ARD Online First, published on May 23, 2017 as 10.1136/annrheumdis-2016-210810

EXTENDED REPORT

Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts

Zhaoli Dai,[1] Jingbo Niu,[1] Yuqing Zhang,[1] Paul Jacques,[2] David T Felson[1,3]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-210810)

[1]Jean Mayer USDA Human Nutrition Research Center on Aging and Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA
[2]Jean Mayer USDA Human Nutrition Research Center on Aging and Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA
[3]University of Manchester and Central Manchester Foundation Trust, Manchester, UK

Correspondence to
Dr Zhaoli Dai, Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, 650 Albany St, Boston, MA 02118, USA; joyzdai@bu.edu

Received 11 November 2016
Revised 8 February 2017
Accepted 20 March 2017

ABSTRACT

Objectives Dietary fibre reduces body weight and inflammation both of which are linked with knee osteoarthritis (OA). We examined the association between fibre intake and risk of knee OA.

Methods We used data from the Osteoarthritis Initiative (OAI) of 4796 participants and Framingham Offspring Osteoarthritis Study (Framingham) of 1268 persons. Dietary intake of fibre was estimated at baseline, and incident radiographic OA (ROA) and symptomatic OA (SxOA) were followed annually until 48 months in OAI and assessed 9 years later in Framingham. Knee pain worsening was also examined in OAI. Generalised estimating equations were applied in multivariable regression models.

Results In OAI, we identified 861 knees with SxOA, 152 knees with ROA and 1964 knees with pain worsening among 4051 subjects with valid dietary intake (baseline mean age: 61.2 years; mean body mass index (BMI): 28.6). In Framingham, 143 knees with SxOA and 175 knees with ROA among 971 such subjects (baseline mean age: 53.9 years; mean BMI: 27.0) were identified. In both cohorts, dietary total fibre was inversely associated with risk of SxOA (p trend <0.03) with significantly lower risk at the highest versus lowest quartile (OR (95% CI): 0.70 (0.52, 0.94) for OAI and 0.39 (0.17, 0.88) for Framingham). Furthermore, dietary total and cereal fibre were significantly inversely associated with knee pain worsening in OAI (p trend <0.02). No apparent association was found with ROA.

Conclusions Findings from two longitudinal studies consistently showed that higher total fibre intake was related to a lower risk of SxOA, while the relation to ROA was unclear.

Dietary fibres are carbohydrates, primarily from plant-based foods such as cereal grains, fruits and vegetables, and nuts and legumes. Fibre is not digestible or absorbable in the small intestine but is partially or fully fermented in the colon.[1] Epidemiological studies suggest that fibre is associated with lower risks of cardiovascular diseases,[2] type 2 diabetes[3 4] and mortality.[5] Furthermore, clinical trials have shown the beneficial effect of dietary fibre in reducing body weight,[6–8] blood pressure[9] and circulating C reactive protein (CRP),[10] and in improving glycaemic control.[11 12] Such protective effects of dietary fibre are likely attributed to its intrinsic property of entrapping sugars and fats to promote satiety and reduce calorie intake,[13] reduce serum cholesterol[2] and improve glycaemic control[12] as well as to its prebiotic function through fermentation in the gut to stimulate desirable microbiome to lower infection and inflammation.[14]

As the most common joint disorder, osteoarthritis (OA) is highly prevalent among adults aged ≥60 years.[15 16] Largely due to pain and limited physical function, OA is a leading cause of disability and impairment of quality of life;[17] however, no effective structure-modifying treatment is available to date. Like metabolic diseases, there is a strong link between obesity, inflammation and knee OA, where obesity both increases loading in weight-bearing joints[18–21] and proinflammatory cytokines and adipokines;[22] and increased inflammation and synovitis[23 24] have been shown to be associated with joint pain.

In light of the relation of dietary fibre to body weight and inflammation, we initially examined the association between fibre intake and knee OA in the Osteoarthritis Initiative (OAI) and, as shown below, found a protective association of fibre intake with symptomatic OA (SxOA) and knee pain worsening. We sought confirmation using a second cohort in hope of replicating these results and better addressing dietary confounders in the Framingham Offspring Study, which was designed to more comprehensively assess diet. The objective of this study was to examine the association between dietary fibre and knee OA phenotypes including symptomatic knee OA (SxOA), radiographic knee OA (ROA) and knee pain worsening in two US cohorts.

METHODS

Study population

Osteoarthritis Initiative (OAI)

OAI is a multi-centre, longitudinal prospective cohort of 4796 US men (41.5%) and women aged 45–79 years with or at risk of knee OA recruited from 2004 to 2006 to investigate OA risk factors. Details of the study protocol can be found elsewhere.[25] After enrolment, participants were followed for OA assessment annually until 48 months.

Framingham Offspring cohort (Framingham)

Participants from the Framingham Offspring cohort, which was assembled in 1971 consisting of adult children of the Original Framingham Study and spouses of the offspring participants.[26] The goal of the Offspring OA study was to investigate inheritance of OA among study participants who represent a community-based population unselected for OA or knee pain.[27] During a callback visit after the Offspring exam 5 (1993–1994), 1268

To cite: Dai Z, Niu J, Zhang Y, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2016-210810

eligible subjects (men: 43.9%, mean age 53.2 years) as baseline of the OA study, weight-bearing radiographs of both knees and surveys about knee pain were obtained. The same assessments were performed among the same subjects after an average of 9.5 years at exam 7 (2002–2005).[28]

In both studies, we excluded those who had rheumatoid arthritis or other forms of inflammatory arthritis. Institutional Review Board approval was obtained from all OAI study sites in OAI and from Boston University for the Framingham Study.

Baseline assessment

In both studies, information was collected including demographics, history of knee injury and surgery (including total knee replacement), medication use, tobacco and alcohol use, physical activity assessed by the Physical Activity in the Elderly Scale (PASE) and habitual diet recorded using the validated food frequency questionnaires (FFQs). Based on the major food sources of fibre, total dietary fibre was derived as sum of fibre from cereal grain, fruits and vegetables, and nuts and legumes. We only included participants with valid fibre (no missing values for total dietary fibre) and calorie intake (≥500 kcal and <4200 kcal for men and <4000 kcal for women). Anthropometric parameters including body weight, height and abdominal (OAI)/waist (Framingham) circumference were measured.[25 26] Knee symptom assessment using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was available at all exams in OAI but was only assessed in exam 7 in Framingham.

Baseline dietary fibre estimation

Osteoarthritis Initiative

Dietary fibre intake was estimated using the Block Brief 2000 FFQ of 60 food items.[29 30] For each food item, frequency consumption was surveyed according to nine predetermined categories ranging from never to everyday with illustrations of standard portion sizes. Estimation of nutrient intake was calculated based on the nutrient composition values developed in the Second National Health and Nutrition Examination Survey.[29]

Framingham Study

Habitual dietary intake was recorded at baseline (exam 5) and 4 years later at exam 6 (1998–2001) via the Harvard validated semi-quantitative FFQ.[31] The FFQ listed 126 items of foods in standard serving sizes and nine frequency categories ranging from 'never or less than once per month' to '6+ per day.' Participants were allowed to add up to three additional foods, types of breakfast cereal and cooking oil that are not listed in the FFQ. Nutrient values were estimated and primarily relied on the US Department of Agriculture food composition database and supplemented by other published data.[31] Additionally, glycaemic load for each food was calculated to estimate glucose effect. The Dietary Guidelines Adherence Index (DGAI-2010) score was applied to the baseline FFQ to determine diet quality according to the Dietary Guidelines for Americans 2010.[32] Detail of the DGAI-2010 has been described[33] and scores range from 0 (lowest adherence) to 100 (highest adherence). Because dietary fibre is one of the 24 components in the DGAI-2010, the modified DGAI-2010 used in this study excluded fibre.

Assessment of knee OA outcomes

Osteoarthritis Initiative

At each exam, subjects were asked about knee pain using the following question: 'During the past 30 days, have you had pain, aching, or stiffness in your right/left knee on most days?' and a positive response was used to define a painful knee. Knee pain was also assessed using the WOMAC pain subscale ranging from 0 (no pain) to 20 (most pain) points. All subjects obtained a fixed flexion posterior–anterior radiograph, which was read centrally for Kellgren and Lawrence (KL) grade. OA outcomes of interest included incident (1) ROA if a knee developed a KL grade ≥2 at follow-up, (2) SxOA, new onset of a combination of a painful knee and ROA and (3) knee pain worsening, if WOMAC pain score difference of a knee between baseline and each annual exam ≥14% of the base score defined in the published estimates for the minimal clinical important difference in WOMAC.[34] Additional detail for knee pain worsening can be found in online supplementary file text 1. For incident SxOA or ROA, we excluded those with prevalence at baseline for the corresponding outcome.

Framingham Study

After subjects had completed the baseline and follow-up exams, radiographs at both exams were read independently by two study readers among a sample of 1268 eligible subjects.[28] The same definitions as OAI were applied to Framingham to define incident ROA and SxOA after excluding prevalent knees with these conditions.

Statistical analysis

For both studies, we calculated the residual of dietary fibre by regressing fibre intake on total calories within each cohort.[35] Quartile cut-offs for dietary fibre were created based on the calculated residuals[35] within men and women separately to account for sex differences in dietary intake. The rationale to use the residual method is described in online supplementary file text 2. Dietary intake was estimated by a semi-quantitative FFQ, which is suitable to rank individuals with regard to their intake.[36] We examined the relation of dietary fibre to the risk of knee OA by comparing a higher quartile (Q2, Q3 and Q4) to the lowest quartile (Q1: reference category), using generalised estimating equations to account for correlation between two knees for each participant[37] in both studies and for the analysis of pain worsening to account for repeated WOMAC pain measures annually in OAI.

In the base model (model 1), we adjusted for age (years), sex (men vs women), race (white vs non-white in OAI) and total energy intake (kcal); model 2 was further adjusted for education attainment (below vs college or above), annual household income (<US$50 000 vs ≥US$50 000), smoking status (never, former and current smokers), physical activity (PASE, continuous) and other dietary factors including dietary vitamin C (mg/day), K (μg/day), polyunsaturated fat (g/day), saturated fats, which have been shown to relate to OA in previous studies.[38–42] Non-steroidal anti-inflammatory drugs use (yes vs no) was further adjusted for pain worsening in OAI. In Framingham, we also controlled for glycaemic load, which has been found to be inversely related to the Mediterranean diet in model 2.[43 44] In a separate model (model 3), we adjusted for the same covariates in model 2 except replacing the dietary variables with DGAI-2010 to account for diet quality. In addition, we further adjusted for baseline body mass index (BMI) (kg/m^2) in addition to the full model in both studies. Linear trends were tested using the median value of each quartile of dietary fibre as a continuous variable in the model. Because there was no significant difference between genders in the fibre–OA associations, we combined men and women for the descriptive characteristics and regression analysis.

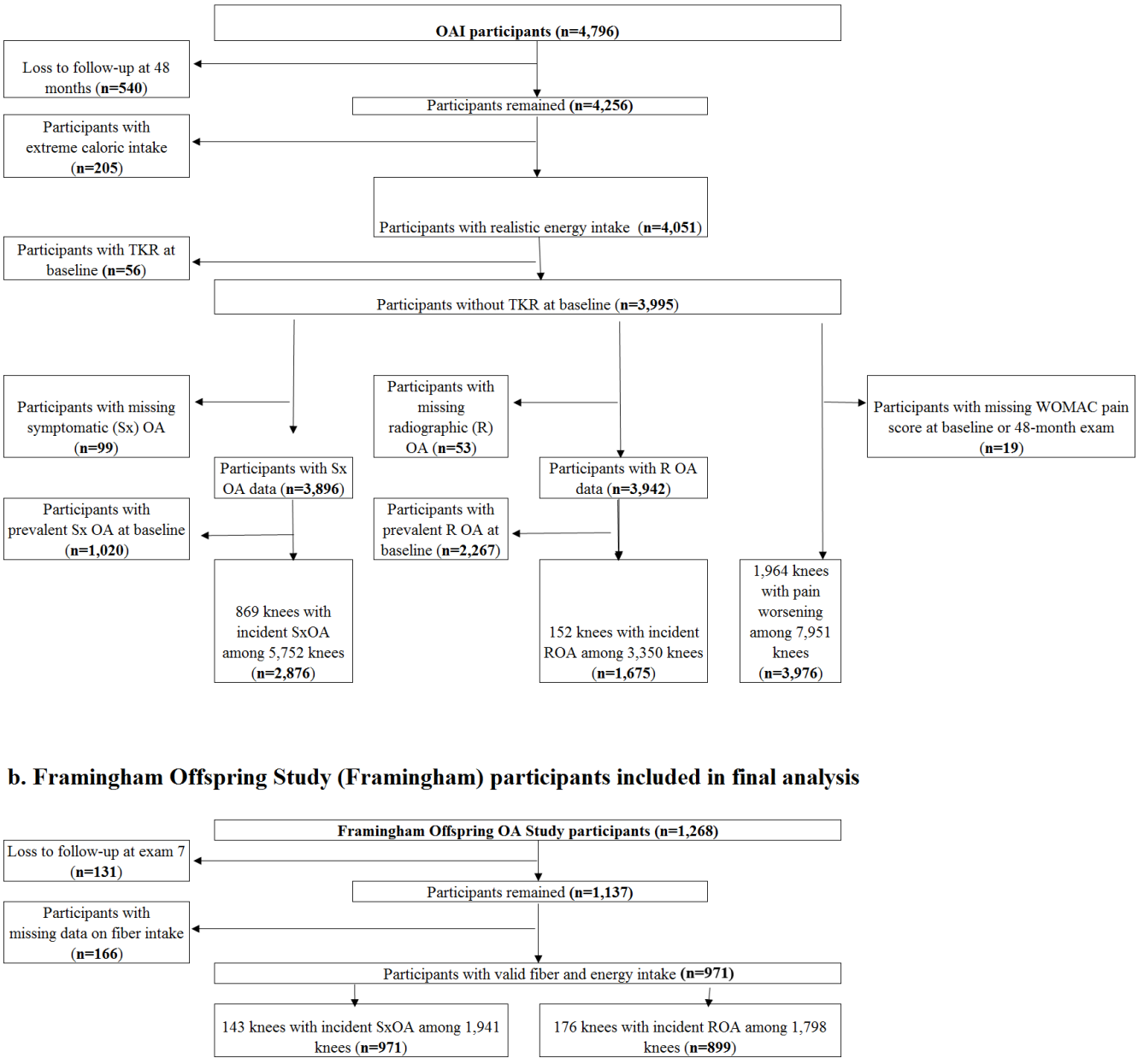

Figure 1 Eligible participants in (A) OAI and (B) Framingham Offspring Study. OAI, Osteoarthritis Initiative; ROA, radiographic OA; SOA, symptomatic OA; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Consistency of our results was tested by stratifying socioeconomic status and replacing BMI with abdominal/waist circumference (cm) as a covariate in the full model. All statistical analysis was conducted using SAS V.9.3. A p value <0.05 (two sided) was considered statistically significant.

RESULTS

At the end of the study course, 540 (11%) among 4796 participants in OAI and 131 persons (11.9%) among 1268 persons in Framingham were lost to follow-up. Figure 1 describes the eligible participants and knees included in the final analyses.

We summarised baseline characteristics across quartiles of total fibre intake by each cohort study (table 1). In both studies, those who consumed more fibre were older, had lower BMI and were more educated. They were less likely to have knee pain symptoms and consumed higher amount of vitamins C and K and less dietary saturated fats.

The associations between dietary fibre and phenotypes of knee OA in OAI are presented in table 2. For total dietary fibre, compared with the lowest quartile (Q1), there was a significant dose-dependent inverse relationship for the risks of SxOA and knee worsening (p trend ≤0.005): at the highest quartile (Q4), risks of SxOA and knee pain worsening were lowered significantly by 30% (OR (95% CI): 0.70 (0.52 to 0.94)) and 19% (OR (95% CI): 0.81 (0.71 to 0.94)), respectively. Although non-statistically significant, similar results for fibre from cereal grains and from fruits and vegetables were observed. Significant inverse relationship was also found between cereal fibre and pain worsening (p trend <0.02) with a 14% lower risk in those at Q4 relative to Q1. No association was found for

Table 1 Participants' baseline characteristics according to quartile intake of total fibre in OAI and Framingham OA Study

	OAI (n=4051)				Framingham (n=971)			
	Q1 (n=1013)	Q2 (n=1012)	Q3 (n=1013)	Q4 (n=1013)	Q1 (n=242)	Q2 (n=244)	Q3 (n=242)	Q4 (n=243)
Age at baseline (years)*	59.8 (9.0)	60.9 (9.1)	62.0 (9.1)	62.8 (9.1)	51.5 (7.8)	53.4 (7.6)	54.5 (8.1)	56.0 (8.0)
Sex (men) n (%)	422 (41.7)	421 (41.6)	422 (41.7)	422 (41.7)	109 (45.1)	112 (45.9)	110 (45.3)	111 (45.7)
Race (Caucasian), n (%)	807 (79.7)	848 (83.8)	836 (82.5)	819 (80.8)	-	-	-	-
BMI (kg/m^2)	29.4 (4.9)	28.7 (4.7)	28.6 (4.8)	27.6 (4.4)	27.2 (5.0)	27.1 (4.5)	27.0 (4.1)	26.6 (4.6)
Tobacco use, n (%)								
Never	803 (79.3)	803 (79.3)	787 (77.7)	810 (80.0)	185 (76.4)	209 (85.8)	221 (91.3)	226 (93.0)
Current smokers	210 (21.7)	209 (21.7)	226 (23.3)	203 (20.0)	210 (21.7)	209 (21.7)	226 (23.3)	203 (20.0)
Education, n (%)								
< College level	463 (45.7)	404 (39.9)	360 (35.5)	337 (33.3)	175 (72.2)	168 (68.9)	159 (65.6)	150 (61.9)
College level or above	550 (54.3)	608 (60.1)	653 (64.5)	676 (66.7)	67 (27.8)	76 (31.1)	83 (34.4)	93 (38.1)
PASE	155.6 (79.8)	161.2 (82.2)	164.6 (80.7)	168.0 (84.4)	36.0 (4.8)	35.3 (4.2)	36.0 (5.6)	35.6 (4.4)
Prevalence of ROA, n (%)	116 (11.5)	113 (11.2)	110 (10.9)	104 (10.3)	14 (5.6)	21 (8.5)	14 (5.8)	17 (6.9)
Pain, aching or stiffness† n (%)	115 (11.4)	105 (10.4)	99 (9.8)	99 (9.8)	45 (18.7)	38 (15.7)	36 (14.9)	32 (13.0)
Total energy, kcal/day	1407.0 (566.8)	1443.7 (553.3)	1399.4 (536.3)	1363.6 (507.3)	2041.4 (632.4)	1698.5 (557.8)	1818.8 (586.0)	1867.8 (575.9)
Total dietary fibre, g/day	9.1 (3.7)	13.0 (4.3)	16.0 (5.2)	21.9 (8.0)	14.1 (5.4)	15.1 (5.0)	19.2 (5.3)	26.6 (8.2)
Cereal fibre	4.2 (2.2)	5.3 (2.6)	6.3 (3.2)	7.8 (4.7)	5.0 (2.6)	5.1 (2.5)	6.3 (3.0)	8.2 (4.2)
Fruit and vegetable fibre	4.2 (2.0)	6.5 (2.7)	8.2 (3.3)	11.5 (5.6)	4.9 (2.3)	6.0 (2.6)	8.1 (2.8)	12.7 (5.3)
Nut and legume fibre	1.0 (0.9)	1.6 (1.1)	2.0 (1.6)	2.9 (2.6)	1.8 (1.3)	2.0 (1.4)	2.5 (1.6)	3.4 (2.3)
Median glycaemic load (ref: bread), g/day	-	-	-	-	170.4	147.0	170.0	199.2
Saturated fats, g/day	21.5 (10.2)	20.2 (9.4)	18.0 (8.6)	14.8 (7.4)	26.6 (10.8)	21.5 (9.3)	21.5 (9.4)	18.2 (8.4)
Polyunsaturated fatty acids, g/day	11.0 (5.6)	11.5 (0.7)	10.8 (5.3)	10.0 (5.2)	14.5 (6.6)	12.8 (5.6)	13.8 (5.6)	13.1 (5.3)
Vitamin C, mg/day	87.9 (57.6)	106.6 (56.0)	116.4 (60.7)	137.7 (68.4)	201.0 (210.2)	208.0 (245.4)	221.4 (228.4)	293.6 (275.3)
Vitamin K, µg/day	100.2 (68.3)	148.3 (100.5)	185.0 (119.9)	286.0 (222.5)	120.1 (62.7)	132.9 (69.1)	165.1 (83.0)	230.2 (134.2)
DGAI-2010 score	-	-	-	-	50.1 (8.8)	54.9 (8.5)	60.7 (7.6)	66.7 (8.0)

*All such values are mean±SD.
†Pain more than half day for most days in past month.
‡KL, Kellgren-Lawrence grading scale.
DGAI-2010, Dietary Guidelines Adherence Index; PASE, Physical Activity in the Elderly Scale; OAI, Osteoarthritis Initiative; OA, osteoarthritis; ROA, radiographic OA.

Table 2 OR (95% CI) to estimate total effect of dietary fibre on knee incident SxOA (n=2876 persons), incident ROA (n=1675 persons) and knee pain worsening (n=3976 persons) for all eligible participants in OAI

Fibres in quartile	Q1	Q2	Q3	Q4	p Trend*
Total fibre (g/day)					
Median	8.6	12.5	15.1	20.6	
SxOA knees†	208/1346	256/1440	206/1472	199/1494	
Model 1‡	1.00	1.14 (0.90 to 1.45)	0.83 (0.65 to 1.07)	0.78 (0.61 to 1.00)	<0.02
Model 2§	1.00	1.12 (0.87 to 1.42)	0.79 (0.61 to 1.03)	0.70 (0.52 to 0.94)	<0.002
Model 3¶	1.00	1.14 (0.89 to 1.46)	0.81 (0.62 to 1.06)	0.80 (0.60 to 1.07)	0.03
ROA knees	29/796	44/828	44/864	35/862	
Model 1	1.00	1.51 (0.85 to 2.68)	1.44 (0.83 to 2.48)	1.11 (0.61 to 2.02)	0.93
Model 2	1.00	1.41 (0.78 to 2.55)	1.24 (0.69 to 2.24)	0.83 (0.40 to 1.73)	0.46
Model 3	1.00	1.44 (0.80 to 2.60)	1.25 (0.70 to 2.23)	0.91 (0.44 to 1.87)	0.64
Pain worsening knees	526/1970	512/1988	514/1994	412/1999	
Model 1	1.00	0.95 (0.85 to 1.07)	0.92 (0.81 to 1.03)	0.77 (0.68 to 0.87)	<0.001
Model 2	1.00	0.96 (0.85 to 1.08)	0.94 (0.83 to 1.06)	0.81 (0.71 to 0.94)	0.005
Model 3	1.00	0.98 (0.87 to 1.10)	0.96 (0.84 to 1.08)	0.85 (0.74 to 0.99)	0.03
Cereal fibre (g/day)					
Median	2.8	4.5	6.0	8.4	
SxOA knees	211/1348	226/1420	215/1450	217/1534	
Model 1	1.00	1.03 (0.82 to 1.31)	0.96 (0.76 to 1.22)	0.88 (0.69 to 1.12)	0.26
Model 2	1.00	1.03 (0.81 to 1.32)	0.97 (0.76 to 1.24)	0.85 (0.66 to 1.09)	0.18
Model 3	1.00	1.05 (0.83 to 1.34)	1.00 (0.79 to 1.28)	0.96 (0.75 to 1.24)	0.79
ROA knees	38/774	36/838	42/850	36/888	
Model 1	1.00	0.89 (0.53 to 1.50)	1.02 (0.61 to 1.73)	0.81 (0.48 to 1.36)	0.38
Model 2	1.00	0.92 (0.55 to 1.56)	1.09 (0.65 to 1.84)	0.78 (0.46 to 1.35)	0.34
Model 3	1.00	0.91 (0.54 to 1.53)	1.07 (0.64 to 1.80)	0.81 (0.47 to 1.38)	0.40
Pain worsening knees	554/1975	474/1974	480/1998	456/2004	
Model 1	1.00	0.91 (0.81 to 1.03)	0.92 (0.82 to 1.04)	0.83 (0.73 to 0.93)	<0.002
Model 2	1.00	0.92 (0.82 to 1.04)	0.94 (0.83 to 1.06)	0.86 (0.76 to 0.97)	<0.02
Model 3	1.00	0.93 (0.83 to 1.04)	0.95 (0.84 to 1.07)	0.89 (0.79 to 1.01)	0.07
Fruit and vegetable fibre (g/day)					
Median	3.4	5.8	7.9	11.5	
SxOA knees	214/1374	238/1504	205/1434	212/1440	
Model 1	1.00	0.99 (0.78 to 1.25)	0.86 (0.67 to 1.10)	0.87 (0.68 to 1.11)	0.19
Model 2	1.00	1.00 (0.78 to 1.27)	0.86 (0.66 to 1.13)	0.85 (0.61 to 1.17)	0.26
Model 3	1.00	1.00 (0.78 to 1.28)	0.89 (0.68 to 1.17)	0.83 (0.60 to 1.15)	0.24
ROA knees	27/828	50/862	35/834	40/826	
Model 1	1.00	1.84 (1.04 to 3.24)	1.32 (0.73 to 2.39)	1.50 (0.84 to 2.69)	0.41
Model 2	1.00	1.80 (1.00 to 3.22)	1.24 (0.67 to 2.32)	1.33 (0.65 to 2.70)	0.78
Model 3	1.00	1.82 (1.02 to 3.25)	1.28 (0.69 to 2.38)	1.34 (0.66 to 2.70)	0.75
Pain worsening knees	496/1982	508/1986	512/1998	448/1985	
Model 1	1.00	0.97 (0.86 to 1.09)	0.96 (0.85 to 1.07)	0.86 (0.76 to 0.97)	0.01
Model 2	1.00	1.00 (0.88 to 1.13)	1.01 (0.89 to 1.15)	0.94 (0.80 to 1.10)	0.50
Model 3	1.00	1.00 (0.89 to 1.13)	1.03 (0.9 to 1.17)	0.95 (0.82 to 1.12)	0.77
Nut and legume fibre (g/day)					
Median	0.5	1.1	1.8	3.2	
SxOA knees	196/1378	222/1436	230/1446	220/1484	
Model 1	1.00	1.09 (0.85 to 1.39)	1.11 (0.87 to 1.42)	1.02 (0.80 to 1.31)	0.96
Model 2	1.00	1.09 (0.85 to 1.40)	1.07 (0.84 to 1.37)	0.95 (0.73 to 1.23)	0.47
Model 3	1.00	1.08 (0.84 to 1.39)	1.08 (0.84 to 1.39)	1.03 (0.79 to 1.34)	0.99
ROA knees	31/830	39/848	35/804	47/862	
Model 1	1.00	1.26 (0.74 to 2.14)	1.19 (0.69 to 2.06)	1.50 (0.88 to 2.54)	0.17
Model 2	1.00	1.19 (0.70 to 2.05)	1.05 (0.60 to 1.84)	1.09 (0.59 to 2.02)	0.96
Model 3	1.00	1.17 (0.68 to 2.01)	1.03 (0.59 to 1.81)	1.15 (0.62 to 2.11)	0.79

Continued

Table 2 Continued

Fibres in quartile	Q1	Q2	Q3	Q4	p Trend*
Pain worsening knees	487/1980	502/1982	493/1979	478/1998	
Model 1	1.00	1.01 (0.90 to 1.14)	1.01 (0.90 to 1.14)	0.94 (0.83 to 1.06)	0.22
Model 2	1.00	1.03 (0.92 to 1.17)	1.03 (0.91 to 1.16)	0.97 (0.86 to 1.10)	0.49
Model 3	1.00	1.04 (0.93 to 1.17)	1.04 (0.92 to 1.17)	1.00 (0.88 to 1.13)	0.82

*Test for trend based on variable containing median value for each quartile.
†Number of OA affected/total number of knees in each quartile of dietary fibre.
‡Model 1 adjusted for age (years), sex (men vs women), race (white vs non-white) and total energy intake (kcal).
§Model 2 further adjusted for education (<college vs ≥college), annual income level (<50 000 US$ vs ≥50 000 US$), tobacco use (never, former and current smokers), physical activity (PASE, continuous), intake of other dietary factors including polyunsaturated fat (g/day), vitamin C (mg/day), vitamin K (µg/day), dairy products (servings/day) and saturated fats, sweets and soda (serving/day) and NSAID use (yes vs no; for pain worsening).
¶Model 3 as for model 2 plus baseline BMI.
BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OAI, Osteoarthritis Initiative; PASE, Physical Activity in the Elderly Scale; ROA, radiographic OA; SxOA, symptomatic OA.

incident ROA or between fibre from nuts and legumes and knee OA.

The association of dietary fibre with knee OA in Framingham is presented in table 3. There was a significant dose-dependent inverse relationship between dietary total fibre and risk of SxOA in all models (p trend <0.03). Participants who consumed the highest quartile (Q4) of total fibre compared with the lowest quartile (Q1) had significantly lower risk by 61% [OR (95% CI): 0.39 (0.17 to 0.88)] in the full model adjusted for diet quality (DQAI-2010). Similarly inverse trends for fibre from other sub-categories were noted although these were not statistical significant. The associations with incident ROA were not apparent.

In the full model with further adjustment for BMI, we found an attenuated but significant inverse relation of dietary total fibre to risk of SxOA (p trend=0.03 in both studies) and to knee pain worsening (p trend=0.03 in OAI). Results for the association between dietary fibre and incident SxOA or knee pain worsening did not differ by stratum of obesity (BMI <30 vs BMI ≥30) as evidenced by a p value for interaction greater than 0.05 between obesity status and quartile dietary total fibre. Secondary analysis showed that dietary fibre was inversely associated with risk of SxOA or knee pain worsening independent of waist circumference in both studies (see online supplementary file tables 1-2) and regardless of socioeconomic status (see online supplementary file tables 3-4).

DISCUSSION

To our knowledge, this was the first study in the literature investigating the association between dietary fibre and OA outcomes. Our results consistently showed that in two prospective US cohorts with different study designs and study populations, those who consumed higher fibre intake were less likely to develop SxOA or to experience worsening knee pain during the study course regardless of socioeconomic or obesity status. These data demonstrate a consistent protective association between total fibre intake and symptom-related knee OA in two study populations with careful adjustment for potential confounders.

There is increasing evidence suggesting that OA shares similar metabolic characteristics including obesity, dyslipidaemia and inflammation with cardiovascular diseases and diabetes.[45] Our findings are consistent with those showing that higher dietary total fibre intake reduced risks of cardiovascular diseases[46] and reduced fasting glucose in type 2 diabetes.[12] The results of non-statistical associations for fibre from other diet sources with OA are similar with findings in cardiovascular diseases[2 47] and mortality[5] after controlling for various risk factors and covariates. Furthermore, these results are consistent with our report on high fibre intake with lower risks of moderate and severe knee pain trajectories over 8 years in OAI.[48] In OAI and Framingham, an inverse relationship was found between dietary fibre and BMI and between BMI and incident SxOA (p<0.01). Additional adjustment for baseline BMI attenuated the results compared with those without such adjustment. We have not tested for whether fibre's association with OA is mediated by BMI which could, in part, explain the dilution of the risk estimates after controlling for BMI.

The study design and participants' characteristics are different between the cohorts. Additionally, there were strengths and weaknesses in the assessment of exposure (fibre intake) and OA outcomes of interest between the studies (see online supplementary file text 3). The inverse association between total fibre intake and knee pain worsening further confirmed the results of SxOA. Using data from two cohorts to assess the relation of detary fibre to OA reduced biases due to potential confounding and misclassification of exposures and outcomes.

The estimation for total fibre intake on average is 18.8 (SD 7.8 g/day) in Framingham and is 15.0 (7.3) in OAI. Such estimated values for daily fibre intake are comparable with the average intake (15 g/day) among Americans.[13] Furthermore, because those who consume more fibre tend to better adhere to the dietary guidelines (table 1), we adjusted for diet quality (DGAI-2010) and found a similar significant inverse association in Framingham. Additionally, a statistically significant inverse relationship was found between the average intake of dietary fibre from baseline to 4 years later and incident SxOA (p trend=0.047) in Framingham. The similar effect estimates in all models further suggest that the association of dietary total fibre and risk of symptom related knee OA may not be affected by the risk factors, lifestyle and dietary confounders we accounted for.

In this study, although we did not find a statistically significant association between dietary fibre and radiographic OA, we cannot rule out the possibility that fibre may reduce the risk of ROA by lowering BMI[20] which may not be detectable because of a bias due to depletion of susceptibility to knee ROA[49] (see online supplementary file text 4). Also, serum CRP level, a marker of systemic inflammation, has been shown to play a greater role in symptoms than radiographic changes in OA.[24] Additionally, synovitis has been related to knee pain in persons with ROA.[50] If one of the biological mechanisms for dietary fibre and knee OA is to lower inflammation, its effect on SxOA may be more

Table 3 OR (95% CI) to estimate total effect of dietary fibre on knee incident SxOA and incident ROA where radiographs are centrally viewed for all eligible participants in the Framingham Offspring OA study (n=971 persons)

Fibres in quartile	Q1	Q2	Q3	Q4	p Trend*
Total fibre (g/day)					
Median	13.7	14.8	19.1	25.5	
SxOA knees†	41/483	50/488	24/484	28/486	
Model 1‡	1.00	1.20 (0.69 to 2.07)	0.47 (0.26 to 0.87)	0.50 (0.27 to 0.94)	0.01
Model 2§	1.00	0.96 (0.51 to 1.81)	0.46 (0.23 to 0.93)	0.34 (0.14 to 0.81)	0.017
Model 3¶	1.00	1.04 (0.56 to 1.94)	0.47 (0.24 to 0.93)	0.39 (0.17 to 0.88)	0.026
Model 4**	1.00	1.03 (0.53 to 2.00)	0.46 (0.22 to 0.95)	0.39 (0.17 to 0.92)	0.03
ROA knees	50/452	43/440	33/457	50/449	
Model 1	1.00	0.83 (0.48 to 1.43)	0.55 (0.32 to 0.95)	0.82 (0.48 to 1.38)	0.64
Model 2	1.00	0.69 (0.38 to 1.26)	0.50 (0.27 to 0.92)	0.65 (0.32 to 1.33)	0.47
Model 3	1.00	0.64 (0.35 to 1.18)	0.44 (0.23 to 0.82)	0.54 (0.26 to 1.13)	0.30
Model 4	1.00	0.63 (0.34 to 1.16)	0.41 (0.21 to 0.78)	0.52 (0.24 to 1.12)	0.29
Cereal fibre (g/day)					
Median	3.7	4.4	5.8	9.7	
SxOA knees	38/453	46/457	25/454	26/454	
Model 1	1.00	1.33 (0.77 to 2.30)	0.63 (0.34 to 1.18)	0.53 (0.29 to 1.00)	0.01
Model 2	1.00	1.33 (0.74 to 2.37)	0.61 (0.31 to 1.16)	0.62 (0.32 to 1.21)	0.07
Model 3	1.00	1.31 (0.71 to 2.43)	0.60 (0.29 to 1.25)	0.59 (0.29 to 1.22)	0.06
Model 4	1.00	1.28 (0.70 to 2.33)	0.62 (0.32 to 1.20)	0.57 (0.28 to 1.17)	0.06
ROA knees	44/412	55/420	27/424	43/432	
Model 1	1.00	1.26 (0.75 to 2.11)	0.55 (0.30 to 1.01)	0.78 (0.46 to 1.33)	0.19
Model 2	1.00	1.13 (0.64 to 1.99)	0.52 (0.27 to 1.02)	0.70 (0.38 to 1.26)	0.20
Model 3	1.00	1.16 (0.67 to 2.00)	0.47 (0.24 to 0.92)	0.73 (0.41 to 1.32)	0.24
Model 4	1.00	1.12 (0.65 to 1.94)	0.48 (0.25 to 0.95)	0.72 (0.39 to 1.32)	0.25
Fruit and vegetable fibre (g/day)					
Median	3.6	5.8	8.3	12.8	
SxOA knees	39/453	16/456	52/453	28/456	
Model 1	1.00	0.33 (0.16 to 0.66)	1.00 (0.58 to 1.72)	0.44 (0.24 to 0.84)	0.12
Model 2	1.00	0.24 (0.11 to 0.54)	0.91 (0.47 to 1.75)	0.37 (0.15 to 0.93)	0.16
Model 3	1.00	0.21 (0.09 to 0.51)	0.87 (0.40 to 1.87)	0.44 (0.17 to 1.16)	0.41
Model 4	1.00	0.17 (0.07 to 0.44)	0.80 (0.35 to 1.79)	0.44 (0.16 to 1.23)	0.57
ROA knees	36/421	31/429	66/417	36/421	
Model 1	1.00	0.78 (0.42 to 1.43)	1.70 (1.00 to 2.90)	0.82 (0.43 to 1.53)	0.94
Model 2	1.00	0.66 (0.35 to 1.27)	1.33 (0.71 to 2.48)	0.64 (0.29 to 1.42)	0.49
Model 3	1.00	0.60 (0.30 to 1.22)	1.16 (0.59 to 2.28)	0.67 (0.28 to 1.58)	0.60
Model 4	1.00	0.54 (0.26 to 1.11)	1.15 (0.57 to 2.28)	0.68 (0.28 to 1.67)	0.74
Nut and legume fibre (g/day)					
Median	0.7	1.6	2.4	4.4	
SxOA knees	40/453	37/457	24/452	34/456	
Model 1	1.00	0.75 (0.42 to 1.34)	0.42 (0.22 to 0.80)	0.56 (0.29 to 1.07)	0.09
Model 2	1.00	0.69 (0.37 to 1.27)	0.32 (0.16 to 0.64)	0.50 (0.24 to 1.04)	0.07
Model 3	1.00	0.71 (0.38 to 1.31)	0.32 (0.16 to 0.64)	0.46 (0.23 to 0.91)	0.03
Model 4	1.00	0.59 (0.31 to 1.14)	0.29 (0.14 to 0.59)	0.41 (0.20 to 0.82)	0.03
ROA knees	46/425	44/419	39/426	40/418	
Model 1	1.00	0.87 (0.51 to 1.48)	0.69 (0.39 to 1.22)	0.71 (0.38 to 1.34)	0.32
Model 2	1.00	0.87 (0.49 to 1.54)	0.52 (0.28 to 0.96)	0.68 (0.34 to 1.35)	0.28
Model 3	1.00	0.82 (0.47 to 1.45)	0.47 (0.25 to 0.87)	0.52 (0.27 to 1.01)	0.06
Model 4	1.00	0.75 (0.42 to 1.31)	0.45 (0.24 to 0.86)	0.49 (0.25 to 0.95)	0.06

*Test for trend based on variable containing median value for each quartile.
†Number of OA affected/total number of knees in each quartile of dietary fibre.
‡Model 1 adjusted for age (years), sex (men vs women) and total energy intake (kcal).
§Model 2 further adjusted from model 1 for education (<college vs ≥college), current cigarette smoking intensity (0, 1–5, 6 or above per day), PASE for physical activity level (continuous), intake of other dietary factors including polyunsaturated fat (g/day), saturated fat (g/day), vitamin C (mg/day), vitamin K (µg/day) and glycaemic load (white bread as reference); for subgroup fibre, other two groups of fibre were simultaneously controlled for.
¶Model 3 further adjusted from model 1 for education (<college vs ≥college), current cigarette smoking intensity (0, 1–5, 6 or above per day), PASE for physical activity level (continuous), and the DGAI-2010; for subgroup fibre, other two groups of fibre were simultaneously controlled for.
**Model 4 as model 3 plus BMI at baseline (kg/m^2).
BMI, body mass index; DGAI-2010, Dietary Guidelines Adherence Index; OA, osteoarthritis; PASE, Physical Activity in the Elderly Scale; ROA, radiographic OA; SxOA, symptomatic OA.

apparent compared with structural deterioration presented by ROA.

Strengths of this study included using data from two prospective cohorts where one is a multicentre and multiethnic cohort targeting to older Americans at risk or with OA and the other is a community-based population study. Therefore, using two different studies to assess fibre intake and OA outcomes in studying the association between dietary fibre and risk of knee OA improves internal validity. However, as a limitation, participants in OAI had higher BMI, and those in Framingham were selected regardless of their risk for OA. Such selection criteria in OAI might introduce collider bias by conditioning on BMI, where an unknown confounder (say, a genetic factor for obesity) affects BMI and knee OA and may negatively relate to dietary fibre. Our reported risk estimates for the association between fibre intake and knee OA could be diluted towards the null due to such collider bias. However, this would not have been true for analyses of Framingham data. Another limitation is that self-reported dietary data are prone to biases and potentially results in non-differential misclassification of fibre consumption, even though this is likely to lead to an underestimate of the observed associations. Inevitably, results from observational studies do not prove causality and may still raise concerns about residual confounding. Ultimately randomised trials are needed to prove causation, but observational and other studies are needed first to provide empirical evidence. As for dietary fibre, evidence from randomised clinical trials have demonstrated its effects on body weight,[6–8] blood pressure,[9] CRP[10] and glycaemia control.[11 12] Many of these are of relevance to OA. This suggests that the association of fibre with OA uncovered in our data may be genuine and unlikely due to the threats to internal validity.[51] Nonetheless, findings in these two studies need further corroboration.

In conclusion, data from two US prospective cohorts demonstrated that higher dietary total fibre intake was associated with lower risks of SxOA and pain worsening of the knee, while the association with radiographic OA was not apparent. Such results support the current recommended daily fibre for older Americans.[52]

Acknowledgements The authors would like to thank Gail Vanca Rogers, senior statistician at Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University for her generous assistance in expediting the distribution of the fibre variables and DGAI-2010 in the Framingham Study.

Contributors Study design: ZJD, YZ and DF. Data analysis: ZJD and JN. Data interpretation: ZJD, YZ, PJ and DF. Drafting manuscript: ZJD. All authors contributed to the final draft of the manuscript.

Competing interests None declared.

Ethics approval Institutional Review Board from all Osteoarthritis Initiative study sites and from Boston University.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 The American Association of Cereal Chemists. The definition of dietary fiber. *Cereal Food World* 2001:112–26.
2 Satija A, Hu FB. Cardiovascular benefits of dietary fiber. *Curr Atheroscler Rep* 2012;14:505–14.
3 Montonen J, Knekt P, Järvinen R, *et al*. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* 2003;77:622–9.
4 AlEssa HB, Ley SH, Rosner B, *et al*. High fiber and low starch intakes are associated with circulating intermediate biomarkers of type 2 diabetes among women. *J Nutr* 2016;146:306–17.
5 Kim Y, Je Y, intake Dfiber. Dietary fiber intake and total mortality: a meta-analysis of prospective cohort studies. *Am J Epidemiol* 2014;180:565–73.
6 Jull AB, Ni Mhurchu C, Bennett DA, *et al*. Chitosan for overweight or obesity. *The Cochrane database of systematic reviews* 2008;3:CD003892.
7 Ma Y, Olendzki BC, Wang J, *et al*. Single-component versus multicomponent dietary goals for the metabolic syndrome: a randomized trial. *Ann Intern Med* 2015;162:248–57.
8 Grube B, Chong PW, Lau KZ, *et al*. A natural fiber complex reduces body weight in the overweight and obese: a double-blind, randomized, placebo-controlled study. *Obesity* 2013;21:58–64.
9 Evans CE, Greenwood DC, Threapleton DE, *et al*. Effects of dietary fibre type on blood pressure: a systematic review and meta-analysis of randomized controlled trials of healthy individuals. *J Hypertens* 2015;33:897–911.
10 Jiao J, Xu JY, Zhang W, *et al*. Effect of dietary fiber on circulating C-reactive protein in overweight and obese adults: a meta-analysis of randomized controlled trials. *Int J Food Sci Nutr* 2015;66:114–9.
11 Chandalia M, Garg A, Lutjohann D, *et al*. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 2000;342:1392–8.
12 Silva FM, Kramer CK, de Almeida JC, *et al*. Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. *Nutr Rev* 2013;71:790–801.
13 Howarth NC, Saltzman E, Roberts SB, *et al*. Dietary fiber and weight regulation. *Nutr Rev* 2001;59:129–39.
14 Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. *Adv Nutr* 2013;4:16–28.
15 Lawrence RC, Felson DT, Helmick CG, *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the united states. part II. *Arthritis Rheum* 2008;58:26–35.
16 Centers for Disease Control and Prevention. Osteoarthritis (OA). 2015 http://www.cdc.gov/arthritis/basics/osteoarthritis.htm (Accessed 29 Feb 2016).
17 Furner SE, Hootman JM, Helmick CG, *et al*. Health-related quality of life of US adults with arthritis: analysis of data from the behavioral risk factor surveillance system, 2003, 2005, and 2007. *Arthritis Care Res* 2011;63:788–99.
18 Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* 2004;42:1–9.
19 Christensen R, Bartels EM, Astrup A, *et al*. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007;66:433–9.
20 Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. *BMJ Open* 2015;5:e007568.
21 Malfait AM. Osteoarthritis year in review 2015: biology. *Osteoarthritis Cartilage* 2016;24:21–6.
22 Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology* 2015;54:588–600.
23 Stannus OP, Jones G, Blizzard L, *et al*. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. *Ann Rheum Dis* 2013;72:535–40.
24 Jin X, Beguerie JR, Zhang W, *et al*. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:703–10.
25 Nevitt M, Felson DT, Lester G. The osteoarthritis initiative - Protocol for the cohort study. 2005;74.
26 Feinleib M, Kannel WB, Garrison RJ, *et al*. The Framingham offspring study. design and preliminary data. *Prev Med* 1975;4:518–25.
27 Felson DT, Couropmitree NN, Chaisson CE, *et al*. Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham study. *Arthritis Rheum* 1998;41:1064–71.
28 Felson DT, Niu J, Clancy M, *et al*. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. *Arthritis Rheum* 2007;56:129–36.
29 Block G, Hartman AM, Dresser CM, *et al*. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124:453–69.
30 Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology* 1990;1:58–64.
31 Rimm EB, Giovannucci EL, Stampfer MJ, *et al*. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114–26.
32 US Department of Health and Human Services and US Department of Agriculture. *Dietary guidelines for americans 2010*. Washington, DC, 2010:112.
33 Sauder KA, Proctor DN, Chow M, *et al*. Endothelial function, arterial stiffness and adherence to the 2010 dietary guidelines for Americans: a cross-sectional analysis. *Br J Nutr* 2015;113:1773–81.
34 Angst F, Aeschlimann A, Michel BA, *et al*. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol* 2002;29:131–8.
35 Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997;65:1220S–8.
36 Willett W. *Food frequency methods. nutritional epidemiology*. New York, NY: Oxford University Press, 2013:70–95.

37 Zhang Y, Zhang B, Wise B, *et al*. Statistical approaches to evaluating the effect of risk factors on the pain of knee osteoarthritis in longitudinal studies. *Curr Opin Rheumatol* 2009;21:513–9.
38 Peregoy J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. *Public Health Nutr* 2011;14:709–15.
39 McAlindon TE, Jacques P, Zhang Y, *et al*. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum* 1996;39:648–56.
40 Neogi T, Booth SL, Zhang YQ, *et al*. Low vitamin K status is associated with osteoarthritis in the hand and knee. *Arthritis Rheum* 2006;54:1255–61.
41 Wang Y, Davies-Tuck ML, Wluka AE, *et al*. Dietary fatty acid intake affects the risk of developing bone marrow lesions in healthy middle-aged adults without clinical knee osteoarthritis: a prospective cohort study. *Arthritis Res Ther* 2009;11:R63.
42 Lu B, Ahmad O, Zhang FF, *et al*. Soft drink intake and progression of radiographic knee osteoarthritis: data from the osteoarthritis initiative. *BMJ Open* 2013;3:e002993.
43 Rodríguez-Rejón AI, Castro-Quezada I, Ruano-Rodríguez C, *et al*. Effect of a mediterranean diet intervention on dietary glycemic load and dietary glycemic index: the PREDIMED study. *J Nutr Metab* 2014;2014:1–10.
44 Castro-Quezada I, Sánchez-Villegas A, Estruch R, *et al*. A high dietary glycemic index increases total mortality in a mediterranean population at high cardiovascular risk. *PLoS One* 2014;9:e107968.
45 Zhuo Q, Yang W, Chen J, *et al*. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol* 2012;8:729–37.
46 Threapleton DE, Greenwood DC, Evans CE, *et al*. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2013;347:f6879.
47 Harris KA, Kris-Etherton PM. Effects of whole grains on coronary heart disease risk. *Curr Atheroscler Rep* 2010;12:368–76.
48 Dai Z, Lu N, Niu J, *et al*. Dietary intake of fiber in relation to knee pain trajectories. *Arthritis Care Res* 2016. Epub ahead of print.
49 Choi HK, Nguyen US, Niu J, *et al*. Selection bias in rheumatic disease research. *Nat Rev Rheumatol* 2014;10:403–12.
50 Baker K, Grainger A, Niu J, *et al*. Relation of synovitis to knee pain using contrast-enhanced MRIs. *Ann Rheum Dis* 2010;69:1779–83.
51 Zaccai JH. How to assess epidemiological studies. *Postgrad Med J* 2004;80:140–7.
52 Institute of Medicine. *Dietary reference intakes for energy, carbohydrate. fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington, DC: The National Academic Press, 2002/2005.

Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts

Zhaoli Dai, Jingbo Niu, Yuqing Zhang, Paul Jacques and David T Felson

Ann Rheum Dis published online May 23, 2017