

Dietary fibre intake in relation to the risk of incident chronic kidney disease

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Abstract

The purpose of this study was primarily to evaluate the association of total fibre intake with the risk of incident chronic kidney disease (CKD). We also evaluated the association of dietary fibre from fruits, vegetables, cereals and legumes with the incidence of CKD in a population-based prospective study. We followed up 1630 participants of the Tehran Lipid and Glucose Study for 6·1 years, who were initially free of CKD. Baseline diet was assessed by a valid and reliable FFQ. Estimated glomerular filtration rate (eGFR) was calculated, using the Modification of Diet in Renal Disease Study equation, and CKD was defined as eGFR <60 ml/min per 1·73 m². OR using multivariable logistic regression was reported for the association of incident CKD with tertiles of dietary fibre intake. After adjustment for age, sex, smoking, total energy intake, physical activity, diabetes and using angiotensin-converting-enzyme inhibitor, the OR for subjects in the highest compared with the lowest tertile of total fibre intake was 0·47 (95 % CI 0·27, 0·86). In addition, for every 5 g/d increase in total fibre intake, the risk of incident CKD decreased by 11 %. After adjusting for potential confounders, OR for participants in the highest compared with the lowest tertile of fibre from vegetables was 0·63 (95 % CI 0·43, 0·93) and from legumes it was 0·68 (95 % CI 0·47, 0·98). We observed inverse associations between total fibre intake and risk of incident CKD, which demonstrate that high fibre intake, mainly from legumes and vegetables, may reduce the occurrence of CKD.

Key words: Fruits: Vegetables: Legumes: Kidney function

Chronic kidney disease (CKD) is a prevalent complex disease and is fast becoming a growing public health problem, leading to premature mortality or poor quality of life, exposing a heavy burden on healthcare systems^(1,2). Evidence available reveals that the global prevalence of CKD has a sharply increasing trend, affecting 10–15 % of general populations^(3,4). Ageing, hypertension, diabetes, hyperlipidaemia, smoking and poor dietary intake have been identified as risk factors for CKD occurrence^(5,6). Higher dietary intake of plant protein, vitamin C, Mg, K, *n*-6 fatty acids and lower intake of animal protein and Na are documented as the potential factors for prevention of CKD occurrence^(7,8). Yet, dietary guidelines have not been developed for the prevention of kidney dysfunction.

Although a great deal of research has been conducted on the importance of dietary fibre intake in the prevention of CVD, diabetes and cancer, encouraging healthcare organisations to recommend dietary fibre intake^(9,10), findings on the dietary fibre and kidney function are limited and inconsistent^(11–13).

One cohort study indicates that subjects in the highest quartile of dietary cereal fibre, compared with those in the lowest, had a 50 % decreased risk for incidence of CKD; however, total fibre intake was not associated with the occurrence of CKD⁽¹¹⁾. Xu *et al.*⁽¹²⁾ showed that higher total fibre intake was positively associated with estimated glomerular filtration rate (eGFR) among elderly men. In addition, greater dietary total fibre intake was associated with reduced risk of incident kidney stones in postmenopausal women⁽¹³⁾.

Previous studies on dietary fibre intake and kidney function have been conducted in developed countries. The Tehran Lipid and Glucose Study (TLGS) is a large prospective cohort study with different dietary habits required for substantiating and persuasion of preventive dietary recommendations. Current TLGS analyses showed that plant-based diets rich in fibre were related to a decrease in incident CKD^(14,15); total dietary fibre intake was also associated with reduced CVD risk⁽¹⁶⁾, and fruit fibre was associated with decreased the metabolic syndrome⁽¹⁷⁾.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TLGS, Tehran Lipid and Glucose Study.

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The purpose of this study was primarily to evaluate the association of total fibre intake with the risk of incident CKD. We also evaluated the association of dietary fibre from fruits, vegetables, cereals and legumes with the incidence of CKD in a population-based prospective study.

Methods

Study population

This study was conducted within the framework of the TLGS, an ongoing community-based prospective investigation aimed at preventing non-communicable diseases (NCD) by developing programmes promoting healthy lifestyles and reducing NCD risk factors in a sample of residents under coverage of three medical health centres in District No. 13 of Tehran, the capital city of Iran⁽¹⁸⁾. The baseline survey was a cross-sectional study conducted from 1999 to 2001, and surveys II (2002–2005), III (2006–2008), IV (2009–2011) and V (2012–2015) are prospective follow-up surveys.

From among the 12 523 participants examined in the third survey of the TLGS, 3462 were randomly selected for dietary assessment, of whom 2417 participants were aged ≥ 27 years. Subjects with a history of myocardial infarction or stroke due to the possibility of major changes in diet were excluded (n 34). In addition, subjects (n 113) who under- or over-reported energy intakes (<3347 kJ/d (<800 kcal/d) or $>17\,573$ kJ/d (>4200 kcal/d), respectively) and those with missing data on covariates (n 52) were excluded; some individuals fell into more than one exclusion category. To evaluate the incidence, we also excluded subjects

who had CKD at baseline (n 360). Finally, 1630 participants were followed up until survey V (response rate: 87%), with a median duration of 6.1 years (25–75 interquartile range: 5.6–6.5; Fig. 1).

The ethics committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences approved the study protocol and written informed consent was obtained from all participants.

Measurements

Dietary measurements. Habitual dietary intakes were assessed using a valid and reliable semi-quantitative FFQ by expert interviewers^(19–21). Trained dietitians, during face-to-face interviews, asked participants to designate their consumption frequency for each food item consumed during the previous year on a daily, weekly and monthly basis. As the Iranian food composition table (FCT) is incomplete, the United States Department of Agriculture (USDA) FCT was used. For national foods not listed in the USDA FCT, the Iranian FCT was the alternative. We calculated total dietary fibre, as well as fibre contribution from cereals, legumes, vegetables and fruits.

The reliability and validity of the FFQ, which were evaluated against twelve 24-h dietary recalls and two FFQ in a previous study, indicated that the FFQ provides reasonably valid measures of the average long-term dietary fibre intake^(19–21).

Measurement of covariates. Information on physical activity was collected by using the modifiable activity questionnaire (MAQ) to calculate metabolic equivalent task (MET)-minutes

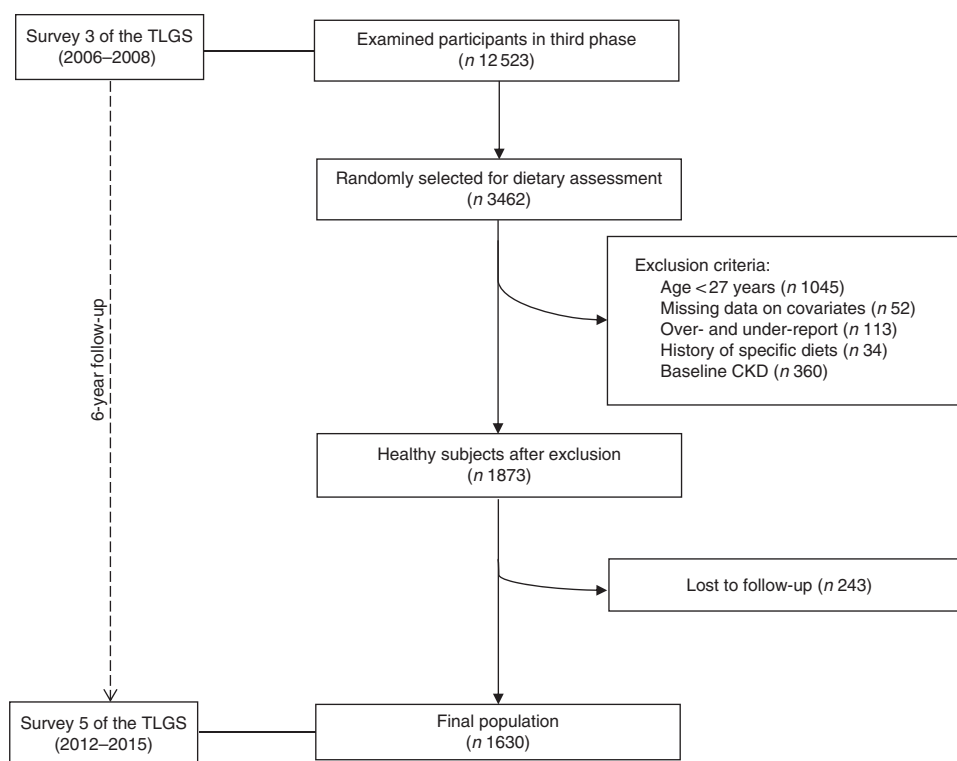


Fig. 1. Flow chart of the Tehran Lipid and Glucose Study (TLGS) participants. CKD, chronic kidney disease.

per week. High reliability (98%) and moderate validity (47%) were found for the Persian translation of MAQ⁽²²⁾. Low levels of physical activity were considered as MET <600 min/week. Weight was recorded in light clothing to the nearest 0.1 kg on a SECA digital weighing scale (Seca 707; Seca Corporation; range 0.1–150 kg) and height was measured without shoes to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by square of height (m²). Arterial blood pressure was measured manually, using a mercury sphygmomanometer with a suitable cuff size for each participant after a 15-min rest in the supine position. Systolic blood pressure (SBP) was determined by the onset of the tapping Korotkoff sound, whereas diastolic blood pressure (DBP) was determined as the disappearance of the Korotkoff sound. Blood pressure was measured twice and the average was considered as the participant's blood pressure.

Blood samples were taken from all participants at the TLGS research laboratory after an overnight fast of 12–14 h. Fasting plasma glucose (FPG) and 2-h plasma glucose (equivalent to 75 g anhydrous glucose; Cerestar EP) were assayed by enzymatic colorimetric method using glucose oxidase, with both inter- and intra-assay CV being <2%. Serum creatinine was measured according to the standard colorimetric Jaffe_Kinetic reaction method at baseline (2006–2008) and after 6 years of follow-up (2012–2015). Both intra- and inter-assay CV were below 3.1%; all analyses were performed using commercial kits (Pars Azmoon Inc.).

Definitions

Hypertension was defined as SBP/DBP ≥ 140/90 mmHg or current therapy for a definite diagnosis of hypertension⁽²³⁾. Diabetes was defined according to the criteria of the American Diabetes Association as FPG ≥ 7.0 mmol/l or 2-h post 75-g glucose load ≥ 11.1 mmol/l or current therapy for a definite diagnosis of diabetes⁽²⁴⁾. We used the Modification of Diet in Renal Disease (MDRD) equation formula to express eGFR in ml/min per 1.73 m² of body surface area⁽²⁵⁾. The abbreviated MDRD study equation is as follows:

$$\text{eGFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American}).$$

Patients were classified based on their eGFR levels by the National Kidney Foundation guidelines⁽²⁶⁾; eGFR ≥ 60 ml/min per 1.73 m² as not having CKD and eGFR < 60 ml/min per 1.73 m² as having CKD.

Statistical analysis

All data were analysed using the Statistical Package for the Social Sciences program (SPSS) (version 15.0; SPSS Inc.) and *P* values < 0.05 were considered statistically significant. Total dietary intake of fibre was categorised into the tertile cut-off points as ≤ 17.7, 17.8–26.0 and > 26.1 g/d; dietary fibre from fruits, vegetables, cereals and legumes was categorised into three groups according to the tertiles of the distribution among the total population. Continuous variables were reported as a mean ± standard deviation and categorical variables as percentages. Tests of a trend for continuous variables across tertiles of the total fibre intake were conducted using ANOVA and for categorical variables χ^2 test was used.

The OR and 95% CI for the incidence of CKD according to tertiles of dietary exposure was assessed with multivariable logistic regression models. In this analysis, the first tertile of dietary exposure was considered as the reference category. To calculate the trend of OR across increasing tertiles of dietary exposure, the median values of each fibre category were considered as continuous variables. Three models were considered to adjust potential confounders (model 1, crude (without any covariate); model 2, age (continuous), sex, smoking (yes/no), total energy intake (continuous), physical activity (low, moderate, heavy); and model 3, diabetes (yes/no) and using angiotensin-converting-enzyme inhibitor (yes/no)). As a further adjustment for intakes of dietary fat, *n*-3 fatty acids, K, Mg and hypertension did not change the relations substantially, these covariates were not considered in the final models.

Results

We recorded 220 (13.5%) cases of incident CKD, with a range of eGFR between 29 and 59 ml/min per 1.73 m², after 6.1 years of follow-up. Mean age and total fibre intake of participants was 42.8 (SD 11.2) years and 23.8 (SD 11.7) g/d. General characteristics of study participants across tertiles of total fibre intake are presented in Table 1. Participants in the highest, compared with the lowest, tertile of total fibre intake were less likely to be women (*P* < 0.05). No significant differences were found by means of age, BMI and eGFR and prevalence of low physical activity, current smoker, diabetes, hypertension and anti-hypertensive drug across tertiles of total fibre intake.

Dietary intakes of participants across tertile categories of total fibre intake are shown in Table 2. Participants in the top tertile of total fibre intake had higher consumption of protein, plant protein, carbohydrate and K than those in the bottom tertile (*P* < 0.05); however, consumption of animal protein, total and SFA tended to decrease across tertiles of total fibre intake (*P* < 0.05).

In the crude model, total fibre intake was inversely associated with an incidence of CKD (Table 3). After adjustment for age, sex, smoking, total energy intake, physical activity, diabetes and using angiotensin-converting-enzyme inhibitor, the OR for subjects in the highest compared with the lowest tertile of total fibre intake was 0.47 (95% CI 0.27, 0.86). A significant decreasing linear trend was noted across tertiles of total fibre intake for risk of incident CKD (*P*_{for trend} < 0.001). In addition, the risk of incident CKD decreased by 11% for every 5 g/d increase in total fibre intake.

We also examined the association between various sources of dietary fibre and incidence of CKD. After adjusting for potential confounders, OR for participants in the highest compared with the lowest tertile of fibre from vegetables was 0.63 (95% CI 0.43, 0.93) and from legumes it was 0.68 (95% CI 0.47, 0.98). In addition, a significant decreasing linear trend was noted across tertiles of dietary fibre from vegetables and legumes for the risk of incident CKD (*P*_{for trend} < 0.05). The risk of incident CKD decreased 50% for every 5 g/d increase in dietary fibre from legumes. Furthermore, there was no significant association of fibre from fruits and cereals with the risk of incident CKD.

Table 1. Baseline characteristics of participants according to tertiles (T) of total fibre intake (Mean values and standard deviations; percentages)

	Tertiles of total fibre						<i>P</i> _{for trend} *
	T1 (<i>n</i> 544)		T2 (<i>n</i> 543)		T3 (<i>n</i> 543)		
	Mean	SD	Mean	SD	Mean	SD	
Median total fibre (g/d)		13.6		21.5		33.5	
Age (years)	42.4	11.1	42.8	11.2	43.3	11.4	0.190
Women (%)		56.8		49.2		45.5	0.001
BMI (kg/m ²)	27.2	4.5	27.6	4.5	27.9	4.6	0.061
Current smoker (%)		9.9		11.2		10.1	0.750
Low physical activity (%)		71.5		69.4		69.2	0.282
Diabetes (%)		8.1		7.6		8.8	0.738
Hypertension (%)		11.6		13.4		12.5	0.635
Antihypertensive drug use (%)		3.1		3.3		2.2	0.564
Angiotensin-converting-enzyme inhibitor use (%)		1.7		2.0		1.3	0.636
eGFR (ml/min per 1.73 m ²)	73.4	8.7	73.3	8.4	74.3	8.6	0.066

eGFR, estimated glomerular filtration rate.

* Tests of trend for continuous variables across tertiles of total fibre intake were conducted using ANOVA, and for categorical variables χ^2 test was used.

Table 2. Baseline dietary intakes of participants, according to tertiles (T) of total fibre intake

	Tertiles of the total fibre								<i>P</i> _{for trend} *
	Total population		T1 (n 544)		T2 (n 543)		T3 (n 543)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total energy (kJ)	9703	3423	7243	1833	9259	2272	12 606	3351	<0.001
Total energy (kcal)	2319	818	1731	438	2213	543	3013	801	<0.001
Protein (% energy)	13.7	2.4	13.5	2.6	13.7	2.2	13.9	2.4	<0.001
Animal protein (g/1000)	18.5	7.0	19.7	7.6	18.6	6.1	17.4	7.2	<0.001
Plant protein (g/1000)	15.9	4.2	14.3	3.3	15.9	3.5	17.6	4.8	<0.001
Carbohydrate (% energy)	57.7	7.2	55.5	7.3	57.8	6.7	59.8	6.9	<0.001
Total fat (% energy)	31.2	7.1	32.8	7.6	31.1	6.9	29.6	6.4	<0.001
SFA (% energy)	10.5	5.5	11.5	8.6	10.3	2.7	9.6	2.7	<0.001
Dietary fibre (g/d)	23.8	11.7	13.1	3.1	21.6	2.4	36.6	10.7	<0.001
K (mg/d)	3861	1792	2601	794	3633	976	5347	2051	<0.001
Cereal fibre (%)	38.2	16.9	36.5	14.4	37.4	16.2	38.7	19.7	0.093
Fruit fibre (%)	26.3	16.9	28.7	16.2	27.5	14.1	22.7	12.7	<0.001
Vegetable fibre (%)	18.3	9.5	16.9	9.8	17.9	8.4	20.0	10.4	<0.001
Legume fibre (%)	5.8	6.10	5.6	5.2	5.8	5.7	6.1	7.2	0.017

* Test of trend across tertiles of total fibre intake was conducted using ANOVA.

Discussion

This population-based prospective study showed that high total fibre intake was related to lower incidence of CKD after 6.1 years of follow-up. Subjects who consumed more than 26.0 g/d of fibre had 50 % lower risk of CKD occurrence compared with those who consumed ≤ 17.7 g/d. We also observed an 11 % lower risk of incident CKD per 5-g/d increase in total fibre intake. Protective associations of specific sources of fibre with the risk of incident CKD were observed for vegetable and legume fibre. No association was observed between the risk of CKD and the cereal or fruit fibre intake.

Relatively limited studies investigated the association of total fibre intake with CKD^(11,12,27,28). Data of 2600 participants aged ≥ 50 years from Blue Mountains Eye Study showed no significant association of fibre intake with the prevalence of moderate CKD⁽¹¹⁾. However, among 1110 participants aged 70–71 years, higher intake of total fibre had desirable association with eGFR⁽¹²⁾. In a cross-sectional study of non-diabetic individuals

from the PREDIMED study, among subjects in the highest quartile of fibre intake the risk of incident CKD decreased by 42 %⁽²⁷⁾. In addition, in 5416 subjects, aged >40 years, dietary fibre consumption was found to be associated with a reduced risk of albuminuria⁽²⁸⁾. Besides studies investigating the association of dietary fibre on CKD, there are studies that show other desirable effects of dietary fibre on kidney-related disorders^(13,29). A recent meta-analysis showed that total fibre intake was associated with 26 % lower risk of renal cell carcinoma⁽²⁹⁾. In addition, women with no history of kidney stones in the highest compared with the lowest categories of dietary fibre intake had a 22 % decreased risk of stone formation⁽¹³⁾.

In our study, participants in the highest tertile of dietary fibre intake showed lower consumption of animal protein and saturated fat and higher consumption of plant protein and K in comparison with those in the lowest tertile. Indeed, higher fibre intake was accompanied by healthier dietary behaviour that may affect kidney function; however, there were no differences between participants in the tertiles of fibre intake according to

Table 3. Incident chronic kidney disease according to the dietary fibre intake and per 5-g increase in intake among participants of the Tehran Lipid and Glucose Study (Odds ratios and 95 % confidence intervals)

	Tertiles of dietary fibre					<i>P</i> _{for trend} *	Per 5-g increase	
	T1	T2		T3				
		OR	95% CI	OR	95% CI		OR	95% CI
Total fibre (median)	13.6	21.5		33.5				
Case/total	81/544	85/543		54/543				
Model 1†	Ref.	1.06	0.76, 1.47	0.63	0.44, 0.91	0.001	0.94	0.88, 1.00
Model 2‡	Ref.	0.98	0.68, 1.39	0.46	0.29, 0.76	0.001	0.88	0.81, 0.97
Model 3§	Ref.	0.97	0.68, 1.38	0.47	0.28, 0.76	0.001	0.89	0.81, 0.97
Fruit fibre (median)	1.96	5.14		10.28				
Case/total	75/543	77/544		68/543				
Model 1†	Ref.	1.03	0.73, 1.45	0.89	0.63, 1.27	0.512	0.93	0.82, 1.07
Model 2‡	Ref.	1.01	0.71, 1.44	0.82	0.56, 1.20	0.291	0.89	0.77, 1.04
Model 3§	Ref.	1.02	0.72, 1.46	0.82	0.56, 1.21	0.312	0.89	0.77, 1.04
Vegetable fibre (median)	1.81	3.51		6.20				
Case/total	79/544	74/543		68/543				
Model 1†	Ref.	0.91	0.65, 1.28	0.84	0.59, 1.19	0.341	0.97	0.77, 1.22
Model 2‡	Ref.	0.76	0.53, 1.09	0.63	0.43, 0.93	0.024	0.86	0.67, 1.11
Model 3§	Ref.	0.75	0.53, 1.08	0.63	0.43, 0.93	0.026	0.87	0.67, 1.12
Cereal fibre (median)	3.83	7.00		13.18				
Case/total	89/544	63/543		68/543				
Model 1†	Ref.	0.67	0.47, 0.95	0.73	0.52, 1.03	0.098	0.94	0.78, 1.13
Model 2‡	Ref.	0.66	0.46, 0.94	0.76	0.51, 1.13	0.211	0.98	0.80, 1.20
Model 3§	Ref.	0.66	0.46, 0.95	0.75	0.50, 1.11	0.180	0.97	0.79, 1.20
Legume fibre (median)	0.30	0.79		2.34				
Case/total	86/544	74/543		60/543				
Model 1†	Ref.	0.84	0.60, 1.17	0.66	0.46, 0.94	0.026	0.48	0.23, 0.98
Model 2‡	Ref.	0.82	0.58, 1.16	0.67	0.46, 0.97	0.035	0.51	0.22, 0.92
Model 3§	Ref.	0.84	0.59, 1.19	0.68	0.47, 0.98	0.038	0.50	0.23, 0.92

Ref., referent values. The tertile range for each category was ≤ 17.7 , 17.8–26.0 and > 26.1 g/d for total fibre; ≤ 3.5 , 3.6–7.2 and > 7.3 g/d for fruit fibre; ≤ 2.6 , 2.7–4.5 and > 4.6 g/d for vegetable fibre; ≤ 5.4 , 5.5–9.4 and > 9.5 g/d for cereal fibre; and ≤ 0.5 , 0.6–1.2 and > 1.3 g/d for legume fibre.

* *P*_{for trend} across tertiles calculated with the exposure modelled as a continuous variable.

† Model 1: crude.

‡ Model 2: adjusted for age, sex, smoking, total energy intake, physical activity.

§ Model 3: additionally adjusted for diabetes and using angiotensin-converting-enzyme inhibitor.

the BMI, current smoker, physical activity and anti-hypertensive drug use. In a previous study, we observed that independent of hypertension and diabetes, higher intakes of plant protein and PUFA had a decreasing effect on risk of CKD, whereas animal protein increased the risk of CKD⁽⁸⁾. Furthermore, the foods rich in fibre are the sources of K as well. K can bind to organic anions and metabolised to bicarbonate, so that the net rate of endogenous acid production in comparison with the rate of acid production from animal foods decreased⁽³⁰⁾. Hence, plant-based diet by providing alkali might decrease the risk of CKD⁽³¹⁾.

According to the present study, fibre from vegetables and legumes, but not from fruits and cereals, was significantly associated with incident CKD. We also found that per 5-g/d increase in intake of fibre from legumes led to 50 % lower risk of incident CKD. Gopinath *et al.*⁽¹¹⁾ observed that participants in the highest compared with those in the lowest quartile of dietary cereal fibre intake had a 50 % reduced risk of incident CKD; however, there were no significant findings between fibre from fruits and vegetables and the risk of CKD. Our results on kidney function are consistent with a previous meta-analysis that showed that the risk of renal cell carcinoma was inversely associated with legume and vegetable fibre intake, but not with fibre intake from fruits and cereals⁽²⁹⁾. Dietary intake of legumes

decreased the risk of incident CKD by 17 %, after 23 years of follow-up⁽³²⁾. People with higher scores of the diet rich in vegetables and legumes such as the Mediterranean diet had 51 % less risk of developing CKD⁽¹⁴⁾. Therefore, on the basis of the findings from our study and others, health benefits of fibre intake on kidney function may depend on the food source of dietary fibre. A previous report on cardiovascular outcomes has similarly shown the effects of fibre from different food sources⁽³³⁾.

In our study, we observed that, contrary to the dietary fibre from vegetables and legumes that simultaneously increased with total dietary fibre, intakes of fibre from cereals and fruits did not have a similar trend with that of total dietary fibre intake. Therefore, we found no significant relation of cereals and fruits with the incidence of CKD.

The beneficial effects of dietary fibre from legumes and vegetables on kidney function can be explained by several potential factors: first, dietary fibre from legumes may decrease the glycaemic index of consumer foods leading to a delay in the postprandial glycaemia⁽³⁴⁾. Second, dietary fibre sources (vegetables and legumes) are also rich in antioxidants and vitamins. Third, vegetable and legume fibre consumption can decrease the risk of incident CKD by attenuating known risk factors such as diabetes, hypertension, hyperlipidaemia

and low-grade inflammation^(35–37). Higher dietary fibre intake was inversely associated with improved glycaemic control, increased insulin sensitivity and reduced risk of type 2 diabetes, all of which are well known for their harmful effects on kidney function^(38,39). Another potential risk factor for CKD is hypertension. The blood pressure-lowering effect of dietary fibre was demonstrated in a recent meta-analysis⁽⁴⁰⁾.

There are some limitations to this study that need to be mentioned. First, as in most epidemiological studies, our definition of CKD is based on a limited number of isolated creatinine measurements that were not repeated within 3 months to confirm a chronic reduction in GFR. Second, despite controlling for various confounders in our analysis, residual confounding due to unknown or unmeasured confounders cannot be excluded.

Of the study's noteworthy strengths are the use of a complex validated 168-question FFQ and a prospective cohort design with high-quality data and low loss to follow-up. In addition, unlike previous studies, the present study provided data based on habitual dietary intakes in a population-based sample of participants, thereby increasing the generalisability of its results.

We observed inverse associations between total fibre intake and risk of incident CKD – results that show that high fibre intake, mainly from legumes and vegetables, may reduce the occurrence of CKD. This study provides important insight into the beneficial effects of the nutritional management for prevention of CKD and the desirable effects of dietary fibre intake in a Middle-Eastern population that is distinctly different from developed countries. Prospective studies in other populations are needed to confirm these associations and provide the evidence needed to translate these findings into clinical results.

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