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ORIGINAL RESEARCH

Food sources of dietary fibre and risk of total knee replacement related to severe osteoarthritis, the Singapore Chinese Health Study

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ABSTRACT

Objectives We aimed to evaluate the association between fibre intake and its food sources, and the risk of total knee replacement (TKR) due to severe knee osteoarthritis (KOA).

Methods We used data from the Singapore Chinese Health Study, a prospective cohort study that recruited 63 257 participants aged 45–74 years from 1993 to 1998. At baseline, we assessed diet using a validated 165-item semiquantitative food frequency questionnaire, together with body mass index (BMI) and lifestyle factors. Incident TKR cases were identified via record linkage with nationwide hospital discharge database through 2017.

Results There were 2816 cases of incident TKR due to severe KOA. The total fibre intake at baseline was not associated with the risk of TKR after adjustment for confounders. Among the food sources of fibre, higher intake of legumes was associated with a lower risk of TKR in a dose-dependent manner; compared with those having the lowest quartile intake, HR (95% CI) was 0.86 (0.76, 0.96) for those having the highest quartile intake (p for trend=0.004). This association was consistent after including BMI in the model and homogeneous across BMI categories. The consumption of other fibre sources, namely grain products, nuts and seeds, soy food, fruits and vegetables, was not associated with the risk of TKR.

Conclusion Intake of legumes, but not total fibre, was associated with a reduced risk of TKR. Further research is needed to replicate our findings and to evaluate possible biological mechanisms that could explain the effect of dietary legumes on pathogenesis or progression of KOA.

Key messages

What is already known about this subject?

- The association between diet and development of knee osteoarthritis (KOA) may be confounded or mediated by body mass index, the latter being a strong risk factor.
- Recent finding that dietary fibre may reduce the risk of KOA in Western populations needs to be replicated in leaner Asian populations.

What does this study add?

- In a relatively lean Asian population, total fibre intake was not associated with the risk of total knee replacement (TKR) for severe KOA.
- Among the food sources of fibre, higher intake of legumes was associated with a lower risk of TKR in a dose-dependent manner.

How might this impact on clinical practice or further developments?

- Further studies are needed to replicate this finding and also to study biological plausibility underlying the effect of dietary legumes on development of osteoarthritis.

INTRODUCTION

Knee osteoarthritis (KOA) is the most prevalent arthritis affecting 10% of the general population and up to 30% of elderly.[1 2] KOA causes knee pain, swelling and stiffness, leading to activity limitation, participation restriction, emotional disturbance and eventual loss of independence. It is one of the leading causes of disability worldwide.[3 4] Despite the huge impact on affected individuals and the society, there is a dearth of effective and safe pharmacological treatment,[5] and total knee replacement (TKR) is often the only option for end-stage severe KOA[6] Obesity is the major risk factor for KOA, associated with a 2-fold to over 10-fold increase in the risk of KOA.[7 8] Apart from the increase in biomechanical loading, obesity may also increase systemic inflammation, which is thought to play an important role in the pathoetiologies of KOA.[9] Dietary fibre is the edible parts of plants that are resistant to digestion in the small intestine and partially fermented in the colon. Dietary patterns rich in food sources of fibre, such as vegetables, legumes and fruits, have been associated with a lower risk of KOA and higher cartilage

thickness.[10 11] Clinical trials have demonstrated the beneficial effect of dietary fibre on weight loss and reducing systemic inflammation.[12 13] Thus, dietary fibre may have biological effects on the preservation of cartilage and reduction in the risk of KOA.

Recently, data from the Osteoarthritis Initiative (OAI) of 4796 participants and from the Framingham Offspring Osteoarthritis Study of 1268 persons in the USA showed that dietary fibre was associated with a lower risk of incident symptomatic KOA after adjustment for body mass index (BMI).[14] Specifically, in the OAI study, the mean BMI of those in the lowest quartile intake of fibre (29.4 kg/m^2) was 1.8 kg/m^2 higher than those in the highest quartile (27.6 kg/m2).[14] BMI is a well-established major risk factor of KOA,[7 8 15] and while overweight or obesity obviously increases biomechanical loading onto weight-bearing joints, chronic inflammation associated with obesity has also been hypothesised to be an additional mechanism for the biological plausibility linking increased BMI to the development of KOA.[16] As those with higher fibre intake had lower body weight in the OAI study, the authors later reported that after controlling for BMI, this inverse association between fibre and incident symptomatic KOA, though still reaching statistical significance, was attenuated. Hence, they concluded that this inverse association was partially mediated by BMI.

As diet is integrally related to BMI, the association between diet and KOA may indeed be confounded or mediated by BMI in observational studies conducted in populations with a wide BMI range. As BMI is such a strong risk factor of KOA, it is difficult to eliminate residual confounding effect attributed by adjusting for BMI with statistical modelling alone, and this is particularly problematic when there is a wide disparity in BMI among the ordinal categories of dietary intake.

In this study, we evaluated the association between fibre intake and the risk of TKR due to severe KOA in a relatively lean population nested in the Singapore Chinese Health Study. In a leaner population with a lower variability in BMI, differences in the mean BMI by dietary intake will be comparatively smaller, thereby reducing the confounding effect of BMI on the diet–KOA risk association. In addition, we evaluated the individual association between specific food sources of fibre in this population, namely grain products, legumes, nuts and seeds, soy food, fruits and vegetables, and the risk of TKR.

RESEARCH DESIGN AND METHODS

Study population

The Singapore Chinese Health Study is a prospective cohort of 63 257 Singaporean Chinese, aged 45–74 years during recruitment between 1993 and 1998 in Singapore. Participants were recruited from public housing estates, where 86% of Singapore's population lived during the time of recruitment. Study participants were restricted to two major dialect groups in Singapore, the Hokkien and Cantonese, who originated from the Fujian and Guangdong Provinces in Southern China, respectively.

Baseline exposure assessment

Information at baseline was collected by face-to-face interviews using structured questionnaires.[17] Information collected included age at recruitment, sex, education level, alcohol consumption, cigarette smoking, habitual physical activity, hours of sitting, sleeping hours and comorbidities. Habitual dietary intake of the past year was collected using a validated 165-item semi-quantitative Food Frequency Questionnaire (FFQ) that covered food in the following categories: rice, noodles, bread and cereals, meats (red meat comprising pork, beef and mutton; poultry comprising chicken and duck; and seafood comprising fish and shellfish), soy foods, legumes, nuts and seeds, fruits, vegetables, dairy products, beverages, condiments and preserved foods. For major food items, participants were asked to report their habitual intake with eight food-frequency categories (from never or hardly ever to two or more times a day) and three portion sizes that were illustrated using actual eating utensils and accompanying photographs. Daily nutrient and energy intakes were computed from the Singapore Food Composition Table that was developed specifically for this cohort.[17] The FFQ was subsequently validated in a subset of 810 participants by performing a repeat administration of the FFQ and comparing results from two 24-hour recalls with their results from the FFQ. The validation study using these two methods showed similar distributions, with the majority of the mean values of energy and nutrients obtained from the FFQ and from the 24-hour recalls falling within 10% of each other. For energy and nutrients, the correlation coefficients between these two methods ranged from 0.24 to 0.79,[17] which were comparable to those from previous validation studies in diverse populations.[18]

In this Chinese cohort in an Asian country, the main contributors of fibre were grain products (30.6%), fruits and related juices (27.6%), vegetables and related juices (21.0%), soy (3.4%), nuts and seeds (1.2%) and legumes (0.8%), which accounted for 84.6% of the total dietary fibre. The grain products included noodles and pasta, rice, bread and pancakes, breakfast cereals, biscuits and crackers. Compared with the percentage contribution from food sources of dietary fibre in three US-based studies,[14 19] the contributions from grains, nuts and legumes were considerably lower in this Singapore Chinese cohort. Instead, contributions from fruits, vegetables and other miscellaneous food sources were higher in our cohort. In the validation study, the mean daily intakes of total fibre assessed by 24-hour recalls and the FFQ were 12.2 g and 12.5 g, respectively. The correlation coefficients between FFQ-based and 24-hour recall-based intakes for dietary fibre (kcal-adjusted) were 0.72, 0.67, 0.66 and 0.65 among Cantonese men, Cantonese women, Hokkien men and Hokkien women, respectively. Furthermore, the intake of fibre in this cohort was comparable to

the intake level of the participants in the Third National Health and Nutrition Examination Survey data in the USA.[17]

BMI was calculated from weight and height, which were self-reported at baseline interview. A total of 10 349 cohort subjects (16%) did not report either weight or height. For participants with either missing weight or height, missing values were imputed using this equation: weight=y-intercept+gradient×height. The values for y-intercept and gradient were obtained from sex-specific weight–height regression lines drawn from all participants in the cohort with known weights and heights. If both weight and height were missing, the missing height was assigned as the sex-specific median and the missing weight was calculated from the equation.[20]

Identification of incident cases of severe KOA

We first identified TKR cases in this cohort and only included those that were first-occurrence as incident cases. We then used the diagnosis codes to include primary KOA and exclude cases with diagnosis codes that indicated or suggested that the TKR was done for other diseases or injuries of the knee joint. We identified participants who underwent TKR due to severe KOA via record linkage with the nationwide MediClaim System hospital discharge database.[21 22] Although it is used for subsequent financial claims, and hence its name, this database, regardless of the claim status, has captured surgical procedures and up to three diagnoses per patient for hospital admissions in all public and private hospitals in Singapore since 1990. The Singapore Ministry of Health conducts regular check on the MediClaims Database to ensure its completeness.[23] We identified cases of TKR in this cohort using the operation codes SB010K, SB012K and SB013K (unilateral right, unilateral left and bilateral TKR) for linkage up to December 2011 and operation codes SB716K and SB809K (TKR unilateral and TKR bilateral) for linkage from January 2012 to December 2017. We only included information for the first TKR in cases with more than one episode. Among the TKR cases, we further included only cases with a diagnosis of KOA using International Classification of Diseases (ICD)-9 code 715 and all subcategories for linkage up to December 2011, and ICD-10 code M17 and all subcategories for linkage from January 2012 to December 2017. We excluded all cases with any mention of diagnoses that included septic arthritis, osteomyelitis, villonodular synovitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other inflammatory arthritis, or a secondary cause of KOA, such as avascular or aseptic necrosis of joint, meniscus or ligament injuries, old tear or rupture or injuries, delay in development, other acquired deformities of knee and neuritis. Although we did not ask for the history of knee injury in our study, we excluded TKR cases with osteoarthritis secondary to other underlying conditions, including severe injury, if this was mentioned in the medical records, so that we could focus on TKR done for primary KOA. After excluding 128 participants who had undergone TKR prior to recruitment, we identified 2816 cases of incident TKR due to severe KOA in this cohort. Deaths in this cohort were ascertained through record linkage analysis with the nationwide Singapore Registry of Births and Deaths. As of 31 December 2011, only 47 (0.07%) subjects from this cohort were known to be lost to follow-up due to migration out of Singapore or for other reasons ascertained from our follow-up interviews in this cohort.

Statistical analysis

We calculated person-years for each participant from date of recruitment until TKR, time of death, lost-to-follow-up or 31 December 2017, whichever came first. We used the residual method to derive energy-adjusted intake of food and fibre for each participant.[24] We used Cox proportional hazards regression to estimate the HRs and 95% CIs for the association of quartiles of total fibre intake, as well as food sources of fibre, with the risk of TKR. Proportional hazards assumption was tested using Schoenfeld residuals test, and no violation was observed. The linear trend was tested by assigning participants the median value of the quartile they belonged to and treating this as a continuous variable in the model.[24 25] As total energy intake is often related to disease risk because of their associations with body size and physical activity, we further adjusted for total energy intake as a covariate in a multivariate nutrient density model to address the potential problem of confounding by total energy intake in the nutrient density approach.[24] In model 1, we adjusted for sex, age at interview, years of interview (1993–1995, 1996–1998), total energy intake (kcal/day), dialect (Hokkien, Cantonese) and educational level (none, primary, secondary and more). In model 2, we further adjusted for BMI (kg/m^2), total physical activity duration (hours/week), sleep duration (hours/day) and sitting duration (hours/day), smoking status (never, past, current) and a history of hypertension, diabetes, heart attack and stroke (yes/no). These covariates were chosen because they either are known risk factors of KOA in the literature[15] or have been reported to affect the risk of TKR in our cohort.[8 21 26 27] Finally, to investigate the association between individual food sources of fibre and the risk of TKR, we added a model 3 that included mutual adjustment for all the other food sources.

We tested for interaction between dietary variables and BMI or sex by adding their cross-product terms into regression models. For BMI, we used the cut-point of 23 kg/m^2 to divide participants into lean and heavy categories. This cut-point was recommended for the definition of cardiovascular risk for Asians by the WHO.[28] Finally, sensitivity analysis was conducted by excluding participants with imputed BMI (10 349 participants), those with an extreme energy intake of <600 or >3000 kcal/day for women (n=584) and <700 or>3700 kcal/day for men (n=476), and those with a follow-up time of less than 5 years (333 TKR cases and 3495 non-cases). We also conducted an analysis that only included cases with

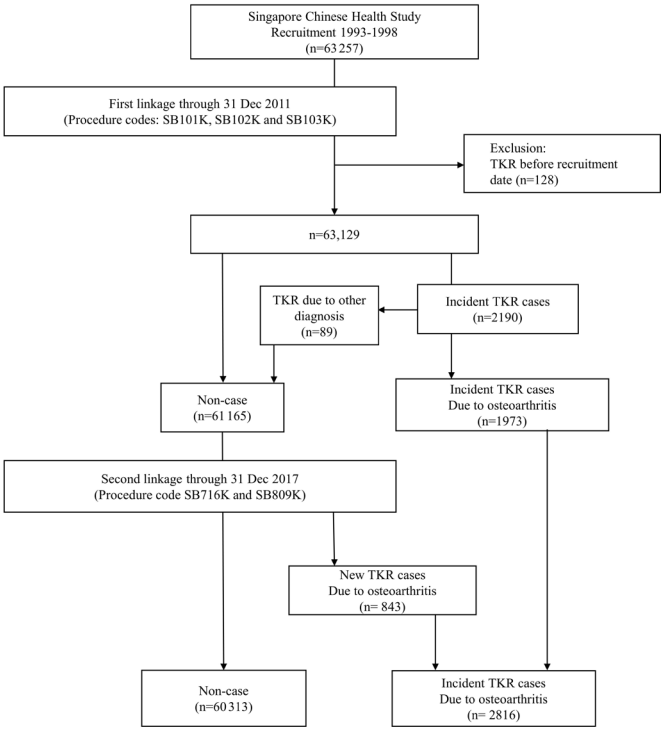

Figure 1 Flow diagram of Singapore Chinese Health Study, recruitment and case selection. TKR, total knee replacement.

TKR done 5–10 years after recruitment and the rest of the cohort participants with 5–10 years of follow-up. To further examine for the confounding effect of BMI and comorbidities separately, we conducted sensitivity analyses to compare the risk estimates from models with and without the inclusion of BMI or comorbidities. We also used the method described by Lange *et al*[29] in mediation analysis to estimate the direct effects in the association between dietary fibre/legumes and the risk of TKR, as well as the indirect effects mediated by BMI. We conducted all statistical analyses using SAS V.9.4 (SAS Institute). All reported p values were two-sided, and $p<0.05$ was considered statistically significant in the models for total fibre. To adjust for multiple testing, the Bonferroni-adjusted $p<0.008$ was considered statistically significant in models that studied the association between six fibre food sources and the risk of KOA.

RESULTS

After a median follow-up of 19.6 years, 2816 cases of incident TKR due to severe KOA were identified among 63 129 participants included in the analysis (figure 1). The mean (SD) age at TKR was 55.7 (6.9) years, and women accounted for 82% of TKR cases (table 1). Participants who had TKR had higher BMI (25.0 (3.0) kg/m^2) at baseline compared with the rest of the cohort (23.0 (3.2) kg/m^2). Participants with TKR had higher prevalence of hypertension and smoking, but lower prevalence of diabetes than those without TKR. Participants who had TKR participated in less physical activity, sitting for longer duration, but sleeping about the same amount of time compared with those without TKR.

Table 2 shows the comparison of the demographic, lifestyle and dietary factors by quartiles of total fibre intake. Compared with those with the lowest quartile,

Table 1 Baseline characteristics of cohort participants who had incident TKR due to severe KOA and who did not have TKR: the Singapore Chinese Health Study (1993–2017)

Characteristics	TKR cases	Participants without TKR
Number of participants	2816	60 313
Women, n (%)	2313 (82.1)	32 878 (54.5)
Age, years*	55.7 (6.9)	56.5 (8.1)
Body mass index, kg/m^2*	25.0 (3.5)	23.0 (3.2)
Dialect group, n (%)		
Hokkien	1578 (56.0)	32 335 (53.6)
Cantonese	1238 (44.0)	27 978 (46.4)
Secondary school or higher, n (%)	555 (19.7)	17 311 (28.7)
Ever smoker, n (%)	350 (12.4)	18 965 (31.4)
Hypertension, n (%)	831 (29.5)	14 153 (23.5)
Diabetes, n (%)	143 (5.1)	5528 (9.2)
Coronary heart disease, n (%)	84 (3.0)	2504 (4.2)
Stroke, n (%)	28 (1.0)	914 (1.5)
Physical activity, hours/week*	1.39 (3.8)	1.60 (4.2)
Sitting, hours/day*	5.87 (3.1)	6.54 (3.6)
Sleep, hours/day*	6.88 (1.1)	7.02 (1.1)

*Mean (SD).
KOA, knee osteoarthritis; TKR, total knee replacement.

Table 2 Baseline characteristics of cohort participants stratified by quartiles of total fibre intake: the Singapore Chinese Health Study (1993–2017)

	Quartile of total fibre intake			
Characteristics	**Q1**	**Q2**	**Q3**	**Q4**
Number of participants	15 796	15 775	15 785	15 773
Number of TKR cases	528	712	767	809
Women, n (%)	5923 (37.5)	9241 (58.6)	9892 (62.7)	10 135 (64.3)
Age, years*	56.6 (8.0)	56.8 (8.1)	56.5 (8.0)	56.0 (7.9)
Body mass index, kg/m*†	23.0 (3.3)	23.2 (3.3)	23.2 (3.2)	23.2 (3.3)
Dialect group, n (%)				
Hokkien	8812 (55.8)	8760 (55.5)	8314 (52.7)	8027 (50.9)
Cantonese	6984 (44.2)	7015 (44.5)	7471 (47.3)	7746 (49.1)
Secondary school or higher, n (%)	3610 (22.9)	3770 (23.9)	4605 (29.2)	5881 (37.3)
Ever smoker, n (%)	7634 (48.3)	4769 (30.2)	3805 (24.1)	3107 (19.7)
Hypertension, n (%)	3227 (20.4)	3799 (24.1)	3881 (24.6)	4077 (25.9)
Diabetes, n (%)	1150 (7.3)	1429 (9.1)	1511 (9.6)	1581 (10.0)
Coronary heart disease, n (%)	512 (3.2)	624 (4.0)	672 (4.3)	780 (5.0)
Stroke, n (%)	207 (1.3)	223 (1.4)	229 (1.5)	283 (1.8)
Physical activity, hour/week*	1.9±5.1	1.3±3.8	1.4±3.8	1.8±3.9
Sitting, hours/day*	6.6±3.8	6.3±3.5	6.4±3.5	6.7±3.6
Sleep, hours/day*	7.04±1.2	7.03±1.1	6.99±1.1	6.98±1.1
Total energy intake, kcal/day*‡	1,697.3±622.9	1,411.3±524.6	1,462.0±497.3	1,646.5±553.3
Total fibre, g/day*‡	9.1±4.0	10.1±3.9	12.8±3.7	18.8±5.8
Grain products, g/day*†‡	649.7±254.6	497.9±198.7	485.5±191.5	507.3±203.8
Legumes, g/day*‡	2.5±3.8	2.7±3.9	3.2±4.7	4.2±6.1
Nuts and seeds, g/day*‡	2.4±3.7	2.3±3.5	2.5±3.8	3.1±4.9
Soy food, g/day*‡	90.7±76.8	95.9±75.6	112.4±86.0	147.8±119.4
Fruits, g/day*‡	97.3±89.0	139.3±95.9	207.5±113.1	366.0±207.0
Vegetables, g/day*‡	86.7±46.6	95.2±47.8	112.1±54.3	148.4±80.8

Statistical testing based on the χ^2 test for categorical variables and analysis of variance for continuous variables; all p values <0.001 except for stroke (p=0.027).
*Mean±SD.
†Grain products included noodles and pasta, rice, bread and pancakes, breakfast cereals, biscuits and crackers.
‡Fibre food sources are shown in energy-adjusted units using the residual method.
Q, quartile; TKR, total knee replacement.

participants with the highest quartile of total fibre intake were more likely to be women, have higher education and abstain from smoking. The mean BMI was very similar among quartiles of total fibre intake, being 23.0 kg/m^2 for those in the lowest quartile and 23.2 kg/m^2 for those in the highest quartile. The characteristics of participants by various food sources of dietary fibre are summarised in online supplemental tables 1 and 2.

In model 1, which included adjustment for sociodemographic variables and total energy intake, the total fibre intake was associated with a stepwise increase in the risk of TKR (p for trend=0.003); compared with those in the lowest quartile, the HR (95% CI) for the risk of TKR for participants in the highest quartile of total fibre intake was 1.18 (1.05 to 1.32) (table 3). In model 2, after further adjustment for BMI and other lifestyle factors, the risk estimates in the higher quartiles of total fibre intake were attenuated, and the associations were no longer statistically significant in any of the higher quartiles or in the overall trend. The HRs (95% CIs) for second, third and fourth quartiles of total fibre intake were 1.06 (0.95 to 1.19), 1.09 (0.97 to 1.22) and 1.11 (0.99 to 1.24) compared with the lowest quartile.

In the evaluation of various food sources of fibre, we noted a stepwise reduction in the risk of TKR with increasing intake of legumes; compared with the lowest quartile of legume intake (referent), HR (95% CI) was 0.98 (0.86 to 1.09) for the second quartile, 0.95 (0.84 to 1.06) for the third quartile and 0.86 (0.76 to 0.96) for the highest quartile (p for trend=0.004) in model 3 (table 3). There was initially a stepwise reduction in the risk of TKR with increasing intake of nuts and seeds in model 1, but

Table 3 HRs (95% CIs) for risk of total knee replacement according to intake of fibre: the Singapore Chinese Health Study (1993–2017)

Quartiles of energy-adjusted food intake	Q1	Q2	Q3	Q4	P for trend*
Total fibre					
Median, g/day†	8.55	9.43	12.19	17.70	
Cases/ person-years	528/2 75 050	712/280 456	767/284 394	809/287 955	
Multivariate model 1	1.00	1.08 (0.96 to 1.21)	1.12 (1.00 to 1.26)	1.18 (1.05 to 1.32)	0.003
Multivariate model 2	1.00	1.06 (0.95 to 1.19)	1.09 (0.97 to 1.22)	1.11 (0.99 to 1.24)	0.088
Grain products‡					
Median, g/day†	374.45	420.21	507.04	793.28	
Cases/person-years	744/289 413	808/283 836	684/280 047	580/274 558	
Multivariate model 1	1.00	1.07 (0.96 to 1.18)	0.93 (0.83 to 1.03)	0.91 (0.82 to 1.02)	0.024
Multivariate model 2	1.00	1.09 (0.98 to 1.21)	0.96 (0.86 to 1.06)	0.95 (0.85 to 1.06)	0.110
Multivariate model 3	1.00	1.09 (0.98 to 1.21)	0.95 (0.85 to 1.06)	0.94 (0.82 to 1.06)	0.120
Legumes					
Median, g/day†	0.11	0.43	2.11	7.01	
Cases/ person-years	638/ 80 170	754/278 001	756/280 407	668/289 275	
Multivariate model 1	1.00	0.97 (0.87 to 1.09)	0.95 (0.84 to 1.06)	0.84 (0.76 to 0.94)	<0.001
Multivariate model 2	1.00	0.98 (0.87 to 1.09)	0.94 (0.84 to 1.06)	0.86 (0.77 to 0.96)	0.004
Multivariate model 3	1.00	0.98 (0.87 to 1.09)	0.95 (0.84 to 1.06)	0.86 (0.76 to 0.96)	0.004
Nuts and seeds					
Median, g/day†	0.51	0.65	1.38	5.14	
Cases/ person-years	687/284 256	689/280 907	773/278 760	667/282 854	
Multivariate model 1	1.00	0.84 (0.75 to 0.94)	0.91 (0.81 to 1.02)	0.87 (0.78 to 0.97)	0.033
Multivariate model 2	1.00	0.83 (0.74 to 0.92)	0.90 (0.08 to 1.01)	0.88 (0.79 to 0.98)	0.175
Multivariate model 3	1.00	0.83 (0.74 to 0.93)	0.92 (0.82 to 1.03)	0.89 (0.79 to 1.00)	0.246
Soy food					
Median, g/day†	43.60	61.05	98.94	197.60	
Cases/ personyears	568/276 720	725/2 79 030	760/283 782	763/288 322	
Multivariate model 1	1.00	1.06 (0.94 to 1.19)	1.05 (0.93 to 1.17)	1.04 (0.93 to 1.16)	0.742
Multivariate model 2	1.00	1.09 (0.97 to 1.22)	1.05 (0.94 to 1.17)	1.01 (0.91 to 1.13)	0.717
Multivariate model 3	1.00	1.10 (0.98 to 1.23)	1.05 (0.94 to 1.18)	1.00 (0.89 to 1.12)	0.494
Fruits					
Median, g/day†	57.47	114.79	194.87	369.31	
Cases/ person-years	579/270 253	677/278 859	762/286 424	798/292 317	
Multivariate model 1	1.00	1.01 (0.90 to 1.13)	1.14 (1.02 to 1.27)	1.21 (1.08 to 1.35)	<0.001
Multivariate model 2	1.00	0.99 (0.88 to 1.10)	1.08 (0.96 to 1.20)	1.10 (0.98 to 1.23)	0.037
Multivariate model 3	1.00	0.99 (0.88 to 1.11)	1.07 (0.96 to 1.20)	1.08 (0.96 to 1.21)	0.134
Vegetables					
Median, g/day†	59.58	76.87	106.49	170.56	
Cases/person-years	544/271 912	678/280 181	761/285 676	833/290 085	
Multivariate model 1	1.00	1.02 (0.90 to 1.14)	1.06 (0.95 to 1.19)	1.13 (1.01 to 1.26)	0.011
Multivariate model 2	1.00	1.01 (0.90 to 1.13)	1.01 (0.91 to 1.14)	1.05 (0.94 to 1.17)	0.332
Multivariate model 3	1.00	1.01 (0.90 to 1.13)	1.00 (0.89 to 1.12)	1.02 (0.91 to 1.15)	0.738

Multivariate model 1: adjusted for age at interview, sex, year of interview, total energy intake, dialect and education level.
Multivariate model 2: model 1 plus body mass index, sitting duration, sleep, physical activity, smoking, history of hypertension, diabetes, coronary artery disease and stroke.
Multivariate model 3: model 2 plus grain products, legumes, nuts and seeds, soy food, fruits and vegetables (except the exposure of interest).
*Linear trend was tested by assigning to participants the median value of the quartile they belonged to and treating this as a continuous variable.
†Fibre food sources are shown in energy-adjusted units using the residual method.
‡The grain products included noodles and pasta, rice, bread and pancakes, breakfast cereals, biscuits and crackers.
Q, quartile.

the association was no longer statistically significant after adjustment with other confounders and food sources of fibre. The other sources of fibre, namely grain products, soy food, fruits and vegetables, were not significantly associated with the risk of TKR.

In the analysis stratified by BMI or sex, the intake of total fibre was not associated with the risk of TKR in any stratum, and the risk estimates were not dissimilar by sex or BMI categories (p for interaction ≥0.32). Conversely, the inverse association between the intake of legumes and the risk of TKR remained statistically significant in women and also in those with a BMI ≥23 kg/m^2. Although the inverse associations in men and in those with BMI <23 kg/m^2 were not statistically significant, likely due to small case numbers, the differences in risk estimates between men and women, or between the two BMI categories, were not statistically significant (p for interaction ≥0.53) (online supplemental table 3).

In sensitivity analyses that excluded participants with imputed BMI (online supplemental table 4), those with extreme energy intake (online supplemental table 5) and those with less than 5 years of follow-up (online supplemental table 6), we also did an analysis including only participants with 5–10 years of follow-up (online supplemental table 7); the results remained materially unchanged compared with the findings based on the whole cohort.

In the sensitivity analysis comparing models with and without adjustment for BMI, the risk estimates in these two models were essentially unchanged, indicating that BMI did not have a significant mediation effect on the fibre–TKR association. Specifically, comparing extreme quartiles, the HR (95% CI) for the association between total fibre and risk of TKR was 1.11 (0.99 to 1.24) in both models, whereas the HR (95% CI) for the association between legumes and risk of TKR was 0.82 (0.73 to 0.92) in the model without BMI and 0.86 (0.76 to 0.96) in the model that adjusted for BMI. Predictably, in the mediation analysis, there was no significant indirect effect mediated by BMI for the association between intake of fibre or legumes and the risk of TKR (data not shown). Finally, we repeated the analysis using models with and without comorbidities (hypertension, diabetes, heart attack and stroke), and the risk estimates from these two models were materially the same (online supplemental table 8).

DISCUSSION

In this prospective cohort of a relatively lean population, we did not observe any association between total dietary fibre and risk of TKR due to severe KOA after adjusting for BMI and other confounders. However, among the food source of fibre, higher intake of legumes was associated with a lower risk of TKR in a dose-dependent manner. These results remained robust to different sensitivity analyses.

The strength of our study is that the BMI levels across quartiles of fibre intake were quite homogeneous among the relatively leaner participants in this prospective cohort study in Singapore. Hence, expectantly, the associations between total fibre or food intake and risk of TKR were essentially unchanged in the models with and without BMI adjustment, thus indicating that any mediation or confounding effect from BMI was minimal. Another strength of our study is its prospective population-based cohort design with a large sample size over a long follow-up time. TKR cases were identified via linkage with a comprehensive nationwide database that had essentially captured a high number of incident TKR cases for severe KOA in this cohort.

To our best knowledge, this is the first study to specifically report an inverse relationship between legume intake and risk of TKR due to severe KOA. The association remained the same after adjusting for BMI and other food sources of fibre. Although Dai *et al* also reported a dose-dependent inverse association between nut and legumes and incident symptomatic and incident radiographic KOA from the Framingham Offspring cohort,[14] nuts and legumes were studied as a single item. In this study, we studied nuts and legumes as separate food items, and although we observed an inverse association of nuts and seeds with the risk of TKR in the preliminary multivariable model, this association was not statistically significant in the fully adjusted model. On the contrary, the inverse association between legumes and the risk of TKR was robust and remained statistically significant in the fully adjusted model.

Legumes are edible seeds or pods of the plant family Fabaceae (or Leguminosae). Examples of common legumes are beans, peas, chickpeas, lentils and lupin beans. Legumes are a rich source of saponin, phenolic compounds, phytochemicals, vitamins and minerals that have antioxidant properties[30–32] and anti-inflammatory effects that could possibly reduce low-grade systemic inflammation[33] and activate mitochondrial oxidation.[34] The generation of reactive oxygen species (ROS) and lipid peroxidation products has been an implication in the pathogenesis of the arthritic joint.[35] Hence, it is possible that phytochemicals in legumes could reduce ROS production and salvage mitochondria dysfunction[36 37] to slow down progression of osteoarthritis. However, further research is dreadfully needed to evaluate these hypotheses.

We acknowledge a few limitations in the study. First, we studied TKR as a surrogate for severe KOA, and although it represented a relevant clinical state of KOA when surgical intervention is indicated due to symptomatic, functional and structural severity in addition to pain,[38] we could have missed severe cases of KOA that did not undergo TKR. Second, dietary intakes, BMI and comorbidities were self-reported, and measurement errors may likely lead to non-differential misclassification and an underestimation of the observed association. Nonetheless, self-reported BMI has generally been reported to be

valid for epidemiological studies across different populations.[39] Third, diet and BMI were only assessed once at baseline; therefore, we lacked information about potential changes in these exposures that could have occurred during the follow-up period. Although FFQs tend to overestimate and underestimate the absolute intake of various nutrients and foods, for most nutrient and foods, the ability of the FFQ to rank subjects according to their dietary intake has been shown to be acceptable to good, and this is the basis of all epidemiological studies that have used FFQ to study diet–disease relationships.[40] There was a 64-fold difference in the median intake of legumes between the lowest and the highest quartile in the Singapore Chinese Health Study cohort that was sufficient to demonstrate the inverse legume–TKR association in a dose-dependent manner. Finally, residual confounding cannot be completely ruled out in our study due to the limitation of the observational design.

In conclusion, in this prospective cohort study, we provided novel epidemiology evidence that although total fibre intake was not associated with severe KOA, increased intake of legumes could possibly reduce the risk of severe KOA in a dose-dependent manner. Further research is needed to replicate our findings, and the biological mechanisms underlying the effect of dietary legumes on pathogenesis or progression of osteoarthritis warrant further investigations.

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