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Cereal fibre intake and risk of mortality from all causes, CVD, cancer and inflammatory diseases: a systematic review and meta-analysis of prospective cohort studies

Maryam Hajishafiee[1,2], Parvane Saneei[1,2,3], Sanaz Benisi-Kohansal[1,2] and Ahmad Esmaillzadeh[4,5]*

[1]*Food Security Research Center, Isfahan University of Medical Sciences, PO Box 81745-151, Isfahan, Iran*
[2]*Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, PO Box 81745-151, Isfahan, Iran*
[3]*Students' Research Committee, Isfahan University of Medical Sciences, PO Box 81745-151, Isfahan, Iran*
[4]*Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, PO Box 14155/6117, Tehran, Iran*
[5]*Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, PO Box 14155/6117, Tehran, Iran*

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Abstract

Dietary fibre intake has been associated with a lower risk of mortality; however, findings on the association of different sources of dietary fibre with mortality are conflicting. We performed a systematic review and meta-analysis of the prospective cohort studies to assess the relation between cereal fibre intake and cause-specific mortality. Medline/PubMed, SCOPUS, EMBASE, ISI web of Science and Google scholar were searched up to April 2015. Eligible prospective cohort studies were included if they provided hazard ratios (HR) or relative risks (RR) and corresponding 95 % CI for the association of cereal fibre intake and mortality from all causes, CVD, cancer and inflammatory diseases. The study-specific HR were pooled by using the random-effects model. In total, fourteen prospective studies that examined the association of cereal fibre intake with mortality from all causes (*n* 48 052 death), CVD (*n* 16 882 death), cancer (*n* 19 489 death) and inflammatory diseases (*n* 1092 death) were included. The pooled adjusted HR of all-cause mortality for the highest *v.* the lowest category of cereal fibre intake was 0·81 (95 % CI 0·79, 0·83). Consumption of cereal fibre intake was associated with an 18 % lower risk of CVD mortality (RR 0·82; 95 % CI 0·78, 0·86). Moreover, an inverse significant association was observed between cereal fibre intake and risk of death from cancer (RR 0·85; 95 % CI 0·81, 0·89). However, no significant association was seen between cereal fibre intake and inflammation-related mortality. This meta-analysis provides further evidence that cereal fibre intake was protectively associated with mortality from all causes, CVD and cancer.

Key words: Cereal fibres: Mortality: CVD: Cancer: Inflammation

Non-communicable diseases (NCD) are the main causes of death worldwide. CVD, cancers, chronic respiratory diseases and diabetes account for 60 % of all deaths worldwide and 80 % in low- or middle-income countries[1]. Several dietary factors including whole grains, fruits and vegetables have been shown to contribute to the risk for NCD[2–5]. Moreover, it seems that fibres from these dietary components have an important role in the aetiology of NCD and mortality[5–9].

Earlier studies have shown that fibre intakes are inversely associated with all-cause mortality and CVD and cancer mortalities[3,7,10,11]. A pooled analysis of ten prospective studies indicated that a 10 g/d higher intake of total dietary fibre was associated with 17 and 27 % reductions in the risk of all coronary events and coronary mortality, respectively[9]. However, the results are inconsistent based on different food sources of dietary fibres[3–6,9]. It is suggested that greater intakes of cereal fibre are associated with a lower risk of CVD and all-cause mortalities[9,10,12]. Similar results have been reported by the National Institutes of Health (NIH)-AARP Diet and Health Study, which found that dietary fibre from grains, but not from other sources, was inversely related to cause-specific death in men and women[8]. In addition, in a cohort study on 3588 elderly, cereal fibre consumption was associated with a lower risk of CVD events[5]. However, some observational studies have not found a significant association between cereal fibre intake and CVD mortality[5,13]. Threapleton *et al.*[14] in UK Women's Cohort Study observed no significant association between cereal fibre intake and CVD mortality. Moreover, in

Abbreviations: HR, hazard ratio; MI, myocardial infarction; RR, relative risk.

* **Corresponding author:** A. Esmaillzadeh, fax +98 31 3668 1378, email esmaillzadeh@hlth.mui.ac.ir

the cohort study of Women's Health Study among the US population, no significant association was observed between cereal fibre intake and CVD-specific death[4]. It is also suggested by the Blue Mountain Eye Study that cereal fibre intake is not associated with CHD or stroke mortality[15]. Two recent meta-analyses of cohort studies[16,17] have reported the inverse associations of total dietary fibre intake with all-cause mortality; however, some relevant cohort studies were not included in these meta-analyses[3,10,12]. In addition, the relation between cereal fibre intake and cause-specific mortality was not examined in these meta-analyses. Nevertheless, in another meta-analysis by Liu *et al.*[18], which assessed the association of total dietary fibre intake with cause-specific mortality, different sources of dietary fibres were not considered. Given the lack of any clear meta-analysis of the association of cereal fibre intake with cause-specific mortality, as well as the conflicting evidence in this regard, we aimed to conduct a systematic review and meta-analysis of the prospective cohort studies to assess the relation between cereal fibre intake and mortality from all causes, CVD, cancer and inflammatory diseases.

Methods

Search strategy

A systematic literature search was conducted in medical databases including Medline/PubMed, SCOPUS, EMBASE, ISI web of Science and Google scholar up to April 2015 using the following medical subject headings (MeSH) and non-MeSH keywords relevant to 'whole grain', 'cereals' and 'dietary fiber' in combination with 'mortality', 'fatal', 'death' and 'survive'. No restriction was set on the time of publication and language. The reference lists of related articles were hand-searched for additional relevant studies. Titles/abstracts were screened for relevant studies by two independent investigators (M. H. and P. S.).

Inclusion criteria

Published studies were included if they were prospective cohort studies that reported relative risks (RR) or hazard ratio (HR) for the association of cereal fibre intakes and mortality from all causes, CVD, cancer and inflammatory diseases as the main outcomes of interest. In case of multiple published reports from the same study population, we included the one reporting the largest number of mortality cases[10,15].

Excluded studies

We excluded editorial letters, comments, ecological studies and meta-analyses. The study selection process is illustrated in Fig. 1. Our search strategy identified 9895 human studies. After removing duplicates, 4798 abstracts were selected for a more detailed review; 181 citations were left after screening for title and abstracts. After scrutinising the full-text papers and based on our inclusion criteria, eighteen prospective studies were selected for the systematic review. However, we included only fourteen studies[3–5,9,10,12–14,15,19–23] in the meta-analysis, and the other four studies were excluded from the meta-analysis because of the following reasons. Two studies conducted by Rimm *et al.*[24] and Wolk *et al.*[25] were not included because they had reported RR or HR for all CVD events simultaneously and had not separated the findings for fatal and non-fatal outcomes. Moreover, two studies were excluded because they had duplicated data from the same cohort studies[8,26].

Data extraction

Two authors (M. H. and P. S.) extracted the required information independently. We used HR or RR as a measure of the association. First author's last name, publication year, cohort name, the country in which the study was conducted, sample size, age range of participants at baseline, methods of assessment of cereal fibre intake, duration of follow-up, main outcome, covariates adjusted for in the analyses and RR or HR with the corresponding 95 % CI were extracted. From each study, we extracted RR or HR estimates that reflected the greatest degree of adjustments for potential confounders. In case of disagreements between the two investigators, principal investigator (A. E.) was consulted.

Quality assessment

We assessed study quality with the Newcastle–Ottawa quality assessment scale[27]. This system allowed a total score of up to 9 points as the highest quality. Scores were derived through three aspects of each study including selection, comparability and outcome in eight questions. Each study could be awarded a maximum score of 1 for each question in selection and outcome categories. However, a maximum score of 2 could be given for comparability.

Statistical methods

RR and HR, and their 95 % CI for the comparison of the highest *v.* the lowest category of cereal fibre intake, were used to calculate log RR and its standard error. The analyses were performed using random-effects model, calculating both Q-statistic and I^2 as indicators of heterogeneity. In case of significant between-study heterogeneity, we performed subgroup analysis, based on the location of the study, participants' sex, duration of follow-up and adjustment for energy intake, to find out possible sources of heterogeneity. Between-subgroup heterogeneity was examined through fixed-effects modelling. We also performed random-effects meta-regression analysis to assess the overall linear relationship between cereal fibre intake and mortality. RR (95 % CI) comparing mortality from all causes, CVD, cancer and inflammatory diseases, in different categories of cereal fibre intake compared with the reference group, were extracted, converted to log RR (SE) and used in this meta-regression. Depending on the available information in the included studies, the median or means of cereal fibre intake (g/d) in the categories were used. For studies in which a range of cereal fibre intake was reported, the mid-point of each category of intake was calculated. For categories with the open-ended ranges, half the width of the adjacent category was used. One study by Holmes *et al.*[21] was not included in the meta-regression, because they had not reported the amount of cereal fibre intake across different

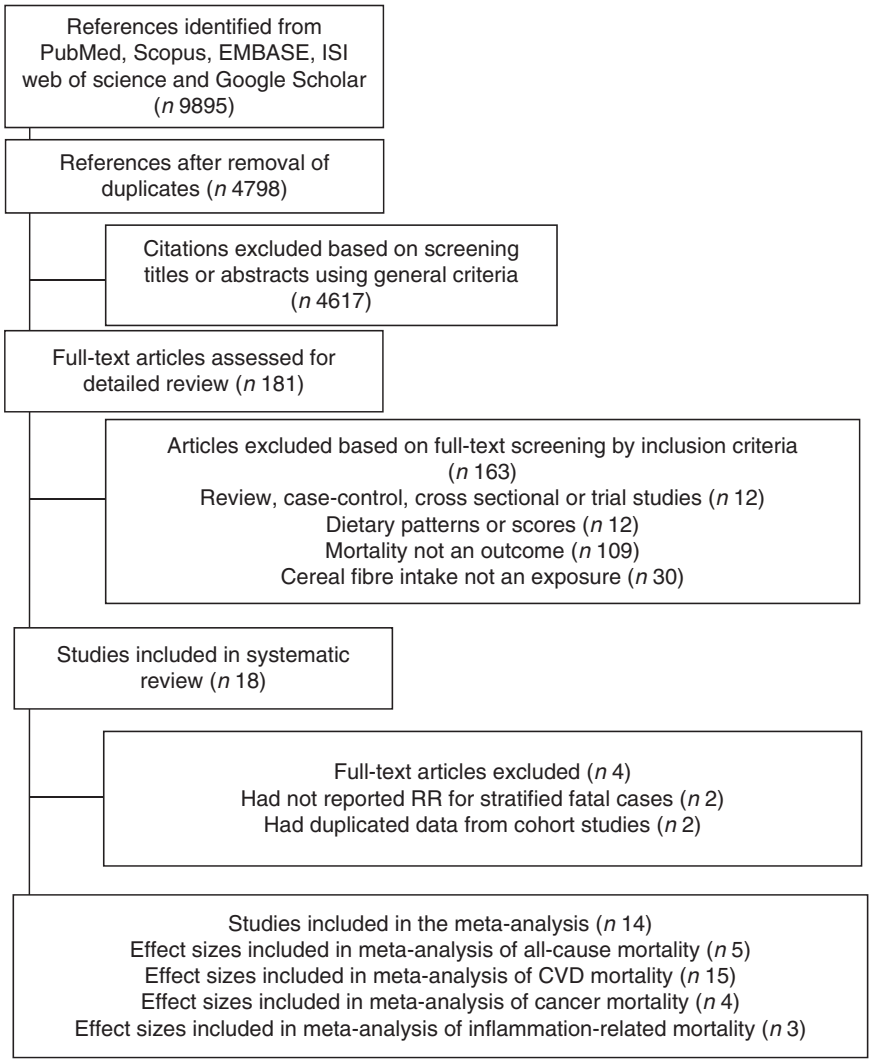

Fig. 1. The flow diagram of study selection. RR, relative risk.

categories. Moreover, the studies by Baer *et al.*[23], Streppel *et al.*[13] and Pereira *et al.*[9], which had reported linear estimates (RR or HR for 4 or 10 g/d increment in cereal fibre intake), were included in the meta-regression but not in the meta-analysis of the highest *v.* lowest intake. The publication bias was examined by visual inspection on Begg's funnel plots. Formal statistical assessment of funnel plot asymmetry was also carried out using Egger's regression asymmetry test. We also conducted a sensitivity analysis in which each prospective cohort study was excluded to examine the influence of that study on the overall estimate. Statistical analyses were conducted using Stata version 11.2 (StataCorp LP). P values $< 0{\cdot}05$ were considered statistically significant for all tests including Cochran's Q test.

Results

Findings from the systematic review

The characteristics of the studies included in the systematic review are presented in Table 1. Out of eighteen cohort studies published between 1996 and 2015, ten were conducted in the USA[3–5,8,10,12,21,23–25], two in the UK[14,19], two in Australia[15,26] and the rest in Japan[20], Finland[22] and Netherlands[13], and one pooled analysis based on cohorts in the USA and UK[9]. The total number of participants in these studies ranged from 1373[13] to 388 122[8], with age ranging from 30 to 99 years. Three[13,22,24] studies were restricted to male subjects and six others to female subjects[3,4,14,21,23,25]. However, the remaining nine papers had examined both sexes, with three examining males and females separately[8,15,20] and six in combination[5,9,10,12,19,26]. From eighteen studies included in the systematic review, one study was conducted exclusively in patients with myocardial infarction (MI)[12], and two studies were conducted in patients with type 2 diabetes and breast cancer, respectively[3,21]. From eighteen citations, six papers had reported RR for all-cause mortality[3,8,10,12,13,23], seventeen publications for CVD mortality[3–5,8–10,12–15,19,20,22,23–26], four studies for cancer mortality[8,10,21,23] and three papers for inflammation-related mortality[8,10,15]. In some publications, cereal fibre was defined as fibre or NSP from flour, rice, pasta,

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Table 1. Main characteristics of prospective studies examined the association of cereal fibre intake with all-cause, CVD, cancer and inflammation-related mortalities (Mean values and standard errors; odds ratios (OR) or relative risk (RR) and 95 % confidence intervals)

First author (year)	Cohort name	Country	Age range/ mean age	Sex	Sample size	Cases	Duration of follow-up (years)	Person-year	Exposure and outcome assessment	Outcome	Comparison	OR or RR	95 % CI	Score	Adjustments
Huang (2015)[10]	NIH-AARP Diet and Health Study	USA	50–71	M/F	367 442	46 067	14	5 148 760	FFQ: 124-item/NDI, Social Security Administration Death Master File, cancer registry linkage	All-cause mortality	Cereal fibre (ready to eat cereals, high fibre cereals, cooked cereals, grain-based cereals) Q5 *v.* Q1 (10·22 *v.* 2·02 g/d)	0·81	0·79, 0·84	8	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
						11 283				CVD mortality		0·80	0·75, 0·85		
						19 043				Cancer mortality		0·85	0·81, 0·89		
						922				Infectious diseases-mortality		0·83	0·67, 1·03		
Li (2014)[12]	NHS + HPFS (patients with MI)	USA	30–75	M/F	4098	1133	8·7–9	37 079	FFQ/vital records, NDI, family reports, medical records or autopsy	All-cause mortality	Cereal fibre Q5 *v.* Q1 (M: 11·2 *v.* 5·3; F: 8·4 *v.* 4·0)	0·73	0·58, 0·91	7	1, 2, 3, 4, 5, 6, 7, 9, 10, 11
						558				CVD mortality		0·72	0·52, 0·99		
Threapleton (2013)[14]	United Kingdom Women's Cohort Study	UK	51·8 (SE 9·2)*	F	31 036	258	14·3	–	FFQ: 217-item/National death registry	CVD mortality	Cereal fibre (total cereal foods, breakfast cereals) Q5 *v.* Q1 (15·7 *v.* 2·8 g/d)	0·91	0·56, 1·48	7	1, 2, 3, 4, 5, 6, 8
Crowe (2012)[19]	European Prospective Investigation into Cancer and Nutrition-Heart study	8 European countries	53·8 (SE 8)*	M/F	30 6311	2381	11·5	3 532 887	FFQ/Mortality registries at the regional or national level	IHD mortality	Cereal fibre (flour, pasta, rice, other grains, bread, crisp breads, rusks, breakfast cereals, crackers, pastry, pizza dough) g/d (≥11 *v.* <5 g/d)	0·83	0·72, 0·96	8	1, 2, 4, 5, 6, 7, 8, 9, 10
Baer (2011)[23]	NHS	USA	52·5 (SE 7·1)*	F	50 112	4893	18	–	FFQ/family reports, NDI, medical records	All-cause mortality	Cereal fibre (per 4 g)	0·84	0·78, 0·91	6	1, 2, 3, 4, 5, 7, 10
						1026				CVD mortality		0·82	0·69, 0·97		
						931				Smoking-related cancers-mortality		0·86	0·72, 1·03		
						1430				Other cancers-mortality		0·82	0·71, 0·95		
Park (2011)[8]	NIH-AARP Diet and Health Study	USA	50–71	M	219 123	20 126	9	–	FFQ: 124-item/NDI, Social Security Administration Death Master File, cancer registry linkage	All-cause mortality	Cereal fibre Q5 *v.* Q1	0·77	0·73, 0·81	7	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
						5248				CVD mortality		0·77	0·71, 0·85		
						8244				Cancer mortality		0·83	0·77, 0·89		
						275				Infectious diseases-mortality		0·48	0·31, 0·75		
				F	168 999	11 330				All-cause mortality		0·81	0·76, 0·86		
						2417				CVD mortality		0·72	0·63, 0·82		
						4927				Cancer mortality		0·88	0·80, 0·97		
						223				Infectious diseases-mortality		0·89	0·60, 1·34		
Buyken (2010)[15]	BMES	Australia	> 49	M	1245	86	13	–	FFQ: 145-item/Australian National Death Index, family reports	Inflammatory diseases-mortality	Cereal fibre (breads and cereals, pasta, rice) g/d T3 *v.* T1 (M: 11·5 *v.* 3·0 g/d; F: 10·9 *v.* 2·9 g/d)	0·98	0·57, 1·67	8	1, 3, 4, 6, 7, 10
				F	1490	84						0·72	0·41, 1·27		
				M	1245	151				CVD mortality		1·04	0·67, 1·61		
				F	1490	109						0·87	0·55, 1·38		
Eshak (2010)[20]	The Japan Collaborative Cohort Study for Evaluation of Cancer Risks	Japan	40–79	M	23 119	231	14·3	288 518	FFQ: 40-item/death certificates	CHD mortality	Cereal fibre (miso soup, rice) g/d Q5 *v.* Q1 (>2·1 *v.* <1·4 g/d)	0·89	0·65, 1·01	7	1, 2, 3, 4, 5, 7, 10
				F	35 611	191		454 653			(>1·7 *v.* <1·1 g/d)	0·76	0·59, 0·97		
He (2010)[3]	NHS (type 2 diabetic patients)	USA	30–55	F	7822	852	26	70 102	FFQ/NDI, family reports, postal system	All-cause mortality	Cereal fibre (rice, pasta, bread, breakfast cereals) Q5 *v.* Q1 (6·29 *v.* 1·9 g/d)	0·86	0·66, 1·12	7	1, 2, 3, 4, 5, 6, 7, 10, 11
						295				CVD mortality		0·89	0·57, 1·41		
Holmes (2009)[21]	NHS (patients with breast cancer)	USA	30–55	F	3846	446	25	–	FFQ/NDI, family reports, postal system	Breast cancer-mortality	Cereal fibre Q5 *v.* Q1	1·00	0·71, 1·40	6	1, 2, 3, 5, 6, 11

Table 1. *Continued*

First author (year)	Cohort name	Country	Age range/ mean age	Sex	Sample size	Cases	Duration of follow-up (years)	Person-year	Exposure and outcome assessment	Outcome	Comparison	OR or RR	95 % CI	Score	Adjustments
Kaushik (2009)[26]	BMES	Australia	≥49	M/F	2897	95	13	–	FFQ: 145-item/Australian National Death Index	Stroke mortality	Cereal fibre T1 *v.* T3	2·13	1·19, 3·80	7	1, 2, 3, 6, 8, 10
										CHD mortality		0·94	0·73, 1·22		
Streppel (2008)[13]	The Zutphen Study	Netherlands	80 (SE 3)*	M	1373	348	40	–	Dietary history/clinical epidemiologist	CHD mortality	Cereal fibre (bread and other cereal products) (per 10 g/d increment)	Recent intake 0·84 (95 % CI 0·64, 1·10) Long-term intake 0·86 (95 % CI 0·64, 1·15)		8	2, 3, 4, 6, 7, 8
						1130				All-cause mortality		Recent intake 0·92 (95 % CI 0·79, 1·07) Long-term intake 0·90 (95 % CI 0·77, 1·05)			
Pereira (2004)[9]	8 prospective cohort studies	USA, Europe	35–98	M	91 058	2011	6–10	2 506 581	FFQ or diet history/ standardised criteria were used for case ascertainment in all studies	CVD mortality	Cereal fibre (per 10 g/d increment)	0·75	0·63, 0·91	6	1, 2, 3, 4, 5, 6, 7, 8, 10
Mozaffarian (2003)[5]	Cardiovascular Health Study	USA	35–99 ≥65	F M/F	245 186 3588	220	8·6	–	FFQ: 99-item/Medical records, physician questionnaires, death certificates, medical examiner forms, Health Care Financing Administration hospitalisations	IHD mortality	Cereal fibre (dark breads, high fibre or bran cereals) Q5 *v.* Q1 (> 6·3 *v.* <1·7 g/d)	0·87	0·67, 1·13	6	1, 3, 4, 5, 7, 8
Liu (2002)[4]	Women's Health Study	USA	≥45	F	38 480	570	6	230 006	FFQ: 131-item/medical records, autopsy reports, death certificates	CVD mortality	Cereal fibre Q5 *v.* Q1 (6·5 *v.* 3·0 g/d)	1·11	0·84, 1·46	7	1, 2, 3, 4, 5, 6, 7, 10, 11
Wolk (1999)[25]	NHS	USA	37–64	F	68 782	591	10	641 515	FFQ/NDI, family reports, postal system	CHD-events	Cereal fibre (median, g/d) Q5 *v.* Q1	0·66	0·49, 0·88	7	1, 2, 3, 4, 5, 6, 7, 10, 11
Pietinen (1996)[22]	Alpha-Tocopherol, Beta-Carotene cancer prevention study	Finland	50–69	M	21 930	635	6·1	129 388	FFQ: 276-item/central population register, death certificates	Coronary mortality	Cereal fibre Q5 *v.* Q1 (26·3 *v.* 8·8 g/d)	0·74	0·57, 0·96	6	1, 2, 3, 4, 5, 6, 7, 8, 10
Rimm (1996)[24]	HPFS	USA	40–75	M	43 757	734	6	–	Dietary questionnaire: 131-item/ NDI, family reports, postal system, medical records, autopsy reports	Total MI (fatal and non-fatal)	Cereal fibre Q5 *v.* Q1 (9·7 *v.* 2·2 g/d)	0·73	0·56, 0·94	6	1, 2, 3, 4, 5, 6, 7, 10

NIH, National Institutes of Health; M, male; F, female; MI, myocardial infarction; NDI, national death index; NHS + HPFS, Nurse's Health Study + Health Professionals Follow-up Study; BMES, Blue Mountains Eye Study; 1, age; 2, BMI; 3, smoking status; 4, alcohol consumption; 5, physical activity; 6, energy intake; 7, dietary intakes; 8, education or socio-economic status; 9, marital status; 10, diseases history; 11, hormone therapy or using drugs; Q1, quartile 1; Q5, quartile 5; T1, tertile 1; T3, tertile 3.
* Mean age.

pastry, bread, dark bread and breakfast cereals[3,5,10,13,14,15,19,20]. However, others did not precisely report how they defined cereal fibre[4,8,9,12,21,22,23–26]. Most studies had assessed dietary intakes by using a validated FFQ, whereas the remaining studies had used dietary questionnaire[24] and diet history[13]. During the follow-up periods ranging from 6[4,24] to 40 years[13], there was a report of total number of 85 531 death from all causes, 29 352 from CVD, 35 021 from cancer and 1590 inflammation-related deaths. Corresponding HR for all-cause mortality across the highest *v.* lowest categories of cereal fibre intake were between 0·73 and 0·92. HR for CVD and cancer mortalities ranged from 0·66 to 2·13 and 0·82 to 1, respectively. Moreover, reported HR for inflammation-related mortality ranged from 0·48 to 0·98. Out of six citations with HR for all-cause mortality as the main outcome, four studies found a significant inverse association between cereal fibre intake and all-cause mortality in men and women[8,10,12,23]. However, the remaining two studies did not show a significant association[3,13]. From seventeen publications that reported HR for CVD mortality, nine studies reported a significant inverse association between cereal fibre intake and CVD mortality[8–10,12,19,22–25], whereas seven others did not[3–5,13–15,26]. It is worth noting that one study found an inverse association between cereal fibre intake and CVD mortality in women but not in men[20]. Two out of four studies that examined the association of cereal fibre intake with cancer mortality reported a significant inverse association[8,10]. From three publications that reported HR for inflammation-related mortality, two studies did not find any significant association[10,15], whereas one study reported a significant inverse association between cereal fibre intake and inflammation-related mortality in men but not in women[8]. Most studies had performed adjustments for important confounding factors including age (*n* 17), BMI (*n* 16), smoking (*n* 17) and alcohol consumption (*n* 16). Moreover, some studies had also made adjustments for physical activity (*n* 15) and energy intake (*n* 15) or other dietary variables or nutrients (*n* 15). In terms of the quality of the study, out of eighteen publications included in the systematic review six studies had a score <7 (0–6) and the rest had a score of ≥7 (7–9).

Findings from the meta-analysis on cereal fibre intake and all-cause mortality

Three effect sizes from three publications[3,10,12], including 379 362 participants and 48 052 cases of death, were included in this analysis (Fig. 2). Subjects with the highest intake of cereal fibre had 19 % lower risk of all-cause mortality (RR 0·81; 95 % CI 0·79, 0·83), compared with those with the lowest intake. It should be taken into account that two studies from these three publications had been conducted on diabetic patients[3] and individuals with MI[12]. No significant between-study heterogeneity was seen ($I^2 = 0{\cdot}0$ %, $P = 0{\cdot}60$). Meta-regression of the five observational studies[3,10,12,13,23] revealed that there is a significant inverse linear trend between cereal fibre intake (g/d) and risk of all-cause mortality ($\beta = -0{\cdot}019$, $P = 0{\cdot}02$) (Fig. 3(a)). Findings from the sensitivity analysis revealed that the exclusion of any single study from the analysis did not alter the overall association. Moreover, no evidence of publication bias was observed ($P = 0{\cdot}80$ by Egger's test, $P = 0{\cdot}60$ by Begg's test).

Findings from the meta-analysis on cereal fibre intake and CVD mortality

Results from the meta-analysis on cereal fibre intake and CVD mortality are presented in Fig. 4. Overall, twelve effect sizes from ten studies[3–5,10,12,14,15,19,20,22] were included. These studies had totally included 842 172 participants at the time of study, out of which 16 882 incident CVD deaths were reported. A significant inverse association was seen between highest consumption of cereal fibre and CVD mortality (RR 0·82; 95 % CI 0·78, 0·86). After excluding two studies that had been performed on patients with MI[12] and diabetes[3], no significant changes occurred in the overall effect size (RR 0·82; 95 % CI 0·78, 0·86). Although no evidence of between-study heterogeneity was found ($I^2 = 0{\cdot}0$ %, $P = 0{\cdot}62$), we performed a subgroup analysis based on sex, study location, follow-up duration and energy adjustment (Table 2). By sex, the inverse association tended to be stronger for men and women combined (RR 0·80; 95 % CI 0·76, 0·85) compared with women (RR 0·90; 95 % CI 0·77, 1·04) or men (RR 0·85; 95 % CI 0·72, 1·00) separately. However, the difference was not statistically significant ($P = 0{\cdot}38$). According to study location, no significant difference was found between US and non-US countries ($P = 0{\cdot}71$). For the duration of follow-up, no statistical differences was seen between long-term (≥10 years) and short-term (<10 years) studies ($P = 0{\cdot}53$). On the basis of energy adjustments, RR for studies with energy adjustments tended to be stronger (RR 0·82; 95 % CI 0·77, 0·86) than studies without energy adjustments (RR 0·84; 95 % CI 0·73, 0·97). However, there was no statistically significant difference ($P = 0{\cdot}68$). As shown in Fig. 3(b), meta-regression of the studies[3–5,9,10,12–15,19,20,22,23] indicated that cereal fibre intake (g/d) was marginally associated with a lower risk of CVD mortality in a dose–response manner ($\beta = -0{\cdot}007$, $P = 0{\cdot}06$). No single study influenced the final association, and no evidence of publication bias was found ($P = 0{\cdot}16$ by Egger's test, $P = 0{\cdot}34$ by Begg's test).

Findings from the meta-analysis on cereal fibre intake and cancer mortality

Results from two studies[10,21], including 371 288 participants and 19 489 cancer death cases, revealed a significant inverse relationship between cereal fibre consumption and cancer mortality (RR 0·85; 95 % CI 0·81, 0·89). However, one of these studies had included patients with breast cancer[21]. No evidence of between-study heterogeneity was found ($I^2 = 0{\cdot}0$ %, $P = 0{\cdot}35$). Findings from the meta-regression, using log RR of two studies[10,23], demonstrated a marginally significant inverse relationship between cereal fibre intake (g/d) and risk of mortality from cancer ($\beta = -0{\cdot}016$, $P = 0{\cdot}09$) (Fig. 3(c)). Excluding any single study did not affect this finding. In addition, no evidence of publication bias was seen ($P = 0{\cdot}32$ by Begg's test).

Findings from the meta-analysis on cereal fibre intake and inflammation-related mortality

Results from the meta-analysis on cereal fibre consumption in relation to mortality from inflammatory diseases are presented in Fig. 5. No significant association was observed between

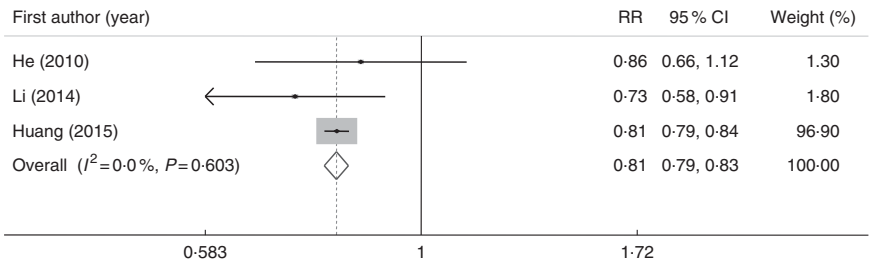

Fig. 2. Forest plots of the association between cereal fibre intake and risk of all-cause mortality. RR, relative risk.

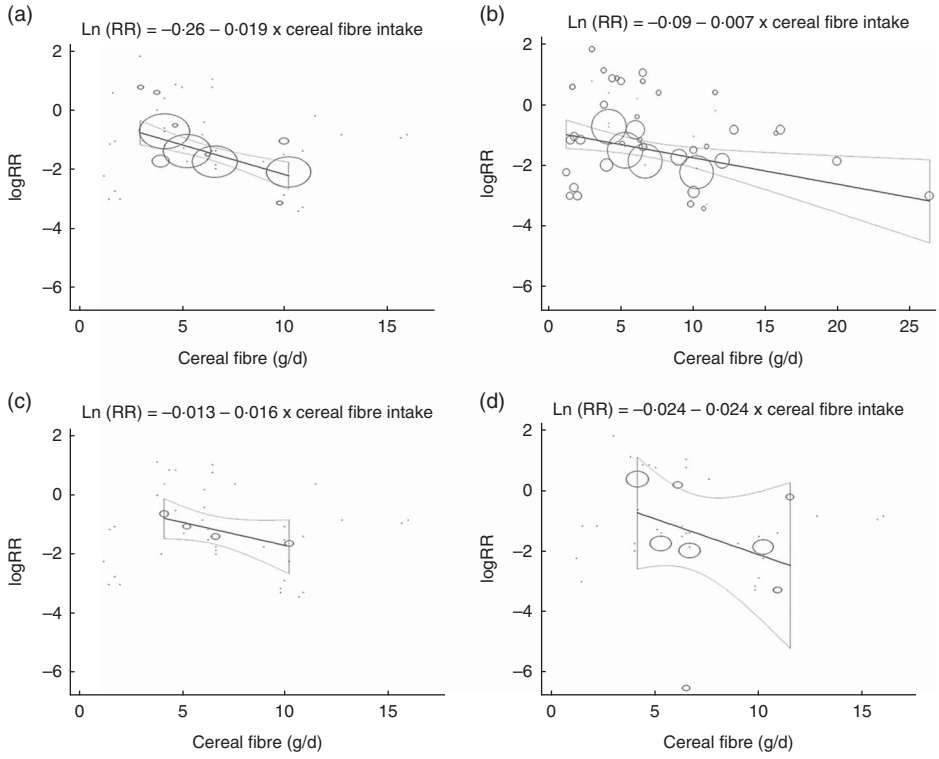

Fig. 3. (a) Association between the risk of all-cause mortality and cereal fibre intake: dose–response meta-regression. The levels of cereal fibre intake (g/d) were modelled using a linear trend with random-effects meta-regression models. ——, Weighted regression line based on variance-weighted least squares. ——, 95 % CI around the regression line. ○, Relative risk (RR) in each study. The circle size is proportional to the precision of the RR. The vertical axis is on a log scale. For all-cause mortality, $\beta = -0{\cdot}019$, $P = 0{\cdot}02$, I^2 residual = 50·77 %. (b) Association between the risk of CVD mortality and cereal fibre intake: $\beta = -0{\cdot}007$, $P = 0{\cdot}06$, I^2 residual = 0·00 %. (c) Association between the risk of cancer mortality and cereal fibre intake: $\beta = -0{\cdot}016$, $P = 0{\cdot}09$, I^2 residual = 0·00 %. (d) Association between the risk of mortality from inflammatory diseases and cereal fibre intake: $\beta = -0{\cdot}024$, $P = 0{\cdot}31$, I^2 residual = 3·86 %.

cereal fibre intake and inflammation-related mortality (RR 0·83; 95 % CI 0·69, 1·01). Between-study heterogeneity was not statistically significant ($I^2 = 0{\cdot}0$ %, $P = 0{\cdot}73$). We found that for the included studies[10,15] there was no significant linear association between cereal fibre intake and inflammation-related mortality ($\beta = -0{\cdot}024$, $P = 0{\cdot}32$) (Fig. 3(d)). Moreover, excluding no single study affected the overall effect size. No evidence of publication bias was found ($P = 0{\cdot}96$ by Egger's test, $P = 0{\cdot}60$ by Begg's test).

Discussion

We found that high cereal fibre intake was inversely associated with mortality from all causes, CVD and cancer. However, no significant association was found between cereal fibre intake and inflammation-related mortality. The inverse association with CVD mortality did not vary by sex, study location, follow-up duration and energy adjustment.

In the interpretation of our findings, it should be taken into account that in this meta-analysis the highest *v.* the lowest categories of cereal fibre intake have been used to demonstrate potentially important biological effects. We have also provided linear associations between cereal fibre intake and mortality. However, most nutritionists are wanting to know the appropriate amount of cereal fibre to recommend to the general population. As the range of intakes appeared to vary considerably between included studies, with the highest values in some studies being below the lowest values in other studies, current limited data did not allow us to determine a certain

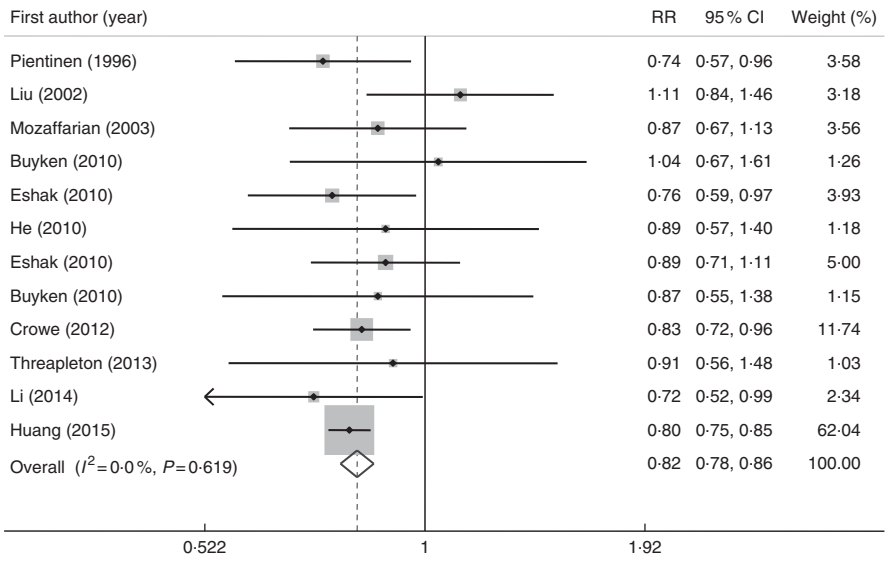

Fig. 4. Forest plots of the association between cereal fibre intake and risk of CVD mortality. RR, relative risk.

Table 2. Subgroup analysis for the association of cereal fibre intake and CVD mortality in prospective studies (Relative risks (RR) and 95% confidence intervals)

	Effect sizes	No	I^2	Q-test	RR	95% CI	$P_{Between}$
Sex							
Male[15,20,22]	3	46 294	3·2	0·35	0·85	0·72, 1·00	0·38
Female[3,4,14,15,20]	5	114 439	0·3	0·40	0·90	0·77, 1·04	
Both[5,10,12,19]	4	681 439	0·0	0·79	0·80	0·76, 0·85	
Location							
USA[3–5,10,12]	5	421 430	34·3	0·19	0·85	0·75, 0·96	0·71
Non-US[14,15,19,20,22]	7	420 742	0·0	0·83	0·83	0·76, 0·91	
Duration							
<10 years[4,5,12,22]	4	68 096	47·5	0·12	0·85	0·70, 1·03	0·53
≥10 years [3,10,14,15,19,20]	8	774 076	0·0	0·89	0·81	0·77, 0·86	
Energy adjustment							
Yes[3,4,10,12,14,15,19,22]	9	779 854	0·0	0·44	0·82	0·77, 0·86	0·68
No[5,20]	3	62 318	0·0	0·62	0·84	0·73, 0·97	

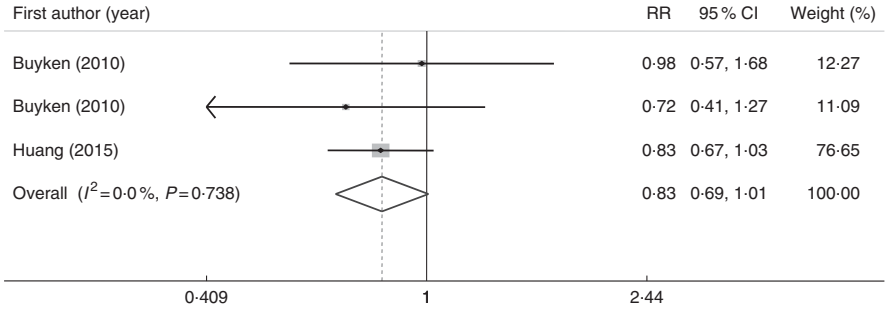

Fig. 5. Forest plots of the association between cereal fibre intake and risk of mortality from inflammatory diseases. RR, relative risk.

value to recommend. It seems that further studies are required to shed light on this issue in the future.

Several observational studies have shown that dietary fibre intake, in particular cereal fibres, have protective effects against all-cause mortality, CVD events and different types of cancers[3,5,12,20,21,24,25]. Findings of our meta-analysis were also in line with most previous publications. However, our findings about all-cause mortality, cancer mortality and inflammation-related mortality should be interpreted with caution, because few studies were available to be included in the analysis. In addition, some studies had included subjects with diabetes and MI in their analysis[3,12]. Although the majority of studies that

were included in our systematic review had reported a significant inverse association between cereal fibre intake and all-cause and CVD mortalities[8–10,12,19,22,23–25], some studies did not reach a protective effect of cereal fibre intake on cancer and inflammation-related mortalities[10,15,21,23]. Such results were also seen in the NIH-AARP Diet and Health Study, in which cereal fibre intake was associated with a lower risk of total and cause-specific death in healthy men and women[8]. Findings from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study revealed that cereal fibre intake had stronger inverse association with coronary death than fibre from other sources in Finnish men[22]. Moreover, a study from the European Prospective Investigation into Cancer and Nutrition revealed a protective association between cereal fibre intake and CVD mortality. However, there was no significant difference in the association with outcome for fibre from different sources[19]. These findings are consistent with a recent meta-analysis in which cereal fibre intake, compared with other sources of dietary fibre, had the strongest inverse association with total mortality[16]. Mozaffarian *et al.*[5] showed that cereal fibre intake was related to a lower risk of CVD events in the elderly, but reported no significant association between cereal fibre intake and CVD mortality. Other investigators have also failed to find a significant association between cereal fibre intake and CVD mortality[4,15]. Similar results have also been reached in UK Women's Cohort study in which neither total dietary fibre nor cereal fibre intake was associated with CVD mortality[14]. In the Nurses' Health Study and Health Professionals Follow-up study with a large healthy population and long-term follow-up duration, an inverse association was seen between cereal fibre intake and mortality[23,24]. Moreover, pooled data of survivors of MI in these two large cohort studies revealed an inverse significant association between cereal fibre intake and all-cause and CVD mortalities[12]. Small study population, small number of events[5,15] and short-term follow-up duration[5] in some of these mentioned studies might explain the lack of a significant association between cereal fibre intake and CVD mortality. It must be noted that when FFQ was used to assess fibre intake in earlier studies an inverse association of dietary fibre intake with risk of mortality from all-causes, CVD and cancer[4,5,14,15] was found; however, this protective effect was not reached when diet history was applied for assessment of dietary fibre[13]. Moreover, different dietary fibre definitions among included studies could be problematic, and it might affect the estimates.

Mechanisms by which cereal fibre intake might lower mortality from different causes are unknown. Cereals are one of the richest sources of insoluble fibres with laxative benefits[28]. Dietary fibres have particular effects on the composition of intestinal microbiota[10]. Decreased faecal transit time and stool-bulking effect of insoluble fibre might also result in a lower contact of potential carcinogens to the colon[7,29,30]. Cereal fibre intake is a marker of other micronutrient and mineral-rich diet related to death caused by chronic diseases[2,5,7,12]. Diets high in cereal fibre are rich in folate, antioxidants, Se, Mg, Cu, phenolic acids, lignans and phytochemicals[31,32], which might have a role in the protective association of cereal fibre with mortality. Cereal fibre might lead to lower levels of inflammatory markers including C-reactive protein and TNF-α receptor 2[10,15]. Lower levels of inflammation markers might explain, at least in part, the inverse association of cereal fibre intake with death. Moreover, it has been shown that high intake of cereal fibre was associated with a lower risk of type 2 diabetes[28]. High intake of cereals rich in insoluble fibres also has protective effects on postprandial blood glucose responses and insulin sensitivity[33]. The interference of cereal fibres with the absorption and digestion of dietary protein and the modulation of the metabolic signature of amino acids by inhibiting the activation of rapamycin/S6 kinase 1 signalling pathway are among the possible mechanisms[34,35].

This study had several strengths. The first strength is the inclusion of prospective cohort studies that resulted in a large sample size with high statistical power. Although some studies had included patients as subjects in their analysis, we excluded them to reach findings generalisable to a healthy population. Most studies included in our meta-analysis had adjusted for confounding factors. However, the possibility of residual confounders cannot be excluded. Some limitations also need to be considered. Differences in sampling methods and dietary intake assessment tools might contribute to the variation in study findings. Because cereal fibre intake was assessed by FFQ in most included studies, measurement errors were inevitable. Moreover, different definitions used for categorisation of fibre consumption might result in mis-classifications. In addition, different definitions of cereal fibre among studies might also affect the associations. The possible relationship between cereal fibre consumption and healthier lifestyle might also attenuate true associations. Although we did not find publication bias, it is not easy to exclude such bias in any meta-analysis.

In conclusion, we found an inverse association between cereal fibre intake and mortality from all causes, CVD and cancer. No significant association was observed between cereal fibre and inflammation-related mortality.

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