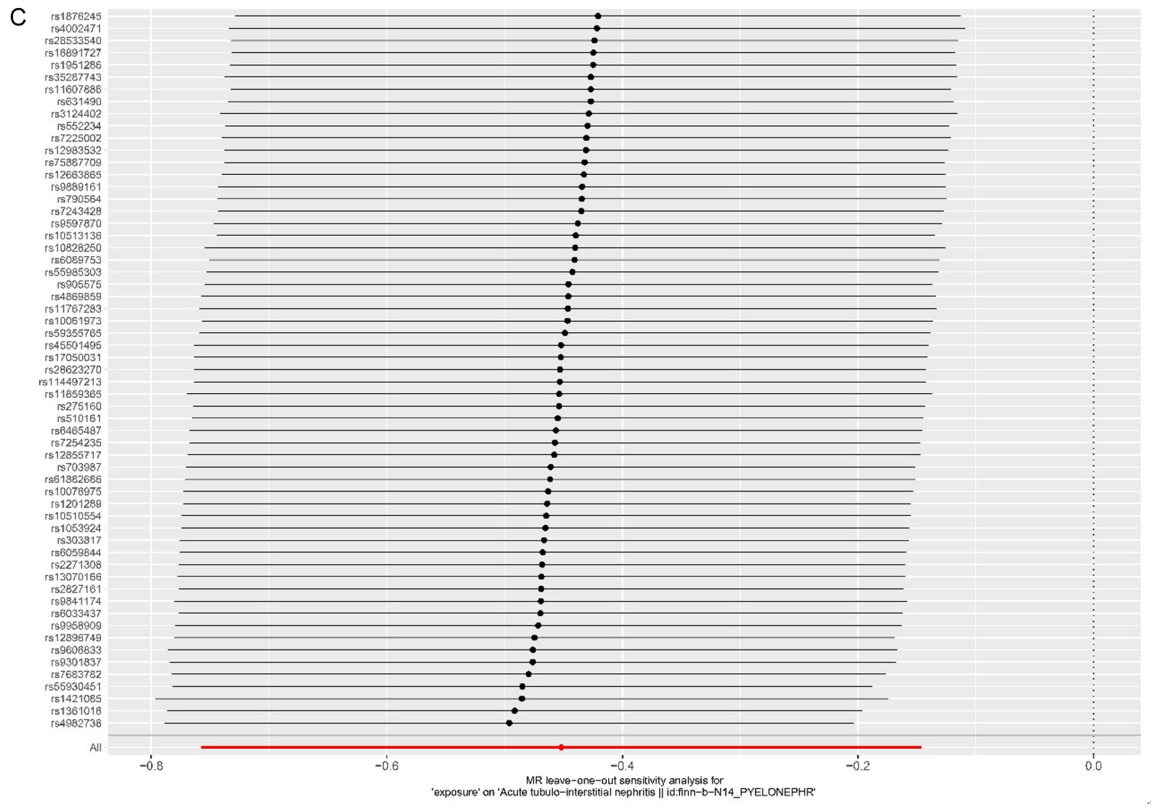
rs12296440
rs13107325
rs78876700
rs4660341
rs1434511
All
−0.6
−0.4
−0.2
0.0
MR leave−one−out sensitivity analysis for
'Cheese intake || id:ukb−b−1489' on 'IgA nephropathy || id:ebi−a−GCST90018866'

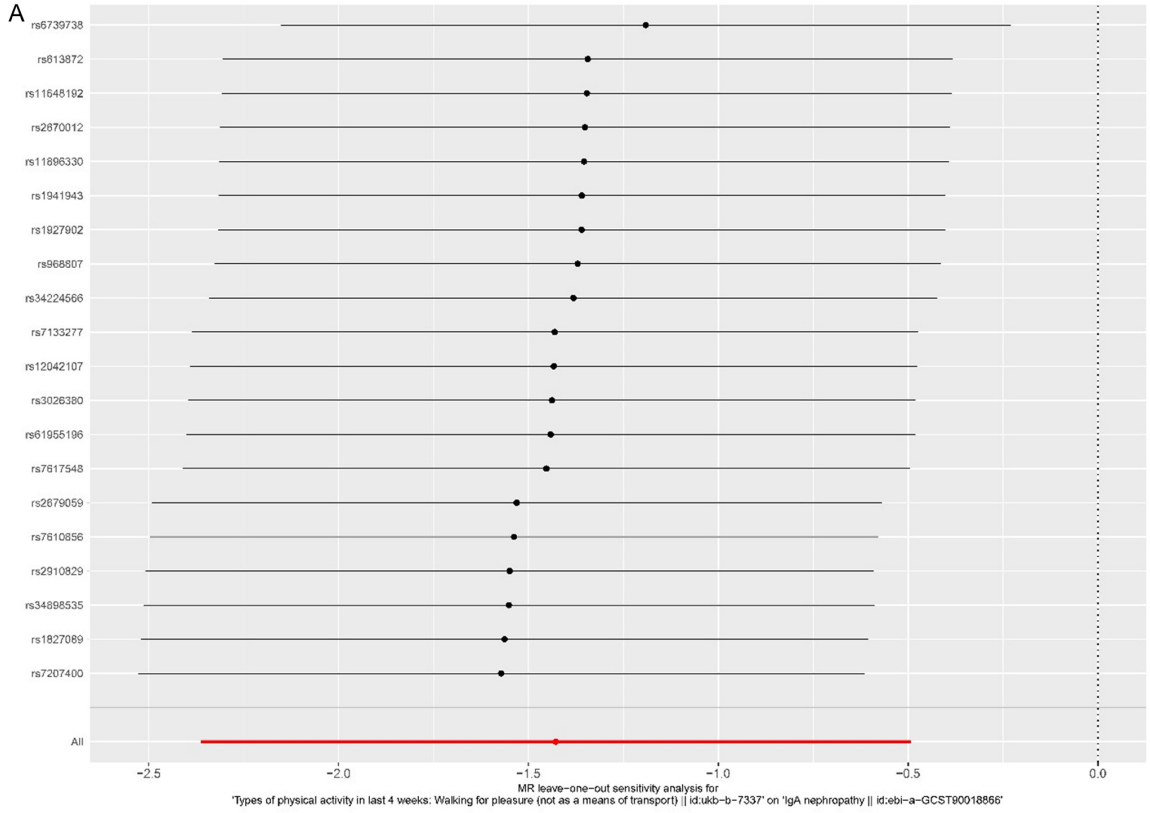
Supplementary Figure 3-4. Leave-one-out sensitivity test plots for Mendelian randomization (MR) analyses of the causal relationship between Fresh Fruit Intake (A), Cheese Intake (B) and Immunoglobulin A Nephropathy (IgA-N).

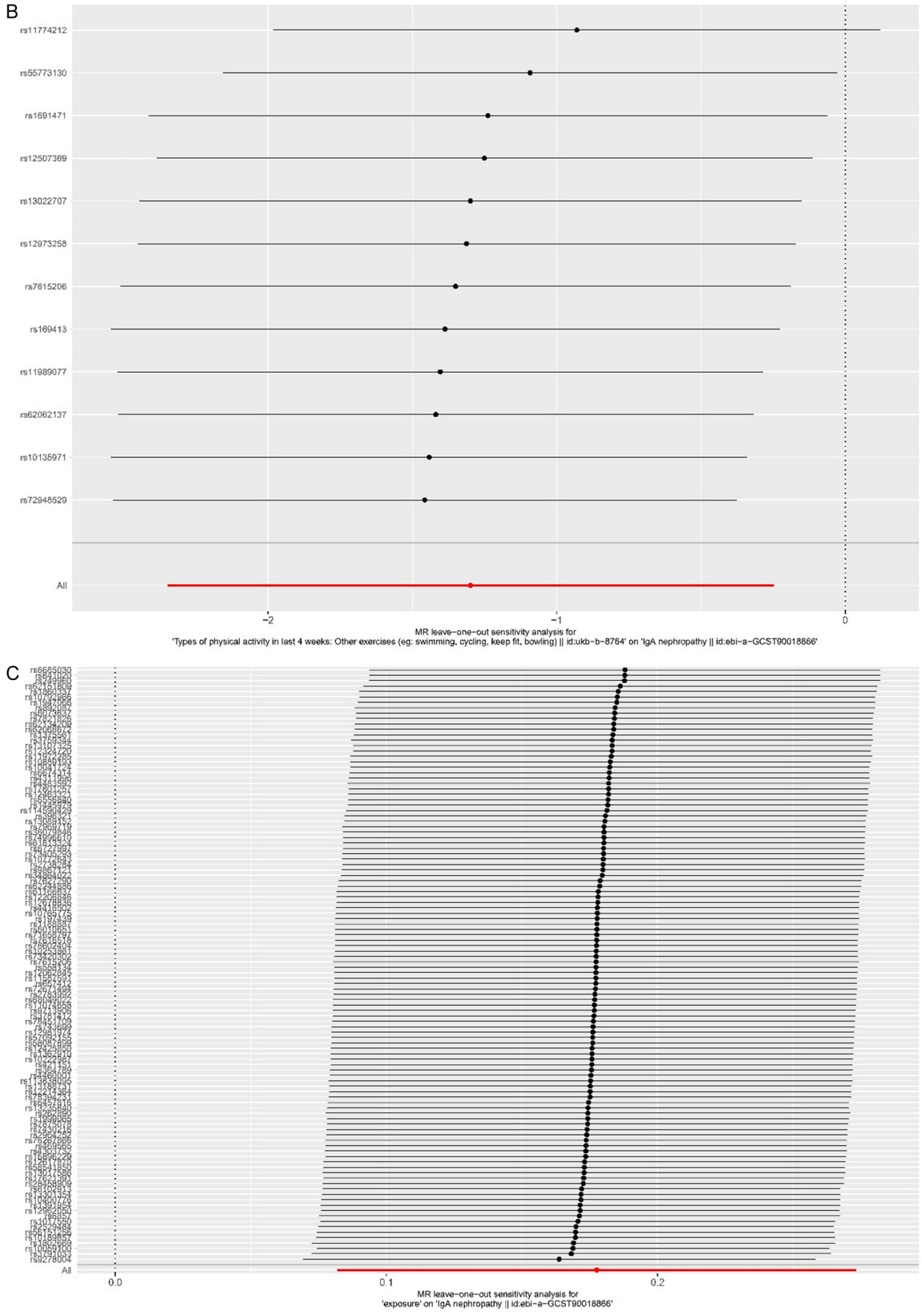




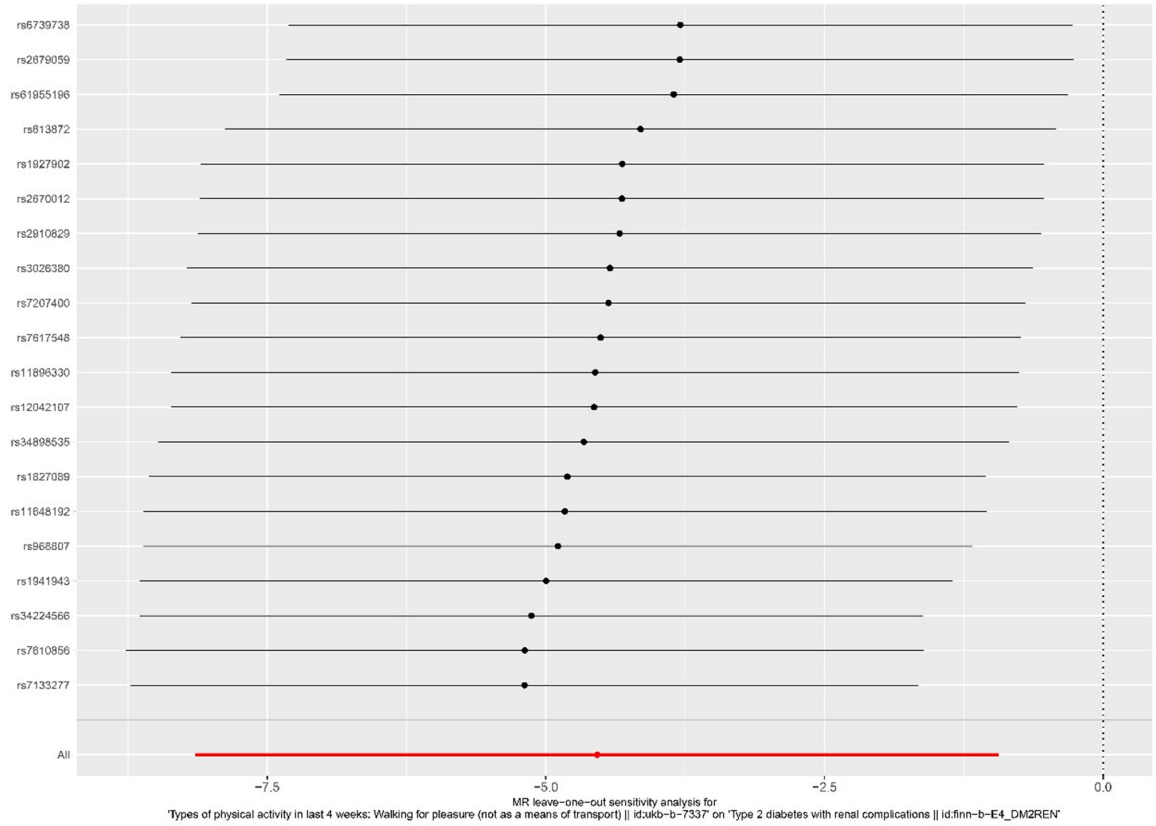


Supplementary Figure 3-5. Leave-one-out sensitivity test plots for Mendelian randomization (MR) analyses of the causal relationship between Dried fruit intake (A), Non-oily fish intake (B), Oily fish intake (C) and Acute tubulointerstitial nephritis (ATIN).





Supplementary Figure 3-6. Leave-one-out sensitivity test plots for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure, Other Exercises, Leisure Screen Time and Immunoglobulin A Nephropathy (IgA-N).



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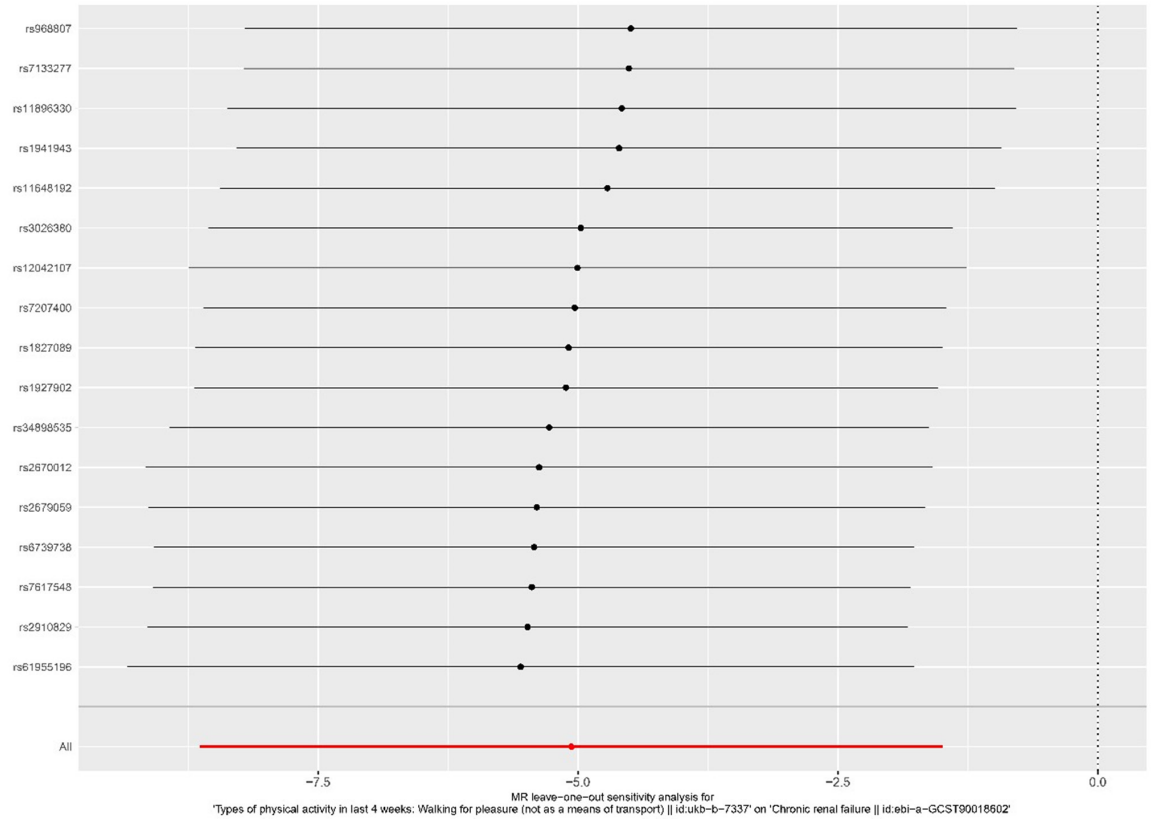

Supplementary Figure 3-8. Leave-one-out sensitivity test plot for Mendelian randomization (MR) analyses of the causal relationship between Walking for Pleasure and Chronic Renal Failure.