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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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Abstract

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

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

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

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

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

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

Introduction

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

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

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

Two recent meta-analyses identified a small number of studies addressing the question of dietary 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.

Covariate assessment

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

Ascertainment of stroke events

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

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

Statistical methods

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

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

Model covariates were identified using a directed acyclic graph (DAG) to identify the minimal sufficiency set of adjustments (20) in addition to examining the potential for over-adjustment through correlation, χ^2 or analysis of variance tests for each potential pair of confounders. For example, saturated fat intake was highly correlated with energy intake (0.76) and was therefore not 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 24.8kg/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.

Overweight or obese women

Lower relative risk for total stroke was observed in obese women with greater legume fibre intake 0.60 (95% CI: 0.41 to 0.87) p<0.01. Overweight and obese participants were combined for haemorrhagic stroke due to small case numbers and total fibre (AOAC) (0.76 (95% CI: 0.59 to 0.97) 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: 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 lower relative risk. Fibre from nuts or seeds was additionally associated with lower relative risk of unspecified stroke 0.78 (95% CI: 0.62 to 0.97) p=0.03.

Healthy weight women

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

In healthy weight women, greater legume fibre intake (per 1g/day) was associated with increased risk of haemorrhagic stroke HR 1.11 (95% CI: 1.00 to 1.24) p=0.05 in the fully adjusted models. For ischaemic stroke, unlike with the full sample, lower relative risk was observed with greater total 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 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% 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% 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 lower relative risk of unspecified type stroke in healthy weight women.

Postmenopausal women

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

Hypertensive status

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

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

Discussion

Total stroke

The estimated relative risk reduction of 13% observed here for total stroke and total dietary fibre (AOAC) intake (per 11g/day increase) HR 0.87 (95% CI: 0.76 to 0.99) is of a similar magnitude to the 7% reduction per 7g/day seen in the recent systematic review and meta-analysis of other prospective cohort studies (14). In this systematic review and meta-analysis, whilst there was also 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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Conflict of Interest

The PhD studentship for D Threapleton was sponsored by Kellogg Sales and Marketing UK Ltd. DCG has held an unrelated research grant (a study of infant diet) funded by Danone and has received personal fees from American Institute for Cancer Research / World Cancer Research Fund, outside the submitted work. Funding bodies played no part in data collection, analysis, interpretation, or decision to publish.

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