Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis

Diane E Threapleton,[1] Darren C Greenwood,[2] Charlotte E L Evans,[1] Christine L Cleghorn,[1] Camilla Nykjaer,[1] Charlotte Woodhead,[1] Janet E Cade,[1] Christopher P Gale,[2] Victoria J Burley[1]

EDITORIAL by Baron

[1]Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds LS2 9JT, UK
[2]Centre for Epidemiology and Biostatistics, University of Leeds, UK
Correspondence to: V J Burley
v.j.burley@leeds.ac.uk

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STUDY QUESTION

Is greater intake of dietary fibre related to lower risk of cardiovascular or coronary heart disease, using a dose-response approach?

SUMMARY ANSWER

For each increase of 7 g/day intake of fibre, separate risks for cardiovascular disease and coronary heart disease were each 9% lower.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous observational studies have reported greater fibre intake being associated with lower risk of cardiovascular disease, with others reporting no such associations. This work explores potential dose-response associations and attempts to quantify the potential sources of heterogeneity between included studies.

Selection criteria for studies

We searched the Cochrane Library, Medline, Medline in-process, Embase, CAB Abstracts, ISI Web of Science, and BIOSIS; hand searched appropriate journals; and cross checked bibliographies of relevant review articles to identify studies published between 1 January 1990 and 6 August 2013. Included articles reported on prospective observational studies, with at least three years' follow-up and were reported in English language. Included studies reported intake of total dietary fibre, soluble or insoluble fibre, or fibre from food sources in relation to risk of coronary heart disease or cardiovascular disease.

Primary outcome(s)

Fatal, non-fatal, or total primary (first occurrence) event of coronary heart disease or cardiovascular disease.

Main results and role of chance

Evidence from 19 included studies, which had accounted for influences of appropriate potential confounders, indicated that lower risk of cardiovascular disease and coronary heart disease was associated with greater intake of total fibre, insoluble fibre, and fibre from cereals and vegetables. Greater fruit fibre was also associated with lower risk for cardiovascular disease. With each increase of 7 g/day in intake of total fibre, relative risks were 0.91 (95% confidence interval 0.88 to 0.94) and 0.91 (0.87 to 0.94) for cardiovascular disease and coronary heart disease, respectively.

Bias, confounding, and other reasons for caution

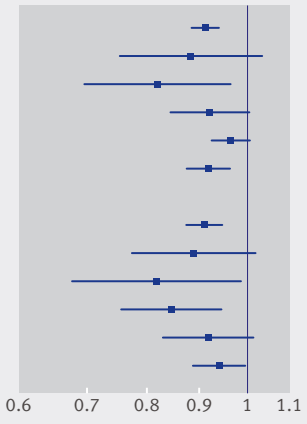
Fibre intake could be a surrogate marker for another healthy lifestyle or dietary behaviour, however there are plausible mechanisms and trial evidence for the action of dietary fibre on key risk factors for the development of cardiovascular disease and coronary heart disease. Adjustments used in the included studies may not have fully accounted for potential confounding influences. Dietary assessment is notoriously challenging, with measurement error being a particular difficulty. The bias can be large and in either direction, and hence we focused on the general direction and relative magnitude of associations. Studies were from a range of countries and reported on participants with wide variations in dietary fibre intakes.

Study funding/potential competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Department of Health for England and support for DET from Kellogg Marketing and Sales Company (UK) for the submitted work; DCG, CELC, CLC, CN, CW, JEC, CPG, and VJB have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Funding bodies played no part in article selection, analysis, interpretation, or decision to publish.

Risk of cardiovascular and coronary heart disease and fibre intake

Outcome and exposure	No of studies	I^2 (%)	Risk ratio (95% CI)
Total cardiovascular disease			
Total fibre (per 7 g/day)	10	45	0.91 (0.88 to 0.94)
Soluble fibre (per 4 g/day)	4	58	0.88 (0.75 to 1.03)
Insoluble fibre (per 7 g/day)	3	46	0.82 (0.70 to 0.96)
Fibre in cereals (per 7 g/day)	5	15	0.92 (0.84 to 1.00)
Fibre in fruit (per 4 g/day)	4	0	0.96 (0.93 to 1.00)
Fibre in vegetables (per 4 g/day)	4	0	0.92 (0.87 to 0.96)
Coronary heart disease			
Total fibre (per 7 g/day)	12	33	0.91 (0.87 to 0.94)
Soluble fibre (per 4 g/day)	6	47	0.89 (0.78 to 1.02)
Insoluble fibre (per 7 g/day)	5	72	0.82 (0.68 to 0.99)
Fibre in cereals (per 7 g/day)	9	65	0.84 (0.76 to 0.94)
Fibre in fruit (per 4 g/day)	9	62	0.92 (0.83 to 1.01)
Fibre in vegetables (per 4 g/day)	9	0	0.94 (0.89 to 1.00)



Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study

Jacob George,[1] Waseem Majeed,[2] Isla S Mackenzie,[3] Thomas M MacDonald,[3] Li Wei[3 4]

EDITORIAL by Strazzullo

[1]Division of Medical Science, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
[2]NHS Tayside, Ninewells Hospital, Dundee DD1 9SY, UK
[3]Medicines Monitoring Unit and Hypertension Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
[4]Department of Practice and Policy, UCL School of Pharmacy, London WC1H 9JP, UK
Correspondence to: T MacDonald
tom@memo.dundee.ac.uk

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STUDY QUESTION

Do patients taking sodium-containing formulations of prescription drugs have a higher incidence of cardiovascular events than patients taking those same drugs in formulation that do not contain sodium?

SUMMARY ANSWER

Patients prescribed sodium-containing effervescent, dispersible, and soluble drugs had an increased risk of incident non-fatal myocardial infarction, incident non-fatal stroke, or vascular death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous observational studies have shown that excess salt is known to be detrimental to cardiovascular health. This study shows that sodium-containing formulations of commonly prescribed drugs are associated with an increased risk of cardiovascular events in patients who are prescribed them. The increased risk was primarily driven by an increased risk of hypertension and stroke.

Participants and setting

The study population consisted of residents in the United Kingdom who were registered with their general practitioner and had more than one recorded contact from January 1987 to December 2010. All patients who received at least two prescriptions of sodium-containing formulations or matched standard formulations of the same drugs from January 1987 to December 2010 formed the study population. We selected only drugs with more than 1000 prescriptions in the entire Clinical Practice Research Datalink (CPRD) database. For each case, we matched one control using incidence density sampling on year of birth, sex, and general practice attended.

Design, size, and duration

We performed a nested case-control study and included 1 292 337 patients. We included 61 072 incident cardiovascular event cases and matched controls. The mean follow-up time was 7.23 years.

Primary outcome, risks, exposures

Cardiovascular events were defined by the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or vascular death.

Main results and the role of chance

For the primary endpoint of incident non-fatal myocardial infarction, incident non-fatal stroke, or vascular death, the adjusted odds ratio for sodium exposure was 1.16 (95% confidence interval 1.12 to 1.21). The adjusted odds ratios for the secondary endpoints were 1.22 (1.16 to 1.29) for incident non-fatal stroke, 1.28 (1.23 to 1.33) for all cause mortality, 7.18 (6.74 to 7.65) for hypertension, 0.98 (0.93 to 1.04) for heart failure, 0.94 (0.88 to 1.00) for incident non-fatal myocardial infarction, and 0.70 (0.31 to 1.59) for vascular death. The median time from date of first prescription (that is, the date of entry into the cohort) to the first event was 3.92 years. Compared with controls the adjusted odds ratios were 1.10 (0.99 to 1.22) for the lowest third (≤7120 mmol sodium), 1.33 (1.20 to 1.48) for the middle third (7121-30 285 mmol sodium), and 1.31 (1.18 to 1.45) for the high third (>30 286 mmol sodium). A test for linear trend showed there was a significant trend in the dose-response relation (P<0.01). To put these findings into context, the median sodium consumption from sodium-containing drugs alone in our study was 106.8 mmol/day. This amount is higher than the current recommended dietary intake of 104 mmol/day.

Bias, confounding, and other reasons for caution

There could be coding misclassification for the exposures, outcomes, and covariates in the database. The present study is observational, and other potential confounding factors and biases could not be fully controlled. Data on unmeasured or unmeasurable risk factors such as health behaviour and family history were not available. We had no data on dietary sodium and could not control for this. Finally, we could not control for medicines bought over the counter.

Generalisability to other populations

Though the results of this study are generalisable as it is derived from a general practice database, our exclusion criteria should be noted.

Study funding/potential competing interests

This study was funded by Tenovus Scotland (Ref T10/12).

Odds ratios and 95% confidence intervals for composite cardiovascular outcome* and individual outcomes for sodium-containing formulations group compared with standard formulations group (OR=1)

	OR (95% CI)	
	Unadjusted	Adjusted
Composite cardiovascular outcome*	1.13 (1.09 to 1.18)	1.16 (1.12 to 1.21)
Individual outcomes		
Incident non-fatal myocardial infarction	0.90 (0.85 to 0.96)	0.94 (0.88 to 1.00)
Incident non-fatal stroke	1.21 (1.15 to 1.28)	1.22 (1.16 to 1.29)
Vascular death	0.62 (0.31 to 1.24)	0.70 (0.31 to 1.59)
Hypertension	6.80 (6.41 to 7.21)	7.18 (6.74 to 7.65)
Heart failure	0.95 (0.91 to 1.00)	0.98 (0.93 to 1.04)
All cause mortality	1.30 (1.25 to 1.35)	1.28 (1.23 to 1.33)

*Incident non-fatal myocardial infarction, incident non-fatal stroke, and vascular death.

Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis

Sophie Grigoriadis,[1 2] Emily H VonderPorten,[1] Lana Mamisashvili,[1] George Tomlinson,[3] Cindy-Lee Dennis,[4] Gideon Koren,[5] Meir Steiner,[6] Patricia Mousmanis,[7] Amy Cheung,[1 2] Lori E Ross[8]

[1]Department of Psychiatry, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada, M4N 3M5
[2]Department of Psychiatry, Faculty of Medicine, University of Toronto and Sunnybrook Research Institute, Toronto, Ontario, Canada
[3]Department of Medicine, University Health Network/Mount Sinai Hospital, Toronto, Ontario, Canada
[4]Faculties of Nursing and Medicine, University of Toronto and Women's College Research Institute, Toronto, Ontario, Canada
[5]Motherisk Program, Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada
[6]Women's Health Concerns Clinic, St Joseph's Healthcare, Hamilton, Ontario, Canada
[7]Healthy Child Development Program, Ontario College of Family Physicians, Toronto, Ontario, Canada
[8]Health Systems and Health Equity Research Group, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
Correspondence to: S Grigoriadis **sophie.grigoriadis@sunnybrook.ca**

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- Research: Use of antidepressants near delivery and risk of postpartum hemorrhage (*BMJ* 2013;347:f4877)
- Research: Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders (*BMJ* 2013;346:f2059)

STUDY QUESTION

What is the association between antenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn (PPHN)?

SUMMARY ANSWER

Infants seem to be at increased risk for developing PPHN after exposure to selective serotonin reuptake inhibitors (SSRIs) during late pregnancy. A significant relationship for exposure in early pregnancy was not evident.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Treatment decisions regarding antidepressant use during pregnancy are multifactorial and the fetus/neonate must also be considered. The risk for PPHN in infants exposed to SSRIs during late pregnancy was small although significantly increased; however, the absolute risk remained low (286 to 351 women would need to be treated to result in an average of one additional case of PPHN).

Selection criteria for studies

We searched Embase, Medline, PsycINFO, and CINAHL to 30 December 2012. Cohort and case-control English language studies were eligible if they reported on PPHN after any exposure to antidepressants, had a comparison group of unexposed pregnant women, and, if an effect size was not already provided, included enough data from which one could be calculated. We carried out a systematic review and meta-analysis.

Primary outcome

Pooled odds ratio for PPHN after antenatal exposure to antidepressants.

Main results and role of chance

Of 738 articles retrieved, seven studies were included in this meta-analysis. Analyses were limited to exposure to SSRIs. Exposure in early pregnancy was not significant (odds ratio 1.23, 95% confidence interval 0.58 to 2.60; P=0.58; 3 studies), and significant heterogeneity was found across studies (Q_2=9.00, P=0.01) in the high range (I^2=77.8%). Exposure to SSRIs at any time in pregnancy was also not significant (1.55, 0.79 to 3.04; P=0.20; n=2), as was heterogeneity across studies (Q_1=0.14, P=0.71, I^2=0.0%). Exposure to SSRIs for most or all of pregnancy was significant (3.33, 1.58 to 7.02; P=0.002; n=2), and heterogeneity across studies was not significant (Q_1=0.18, P=0.67, I^2=0.0%). Exposure in late pregnancy was also significant (2.50, 1.32 to 4.73; P=0.005; n=5), with study heterogeneity not significant, although the I^2 was in the moderate range of heterogeneity (Q_4=8.31, P=0.08, I^2=51.9%). The analysable potential moderator variables for late exposure (study design, congenital malformations, and meconium aspiration) did not account for significant sources of heterogeneity. Publication bias was indicated, with a slightly higher revised estimate for late exposure (2.84, 1.41 to 5.72; P=0.004). With an estimated PPHN baseline risk of 1.9/1000 livebirths and using our pooled odds ratios we estimated that 286 to 351 women would need to be treated with an SSRI in late pregnancy to result in an average of one additional case of PPHN.

Bias, confounding, and other reasons for caution

Limitations of pooled studies included lack of uniformity in the definition of antidepressant exposure, poor information on the severity and definition of PPHN, lack of control for PPHN risk factors, reliance on prescription registries, and lack of control for underlying psychiatric conditions that may have an independent or moderating effect.

Study funding/potential competing interests

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Risk of persistent pulmonary hypertension of the newborn (PPHN) and number needed to treat to harm (NNTH) for population risk of 1.9/1000 liveborn infants

	Per 1000 liveborn infants (%)		
Pooled odds ratio	Risk of PPHN	Absolute risk difference	NNTH (No of women)
SSRIs in late pregnancy:			
2.84 (trim and fill revised)	5.40 (0.54)	3.50 (0.35)	286
2.5	4.75 (0.48)	2.85 (0.29)	351
SSRIs in early pregnancy:			
1.23	2.34 (0.23)	0.44 (0.04)	2288

Quality of reporting in systematic reviews of adverse events: systematic review

Liliane Zorzela,[1] Su Golder,[2] Yali Liu,[3] Karen Pilkington,[4] Lisa Hartling,[5] Ari Joffe,[6] Yoon Loke,[7] Sunita Vohra[8]

[1]Department of Pediatrics, 4-548 Edmonton Clinic Health Academy, University of Alberta, Edmonton, Canada
[2]Centre for Reviews and Dissemination, University of York, York, UK
[3]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Chengguan District, Lanzhou, Gansu, People's Republic of China
[4]School of Life Sciences, University of Westminster, London, UK
[5]Department of Pediatrics, 4-472 Edmonton Clinic Health Academy, University of Alberta, Canada
[6]Stollery Children's Hospital, Department of Pediatrics, University of Alberta, Edmonton, Canada
[7]University of East Anglia Medical School, Norwich, UK
[8]Department of Pediatrics, University of Alberta, Canada T5K 0L4
Correspondence to: S Vohra
svohra@ualberta.ca

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STUDY QUESTION

What are the weaknesses in reporting adverse events in reviews specifically designed to measure harms?

SUMMARY ANSWER

Systematic reviews compound the poor reporting of harms data in primary studies by failing to report on harms or doing so inadequately; improving the reporting of adverse events in systematic reviews is an important step towards a balanced assessment of an intervention.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Harms are poorly reported in randomised controlled trials, but it is unclear whether weaknesses in reporting are found in systematic reviews of harms. The PRISMA statement has been developed to address suboptimal reporting in systematic reviews, but focuses mainly on efficacy; the present review identifies poor reporting in systematic reviews of harms and the need for developing a specific reporting guideline.

Eligibility criteria

We searched the Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE) for systematic reviews published from January 2008 to April 2011. Reviews were selected if the primary outcome investigated was an unintended effect or effects of an intervention. It could be an adverse event, adverse effect, adverse reaction, harms, or complication associated with any healthcare intervention. Articles with a primary aim to investigate the complete safety profile of an intervention were included.

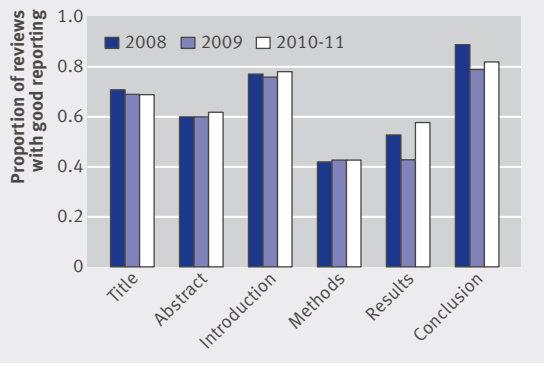
Outcome

A list of 37 items measured the quality of reporting on harms in each review; data were collected as dichotomous outcomes ("yes" or "no" for each item). We also measured the proportion of each "yes" response for each year of the search: 2008, 2009, and 2010-11.

Main results and role of chance

Of 4644 reviews identified, 309 were systematic reviews or meta-analyses primarily assessing harms. Thirteen reviews were identified in CDSR, and 296 were identified in DARE. Despite a short time interval, the comparison between years 2008 and 2010-11 showed no difference in the quality of reporting over time (P=0.079). The overall, unweighted, proportion of reviews with good reporting was 0.56 (95% confidence interval 0.55 to 0.57).

Proportion of reviews with good reporting, by subheading



Bias, confounding, and other reasons for caution

This review included more than 300 systematic reviews looking at harms as a main outcome, using a novel set of 37 items to measure the quality of reporting. A limitation of this review was the lack of a reporting guideline specific for systematic reviews of harms; different formats of reporting were found, and assessing whether the reporting was adequate was challenging. The reviewers were generous in their assessment of reporting quality, which may have underestimated the degree of the problem. Our review was limited exclusively to systematic reviews where harms were the primary focus, to generate a pure sample of reviews focusing on the reporting of such events. The documenting of poor reporting on these reviews would imply poor reporting on adverse events in general. Furthermore, we were inclusive and measured all potentially relevant items; in the future PRISMA Harms guideline (a reporting guideline specifically designed for reviews of harms), we would use a minimum set of essential items for harms reporting in a systematic review.

Study funding/potential competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.