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Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study

Running title: Dietary fibre and risk of stroke

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1 Abstract

2 Background: Stroke risk is modifiable through many risk factors, one being healthy dietary habits.
3 Fibre intake was associated with reduced stroke risk in recent meta-analyses however data were
4 contributed by relatively few studies and few examined different stroke types.

5 Methods: 27 373 disease-free women were followed for 14.4 years. Diet was assessed with a 217-
6 item food frequency questionnaire and stroke cases were identified using English Hospital Episode
7 Statistics and mortality records. Survival analysis was applied to assess risk of total, ischaemic or
8 haemorrhagic stroke in relation to fibre intake.

9 Results: 135 haemorrhagic and 184 ischaemic stroke cases were identified in addition to 138 cases
10 where the stroke type was unknown or not recorded. Greater intake of total fibre, higher fibre
11 density and greater soluble fibre, insoluble fibre and fibre from cereals were associated with
12 significantly lower risk for total stroke. For total stroke, the hazard ratio per 6g/day total fibre intake
13 was 0.89 (95% confidence intervals: 0.81 to 0.99).

14 Different findings were observed for haemorrhagic and ischaemic stroke in healthy weight or
15 overweight women. Total fibre, insoluble and cereal fibre were inversely associated with
16 haemorrhagic stroke risk in overweight/obese participants and in healthy weight women, greater
17 cereal fibre was associated with lower ischaemic stroke risk. In non-hypertensive women, higher
18 fibre density was associated with lower ischemic stroke risk.

19 Conclusion: Greater total fibre and fibre from cereals are associated with lower stroke risk and
20 associations were more consistent with ischaemic stroke. The different observations by stroke type,
21 BMI group or hypertensive status indicates potentially different mechanisms. These may be clarified
22 through randomised controlled trials.

23 Keywords: Dietary fibre, cohort studies, stroke, survival analysis

24 Introduction

25 Across Europe, using the latest available records for each country, there are estimated to be over
26 200 000 premature stroke deaths (under 75 years) in men and around 160 000 in women annually,
27 accounting for 6% and 11% of total premature deaths in men and women respectively (1). Stroke
28 incidence has decreased over the past few decades in many developed countries but because
29 women live longer in general they experience a greater number of strokes (under and over 75 years)
30 than men (2).

31 Risk factors for stroke include the presence of hypertension, smoking, poor glycaemic control,
32 dyslipidaemia, poor diet and physical inactivity (3, 4). Addressing modifiable risk factors is therefore
33 crucial for reducing the frequency and associated burden of stroke (3). Ischaemic and haemorrhagic
34 strokes have distinctly different pathophysiology (5) and different risk factors have been identified
35 for these conditions (6) leading researchers to examine the risks separately.

36 High fibre intake is thought to lower risk through a number of plausible mechanisms. Insoluble-type
37 fibres physically bind to bile acids, which contain cholesterol, and are subsequently prevented from
38 being reabsorbed from the gut back into the body. Soluble fibres are fermented through bacterial
39 action to produce short-chain fatty-acids and this in addition to lower bile acid reabsorption are
40 thought to lower blood cholesterol levels (7-10). The viscous quality of soluble fibres also slows
41 postprandial glucose increases and the viscous gels also aid satiety (11) and are believed to
42 ultimately influence body weight by reducing energy intake (7, 9). Dietary fibre intake has also been
43 linked to lower circulating levels of C-reactive protein, a key indicator of inflammation in cross-
44 sectional analyses (12). Endothelial damage, inflammation and excess lipids are the triggers for
45 atherosclerosis, one of the main causes of cardiovascular disease development (13).

46 Two recent meta-analyses identified a small number of studies addressing the question of dietary
47 fibre and risk of stroke (14, 15). Inconsistent findings were reported for ischaemic and haemorrhagic

stroke and only two studies had considered fruit and vegetable fibre intake. Further work in large cohort studies was recommended to confirm findings (15) and explore fibre types and sources (14). The objective of this study was therefore to evaluate associations between total fibre and different food sources of fibre with risk of total stroke and stroke types, using data from a large cohort study of British women with diverse dietary intakes.

Methods*Study population*

The UK Women's Cohort Study (UKWCS) recruited 35 691 participants in the mid 1990's. Recruitment and characteristics of cohort participants have been detailed previously (16). The cohort was formed from a World Cancer Research mailing register and additional participants were recruited from friends and relatives of registered participants. Recruitment focused on middle aged women (35 to 69 years) and the study was designed to include a high proportion of non meat-eaters to enable assessment of women with diverse dietary habits and therefore include sufficient numbers of women with healthy dietary characteristics.

Dietary assessment

Habitual intake was assessed once at study baseline using a validated 217-item food frequency questionnaire (FFQ) covering intake over the previous 12 months. Total fibre intake was estimated both as non-starch polysaccharide (NSP) and using the Association of Official Analytical Chemist methods (AOAC) as detailed in a previous study (17). Additionally, soluble fibre, insoluble fibre and fibre from key food sources was estimated as in this previous study.

68 ***Covariate assessment***

69 Self-reported lifestyle characteristics were obtained at study baseline and included, weight, height,
 70 smoking and physical activity level which was calculated as metabolic equivalent tasks. United
 71 Kingdom National Statistics-Socio-Economic Classification (NS-SEC) was used to define class and
 72 women were grouped either as (1) Managerial/professional, (2) Intermediate, (3) Routine/manual.
 73 Data on participant ethnicity was collected but not used in analyses as greater than 99% of
 74 participants were white. Hypertensive status was determined using answers to the question: ‘Have
 75 you ever been told by a doctor that you have high blood pressure (hypertension)?’.

76 ***Ascertainment of stroke events***

77 Over 98% of participants provided sufficient information to allow their medical records to be
 78 traceable via the National Health Service Information Centre (NHSIC). Stroke cases were identified
 79 using International Classification of Disease (ICD) 9th edition or 10th edition codes 430–438 and
 80 I600–I69.8, respectively. Haemorrhagic strokes included records with ICD10 I60-I629, Ischaemic
 81 strokes as ICD10 I630 to I639 and I64X was used for identifying strokes where the type had not been
 82 specified in records.

83 Mortality records are available for participants since baseline and Hospital Episode Statistics (HES)
 84 for England were additionally obtained for participants from 1998 to 30th June 2011 to identify non-
 85 fatal stroke cases, using the primary diagnosis field within the HES dataset. Stroke cases were
 86 initially grouped as haemorrhagic, ischaemic or ‘unspecified’, where the type of stroke was
 87 unrecorded. Post-hoc exploration of stroke types was undertaken as estimates from other studies
 88 indicate the majority of first stroke events are ischaemic in type (4, 6). A new case group was created
 89 that included ischaemic plus unspecified strokes, with the assumption being that the majority of
 90 stroke events in this case group would be ischaemic in type.

91

92 ***Statistical methods***

93 Survival analyses were conducted using Cox proportional hazards regression (18) and study time was
 94 calculated from the date of questionnaire receipt until either date of death, date of stroke or the
 95 censor date (30th June 2011). Models were weighted by the inverse of the probability of being
 96 sampled (19). This aimed to provide results representative of the population sampled, but still
 97 benefitting from the increased power gained by using the larger number of high fibre consumers.
 98 Estimates and confidence intervals did not greatly differ in models with or without this weighting
 99 factor.

100 The following exclusions were applied to the sample: insufficient data to allow linkage to NHSIC
 101 (n=695), did not provide both diet and lifestyle information (n=699), died within 1 year of baseline
 102 (n=129), self-reported history of stroke (n=264), heart attack (n=497), cancer (n=2443), diabetes
 103 (n=646) or angina (n=718), implausible energy intake as estimated from FFQ (outside range 500 to 6
 104 000kcal/day or 2.1 to 25.1MJ/day) (n=459) or requested to be removed from study (n=1). Women
 105 whose baseline address was listed outside of England (14%) were additionally removed as HES data
 106 related to English hospitals only (n=3872). Participants with history of chronic diseases were
 107 excluded rather than accounted for through adjustment to avoid potential bias from reverse
 108 causality. Women with known health conditions may be eating a modified diet (e.g. higher in fibre)
 109 and separately be at greater risk of stroke.

110 Model covariates were identified using a directed acyclic graph (DAG) to identify the minimal
 111 sufficiency set of adjustments (20) in addition to examining the potential for over-adjustment
 112 through correlation, χ^2 or analysis of variance tests for each potential pair of confounders. For
 113 example, saturated fat intake was highly correlated with energy intake (0.76) and was therefore not
 114 included as a covariate.

Results are presented for models adjusted only for age (years) or additionally for, BMI (Kg/m^2), calories from carbohydrate, fat and protein (Kcal/day), ethanol intake (g/day), MET (hours/week), smoking status (current vs. not current smoker) and socioeconomic status. An intermediate model was conducted that did not include energy intake or BMI as these are one of the potential mechanisms for the action of fibre on stroke risk. Both the intermediate and fully-adjusted models were derived from the DAG allowing for different potential mechanisms for the action of fibre on stroke risk to be explored. The model without adjustment for BMI and energy intake assumes the action of fibre on stroke risk is via weight gain. The fully adjusted model including these additional covariates explores the association through other routes than weight gain and it was therefore important to account for these factors in analyses. Results from this intermediate model were not substantially different from the fully-adjusted results and are therefore not presented here but are discussed where relevant. Models exploring fibre density were conducted with and without adjustment for energy intake, as suggested for nutrient density analyses (21). The results presented here for fibre density do not include adjustment for energy intake and findings were not appreciably different in the two models.

Relative risk was assessed in fibre intake categories compared to the lowest consumers (sample divided into five approximately equal groups for each fibre exposure). To assess potential linear trends, increments (or dose values) were created for each exposure that approximately matched the mean difference in fibre intake between the fifths, to reflect the increase trend within this sample. Categorical exposures were not examined in subgroups because of too few cases being available within each exposure group.

Pre-defined subgroups were examined where there were a minimum of 50 cases available for models (Supplementary Table 1). BMI category (healthy, overweight or obese), presence of hypertension and menopausal status were explored, although models could only be conducted in postmenopausal women as there were too few cases in the premenopausal subgroup. Subgroup

analyses were conducted for potential effect modifiers, where a biologically plausible mechanism exists for the different effect of fibre on stroke risk within these subgroups. Independent associations with CVD risk have been proposed for menopausal status (22) and BMI (23, 24) and hypertensive status was explored to isolate potential reverse causality caused by knowledge of ill health and modified diet in participants.

For primary analyses (full sample) a 2-sided p value <0.05 was considered statistically significant. However, to mitigate the chance of observing false positive results through conducting multiple tests, the accepted significance level was reduced to $p<0.01$ for subgroups. Stata version 12 (25) was used for all data manipulation and analyses.

Ethical approval

Ethical approval for this work was granted by the National Research Ethics Committee-Yorkshire and the Humber, Leeds East in December 2011.

Results

After exclusions, 27 373 women remained for analyses and 388 incident strokes were identified. After mean follow-up of 14.4 years (SD 1.8) 135 Haemorrhagic, 184 ischaemic and 138 unspecified cases were identified. When ischaemic and unspecified cases were combined 284 cases were available.

Characteristics across increasing fibre intake categories are detailed in Table 1 and indicate average NSP intake in the cohort to be approximately 24g/day, with cereals being the largest contributor to total intake. BMI was lowest in the highest fibre intake group 23.8 kg/m^2 (SD 3.9) and highest in the lowest fibre category 24.8 kg/m^2 (SD 4.5). The lowest fibre intake group included the greatest proportion of smokers (18%), meat-eaters (79%) and had the lowest physical activity level among the groups.

Greater intake of total dietary fibre, assessed as NSP or using the AOAC method, higher fibre density and greater intake of soluble fibre, insoluble fibre and fibre from cereals were all associated with significantly lower risk for total stroke (Table 2). With each 6g/day higher intake of total NSP, risk of total stroke was 11% lower: hazard ratio (HR) 0.89 (95% confidence intervals (CI): 0.81 to 0.99) $p=0.03$.

Total fibre intake, insoluble fibre, soluble fibre and vegetable fibre were all associated with significantly lower risk of unspecified-type stroke in the fully-adjusted dose-response models (Table 3). Each 6g/day higher intake of NSP was associated with 24% lower risk HR 0.76 (95% CI: 0.63 to 0.92) $p<0.01$ and with each 2g/day greater vegetable fibre HR 0.80 (95% CI: 0.68 to 0.92) $p<0.01$.

The majority of estimates for haemorrhagic and ischaemic stroke indicated a protective association but CIs were generally wide and no significant associations were observed in the fully-adjusted models for dose-response associations except with cereal fibre (Table 3). The relative risk of ischaemic stroke was HR 0.89 (95% CI: 0.80 to 1.00) $p=0.05$ with greater cereal fibre intake (each 3g/day).

Estimates of relative risk for 'mostly ischaemic' stroke (ischaemic plus unspecified cases) largely reflect those seen for the unspecified type stroke but tend to be slightly weaker compared to unspecified strokes although CIs were narrower on the whole in this larger case category. For example, with total fibre intake (AOAC), unspecified stroke risk was HR 0.74 (95% CI: 0.57 to 0.94) with each 11g/day greater intake and HR 0.80 (95% CI: 0.68 to 0.95) for 'mostly ischaemic' stroke.

183 ***Overweight or obese women***

184 Lower relative risk for total stroke was observed in obese women with greater legume fibre intake
 185 0.60 (95% CI: 0.41 to 0.87) $p < 0.01$. Overweight and obese participants were combined for
 186 haemorrhagic stroke due to small case numbers and total fibre (AOAC) (0.76 (95% CI: 0.59 to 0.97)
 187 $p = 0.03$), cereal fibre (0.85 (95% CI: 0.72 to 1.00) $p = 0.05$), fibre from breakfast cereals (0.83 (95% CI:
 188 0.69 to 1.00) $p = 0.05$) and insoluble fibre (0.81 (95% CI: 0.69 to 0.97) $p = 0.02$) were associated with
 189 lower relative risk. Fibre from nuts or seeds was additionally associated with lower relative risk of
 190 unspecified stroke 0.78 (95% CI: 0.62 to 0.97) $p = 0.03$.

191 ***Healthy weight women***

192 In contrast to the overweight and obese subgroups, protective associations for the various fibre
 193 exposures (total fibre, fibre density, insoluble fibre, cereal fibre) and relative risk of 'mostly
 194 ischaemic' stroke remained in healthy weight women, reflecting results seen in the full sample of
 195 participants. With greater intake of insoluble fibre (each 4g/day), HR 0.81 (95% CI: 0.70 to 0.95)
 196 $p < 0.01$ and with greater soluble fibre intake (3g/day), risk of 'mostly ischaemic' stroke was 0.83 (95%
 197 CI: 0.67 to 1.02) $p = 0.08$.

198 In healthy weight women, greater legume fibre intake (per 1g/day) was associated with increased
 199 risk of haemorrhagic stroke HR 1.11 (95% CI: 1.00 to 1.24) $p = 0.05$ in the fully adjusted models. For
 200 ischaemic stroke, unlike with the full sample, lower relative risk was observed with greater total
 201 cereal fibre (0.83 (95% CI: 0.71 to 0.98) $p = 0.03$), fibre from breakfast cereals (0.78 (95% CI: 0.66 to
 202 0.92) $p < 0.01$), AOAC fibre density (0.85 (95% CI: 0.73 to 1.00) $p = 0.05$) and insoluble fibre (0.82 (95%
 203 CI: 0.67 to 0.99) $p = 0.04$). Total NSP (0.78 (95% CI: 0.61 to 0.99) $p = 0.04$), vegetable fibre (0.80 (95%
 204 CI: 0.68 to 0.95) $p = 0.01$) and soluble fibre (0.74 (95% CI: 0.55 to 1.00) $p = 0.05$) were associated with
 205 lower relative risk of unspecified type stroke in healthy weight women.

206

207 ***Postmenopausal women***

208 In the postmenopausal subgroup, vegetable fibre per 2g/day increase was associated with increased
 209 risk of haemorrhagic stroke HR 1.08 (95% CI: 1.02 to 1.14) p=0.01 but a decreased risk of unspecified
 210 stroke 0.80 (95% CI: 0.66 to 0.96) p=0.02, in fully adjusted models. As with the full sample analyses,
 211 total fibre, soluble and insoluble fibre were all associated with lower relative risk of unspecified
 212 stroke in this subgroup although not when fibre was calculated using the AOAC method.

213 ***Hypertensive status***

214 There were only sufficient cases to explore associations for 'mostly ischaemic' stroke risk in those
 215 reporting doctor-diagnosed hypertension at baseline. In this subgroup, only greater cereal fibre
 216 intake, per 3g/day increase, was associated with lower risk HR 0.84 (95% CI: 0.70 to 1.00) p=0.05.

217 Results for non-hypertensive women were largely similar to the full sample with various exposures
 218 being associated with lower risk for unspecified or mostly ischaemic stroke and none being
 219 associated with haemorrhagic stroke risk. Unlike the full sample analyses, additional associations
 220 became apparent for risk of ischaemic stroke: greater NSP density (per 2g/1000kcal/day) HR 0.88
 221 (95% CI: 0.77 to 1.00) p=0.05, AOAC density (per 3g/1000kcal/day) 0.86 (95% CI: 0.75 to 0.98) p=0.02
 222 and fibre from breakfast cereals (per 2g/day) 0.81 (95% CI: 0.71 to 0.93) p<0.01.

223 **Discussion**

224 ***Total stroke***

225 The estimated relative risk reduction of 13% observed here for total stroke and total dietary fibre
 226 (AOAC) intake (per 11g/day increase) HR 0.87 (95% CI: 0.76 to 0.99) is of a similar magnitude to the
 227 7% reduction per 7g/day seen in the recent systematic review and meta-analysis of other
 228 prospective cohort studies (14). In this systematic review and meta-analysis, whilst there was also
 229 some indication of lower stroke risk with greater soluble fibre intake, the result did not reach

statistical significance (14). However, in this cohort lower relative risk for stroke was associated with higher soluble fibre intake 0.88 (95% CI: 0.77 to 1.00). This finding may be attributed to study population differences, such as the greater variation in dietary intakes in the UKWCS, compared to other studies.

Protective associations were apparent here for cereal and not fruit or vegetable sources of fibre which may reflect protective benefits of cereal grains generally (26) or the greater relative proportion of insoluble to soluble type fibre (9). Additionally, these observations may simply reflect better measurement of cereal foods compared to fruit and especially vegetables since there is evidence of over-reporting of vegetables in other British cohort studies (27, 28).

The inverse associations observed for greater fibre and stroke risk in the full sample were also observed in the obese but not healthy weight or overweight subsamples. Obesity is a well established risk factor for stroke (3) and results in systemic inflammation which is thought to initiate and mediate the development of vascular damage (29). Additional fibre intake may confer no additional benefit in those who are at lower risk of stroke (i.e. not obese) but could be particularly beneficial where risk is greater because of higher BMI and inflammation.

Haemorrhagic and ischaemic stroke

Only one significant association was observed in the full sample analyses for haemorrhagic or ischaemic types of stroke; an 11% lower relative risk of ischaemic stroke was observed for each 3g/day greater cereal fibre intake. The inverse associations observed with total fibre, soluble, insoluble and cereal fibre in the unspecified type stroke were also apparent when ischaemic cases were combined with the unspecified strokes. Combining cases in this way tended to slightly attenuate the strength of associations but CIs were generally tighter in this larger sample of cases. The narrowing of CIs gives greater certainty to the estimates quantifying the degree of risk reduction seen with each specified fibre type. The marginally larger risk reductions observed for the unspecified strokes may be related to a difference in the nature or severity of events that are

recorded as either haemorrhagic or ischaemic or where the type of event is unknown and unrecorded. Four other cohorts identified during a recent systematic review of literature (14) had also considered the associations between fibre and stroke sub-types (30-33). Findings from these studies do not help to explain observations seen for the UKWCS as they are not consistent between the studies, making it challenging to formulate a consensus on risk of different types of stroke in relation to fibre. The differing observations may result from measurement error in assessing fibre intake from different foods in the various assessment tools. Additionally, the likely large variation in diets and variation in sources of fibre between the UK, US, Finland, Japan and Sweden and the possible variation in magnitude of other stroke risk factors, such as levels of obesity and smoking habits, observed in these different countries may somewhat account for differences.

Inverse associations that were not apparent in the full sample analysis or healthy weight subgroup became apparent for haemorrhagic stroke risk when examining overweight or obese women indicating that the effect of fibre on the relative risk of stroke may be modified with greater BMI.

Strengths and limitations

This large prospective study, with a long period of follow up, provided sufficient cases of each type of stroke to allow these to be examined separately. This approach is especially important for stroke because risk factors for the two main types differ (6). Combining ischaemic with the unknown type stroke cases provided narrower CIs around risk estimates but a limitation with this approach is that some sensitivity may be lost through including a small number of unidentified haemorrhagic stroke cases into this category.

A further unique strength of this cohort is the validated FFQ used in a sample with diverse dietary intakes. However, there are naturally limitations in assessing diet through any method and specific limitations with the use of FFQs (34, 35). Additionally, relying on self-reported height, weight and other lifestyle characteristics is a limitation in this study.

Although the UKWCS includes women with a range of different education and socioeconomic classifications, it is a clear limitation that results from the UKWCS may not directly relate to the general population as participants are likely to be better educated and healthier than the UK population on the whole. A further limitation is the unknown applicability of current findings to men of similar ages.

A major limitation with analysis of data from prospective observational studies is the potential for uncontrolled confounding, either via another lifestyle variable not considered in models or via an included confounder that has been imperfectly measured. It is conceivable that fibre itself is not directly acting to influence stroke risk, despite plausible mechanisms discussed above, but another closely correlated nutrient or food component, or maybe both, may elicit the effect (36).

Uncontrolled confounding may similarly explain the few positive associations between fibre intake and increased stroke risk. Fibre from legumes was associated with greater haemorrhagic stroke risk in healthy weight women but with lower total stroke risk in overweight women. This positive association may relate to some uncontrolled lifestyle or dietary characteristic of high legume consumers.

Meta-analyses prior to this study found protective associations between dietary fibre and stroke although this work identified that there were too few studies exploring stroke subtypes and exploring the key types or food sources of fibre (14, 15) .

This study adds new data to this little studied area and has identified that greater intakes of fibre are associated with lower total stroke risk in a cohort of English middle aged women. The associations were stronger and more consistent with ischaemic stroke, where more cases had been observed, and with cereal sources of fibre. Protective associations were also apparent in non hypertensive women and also in obese participants.

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305 **Conflict of Interest**

306 The PhD studentship for D Threapleton was sponsored by Kellogg Sales and Marketing UK Ltd. DCG
307 has held an unrelated research grant (a study of infant diet) funded by Danone and has received
308 personal fees from American Institute for Cancer Research / World Cancer Research Fund, outside
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References

1. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, et al. European Cardiovascular Disease Statistics. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis. 2012.
2. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, et al. Coronary heart disease statistics. A compendium of health statistics. British Heart Foundation Health Promotion Research Group. Department of Public Health, University of Oxford. [Online]. Available at <http://www.bhf.org.uk/publications/view-publication.aspx?ps=1002097> [Accessed 2013]. 2012.
3. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011 Feb;42(2):517-84.
4. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010 Jul 10;376(9735):112-23.
5. Frizzell JP. Acute stroke: pathophysiology, diagnosis, and treatment. *AACN Clin Issues*. 2005 Oct-Dec;16(4):421-40.
6. Andersen KK, Olsen TS, Dehlendorff C, Kammergaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke*. 2009 Jun;40(6):2068-72.
7. James SL, Muir JG, Curtis SL, Gibson PR. Dietary fibre: a roughage guide. *Internal Medicine Journal*. 2003 Jul;33(7):291-6.
8. British Nutrition Foundation. Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors. Report of the British Nutrition Foundation Task Force. S. S, editor. Oxford: Blackwell Publishing Ltd; 2005.
9. Lunn J, Buttriss JL. Carbohydrates and dietary fibre. *British Nutrition Foundation Nutrition Bulletin*. 2007;32:21-64.
10. Coultate TP. Chapter 3 Polysaccharides. In: Coultate TP, editor. *Food The Chemistry of its components*. Cambridge: The Royal Society of Chemistry; 2009. p. 75.
11. Wanders AJ, van den Borne JJ, de Graaf C, Hulshof T, Jonathan MC, Kristensen M, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev*. 2011 Sep;12(9):724-39.
12. King DE. Dietary fiber, inflammation, and cardiovascular disease. *Mol Nutr Food Res*. 2005 Jun;49(6):594-600.
13. George SJ, Lyon C. Pathogenesis of Atherosclerosis. In: Johnson J, George SJ, editors. *Atherosclerosis: molecular and cellular mechanisms*: Wiley-VCH; 2010.
14. Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary fiber intake and risk of first stroke: a systematic review and meta-analysis. *Stroke*. 2013 May;44(5):1360-8.
15. Zhang Z, Xu G, Liu D, Zhu W, Fan X, Liu X. Dietary fiber consumption and risk of stroke. *Eur J Epidemiol*. 2013 Feb;28(2):119-30.
16. Cade JE, Burley VJ, Greenwood DC. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutrition*. 2004 Oct;7(7):871-8.
17. Threapleton DE, Greenwood DC, Burley VJ, Aldwairji M, Cade JE. Dietary fibre and cardiovascular disease mortality in the UK Women's Cohort Study. *Eur J Epidemiol*. 2013 Apr;28(4):335-46.
18. Cox DR, Oakes D. *Analysis of Survival Data*. London: Chapman & Hall/CRC; 1984.
19. Kohler U, Kreuter F. *Data Analysis Using Stata*. Third ed. Texas: Stata Press; 2012.
20. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999 Jan;10(1):37-48.

21. Willett WW, Stampfer MJ. Implications of total energy intake for epidemiologic analyses. In: Willett WW, editor. *Nutritional Epidemiology*. Second ed. Oxford: Oxford University Press; 1998. p. 273-300.
22. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol*. 2009 Dec 15;54(25):2366-73.
23. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, Davey Smith G, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PLoS Med*. 2012;9(5):e1001212.
24. Logue J, Murray HM, Welsh P, Shepherd J, Packard C, Macfarlane P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. *Heart*. 2011 Apr;97(7):564-8.
25. StataCorp. *Stata Statistical Software: Release 12*. College Station, TX. StataCorp LP. 2011.
26. Slavin J. Why whole grains are protective: biological mechanisms. *Proceedings of the Nutrition Society*. 2003 Feb;62(1):129-34.
27. Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *International Journal of Epidemiology*. 1997;26 Suppl 1:S137-51.
28. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *British Journal of Nutrition*. 2001 Sep;86(3):405-14.
29. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res*. 2005 May 13;96(9):939-49.
30. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *American Journal of Epidemiology*. 2005;161(2):161-9.
31. Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Dietary fiber and fiber-rich food intake in relation to risk of stroke in male smokers. *European Journal of Clinical Nutrition*. 2009;63(8):1016-24.
32. Wallstrom P, Sonestedt E, Hlebowicz J, Ericson U, Drake I, Persson M, et al. Dietary fiber and saturated fat intake associations with cardiovascular disease differ by sex in the Malmo diet and cancer cohort: A prospective study. *PLoS ONE*. 2012 27 Feb;7(2).
33. Kokubo Y, Iso H, Saito I, Yamagishi K, Ishihara J, Inoue M, et al. Dietary fiber intake and risk of cardiovascular disease in the Japanese population: The Japan Public Health Center-based study cohort. *European Journal of Clinical Nutrition*. 2011 November;65(11):1233-41.
34. Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires - a review. *Public Health Nutrition*. 2002 Aug;5(4):567-87.
35. Willett W, Lenart E. Reproducibility and validity of Food Frequency Questionnaires. In: Hofman A, Marmot M, Samet J, Savitz DZ, editors. *Nutritional Epidemiology*. Third ed. Oxford: Oxford University Press; 2013.
36. Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, et al. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *British Journal of Nutrition*. 1994 Oct;72(4):619-43.