Chapter 1. Cardiovascular disease and dietary carbohydrate

Contents

Background

Cardiovascular disease (CVD) includes all diseases that affect the cardiovascular system including the heart and blood vessels (arteries and veins). Typically the term is used in reference to diseases that affect the arterial aspect of the cardiovascular system and therefore often focuses on atherosclerosis and its consequences.

Although rates of CVD are in decline in many developed countries (American Heart Association, 2011;Allender *et al.*, 2008;Unal *et al.*, 2004), it remains a significant worldwide healthcare and financial burden. Cardiovascular disease is the principal cause of death in the United Kingdom (UK) today accounting for almost 191,000 deaths per year (equivalent to one in three deaths) (British Heart Foundation, 2010;British Heart Foundation, 2010). In terms of mortality from CVD, coronary heart disease (CHD) was the primary cause of death in 2008 resulting in 1 in 8 female and 1 in 5 male deaths and totalling 88,000 deaths. In comparison, in the same year, stroke was responsible for over 43,000 deaths in the UK (Scarborough *et al.*, 2010).

In part, improvements in CVD death have been the result of substantial investment in cardiac services (Department of Health Coronary Heart Disease Policy Team, 2008). Recent evidence from English heart attack data suggests substantial temporal improvements in in-hospital mortality rates (Gale *et al.*, 2011b). However, there remain major geographical differences in the risk, treatment and outcome from CHD (Scarborough *et al.*, 2010); (Scarborough *et al.*, 2008;Gale *et al.*, 2011a) and although the mortality from acute coronary syndromes (ACS) in England has declined, it still generates a massive burden of disease (Department of Health, 2000;British Heart Foundation, 2010). Approximately 20% of men and 14% of women die from the disease, and it causes 101,000 deaths in the UK each year (World Health Organization, 2008;British Heart Foundation, 2010). Capewell and colleagues (Capewell *et al.*, 2008) for the British Heart Foundation have recently highlighted the need for continued efforts to tackle cardiovascular problems in the years to come due to the anticipated extra burden this disease will place on health care services in the future.

Whilst some would argue that the association between temporal improvements in outcomes from CVD is related to advances in and the application of evidence-based medicine, others would suggest that there has been a significant contribution from primary prevention strategies which include lifestyle and dietary modification (Unal *et al.*, 2004;Bjorck *et al.*, 2009;Capewell *et al.*, 1999;Laatikainen *et al.*, 2005;Bennett *et al.*, 2006;Unal *et al.*, 2005). The World Health Organization 2003 report ‘Diet, Nutrition and the Prevention of Chronic Diseases’ outlines ‘convincing’ and ‘probable’ associations between diet and prevention of CVD (World Health Organisation, 2003) and in the UK. Dietary changes which would help to reduce rates of coronary heart disease (CHD) were detailed in the 1994 report of the Government's Committee on the Medical Aspects of Food and Nutrition Policy (COMA) (Committee on Medical Aspects of Food Policy, 1994).

The Committee on Medical Aspects of Food Policy concluded that diets high in dietary carbohydrate were associated with higher fasting concentrations of plasma triglyceride and lower HDL cholesterol (Committee on Medical Aspects of Food Policy, 1994). Nonetheless, due to the reciprocal relationship between dietary carbohydrate and dietary fat, such high carbohydrate diets tended to be low in saturated fat and consequently were associated with lower LDL cholesterol levels and low risk of CHD. At that time there was limited evidence that the type of carbohydrate (sugars or starches) was important, although the panel did find evidence that diets rich in non starch polysaccharide were associated with lower post prandial plasma insulin and glucose levels, and LDL cholesterol levels. The panel recommended a reduction in fat intake, particularly saturated fat intake, a reduction in sodium intake and an increase in fruit and vegetable and complex carbohydrate intake. Somewhat more recently, the World Health Organisation summarised the strength of evidence on lifestyle factors and risk of developing cardiovascular diseases, type 2 diabetes and obesity (World Health Organisation, 2003). They found the evidence convincing or probable for a decreased risk of these conditions with diets high in dietary fibre and probable that a high intake of sugar-sweetened beverages increase the risk of obesity. However, at that time the panel concluded that there was insufficient evidence concerning the relationship between total carbohydrate and risk of cardiovascular disease and that the evidence was indicative of a possible decreased risk of obesity with diets composed of low glycaemic index foods.

Cardiovascular disease may become clinically apparent in a variety of ways. It may present as ischaemic heart disease, cerebrovascular disease and /or as peripheral vascular disease. Sometimes it may not be clinically apparent and results in sudden cardiovascular death.

Ischaemic heart disease (IHD) is one of the major components of CVD. It is characterised by a reduced blood supply (ischaemia) to the heart muscle (myocardium), and is usually due to coronary artery disease (CAD) – atherosclerosis of the arteries that supply the myocardium. Atherosclerosis is a chronic inflammatory condition in which the components of an artery wall thicken. Very commonly, it is as the result of the deposition of fats (atheroma) such as cholesterol. Atherosclerosis affects arteries. Plaques are formed on the luminal surface of arteries which may limit the blood flow over time. Plaques may rupture triggering formation of a clot which blocks and severely limits the arterial supply downstream. IHD comprises chronic stable angina, and acute coronary syndromes (ACS).

There are many contributors toward cardiovascular disease including: smoking, high blood pressure, high cholesterol, physical inactivity, obesity, diabetes, a family history of cardiovascular disease, increasing age, and South Asian ethnicity (Bonow *et al.*, 2011). These risk factors may be termed modifiable and non-modifiable and diet may influence many of the components of the modifiable cardiovascular risk factors.

Stroke (cerebrovascular accident) is a condition in which a disturbance in the blood supply to the brain results in a loss of brain function. A stroke may be due to a haemorrhage in the brain, or due to ischemia as a result of a thrombus or embolus. Most (over 80%) of strokes are ischaemic in nature. A transient ischaemic attack (TIA) is defined if the symptoms and signs of a stroke which are due to a change in the blood supply to the brain last less than 24 hours. The risk factors for stoke are very much similar to those for IHD. Haemorrhagic stokes are mostly due to rupture of the microvasculature or rupture of an intracranial aneurysm. The main predictors of risk for haemorrhagic stroke are age, male gender and hypertension. Whilst the modifiable risk factors for ischaemic stroke are similar to those for CVD (that is, diabetes mellitus, hyperlipidaemia, obesity, smoking and physical inactivity) non-modifiable risk factors include history of atrial fibrillation, prior cardiac disease and carotid stenosis (Brainin and Heiss, 2009).

Peripheral vascular disease (PVD) is another component of CVD and concerns the arteries in the limbs and aorta, but not the coronary arteries or cerebral arteries. It occurs as a result of atherosclerosis with clinically apparent endpoints being either a chronic or acute occlusion of the artery. Consequently patients often suffer pain in the legs on walking (claudication), and it may result in gangrene if the blood supply is critically reduced. Peripheral vascular disease affects approximately 12% of the population, and is more common in the elderly, individuals with diabetes mellitus and smokers. It is often coexistent with IHD and cerebrovascular disease, and typically patients with PVD die of a heart attack or stroke. PVD can be classified as asymptomatic, acute limb ischaemic, chronic limb ischaemic and intermittent claudication. The modifiable risk factors associated with PVD include diabetes, smoking, hyperlipidaemia, obesity and hypertension. As with IHD, lifestyle modification plays an impart role in the management of patients with PVD (Shammas, 2007).

Studies referenced in COMA reports concerning incident CVD

The following section provides details of publications referenced in previous Committee of Medical Aspects of Food Policy (COMA) reports which were not eligible for inclusion in this review since they were published prior to 1990 (the cut point for this review). Full text copies of each article referenced in the COMA reports, which were relevant to this review (i.e. concerned dietary carbohydrates or cardiometabolic health outcomes), were obtained and screened independently by two members of the review team by applying the same inclusion and exclusion criteria as used for studies in this review.

Papers from COMA reports not meeting inclusion criteria

Table 1.1 lists those articles from the COMA reports (Committee on Medical Aspects of Food Policy, 1989;Committee on Medical Aspects of Food Policy, 1991;Committee on Medical Aspects of Food Policy, 1994) which concerned incident CVD events but did not meet the inclusion criteria for this review. Reasons for exclusion are detailed within the table.

N.B. Detail relating to other publications concerning different endpoints or outcomes are discussed in the appropriate chapters of this review.

Table 1.1 Publications discussed in COMA reports* not meeting inclusion criteria for this review

Reference	Intervention description	Intervention duration/ follow up	Exclusion code that would be applied in this review	Exclusion detail
(Burr *et al.*, 1989) DART study	1) Fat advice 2) Fish advice 3) Fibre advice	2 years	6	Subjects did not fit the definition of 'healthy' – all were diagnosed with acute myocardial infarction.
(Keys, 1971)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(McGandy *et al.*, 1967a) / (McGandy *et al.*, 1967b)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Walker, 1971)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Yudkin, 1957)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Yudkin, 1964)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Yudkin, 1971)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Yudkin and Morland, 1967)	Not applicable	Not applicable	2	The study was not apparently a randomised controlled trial or a cohort/ prospective study (case-control)

*(Committee on Medical Aspects of Food Policy, 1989;Committee on Medical Aspects of Food Policy, 1994;Committee on Medical Aspects of Food Policy, 1991)

Papers from COMA reports which met inclusion criteria

Table 1.2 lists five articles from the COMA reports (Committee on Medical Aspects of Food Policy, 1989;Committee on Medical Aspects of Food Policy, 1991;Committee on Medical Aspects of Food Policy, 1994) which included incident CVD endpoints and would have met the inclusion criteria for this review, if they had been published after 1990.

N.B. Summaries of findings from these publications are discussed within this chapter in the relevant exposure section.

Table 1.2 Publications discussed in COMA reports* meeting inclusion criteria for this review

Reference	Population characteristics	Length of follow-up (years)	Dietary assessment methods	Initial cohort size	Losses to follow-up (%)
(Fehily *et al.*, 1987) Caerphilly Study	Longitudinal study of a representative population sample of middle-aged men in a town in South Wales Mean age: 45-59 %Male: 100 Country: Wales Ethnicity: Primarily White	5	Diet was assessed using a validated 7-day dietary intake record.	2512	0.3
(Kromhout *et al.*, 1982) Zutphen Elderly Study	Men born between 1900 and 1919 who had lived in Zutphen or surrounding areas for at least 5 years Mean age: 40-59 years %Male: 100 Country: The Netherlands Ethnicity: Not reported	10	A dietary history was used to assess diet; the authors reported this method as validated. Both wives of participants and participants themselves were interviewed about the participants' habitual food consumption patterns.	1,008	13.6
(Kushi *et al.*, 1985) The Ireland-Boston Diet-Heart Study	Men of Irish descent Mean age: Not reported %Male: 100 Country: Ireland Ethnicity: Not reported	20	A FFQ was used to assess diet although no details concerning validation of the dietary assessment method were reported.	1,508	7.6
(Morris *et al.*, 1977)	Middle-aged men Mean age: 30-67 %Male: 100 Country: UK Ethnicity: Not stated	20	Diet was assessed via 7-day weighed dietary surveys administered twice. No details concerning validation of the dietary assessment method were reported.	337	10
(Yano *et al.*, 1978)	Men of Japanese ancestry born 1900-1919 living in Oahu in 1965 Mean age: Not reported %Male: 100 Country: Hawaii Ethnicity: Japanese	6	Diet was assessed using both a dietary acculturation questionnaire and a 24-hour dietary recall, the latter of which was conducted by dieticians. Both methods were reported as validated.	8,006	0

*(Committee on Medical Aspects of Food Policy, 1989;Committee on Medical Aspects of Food Policy, 1994;Committee on Medical Aspects of Food Policy, 1991)

Summary of the evidence base

Cohort studies

Fifty one papers, from 31 separate cohorts provided data on the relationship between dietary carbohydrate consumption and cardiovascular disease outcomes. Details of these cohort studies are provided in Table 1.3.

These cohorts were conducted in the UK (4), the USA (11), the Netherlands (2), Denmark, Australia, Canada, Finland (3), Germany, Greece (2), Sweden (2), Norway, Japan, and Italy. All of these cohort studies were of adults and the majority initially recruited participants who were in middle-age or older (aged 40+ years). Some cohorts recruited participants with a much wider age range, including younger individuals (aged 16-40 years) (Fraser *et al.*, 1992;Trichopoulou *et al.*, 2007;Drogan *et al.*, 2007;Knekt *et al.*, 1994;Esrey *et al.*, 1996;Jakobsen *et al.*, 2004;Bazzano *et al.*, 2001;Jacobs, Jr. *et al.*, 2001;Fung *et al.*, 2009;Appleby *et al.*, 1999;Key *et al.*, 1996;Lagiou *et al.*, 2007). Most cohorts included both men and women, but 8 cohorts were restricted to men and 6 to women only.

The average length of follow-up in these cohorts ranged from 5 years, to a maximum of 40 years, with a median duration of 13 years (taking longest follow-up for multiple papers from one cohort). The size of the cohorts at baseline ranged from 541 to 121,700 participants, with a median size of 13,710 participants. Three cohorts were particularly small, with fewer than 1,000 participants (Sahyoun *et al.*, 2006;Van Dam *et al.*, 2000;Park *et al.*, 2006), but with 11-15 years of follow-up. Some (mainly USA-based) cohorts were particularly large, with in excess of 50,000 participants (Jensen *et al.*, 2004;Fraser *et al.*, 1992;Nagura *et al.*, 2009;Liu *et al.*, 2003;Hu *et al.*, 1999). Due to their large size, these cohort studies have a dominant influence on the pooled estimates of meta-analyses. It should be noted that some of the cohorts include specific types of participant who may not be generally representative of the population as a whole, such as specific religious groups (Fraser *et al.*, 1992), occupational groups (health professionals) (Ascherio *et al.*, 1998;Hu *et al.*, 1999), overtly health conscious individuals (Key *et al.*, 1996;Appleby *et al.*, 1999) and smokers (Larsson *et al.*, 2009).

Dietary habits were assessed mainly by use of food frequency questionnaires (FFQ), but 3 studies employed the dietary recall technique (Park *et al.*, 2006;Esrey *et al.*, 1996;Bazzano *et al.*, 2003), and 3 studies used the dietary history method (Farchi *et al.*, 1995;Knekt *et al.*, 1994;Van Dam *et al.*, 2000). Food diaries were used in 3 studies (Jakobsen *et al.*, 2004;Sahyoun *et al.*, 2006;Laaksonen *et al.*, 2005).

With observational studies, especially in the field of diet and nutrition, there is substantial potential for biases caused by incomplete adjustment for confounding, measurement error in the exposure estimate, and other biases in participant selection or data collection. The bias could be large in

size, and act in either direction, either towards or away from the null. The results from these studies should therefore be interpreted cautiously.

Table 1.3 Characteristics of cohort studies included in the review

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
Adventist Health Study	(Fraser *et al.*, 1992)	California Seventh-Day Adventists Mean age: 52 % Male: 37.4 Country: USA Ethnicity: Primarily white	Community cohort	59081	Diet was assessed once with a validated 65-item FFQ for usual routine intakes.	Self-reported then confirmed by medical records	6	Not reported
Alpha-tocopherol, Beta-carotene Cancer Prevention Study	(Pietinen *et al.*, 1996)	Male smokers Mean age: 59.5 (50-69) % Male: 100 Country: Finland Ethnicity: Primarily white	Community cohort	29133	Diet was assessed using a validated 276 item FFQ referring to diet over previous year	National Register data	6.1	Not reported
	(Larsson *et al.*, 2009)						13.6	Not reported
Atherosclerosis Risk in Communities (ARIC) Study	(Steffen *et al.*, 2003)	Middle-aged adults Mean age: 54 (45-64) % Male: 44 Country: USA Ethnicity: Multi-Ethnic	Community cohort	15792	Diet was assessed twice using a 66-item FFQ (validated). The FFQ referred to diet over the previous year	Self reports, hospital surveillance and death certificates. Validated by medical records & family members	11	2
ATTICA study	(Panagiotakos *et al.*, 2009)	Men and women without any clinical evidence of CVD at baseline Mean age: 45 %Male: 49.8 Country: Greece Ethnicity: Not reported	Population-based cohort	3042	A 156-item FFQ was used once to measure diet; the authors reported this method as validated. The FFQ referred to diet over the previous 12 months	Medical records, verified by physicians	5	31
Blue Mountains Eye Study	(Kaushik *et al.*, 2009)	Older age population cohort Mean age: 65 %Male: 44 Country: Australia Ethnicity: Primarily White	Population-based cohort	3654	Diet was assessed using a validated 145 item FFQ	National death index & family members	13	Not reported
Boston Study of Whole-grains and CVD Risk	(Sahyoun *et al.*, 2006)	Healthy community living-persons Mean age: 73 %Male: 33 Country: USA Ethnicity: Primarily white	Volunteers	747	Diet was measured using a 3-day food diary, which was administered once. No detail was reported concerning validation of the dietary assessment method	National death index, confirmed by medical records	15	Not reported

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
Cardiovascular Health Study	(Mozaffarian *et al.*, 2003)	Randomly selected older participants from US communities Mean age: >65 %Male: 38.8 Country: USA Ethnicity: Primarily white	Population-based cohort	5201	A 99-item FFQ administered once was used to assess diet, and this was reported to be validated. The FFQ referred to diet over the previous year	Hospital records reviewed by clinicians	8.6	Not reported
Cohort of Swedish Men	(Levitan *et al.*, 2007)	Middle-aged and older Swedish men without diabetes or prior cardiovascular disease Mean age: 62 (45-79) %Male: 100 Country: Sweden Ethnicity: Not reported	Community cohort	48850	Diet was assessed from a 96-item FFQ administered once and this was reported to be validated. The FFQ assessed the dietary intakes for the previous year	Hospital discharge lists and death registry	5	0
Crevalcore and Montegiorgio Cohorts Seven Countries Study	(Farchi *et al.*, 1995)	Italian rural cohort of the Seven Countries Study Mean age: 45-64 %Male: 100 Country: Italy Ethnicity: Not reported	Community cohort	1564	Diet was assessed using a validated dietary history which was administered once	Death certificates	20	0
EPIC Greece	(Trichopoulou *et al.*, 2007)	General adult Greek population Mean age: 20-86 %Male: 41 Country: Greece Ethnicity: Not reported	Population-based cohort	28572	A 150-item FFQ consisting of foods commonly consumed in Greece was used to assess dietary intake in this cohort. It was administered once and was reported to be validated. This FFQ referred to diet over the previous year	Death certificates and other official sources	4.9	5
EPIC Potsdam	(Drogan *et al.*, 2007)	Sample of population from the Potsdam area Mean age: 50 (35-65) %Male:40 Country: Germany Ethnicity: Primarily white	Community cohort	27548	Diet was assessed from a validated 148-item self-administered FFQ. The FFQ referred to diet over the past 12 months.	Confirmed self-reports or death certificates	6.4	5
Finnish Mobile Clinic Health Surveys	(Knekt *et al.*, 1994)	Representative sample, free of heart disease at baseline Mean age: 40-69 %Male:53 Country: Finland Ethnicity: Not reported	Population-based cohort	5133	Diet was assessed once with dietary histories and this method was reported to be validated. The dietary history referred to diet over the previous year	National death registry data	14	9

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
Health Professionals' Follow-Up Study (HPFS)	(Rimm *et al.*, 1996)	Male health professionals free of CHD at baseline Mean age: 40-75 %Male:100 Country: USA Ethnicity: Primarily white	Occupational cohort	51529	Diet was assessed from a validated 131-item FFQ. The FFQ referred to the diet over the previous year.	National death index or confirmed self reports for incident events	6	6
	(Ascherio *et al.*, 1998)					Self reports and medical records for incident events. Relative reports or the National death index confirmed by medical records for deaths	8	6
	(Jensen *et al.*, 2004)				Diet was assessed from a validated 131-item FFQ which was administered every 4 years. The FFQ referred to the diet over the previous year.	Self reports and medical records for incident events. Relative reports or the National death index confirmed by medical records for deaths	14	Not reported
Iowa Women's Health Study	(Kelemen *et al.*, 2005)	Postmenopausal women Mean age: 61 (55-69) %Male: 0 Country: USA Ethnicity: Primarily white	Community cohort	41836	Diet was assessed once with a validated semi quantitative 127-item FFQ. The FFQ referred to diet over the previous year.	National death index or health registry for incident events	16.4	Not reported
	(Jacobs, Jr. *et al.*, 2007)					Death records or the National death index	17	Not reported
	(Jacobs, Jr. *et al.*, 1998)					Health registry, National death index and self reports	9	Not reported
Japan Collaborative Cohort Study	(Nagura *et al.*, 2009)	Sample from the general population Mean age: 40-79 %Male: 42.37 Country: Japan Ethnicity: Japanese	Community cohort	110792	A validated 33-item FFQ was used to assess diet over the past year.	Death certificates	14.3	4.2
Kuopio Ischaemic Heart Disease Risk Factor Study	(Laaksonen *et al.*, 2005)	Random sample of men in eastern Finland Mean age: 42-60 %Male: 100 Country: Finland Ethnicity: Not reported	Community cohort	2682	Diet was assessed using 4-day food diary records collected on 3 workdays and 1 weekend day. It was administered once and was not reported to be validated.	National death registry data	14.6	0
Lipid Research Clinics Prevalence Follow-Up Study	(Esrey *et al.*, 1996)	Sample of men and women from Northern American populations Mean age: 46 (30-79) %Male: 52 Country: Canada	Community cohort	4904	Diet was assessed using a 24-hour dietary recall administered once by a trained nutritionist. No details concerning the validation of	Death certificates and then hospital records and reports from informants	12.4	Not reported

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
		Ethnicity: Not reported			this dietary assessment method were reported.			
MONICA I & III Danish Cohorts	(Jakobsen *et al.*, 2004)	Men and women from western suburbs of Copenhagen, Demark Mean age: 30-71 %Male: 70 Country: Denmark Ethnicity: Primarily White	Population-based cohort	3959	Dietary intakes of some subjects were assessed using 7-day weighed food record completed within 3 weeks. The remaining subjects underwent a dietary history interview	National patient registry and cause of death registry and medical records for incident events	16	Not reported
NHANES I	(Bazzano *et al.*, 2001)	Nationally representative sample free of CVD Mean age: 49 (25-74) %Male: 38.34 Country: USA Ethnicity: Not reported	Community cohort	9776	Diet was assessed using a 3-month FFQ and one 24 hour recall including portion size estimates. It was administered once and was reported to be validated.	Medical and death records	19	4
	(Bazzano *et al.*, 2003)			9776	Diet was assessed using 24-hour dietary recall by trained personnel administered once and it was reported to be validated.	Death certificates	19	4
Norwegian County Study	(Jacobs, Jr. *et al.*, 2001)	Men and women in 3 Norwegian counties, not disabled and free of cardiovascular disease. Mean age: 35-56 %Male: 50 Country: Norway Ethnicity: Not reported	Community cohort	47114	Diet was assessed once with a semi-quantitative validated 66-item FFQ for subjects' usual intake.	Medical records or autopsy	17	Not reported
Nurses' Health Study (NHS)	(Liu *et al.*, 2000b)	Health professionals free of CHD at baseline Mean age: 30-55 %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	75521	Diet was assessed three times from a 126-item semi-quantitative FFQ for intakes over the previous year and it was reported to be validated.	Medical records for incident events and the National death index verified by medical records, autopsy reports or death certificates for deaths	10	2
	(Halton *et al.*, 2006)			82802	Diet was assessed six times using validated 61 and 100+ item FFQs.	Confirmed self reports for incidence and relatives/ postal service/ National death index for deaths. Deaths also verified by autopsy, hospital records and death certificates	20	Not reported
	(Wolk *et al.*, 1999)			121700	Diet was assessed at least 3 times using a validated 61 and 116 item FFQ.	Confirmed self/relative reports and national death index, relatives or the postal system	10	20

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
	(Fung *et al.*, 2009)				Validated 61 and 116 item FFQs were used seven times to assess diet.	Confirmed self reports for incidence and relatives/ postal service/ National death index for deaths. Deaths also verified by autopsy, hospital records and death certificates	24	5
	(Hu *et al.*, 1999)				Validated 61 and 116 item FFQs were used to assess diet 4 times between 1980-94	As above	14	Not reported
	(Liu *et al.*, 1999)				Validated 61 and 126 item FFQs were used to assess diet three times between 1980 and 1994	Confirmed self reports for incidence, deaths verified by autopsy, hospital records and death certificates	10	17
	(Oh *et al.*, 2005)				Validated 61 and 116 item FFQs were used to assess diet 4 times between 1980-94	Confirmed self reports for incidence and relatives/ postal service/ National death index for deaths. Deaths also verified by autopsy, hospital records and death certificates	18	Not reported
	(Liu *et al.*, 2000a)				Validated 61 and 126 item FFQs were used to assess diet 4 times between 1980-94	As above	12	Not reported
Nurses' Health Study & Health Professionals' Follow-up Study	(Joshipura *et al.*, 2009)	US Health Professionals Mean age: 60 (30-75) %Male: 36 Country: USA Ethnicity: Not reported	Occupational cohort	173229	Diet was assessed from a 126-item FFQ administered five times in the NHS and four times in the HPFS and it was reported to be validated. The FFQ referred to diet over the previous year.	As above	12	Not reported
	(Joshipura *et al.*, 1999)				Diet was assessed from a 61/116 item FFQ administered four times and from a 116 item FFQ administered twice in the NHS and HPFS, respectively. Both were validated	Self-reported then confirmed by medical records or death register	8 (NHS) 14 (HPFS)	20
Oxford Vegetarian Study	(Appleby *et al.*, 1999)	Vegetarian (50%) and non-vegetarian subjects Mean age: 46 (16-79) %Male: 40 Country: UK Ethnicity: Primarily white	Community cohort	11140	Diet was assessed using a simple validated FFQ administered once.	NHS register-death certificates	13.3	Not reported

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
Physicians' Health Study I	(Liu *et al.*, 2003)	Male Health Professionals Mean age: 54 (40-84) %Male: 100 Country: USA Ethnicity: Not reported	Occupational cohort	104353	Diet was assessed from a simple validated FFQ for intake over the previous year.	National death index and death certificates	5.5	Not reported
Prospect-EPIC Utrecht cohort	(Beulens *et al.*, 2007)	Dutch women without diabetes or CVD Mean age: 49-70 %Male: 0 Country: The Netherlands Ethnicity: Not reported	Community cohort	17357	Diet was assessed using a validated 178-item FFQ for intake over the previous year and it was administered once.	National register data	9	10
Scottish Heart Health Study	(Todd *et al.*, 1999)	Men and women from 25 Scottish districts recruited via GP surgeries Mean age: 40-59 %Male: 51 Country: Scotland Ethnicity: Primarily White	Community cohort	11629	Diet was assessed from a validated 60-item FFQ administered once.	Death registry	9	0.1
The Caerphilly Study	(Fehily *et al.*, 1993)	All middle-aged men in towns in south Wales Mean age: 45-59 %Male: 100 Country: Wales Ethnicity: Primarily White	Community cohort	2512	Diet was assessed from a validated semi-quantitative FFQ (portions were informed from food diary sub-sample).	Medical records and confirmed self-reports	5	0.3
The Health Food Shoppers Study	(Key *et al.*, 1996)	Vegetarians and health conscious subjects Mean age: 46 (16-79) %Male: 40 Country: United Kingdom Ethnicity: Primarily white	Community cohort	11140	Diet was assessed using a short questionnaire.	Death certificates	16.8	4.7
The Women's Health Study	(Liu *et al.*, 2002)	Health professionals in RCT for aspirin and Vitamin E supplementation Mean age: 54 %Male: 0 Country: USA Ethnicity: Primarily White	Occupational cohort	39876	Diet was assessed using a validated semi-quantitative 131-item FFQ.	Incident events confirmed by cardiologists and a neurologist, deaths verified by medical records, autopsy reports and death certificates	6	Not reported
The Women's Lifestyle and Health Cohort Study	(Lagiou *et al.*, 2007)	Swedish women residing in the Uppsala Health Care Region Mean age: 30-49 %Male: 0 Country: Sweden Ethnicity: White	Population-based cohort	42237	Diet was assessed once with a validated 80-item FFQ for intakes over the past 6 months.	National register data	12	0
Zutphen Elderly Study	(Van Dam *et al.*, 2000)	Random sample of men from industrial town in Netherlands Mean age: 64-84 %Male: 100 Country: The Netherland Ethnicity: Not reported	Population-based cohort	646	Diet was assessed several times with a validated dietary history.	National registry	10	0.15

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Initial cohort size	Dietary assessment method	Outcome assessment method	Length of follow-up (years)	Losses to follow-up (%)
	(Streppel *et al.*, 2008)			1373	Diet was assessed several times with a validated dietary history for intake over the past 6-12 months.	National registry	40	0.2

Trial design

One clinical trial provided data on cardiovascular disease events in relation to consumption of a reduced fat diet (higher carbohydrate) which was higher in fruit and vegetables, dietary fibre and whole grains. Details of this study are included in Table 1.4.

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial design (washout duration)	Length of Inter-vention	Intervention style	Total n	Intervention groups	Intervention description	Diet/ Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Howard *et al.*, 2006) The Women's Health Initiative Dietary Modification Trial	Age 50-79y Fat intake >32% Post-menopausal	USA 0% Male Age: (62) BMI: (29)	Parallel Group	6 years	Free living diet plan	48835	1. Low fat 2. Control	1. Advice: reduce fat intake to 20%, increase fruit, vegetables and wholegrains 2. Received information relating to health and healthy diets	1. %E: C 53.9 P 17.7 F 28.8 Energy 1432 kcal/d Fibre g/d: 19.6 2. %E: C 45.9 P 17.1 F 37 Energy 1546 kcal/d Fibre g/d:14.4	yes	National Heart, Lung, and Blood Institute

Table 1.4 Trial characteristics information for incident cardiovascular events

Table 1.5 Risk of bias information for the trial reporting incident cardiovascular events

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome reporting	Selective outcome reporting	Any other bias
(Howard *et al.*, 2006)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias

Nutrients and CVD

This section includes cohorts which report results concerning nutrient intakes and incident cardiovascular events. The nutrient exposures reported by these cohorts include the following: total carbohydrate intake, sugar, polysaccharides, “complex” carbohydrates, cellulose, lignin, total dietary fibre, fibre contained within cereals, fruits, vegetables, potatoes and legumes, soluble fibre and insoluble fibre.

Total carbohydrate and CVD

Total CVD, carbohydrate density and high carbohydrate diets

Summary of cohort results

The European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam cohort study provided data on the relationship between total CVD events and carbohydrate intake (Drogan *et al.*, 2007). Mean intake of total carbohydrate (grams per MJ per day) did not differ between fatal and non-fatal cases of CVD and the other cohort members.

Exposure definition and assessment

Carbohydrate intake was assessed using a 148-item FFQ at baseline.

Adjustment for appropriate confounders

The results provided are unadjusted mean estimates of intake.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Summary of trial results

One randomised controlled trial (RCT) reported total CVD events in relation to high carbohydrate diets, the Women's Health Initiative Dietary Modification Trial (Howard *et al.*, 2006). Participants were randomised to either an intensive intervention group which included individual sessions designed to reduce fat intake to 20% of total energy and increase consumption of fruits, vegetables and grains or a comparison group which received diet-related education materials only. At one year, carbohydrate energy intake as assessed by an FFQ was 58.3% (SD 8.9) in the intervention group and 48.0% in the comparison group and at year 6 this was 53.9 (9.9) and 45.9 (8.8), respectively.

The percent of participants in each group experiencing total CVD events was very similar and the hazard ratios which compared the low-fat intervention group with the comparison did not show any clear direction of association.

Results from this trial should be interpreted with caution as other dietary components other than carbohydrate intake were altered, and the low fat diet group experienced weight loss but the comparison group did not.

Table 1.6 Total CVD and carbohydrate density: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) /Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Units	Mean Exposure (SD)
13465 (Drogan *et al.*, 2007) EPIC Potsdam	Germany, No history of MI/Stroke	35-65 (50) %M 40	(68) /27548	6.4 y (5)	FFQ (148)	Carbohydrate density	Fatal Events	MI/ Stroke, any Medical records/ death certificate	g/MJ/d	Cases: (n=68) 25.3 (3.7) Non-cases: (n=25859) 26.7 (3.7)
14720 EPIC Potsdam			(311) /27548				Non-fatal Events	MI/ Stroke, any Medical records	g/MJ/d	Cases: (n=311) 26.6 (3.8) Non-cases: (n=25859) 26.7 (3.7)

Table 1.7 Total CVD and high carbohydrate diets: RCT data

Result ID/Author	Subgroup detail	Intervention group	Completers/ Allocated	% of group experiencing event	Outcome/ Assessment method	Contrast	RR (95% CI)	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17158 (Howard *et al.*, 2006) The women's health initiative dietary modification trial		Low fat	19541/19541	0.86	Total CVD (fatal and non-fatal) Multiple assessment methods	Control (reference) vs. Low fat	0.98 (0.92, 1.05)	8 years	Decrease	No bias
		Control	29294/29294	0.88					No change	
17159 (Howard *et al.*, 2006)	No history of CVD	Low fat	27925/29294	0.78	Total CVD (fatal and non-fatal) Multiple assessment methods	Control (reference) vs. Low fat	0.96 (0.89, 1.03)	8 years	Decrease	No bias
		Control	18633/19541	0.75					No change	

Coronary events, total carbohydrate and high carbohydrate diets

Summary of cohort results

Six papers from five cohort studies provided evidence concerning the association between total carbohydrate and coronary events: the Lipids Research Clinics Prevalence Follow-up Study, the Seven Countries Study, the Nurses' Health Study (NHS), Prospect-EPIC Utrecht study and the Caerphilly Study (Liu *et al.*, 2000b;Esrey *et al.*, 1996;Halton *et al.*, 2006;Farchi *et al.*, 1995;Beulens *et al.*, 2007;Fehily *et al.*, 1993).

Four of these studies provided risk estimates for cardiovascular disease with carbohydrate consumption (Esrey *et al.*, 1996;Farchi *et al.*, 1995;Halton *et al.*, 2006;Liu *et al.*, 2000b;Beulens *et al.*, 2007). There was no consistent direction of association between these studies, with the NHS and the Lipids Research Clinics Prevalence Follow-up Study reporting risk estimates close to 1 (Esrey *et al.*, 1996;Liu *et al.*, 2000b) and the Seven Countries Study, the NHS and Prospect-EPIC Utrecht study reporting evidence of increased risk of coronary events with increasing carbohydrate intake (Farchi *et al.*, 1995;Beulens *et al.*, 2007;Halton *et al.*, 2006). Only the Lipids Research Clinics Prevalence Follow-up Study reported a significant negative association (lower risk of coronary events with increasing total carbohydrate intake) in a subgroup of participants aged 30-59 years. In this group of participants, risk of CHD decreased by 4% for each 1% increase in percentage of energy from carbohydrate (relative risk (RR): 0.96 (95% confidence interval (CI) 0.94, 0.99)) (Esrey *et al.*, 1996).

Data were extracted from two studies on mean carbohydrate consumption at baseline in participants who later became cases and non-cases: the Lipids Research Clinics Prevalence Follow-up Study and the Caerphilly Study (Esrey *et al.*, 1996;Fehily *et al.*, 1993). Generally, differences in carbohydrate intake were not marked between cases and non-cases in either cohort.

Exposure definition and assessment

Carbohydrate intake was reported as either g/day or percent of total energy and was assessed using a single 24-hour recall in the Lipids Research Clinics Prevalence Follow-up Study (Esrey *et al.*, 1996) and by dietary history in the Seven Countries Study (Farchi *et al.*, 1995). The other studies tended to use FFQs, and the number of FFQ items varied from 122 to 178. In the Caerphilly Study, carbohydrate intake was assessed with a semi-quantitative FFQ, which was validated for portion size against seven-day food diaries which were completed by 30% of the sample. In this cohort, FFQs were taken home by each participant to be filled in with help from their spouse (Fehily *et al.*, 1993).

Adjustment for appropriate confounders

The Crevalcore and Montegiorgio Cohorts Seven Countries Study presented results adjusted only for age (Farchi *et al.*, 1995). The other studies all adjusted for age and gender (where relevant) but there was variability in adjustments for socio-economic status, familial CHD and other nutrients. Most had also adjusted for total energy intake. Unadjusted mean intakes were presented in the Caerphilly Study and the Lipids Research Clinics Prevalence Follow-up Study (Esrey *et al.*, 1996;Fehily *et al.*, 1993).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Summary of RCT data

One RCT only reported total coronary events in relation to high carbohydrate diets. In the Women's Health Initiative Dietary Modification Trial (Howard *et al.*, 2006), participants were randomised to either an intensive intervention group which included individual sessions designed to reduce fat intake to 20% of total energy and increase consumption of fruits, vegetables and grains or a comparison group which received diet-related education materials only. At year 1, carbohydrate energy intake as assessed by an FFQ was 58.3% (SD 8.9) in the intervention group and 48.0% in the comparison group and at year 6 this was 53.9 (9.9) and 45.9 (8.8), respectively.

The percent of participants in each group experiencing coronary events was very similar and the hazard ratios which compared the low-fat intervention group with the comparison group did not show any clear direction of association.

Results from this trial should be interpreted with caution as other dietary components other than carbohydrate intake were altered, and the low fat diet group experienced weight loss but the comparison group did not.

Evidence from COMA reports - Total carbohydrate intake and coronary events

Two papers discussed in previous COMA reports which concerned total carbohydrate intake and coronary events met the inclusion criteria for this review, except publication date was prior to 1990 (Kushi *et al.*, 1985;Yano *et al.*, 1978). Carbohydrate intake was assessed via a dietary history which was coded on a food frequency form in one study (Kushi *et al.*, 1985) and via a dietary acculturation questionnaire and a 24-hour dietary recall in another (Yano *et al.*, 1978). In the Ireland-Boston Diet-Heart Study, a statistically significant lower intake of carbohydrate in cases compared to non-cases was reported (41.2 vs. 42.7% energy, p=0.04) (Kushi *et al.*, 1985). Conversely, in the study of Japanese men in Hawaii, no difference between cases and non-cases was found in terms of carbohydrate intake (Yano *et al.*, 1978).

Table 1.8 Coronary events and total carbohydrate: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
13485 (Beulens *et al.*, 2007) Prospect-EPIC Utrecht	The Netherlands, No CHD, No T2DM	49-70 %M 0	(556) /17357	9 y (10)	FFQ (178)	Carbohydrate, total (g/day)	Fatal + Non-fatal Events	CHD events Registry data		Q4 vs. Q1		1.17 (0.78, 1.77)			0.35	Age, alcohol, BMI, smoking, physical activity, systolic blood pressure, hypercholesterolaemia, hypertension, menopausal status, nutrient intake, oral contraceptive pill
14169 (Farchi *et al.*, 1995) Crevalcore and Montegiorgio Cohorts Seven Countries Study	Italy	45-64 %M 100	(168)/ 1564	20 y (0)	Dietary history	Carbohydrate, total (% energy)	Fatal Events	CHD events Medical records/ autopsy		55-75 vs. <55 (WHO recom-mended intake)	% Energy	1.34 (0.9, 1.99)				Age
*14117 (Esrey *et al.*, 1996) Lipid Research Clinics Prevalence Follow-Up Study	Canada, Age 30-79y, No CHD	30-79 (46) %M 52	(52) /4904	12.4 y	Dietary recall	Carbohydrate, total (% energy)	Fatal Events	CHD events Medical records/ autopsy	Age 30-59y	Continuous risk estimate	1% Energy	0.96 (0.94, 0.99)				Age, BMI, energy intake, impaired glucose tolerance, blood total cholesterol and triacylglycerol, gender, smoking, systolic blood pressure
*14119			(40) /4904				Fatal Events	As above	Age 60-79y	Continuous risk estimate	1% Energy	1.02 (0.98, 1.05)				As above
14110			(52) /4904			Carbohydrate, total (g/day)	Fatal Events	As above	Age 30-59y		g/d		Cases: (n: 52) 201.8g/d (98.6) Non-cases: (n: 3873) 221.2 g/d (104.5)			
14114			(40) /4904				Fatal Events	As above	Age 60-79y		g/d		Cases: (n: 40) 218.5 g/d (92.7) Non-cases: (n: 581) 195.2 g/d (78.7)			
14306 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Carbohydrate, total (g/day)	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/ autopsy, Self report			g/d		Cases: (n: 70) 240.2 g/d (66.3) Non-cases: (n: 1686) 250.5 g/d (73.2)			
17564 (Halton *et al.*, 2006)	USA, Primarily White,	30-55 %M 0	(1994) /82802	20 y	FFQ (122)	Carbohydrate, total (% energy)	Fatal + Non-fatal	Coronary heart disease death, Non-		Q10 vs. Q1		1.22 (0.95, 1.56)			0.06	Age, alcohol, aspirin, BMI, cereal fibre, energy intake,

NHS	No T2DM, No CVD						Events	fatal MI Ascertained using multiple methods						hormone replacement therapy, hypercholesterolaemia, hypertension, parental CHD, physical activity, protein intake, smoking, supplements
*14630 (Liu *et al.*, 2000b) NHS	USA, No T2DM, Without angina or heart attack	38-63 %M 0	(761) /75521	10 y (2)	FFQ (126)	Carbohydrate, total (% energy)	Fatal + Non-fatal Events	Fatal CHD + non-fatal MI Medical records/ autopsy	Continuous risk estimate	5% Energy	1.02 (0.96, 1.08		0.5	Age, alcohol, aspirin, BMI, energy intake, Fibre, folate, Hypercholesterol-aemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements

*This result was used in the meta-analysis of carbohydrate (% energy) and any CVD event

Table 1.9 Coronary events and high carbohydrate diets: RCT data

Result ID/Author	Subgroup detail	Intervention group	Completers/ Allocated	% of group experiencing event	Outcome/ Assessment method	Contrast	RR (95% CI)	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17138 (Howard *et al.*, 2006) The women's health initiative dietary modification trial		Low fat	19541/19541	0.35	Coronary heart disease death Nonfatal MI (Medical records/autopsy Medical testing)	Control (reference) vs. Low fat	0.98 (0.88, 1.09)	8 years	Decrease	No bias
		Control	29294/29294	0.36					No change	
17139	No history of CVD	Low fat	18633/19541	0.3	As above	Control (reference) vs. Low fat	0.93 (0.83, 1.05)	8 years	Decrease	No bias
		Control	27925/29294	0.32					No change	
17140		Low fat	19541/19541	0.28	Myocardial infarction (Non-fatal) (Medical records/Medical testing)	Control (reference) vs. Low fat	0.98 (0.87, 1.11)	8 years	Decrease	No bias
		Control	29294/29294	0.28					No change	
17141	No history of CVD	Low fat	18633/19541	0.23	As above	Control (reference) vs. Low fat	0.91 (0.82, 1.01)	8 years	Decrease	No bias
		Control	27925/29294	0.26					No change	
17142		Low fat	19541/19541	0.1	Fatal coronary heart disease events Medical records/autopsy	Control (reference) vs. Low fat	1.02 (0.84, 1.25)	8 years	Decrease	No bias
		Control	29294/29294	0.1					No change	
17143	No history of CVD	Low fat	18633/19541	0.08	As above	Control (reference) vs. Low fat	1.01 (0.81, 1.27)	8 years	Decrease	No bias
		Control	27925/29294	0.08					No change	
17144		Low fat	19541/19541	0.45	Coronary artery bypass graft/percutaneous coronary intervention (non-fatal events) Multiple assessment methods	Control (reference) vs. Low fat	0.96 (0.88, 1.06)	8 years	Decrease	No bias
		Control	29294/29294	0.47					No change	
17145	No history of CVD	Low fat	18633/19541	0.38	As above	Control (reference) vs. Low fat	0.91 (0.82, 1.01)	8 years	Decrease	No bias
		Control	27925/29294	0.41					No change	
17146		Low fat	19541/19541	0.63	Coronary artery bypass graft/percutaneous coronary intervention and Coronary heart disease death/Nonfatal MI Multiple assessment methods	Control (reference) vs. Low fat	0.97 (0.90, 1.06)	8 years	Decrease	No bias
		Control	29294/29294	0.65					No change	
17147	No history of CVD	Low fat	18633/19541	0.53	As above	Control (reference) vs. Low fat	0.94 (0.86, 1.02)	8 years	Decrease	No bias
		Control	27925/29294	0.57					No change	

Stroke events, total carbohydrate and high carbohydrate diets

Summary of cohort results

Data were extracted from one study of US female nurses, the NHS (Oh *et al.*, 2005). This study provided evidence concerning the association between percentage energy from carbohydrates and fatal and non-fatal stroke. These results were also reported separately for BMI <25kg/m^2 and BMI >25kg/m^2. There was no significant association between total energy from carbohydrates and total or ischaemic stroke in the whole cohort but there was a 25% increased risk of haemorrhagic stroke when comparing the highest quintile of carbohydrate intake with the lowest (p trend = 0.02). No association was seen in those with BMI<25kg/m^2 but there was evidence of a two-three fold increased risk of total stroke or haemorrhagic stroke in women with the highest intakes of carbohydrate, in those with BMI>25kg/m^2.

Exposure definition and assessment

The NHS (Oh *et al.*, 2005) assessed percentage of total energy from carbohydrates using a 116-item FFQ.

Adjustment for appropriate confounders

The NHS (Oh *et al.*, 2005) adjusted for a wide range of covariates including age, smoking, physical activity and family history of certain diseases.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Summary of trial results

One RCT only reported stroke events in relation to high carbohydrate diets. In the Women's Health Initiative Dietary Modification Trial (Howard *et al.*, 2006), participants were randomised to either an intensive intervention group which included individual sessions designed to reduce fat intake to 20% of total energy and increase consumption of fruits, vegetables and grains or a comparison group which received diet-related education materials only. After 1 year, carbohydrate energy intake as assessed by an FFQ was 58.3% (SD 8.9) in the intervention group and 48.0% in the comparison group. After 6 years the difference had diminished to some extent, and was 53.9 (9.9) and 45.9% (8.8), respectively.

The percent of participants in each group experiencing stroke events was very similar and the hazard ratios which compared the low-fat intervention group with the comparison group did not show any clear direction of association for all strokes or for specific stroke types.

Results from this trial should be interpreted with caution as other dietary components were altered other than a switch between fat and carbohydrate content and the low fat diet group experienced weight loss but the comparison group did not.

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments

Table 1.10 Stroke events and total carbohydrates: cohort studies in adults

*13436 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	Carbohydrate, total (% energy)	Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods		(52.9) vs. (32.6)	% Energy	1.25 (0.91, 1.73)	0.16	Age, alcohol, aspirin, BMI, monoun-, polyun- and saturated fatty acid intake, energy from trans fatty acids, energy intake, energy from cereal fibre, family history of DM; hypertriglycerideaemia; hypertension or MI, menopausal status, n-3 fatty acid intake, physical activity, smoking, postmenopausal hormone replacement therapy, Vitamin E
NHS	13495		(528) /121700						BMI <25	Q5 vs. Q1		0.89 (0.58, 1.36)	0.54	As above
NHS	13496		(492) /121700						BMI >25	Q5 vs. Q1		2.13 (1.28, 3.53)	0.002	As above
NHS	13439		(279) /121700					Stroke, haemorrhagic Ascertained using multiple methods		(52.9) vs. (32.6)	% Energy	2.05 (1.1, 3.83)	0.02	As above
NHS	13499		(178) /121700						BMI <25	Q5 vs. Q1		1.57 (0.74, 3.35)	0.2	As above
NHS	13500		(101) /121700						BMI >25	Q5 vs. Q1		3.84 (1.23, 12.05)	0.02	As above
NHS	13438		(515) /121700					Stroke, ischaemic Ascertained using multiple methods		(52.9) vs. (32.6)	% Energy	0.86 (0.54, 1.36)	0.46	As above
NHS	13497		(259) /121700						BMI <25	Q5 vs. Q1		0.58 (0.32, 1.07)	0.05	As above
NHS	13498		(256) /121700						BMI >25	Q5 vs. Q1		1.61 (0.79, 3.28)	0.16	As above

*This result was used in the meta-analysis of carbohydrate (% energy) and any CVD event

Table 1.11 Stroke events and high carbohydrate diets: RCT data

Result ID/Author	Subgroup detail	Intervention group	Completers/ Allocated	% of group experiencing event	Outcome/ Assessment method	Contrast	RR (95% CI)	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17148 (Howard *et al.*, 2006) Women's Health Initiative Dietary Modification Trial		Low fat	19541/19541	0.28	Stroke, any (fatal and non-fatal) Multiple outcome assessment methods	Control (reference) vs. Low fat	1.02 (0.90, 1.15)	8 years	Decrease	No bias
		Control	29294/29294	0.27					No change	
17149	No history of CVD	Low fat	18633/19541	0.25	As above	Control (reference) vs. Low fat	1.02 (0.90, 1.17)	8 years	Decrease	No bias
		Control	27925/29294	0.25					No change	
17150		Low fat	19541/19541	0.03	Stroke, any (fatal) Multiple outcome assessment methods	Control (reference) vs. Low fat	0.97 (0.69, 1.36)	8 years	Decrease	No bias
		Control	29294/29294	0.04					No change	
17151	No history of CVD	Low fat	18633/19541	0.03	As above	Control (reference) vs. Low fat	0.94 (0.65, 1.35)	8 years	Decrease	No bias
		Control	27925/29294	0.03					No change	
17152		Low fat	19541/19541	0.24	Stroke, any (non-fatal) Multiple outcome assessment methods	Control (reference) vs. Low fat	1.03 (0.90, 1.17)	8 years	Decrease	No bias
		Control	29294/29294	0.23					No change	
17153	No history of CVD	Low fat	18633/19541	0.22	As above	Control (reference) vs. Low fat	1.04 (0.90, 1.19)	8 years	Decrease	No bias
		Control	27925/29294	0.22					No change	
17154		Low fat	19541/19541	0.16	Stroke, ischaemic (fatal and non-fatal) Multiple outcome assessment methods	Control (reference) vs. Low fat	1.01 (0.86, 1.18)	8 years	Decrease	No bias
		Control	29294/29294	0.16					No change	
17155	No history of CVD	Low fat	18633/19541	0.15	As above	Control (reference) vs. Low fat	1.03 (0.87, 1.22)	8 years	Decrease	No bias
		Control	27925/29294	0.15					No change	
17156		Low fat	19541/19541	0.04	Stroke, hemorrhagic (fatal and non-fatal) Multiple outcome assessment methods	Control (reference) vs. Low fat	0.90 (0.66, 1.22)	8 years	Decrease	No bias
		Control	29294/29294	0.05					No change	
17157	No history of CVD	Low fat	18633/19541	0.04	As above	Control (reference) vs. Low fat	0.88 (0.64, 1.20)	8 years	Decrease	No bias
		Control	27925/29294	0.05					No change	

Total carbohydrate and CVD summary

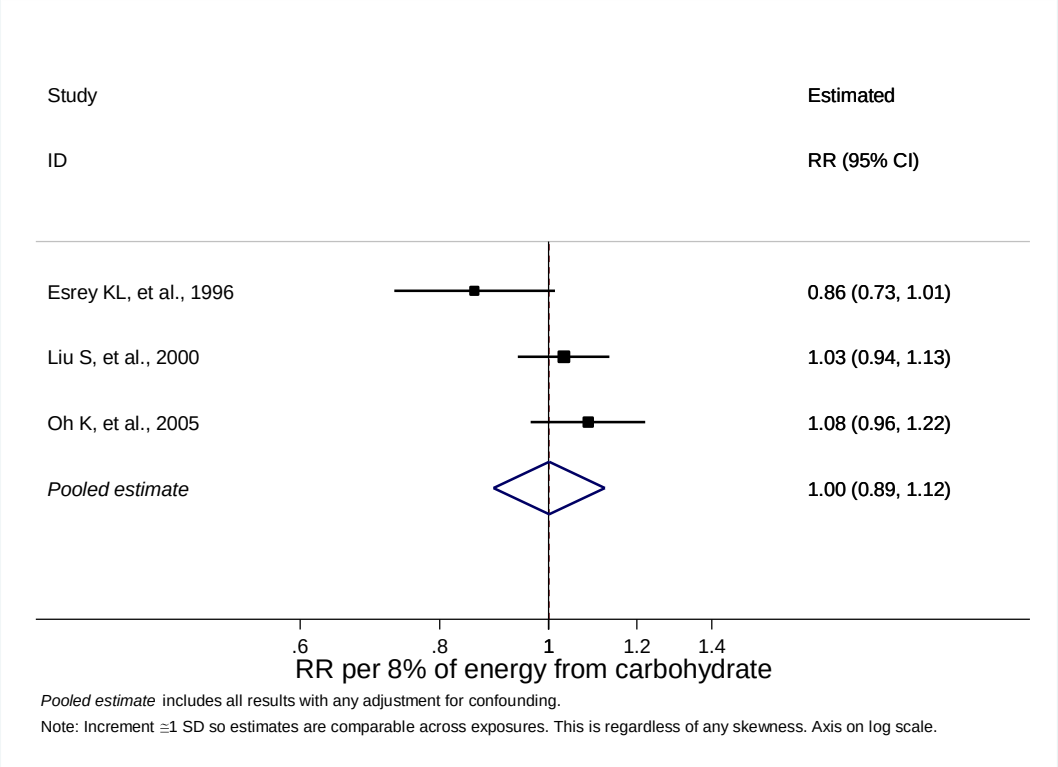
Meta-analysis: Total carbohydrate (% energy) and any incident CVD events

Data were extracted from 6 publications presenting results from 3 cohort studies for total carbohydrate (reported as percent energy) and CVD: the NHS, the Lipid Research Clinics Prevalence Follow-Up Study and the Crevalcore and Montegiorgio Cohorts Seven Countries Study (Halton *et al.*, 2006;Park *et al.*, 2006;Oh *et al.*, 2005;Liu *et al.*, 2000b;Esrey *et al.*, 1996;Farchi *et al.*, 1995). The Crevalcore and Montegiorgio Cohorts from the Seven Countries Study could not be included in the dose-response meta-analysis because of insufficient information presented in the paper (Farchi *et al.*, 1995). Another publication from this study presented results in terms of continuous markers of CHD, so could not be combined with the other studies (Park *et al.*, 2006). One paper from the NHS presented the exposure as a dietary pattern score covering several dietary exposures, and could not be combined with the other studies (Halton *et al.*, 2006). The remaining three papers were included in one meta-analysis for any CVD event, because there were insufficient usable papers to present results separately for CHD and stroke. One publication reporting on the Lipid Research Clinics Prevalence Follow-Up Study presented results stratified by age group (Esrey *et al.*, 1996). These were first combined into one estimate for that study using a fixed effects meta-analysis, before combining with the other studies.

Relative risks are presented for each 8% increase, equivalent to approximately one standard deviation, in percent energy from total carbohydrate (the approximate mean population intake is 44% energy from carbohydrate) as based on UK data from the National Diet and Nutrition Survey (NDNS) (Bates *et al.*, 2009).

The pooled estimate of relative risk was 1.00 (95% CI: 0.89 to 1.12) per 8% of energy from carbohydrate (p=0.97).

Figure 1.1 Forest plot for total carbohydrate (% energy) and any incident CVD event



There was considerable heterogeneity between the cohort studies (I^2=62%, 95% CI: 0% to 89%, Q=5.2, df=2, p=0.07), so the pooled estimate should be interpreted with caution.

There were insufficient studies to explore small-study effects such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

There were insufficient studies to explore the sources of heterogeneity by stratified forest plots or meta-regression.

Meta-analysis: Total carbohydrate (g/day) and any incident CVD events

Data were identified from four publications presenting results from four cohort studies: Prospect-EPIC Utrecht, EPIC Potsdam, the Lipid Research Clinics Prevalence Follow-Up Study and the Caerphilly study (Drogan *et al.*, 2007;Beulens *et al.*, 2007;Esrey *et al.*, 1996;Fehily *et al.*, 1993).

Data relating to carbohydrate density was reported only from EPIC Potsdam, the other three cohorts reported carbohydrate as grams per day. Prospect-EPIC Utrecht could not be included because insufficient information on total carbohydrate intake was presented to estimate category means, medians or midpoints, therefore the dose-response trend could not be estimated (Beulens *et al.*, 2007). This left only the Lipid Research Clinics Prevalence Follow-Up Study and The Caerphilly Study that could be included in a meta-analysis (Esrey *et al.*, 1996;Fehily *et al.*, 1993),

of which the latter only provided unadjusted results (Fehily *et al.*, 1993). Therefore there were an insufficient number of studies to provide a meta-analysis.

Total sugars and sugar fractions and CVD

Coronary events and total sugars and sugar fractions

Summary of cohort results

Data were identified from three studies: the NHS, Prospect-EPIC Utrecht study and the Caerphilly Study. Prospect-EPIC Utrecht and the Caerphilly Study provided evidence concerning the association between total sugars intake and risk of IHD or CHD (Fehily *et al.*, 1993;Beulens *et al.*, 2007) and the NHS provided evidence relating to fructose, sucrose and lactose with CHD events (Liu *et al.*, 2000b).

The NHS and Prospect-EPIC Utrecht provided risk estimates for sugars and CHD events but both reported risk estimates close to 1 and neither study reported any statistically significant associations between intake of sugars and risk of CHD. The Caerphilly Study reported very similar total sugar consumption in cases and non-cases at baseline (Fehily *et al.*, 1993) but as no risk estimates were reported for this cohort, a meta-analysis could not be conducted,

Exposure definition and assessment

Intake of sugars in the Caerphilly Study was assessed with a validated semi-quantitative FFQ. In this cohort, FFQs were taken home by each participant to be filled in with help from their spouse (Fehily *et al.*, 1993). The other studies used FFQs with either 126 or 178 items (Beulens *et al.*, 2007;Liu *et al.*, 2000b). The NHS calculated an energy-adjusted score for each of the sugar fractions (Liu *et al.*, 2000b).

Adjustment for appropriate confounders

Both the NHS and Prospect-EPIC Utrecht adjusted for age, hypercholesterolaemia and menopausal status but there was variability in adjustments for occupation and familial CHD (Beulens *et al.*, 2007;Liu *et al.*, 2000b). The NHS also adjusted for total energy intake (Liu *et al.*, 2000b). Unadjusted mean intakes were presented in the Caerphilly Study (Esrey *et al.*, 1996;Fehily *et al.*, 1993).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Evidence from COMA reports - Total sugars and coronary events

Three cohort studies were identified from previous COMA reports that would have been eligible for inclusion in this review except publication dates were pre-1990. These three provided data concerning sugar (mostly sucrose) consumption and coronary events (Morris *et al.*, 1977;Kushi *et al.*, 1985;Yano *et al.*, 1978). Sugar intake was reported as a percentage of energy (Kushi *et al.*, 1985;Yano *et al.*, 1978) or as grams per day (Morris *et al.*, 1977). All studies differed in their assessment of diet: the British study used 7-day weighed record estimates of sugar (Morris *et al.*, 1977), the Ireland-Boston Diet-Heart study employed a dietary history which was coded on a food frequency form (Kushi *et al.*, 1985) and the study of Japanese men in Hawaii reported intakes using a dietary acculturation questionnaire and a 24-hour dietary recall (Yano *et al.*, 1978). Both US studies reported similar mean age-adjusted intakes of sugar in cases and non-cases (Yano *et al.*, 1978;Kushi *et al.*, 1985). Similarly, no association between consumption of sucrose and coronary events was observed in the British study (Morris *et al.*, 1977).

Table 1.12 Coronary events and total sugars and sugar fractions: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13612 (Beulens *et al.*, 2007) Prospect-EPIC Utrecht	The Netherlands, No CHD, No T2DM	49-70 %M 0	(556) /17357	9 y (10)	FFQ (178)	Sugars, total	Fatal + Non-fatal Events	CHD events Registry data	Q4 vs. Q1		1.04 (0.72, 1.48)		0.7	Age, alcohol, BMI, smoking, physical activity, hypercholesterolaemia, hypertension, menopausal status, nutrient intake, oral contraceptive pill, systolic blood pressure
14308 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Sugars, total	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/autopsy, Self report		g/d		Cases: (n: 70) 92.9 (30.3) Non-cases: (n: 1686) 95.3 (37.6)		
14681 (Liu *et al.*, 2000b) NHS	USA, No T2DM, Without angina or heart attack	38-63 %M 0	(761) /75521	10 y (2)	FFQ (126)	Fructose (Energy adjusted score)	Fatal + Non-fatal Events	All fatal CHD + non-fatal MI Medical records/ autopsy	Q5 vs. Q1	score	1.07 (0.82, 1.4)			Age, alcohol, aspirin, BMI, energy intake, fibre, folate, hypercholesterolaemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements, Vitamin E
14680 NHS						Sucrose (Energy adjusted score)	Fatal + Non-fatal Events	All fatal CHD + non-fatal MI Medical records/ autopsy	Q5 vs. Q1	score	1.22 (0.94, 1.6)			As above
14682 NHS						Lactose (Energy adjusted score)	Fatal + Non-fatal Events	All fatal CHD + non-fatal MI Medical records/ autopsy	Q5 vs. Q1	score	0.94 (0.74, 1.21)			As above

Polysaccharides, starch and CVD

Coronary events, polysaccharides and starch

Summary of cohort results

Data were identified from four studies: the Alpha-tocopherol, beta-carotene (ATBC) study, the NHS, Prospect-EPIC Utrecht study and the Caerphilly Study. The ATBC study provided evidence concerning the association between non-cellulosic polysaccharides and fatal CHD and the Prospect-EPIC Utrecht study between polysaccharide intake and risk of both fatal and non-fatal CHD (Pietinen *et al.*, 1996;Beulens *et al.*, 2007). The NHS and the Caerphilly Study provided evidence relating starch and fatal and non-fatal coronary events (Liu *et al.*, 2000b;Fehily *et al.*, 1993).

The ATBC, NHS and Prospect-EPIC Utrecht studies all provided some evidence of reduced risk with greater polysaccharide intake, although only the Finnish ATBC study found the association to be statistically significant, for highest vs. lowest intake RR: 0.67 (95% CI 0.52, 0.88) (Pietinen *et al.*, 1996).

The Caerphilly Study reported very similar intakes of total starch in cohort participants who subsequently became cases and non-cases (Fehily *et al.*, 1993) but no risk estimates were reported for this cohort.

Due to variation in the exposures reported (a starch score rather than starch in the NHS), and the lack of age-adjustment in the Caephilly cohort study, there were too few studies to undertake a meta-analysis.

Exposure definition and assessment

Intake of starch in the Caerphilly Study was assessed with a semi-quantitative FFQ, which was validated for portion size against seven-day food diaries completed by 30% of the sample. In this cohort, FFQs were taken home by each participant to be filled in with help from their spouse (Fehily *et al.*, 1993). The other studies used FFQs with substantial numbers of food items, ranging from 126 to 276 (Pietinen *et al.*, 1996;Beulens *et al.*, 2007;Liu *et al.*, 2000b). The NHS calculated an energy-adjusted score for starch intake (Liu *et al.*, 2000b).

Adjustment for appropriate confounders

For the Prospect-EPIC Utrecht study, NHS and ATBC studies, appropriate adjustments were applied including age, dietary and anthropometric variables (Beulens *et al.*, 2007;Pietinen *et al.*, 1996;Liu *et al.*, 2000b). Unadjusted mean intakes were presented in the Caerphilly Study (Esrey *et al.*, 1996;Fehily *et al.*, 1993).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Evidence from COMA reports – Polysaccharides and coronary events

Data were identified from one cohort study published before 1990 from the COMA reports concerning the association between mean polysaccharide intake and heart-related events (Kromhout *et al.*, 1982). Findings from this study show a somewhat lower polysaccharide intake in fatal cases compared to non-cases at baseline (180.3 vs. 206.5 g/day), with the difference between these two intakes being statistically significant (p=0.04).

Three studies reporting on starch consumption were also included in COMA reports. Two studies presented data on starch intake as a percentage of energy (Kushi *et al.*, 1985;Yano *et al.*, 1978) whereas one study reported starch consumption as g/d (Fehily *et al.*, 1987). The Ireland-Boston Diet-Heart study (Kushi *et al.*, 1985) reported that cases derived 28% of calories from starchy food compared to the rest of the cohort which derived 29% of calories. Findings from the study of Japanese men in Hawaii (Yano *et al.*, 1978) also showed comparable age- and cohort-adjusted means of starchy food intakes in cases and non-cases (22.9 vs. 23.5% calories). In two regression models, percentage of energy derived from starch was not statistically significantly associated with risk of death from coronary heart disease (Yano *et al.*, 1978). The Caerphilly study (Fehily *et al.*, 1987) reported starch consumption at baseline in participants who subsequently did or did not have develop ischaemic heart disease. There was no evidence to suggest there was an association between starch consumption and heart-related events.

Table 1.13 Coronary events, polysaccharides and starch: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13611 (Beulens *et al.*, 2007) Prospect-EPIC Utrecht	The Netherlands, No CHD, No T2DM	49-70 %M 0	(556) /17357	9 y (10)	FFQ (178)	Polysaccharides (>10), unspecified	Fatal + Non-fatal Events	CHD events Registry data	Q4 vs. Q1		0.99 (0.75, 1.32)		0.78	Age, alcohol, BMI, smoking, physical activity, hypercholesterolaemia, hypertension, menopausal status, nutrient intake, oral contraceptive pill, systolic blood pressure
14307 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Starch, total	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/autopsy, Self report		g/d		Cases: (n: 70) 148.8 (56) Non-cases: (n: 1686) 155.1 (57.2)		
14678 (Liu *et al.*, 2000b) NHS	USA, No T2DM, Without angina or heart attack	38-63 %M 0	(761) /75521	10 y (2)	FFQ (126)	Starch (Energy adjusted score)	Fatal + Non-fatal Events	All fatal CHD + non-fatal MI Medical records/ autopsy	Q5 vs. Q1	score	0.94 (0.69, 1.28)			Age, alcohol, aspirin, BMI, energy intake, fibre, folate, hypercholesterolaemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements, vitamin E
13390 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Questionnaire (276)	Non-cellulosic polysaccharides, (based on Englyst method)	Fatal Events	CHD events Registry data	(15.9) vs. (6.8)	g/d	0.67 (0.52, 0.88)		0.01	Age, alcohol, beta-carotene, BMI, systolic and diastolic blood pressure, education, saturated fatty acid, energy intake, physical activity, smoking, group allocation, vitamin C and E

“Complex” carbohydrates and CVD

Coronary events and “complex” carbohydrates

Summary of cohort results

The Crevalcore and Montegiorgio cohort from the Seven Countries Study reported no significant association between energy from “complex” carbohydrate and risk of fatal CHD (Farchi *et al.*, 1995).

Exposure definition and assessment

The definition of “complex” carbohydrates was not provided in The Crevalcore and Montegiorgio cohort from the Seven Countries Study publication (Farchi *et al.*, 1995), although it is generally recognised that “complex” carbohydrates are composed of complex sugar chains, with these chains acting as an energy store or fibrous structure in plants (Committee on Medical Aspects of Food Policy, 1989). As such, rich food sources include grains, legumes, fruits and vegetables (British Nutrition Foundation, 1990;Shah *et al.*, 1994;Shah *et al.*, 1996;Poppitt *et al.*, 2002). According to the WHO and as stated in The Crevalcore and Montegiorgio cohort from the Seven Countries Study (Farchi *et al.*, 1995), intakes of “complex” carbohydrates should make up 50-70% of total carbohydrate intake.

The mean “complex” carbohydrate intake in the sample was 81.8%. Intake of this exposure was assessed using the dietary history method which was validated against a weighed food record in a small sample of the study population.

Adjustment for appropriate confounders

Insufficient adjustments were made for this result, with age being the only confounder included.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.14 Coronary events and “complex” carbohydrates: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast/Units	RR (CI)	Adjust-ments
14172 (Farchi *et al.*, 1995) Crevalcore and Montegiorgio Cohorts Seven Countries Study	Italy	45-64 %M 100	(168) /1564	20 y (0)	Dietary history	“complex” carbohydrates (% energy)	Fatal Events	CHD events Medical records/ autopsy	>70 vs. 50-70 % Energy (WHO recommendation)	1.2 (0.76, 1.88)	Age

Cellulose, lignin and CVD

Coronary events and cellulose and lignin

Summary of cohort results

One cohort study reported data concerning fibre fractions and risk of coronary heart disease. The Finnish ATBC study provided risk estimates for fatal and non-fatal CHD events in association with cellulose and lignin consumption (Pietinen *et al.*, 1996). While fibre fractions tended to be inversely associated with risk of CHD (reduced risk with greater consumption), there was some variation in the size and statistical significance of the risk estimates according to the nature of the outcome. For fatal CHD events, individuals in the highest quantile of consumption of both cellulose and lignin had a 25% reduction in risk compared to those in the lowest intake quantile (p for trend 0.006 and 0.002 respectively). The associations were weaker for a combination of first non-fatal myocardial infarction and coronary heart disease death.

Exposure definition and assessment

The ATBC study assessed food intake at baseline using a 276-item FFQ and estimated fibre fractions using a modified Englyst method (Pietinen *et al.*, 1996).

Adjustment for appropriate confounders

The fully adjusted models in the ATBC study analyses included all important confounders, including age, various dietary variables, anthropometry and indices of socio-economic status (SES).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.15 Coronary events, cellulose and lignin: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13392 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Questionnaire (276)	Cellulose (Englyst method)	Fatal Events	CHD events Registry data	(6.3) vs. (3.1)	g/d	0.72 (0.54, 0.97)	0.006	Age, alcohol, beta-carotene, BMI, systolic and diastolic blood pressure, education, saturated fatty acid, energy intake, physical activity, smoking, group allocation, vitamin C and E
13383 ATBC Study			(1399) /29133			Cellulose (Englyst method)	Fatal + Non-fatal Events	Fatal CHD, MI Registry data	(6.3) vs. (3.1)	g/d	0.9 (0.75, 1.1)	0.07	As above
13382 ATBC Study			(1399) /29133			Lignin (Englyst method)	Fatal + Non-fatal Events	Fatal CHD, MI Registry data	(5.8) vs. (2.1)	g/d	0.89 (0.75, 1.06)	0.21	As above
13391 ATBC Study			(635) /29133			Lignin (Englyst method)	Fatal Events	CHD events Registry data	(5.8) vs. (2.1)	g/d	0.75 (0.58, 0.97)	0.002	As above

Dietary fibre and CVD

The following sections include studies which have examined cardiovascular disease in association with total dietary fibre intake or fibre from a number of food sources.

The Association of Official Analytical Chemists (AOAC) methods of dietary fibre estimation include polysaccharides, oligosaccharides, lignin and associated plant substances that are resistant to digestion. This is the most commonly applied enzymatic-gravimetric method throughout most of Europe and the Americas. However, in the UK until recently, the Englyst method of dietary fibre analysis has been the preferred approach. This method, developed by Hans Englyst and colleagues, is based on an enzymatic-chemical approach and includes only non-starch polysaccharides (NSP), which are considered to be the dominant and most active fraction of 'dietary fibre'. Since it includes only NSP, this approach produces smaller estimates than AOAC. The Southgate method (Southgate, 1969) used in earlier editions of the UK Composition of Foods tables, produces dietary fibre estimates for foods which are greater than the Englyst method as it includes the sum of polysaccharides (including pectins, hemicelluloses and cellulose) and lignin.

Total CVD and dietary fibre/ fibre density

Summary of cohort results

Four cohorts in Finland, USA and Germany provided data on total CVD events and dietary fibre intake: Kuopio Ischaemic Heart Disease Risk Factor Study, NHANES I, The Women's Health Study and the EPIC Potsdam (Laaksonen *et al.*, 2005;Bazzano *et al.*, 2003;Liu *et al.*, 2002;Drogan *et al.*, 2007).

The German cohort tended to show lower mean intakes of dietary fibre expressed as grams per MJ per day in both fatal and non-fatal cases of CVD compared to the other members of the cohort, although this difference is likely not statistically significant (significance not provided). The Finnish cohort showed much lower mean baseline estimates of dietary fibre intake (grams per day) in cases of fatal CVD than in the non-cases, although again statistical significance was not provided. The 2 US cohorts provided some evidence of reduced risk of CVD with increasing intakes of dietary fibre. In the NHANES I cohort there was a 7% reduction in risk of fatal and non-fatal CVD per 10g increment of dietary fibre ($p<0.001$), although the reduction in risk was not so marked for fatal events only. Similarly, the Women's Health Study also reported a 7% reduction in risk associated with each 10g/d increment in dietary fibre (unadjusted model – data not in table), although this estimate was not statistically significant in the fully adjusted model ($p=0.17$).

Exposure definition and assessment

The NHANES I cohort study estimated intakes of dietary fibre density using 24 hour recall data (Bazzano *et al.*, 2003), and the Kuopio Ischaemic Heart Disease Risk Factor Study (Laaksonen *et al.*, 2005) used 4-day food diary estimates of dietary fibre intake. The EPIC Potsdam and Women's Health Study both reported dietary fibre intakes (AOAC) as assessed by FFQ as grams per day and grams per MJ per day respectively (Liu *et al.*, 2002;Drogan *et al.*, 2007).

Adjustment for appropriate confounders

Mean consumption data reported in the EPIC Potsdam and Kuopio Ischaemic Heart Disease Risk Factor Study cohorts was unadjusted. The other cohorts appear to be appropriately adjusted for important confounders. In the Women's Health Study, analyses excluding participants with BMI <25 or ever smokers were conducted to improve control of residual confounding (data not in tables). This provided evidence of stronger inverse associations of CVD with dietary fibre e.g. for never smokers the highest quintile of fibre consumers experienced a 46% reduction in risk of CVD compared to those in the lowest quintile (p trend 0.03).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.16 Total CVD and dietary fibre/ fibre density: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) /Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	Adjustments
14016 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(1198) /14407	19 y (4)	Dietary recall	Dietary Fibre (method unclear, likely AOAC)	Fatal Events	Total CVD Medical records/ autopsy	Continuous risk estimate	10 g/ 1735 kcal/d	0.96 (0.9, 1.03)		0.29	Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, diabetes mellitus, physical activity, gender, systolic blood pressure , saturated fatty acid intake
14015 NHANES I			(3762) /14407				Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	Continuous risk estimate	10 g/ 1735 kcal/d	0.93 (0.89, 0.97)		<0.001	As above
13464 (Drogan *et al.*, 2007) EPIC Potsdam	Germany, No history of MI/Stroke	35-65 (50) %M 40	(68) /27548	6.4 y (5)	FFQ (148)	Fibre density (AOAC method)	Fatal Events	MI/ Stroke, any Medical records/ death certificate		g/MJ/d		Cases: (n=68) 2.4 (0.6) Non-cases: (n=25859) 2.6 (0.7)		
14719 EPIC Potsdam			(311) /27548				Non-fatal Events	MI/ Stroke, any Medical records		g/MJ/d		Cases: (n=311) 2.5 (0.6) Non-cases: (n=25859)2.6 (0.7)		
14040 (Laaksonen *et al.*, 2005) Kuopio Ischaemic Heart Disease Risk Factor Study	Finland, Cancer free, No CHD, No T2DM	42-60 %M 100	(78) /2682	14.6 y (0)	Food diary	Dietary Fibre (AOAC method)	Fatal Events	Total CVD Registry data		g/d		Cases: (n=68) 33.9 (51.9) Non-cases: (n=25859) 45.5 (54.6)		

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) /Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	Adjustments
13515 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(570) /39876	6 y	FFQ (131)	Dietary Fibre (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	Continuous risk estimate	26.3 vs. 12.5 g/d	0.79 (0.58, 1.09)		0.17	Age, alcohol, BMI, energy intake, family history MI, fat intake, folate, diabetes mellitus, supplements, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, postmenopausal hormone replacement therapy

Coronary events and dietary fibre/fibre density

Summary of cohort results

Eleven studies presented data on dietary fibre intake and coronary events: Zutphen Elderly Study, Finnish Mobile Clinic Health Surveys, Oxford Vegetarian Study, ATBC Study, NHANES I, Health Professionals' Follow-up Study (HPFS), Cardiovascular Health Study, The Women's Health Study, NHS, The Caerphilly Study, and the Scottish Heart Health Study (Streppel *et al.*, 2008;Knekt *et al.*, 1994;Appleby *et al.*, 1999;Pietinen *et al.*, 1996;Bazzano *et al.*, 2003;Rimm *et al.*, 1996;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Fehily *et al.*, 1993;Todd *et al.*, 1999).

Risk estimates were extracted from 10 studies and all but one study provided evidence of reduced risk for fatal, non-fatal or combined coronary events with greater intake of fibre (Streppel *et al.*, 2008;Knekt *et al.*, 1994;Appleby *et al.*, 1999;Pietinen *et al.*, 1996;Bazzano *et al.*, 2003;Rimm *et al.*, 1996;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Todd *et al.*, 1999). Many of these negative risk estimates were not statistically significant, however this evidence for reduced risk with greater intake was statistically significant in five of the studies and related to the following outcomes: fatal CHD in HPFS, ATBC, NHS (Rimm *et al.*, 1996;Pietinen *et al.*, 1996;Wolk *et al.*, 1999), fatal and non-fatal CHD in NHANES I and the Scottish Heart Health Study (Todd *et al.*, 1999;Bazzano *et al.*, 2003), non-fatal MI in NHS and HPFS (Rimm *et al.*, 1996;Wolk *et al.*, 1999) and fatal and non-fatal MI in the HPFS (Rimm *et al.*, 1996).

The Caerphilly Study and Finnish Mobile Clinic Health Surveys reported very similar intakes of dietary fibre in cases and non-cases at baseline in men, although the female cases in the Finnish study consumed significantly less fibre compared to the rest of the cohort (22 vs. 25g/d p=0.02) (Knekt *et al.*, 1994;Fehily *et al.*, 1993).

Exposure definition and assessment

Fibre intake was calculated as either g/day or g/unit energy and was assessed using a single 24hour recall in NHANES I (Bazzano *et al.*, 2003), and by dietary history in the Zutphen Elderly Study and in the Finnish Mobile Clinic Health Surveys (Streppel *et al.*, 2008;Knekt *et al.*, 1994). In the Caerphilly Study, fibre intake was assessed with a semi-quantitative FFQ, which was validated for portion size against seven-day food diaries completed by 30% of the sample. The rest of the studies tended to use FFQs (Rimm *et al.*, 1996;Appleby *et al.*, 1999;Pietinen *et al.*, 1996;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Todd *et al.*, 1999). In the Scottish Heart Health Study only 60 foods or food groups were included on the FFQ; this may be too few to accurately estimate total fibre intake (Todd *et al.*, 1999).

The Oxford Vegetarian and ATBC cohorts calculated fibre intakes using Englyst values (Appleby *et al.*, 1999;Pietinen *et al.*, 1996), the Caerphilly and Scottish cohorts used Southgate methods (Todd *et al.*, 1999;Fehily *et al.*, 1993) and AOAC values were used in the remaining cohorts (Knekt *et al.*, 1994;Liu *et al.*, 2002;Mozaffarian *et al.*, 2003;Rimm *et al.*, 1996;Streppel *et al.*, 2008;Wolk *et al.*, 1999) except NHANES I, which did not report the method (Bazzano *et al.*, 2003).

In the NHS, dietary fibre intake was reported as a measure of cumulative average intake from questionnaires which were sent at two year intervals (Wolk *et al.*, 1999). All other studies assessed fibre intake at baseline.

Adjustment for appropriate confounders

The Finnish Mobile Clinic Health Surveys study provided data on fibre intake in cases and non-cases adjusted by age (Knekt *et al.*, 1994). The Oxford Vegetarian Study did not adjust for any anthropometric or diet-related variables (Appleby *et al.*, 1999). The other studies all adjusted for appropriate confounders including age and nutrients/energy intake, and most included adjustments for class/socioeconomic status.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Evidence from COMA reports - Dietary fibre and coronary events

Three cohorts in the UK, Ireland/Boston(US) and the Netherlands were discussed in prior COMA reports but were not included in this review as they were published before 1990 (Morris *et al.*, 1977;Kromhout *et al.*, 1982;Kushi *et al.*, 1985). The UK cohort tended to show lower dietary fibre intakes in cases of coronary heart disease compared to non-cases, although statistical significance values were not reported (Morris *et al.*, 1977). The Netherlands cohort also reported a lower intake of dietary fibre in cases compared to non-cases (27.2 vs. 30.8 g/d), but this difference did not reach statistical significance (p=0.06). The authors showed that the coronary heart disease-death rate in those in the lowest quintile of intake of dietary fibre was four times higher than those in the highest quintile, yet this relation disappeared following multiple logistic regression analysis (Kromhout *et al.*, 1982). Finally the Ireland-Boston cohorts showed lower intakes of dietary fibre in fatal cases of coronary heart disease than non-fatal cases (0.81 vs. 0.75g/1,000 kcal, p=0.04) (Kushi *et al.*, 1985). Participants in the upper third of fibre intake had a significantly lower risk of coronary heart disease than those in the lowest third (RR 0.57 95% CI 0.33 to 0.97) (Kushi *et al.*, 1985). The study also provided evidence of a negative association of dietary fibre with CHD death (p=0.05) (Kushi *et al.*, 1985).

Table 1.17 Coronary events and dietary fibre/fibre density: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
*13133 (Appleby *et al.*, 1999) Oxford Vegetarian Study	UK, Primarily White	16-79 (46) %M 40	(525) /11140	13.3 y	FFQ	Dietary Fibre (not reported, likely Southgate method)	Fatal Events	Ischaemic heart disease Medical records/ autopsy		Q3 vs. Q1		2.25 (0.92, 5.53)			NS	Age, socio-economic status/class, gender, smoking
14014 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(668) /14407	19 y (4)	Dietary recall	Fibre Density (method unclear, likely AOAC method)	Fatal Events	CHD events Medical records/ autopsy		Continuous risk estimate	10 g/17 35 kcal	0.91 (0.83, 1)		0.06		Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, DM, physical activity, saturated fatty acid intake, gender, SBP
*14013 NHANES I			(1843) /14407				Fatal + Non-fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/17 35 kcal	0.92 (0.86, 0.98)		0.01		As above
14309 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Dietary Fibre (not reported, likely Southgate method)	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/autopsy, Self report			g/d		Cases: (n: 70) 15.1 (5.7) Non-cases: (n: 1686) 16.4 (5.7)			
13141 (Knekt *et al.*, 1994) Finnish Mobile Clinic Health Surveys	Finland, No CHD	30-69 %M 53	(186) /5133	14 y (9)	Dietary history	Dietary Fibre (AOAC method)	Fatal Events	CHD events Registry data	Men		g/d		Cases: (n: 186) 32 Non-cases: (n: 2264) 32	0.84		Age
13142 Finnish Mobile Clinic Health Surveys			(58) /5133						Women		g/d		Cases: (n: 58) 22 Non-cases: (n: 2183) 25	0.02		Age
*13563 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(177) /39876	6 y	FFQ (131)	Dietary Fibre (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods		(26.3) vs. (12.5)	g/d	0.68 (0.39, 1.22)			0.13	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolae

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
																mia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
*14135 (Mozaffarian *et al.*, 2003) Cardiovascular Health Study	USA, Primarily White, Age >65y, No CHD	65- %M 38.8	(811) /5201	8.6 y	FFQ (99)	Dietary Fibre (AOAC method)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy		Q5 vs. Q1	g/d	0.84 (0.66, 1.07)			0.23	Age, alcohol, cereal fibre, education, fibre from fruit, fibre from veg, DM, smoking, physical activity, gender, smoking
13378 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(1399) /29133	6.1 y	FFQ / Question-naire (276)	Dietary Fibre (Englyst method)	Fatal + Non-fatal Events	Fatal CHD, MI Registry data		(34.8) vs. (16.1)	g/d	0.87 (0.73, 1.04)			0.8	Age, alcohol, Beta-carotene, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP, Vit C, Vit E
*13387 ATBC Study			(635) /29133				Fatal Events	CHD events Registry data		(34.8) vs. (16.1)	g/d	0.73 (0.56, 0.95)			0.004	As above
*13477 (Rimm *et al.*, 1996) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(232) /51529	6 y	FFQ (131)	Dietary Fibre (AOAC method)	Fatal Events	CHD events Registry data		(28.9) vs. (12.4)	g/d	0.45 (0.28, 0.72)			<0.001	Age, alcohol, BMI, saturated fatty acid intake, family history of MI, hypercholesterolaemia, occupation, physical activity, hypertension, smoking, Vit E
13478 HPFS			(734) /51529				Fatal + Non-fatal Events	MI Medical records/ autopsy, Registry data, Self report		(28.9) vs. (12.4)	g/d	0.59 (0.46, 0.76)			<0.001	As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
*13476 HPFS			(511) /51529				Non-fatal Events	MI Confirmed self report		(28.9) vs. (12.4)	g/d	0.65 (0.49, 0.88)			0.02	As above
*13615 (Streppel *et al.*, 2008) Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	Dietary Fibre AOAC method (Energy adjusted, recent intake)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.83 (0.75, 1.7)				TFA, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake, SES/class, alcohol
13414 Zutphen Elderly Study						Dietary Fibre AOAC method (Intake during middle age. Energy adjusted, long term intake)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.87 (0.71, 1.07)				As above
14130 (Todd *et al.*, 1999) Scottish Heart Health Study	Scotland, Primarily White	40-59 %M 51	(296) /11629	9 y (0.1)	FFQ (60)	Fibre density (not reported, likely Southgate method – NSP, resistant starch and lignin)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy	Men	Q4 vs. Q1		0.64 (0.45, 0.9)				Age, alcohol, BMI, dietary cholesterol, energy intake, fibrinogen, HDL-C, DM, personality score, physical activity, smoking, SBP, blood TG
14136 Scottish Heart Health Study			(97) /11629						Women	Q4 vs. Q1		0.56 (0.29, 1.08)				As above
13626 (Wolk *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM, Not hyper-lipidaemic/ hyperholest-erolaemic	30-55 %M 0	(429) /121700	10 y (20)	FFQ (116)	Dietary Fibre (Long-term intake over 6 years. AOAC method)	Non-fatal Events	MI Confirmed self reports		(22.9) vs. (11.5)	g/d	0.57 (0.42, 0.77)			<0.001	Age, alcohol, aspirin, BMI, carbohydrate intake, saturated fatty acid intake, energy intake, hypertension, menopausal status, parental MI, Period of exposure, physical activity, smoking,

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
																postmenopausal HRT, Vit intake
NHS 13627			(162) /121700				Fatal Events	CHD events Registry data, Records/ autopsy		(22.9) vs. (11.5)	g/d	0.41 (0.23, 0.7)			0.002	As above
NHS *13628			(591) /121700				Fatal + Non-fatal Events	Non-fatal MI, fatal CHD Registry data, Medical records/ autopsy, Confirmed self reports		(22.9) vs. (11.5)	g/d	0.77 (0.57, 1.04)			0.07	As above

*This result was used in the meta-analysis of dietary fibre and CHD events

Stroke events and dietary fibre/fibre density

Summary of cohort results

Data were identified from four studies: the NHS (Oh *et al.*, 2005), HPFS (Ascherio *et al.*, 1998), ATBC study (Larsson *et al.*, 2009), and NHANES I (Bazzano *et al.*, 2003). These studies provided evidence concerning the association between dietary fibre and fatal and non-fatal stroke (total stroke/ ischaemic/ haemorrhagic/ haemorrhagic – subarachnoid/ haemorrhage – intracerebral). One study reported a borderline significant association between dietary fibre and any stroke with a significant p for trend (0.028) (Ascherio *et al.*, 1998). The remaining studies reported non-significant relative risks for dietary fibre and any stroke (Oh *et al.*, 2005;Bazzano *et al.*, 2003), haemorrhagic stroke (Oh *et al.*, 2005;Larsson *et al.*, 2009) and ischaemic stroke (Oh *et al.*, 2005;Larsson *et al.*, 2009). In summary, these studies do not provide evidence of an association between dietary fibre and risk of stroke.

Exposure definition and assessment

The four cohort studies presented data on dietary fibre reported as total grams per day (Oh *et al.*, 2005;Ascherio *et al.*, 1998;Larsson *et al.*, 2009), and as fibre density (Bazzano *et al.*, 2003). Dietary fibre was measured using the AOAC method for HPFS and NHS, (Oh *et al.*, 2005;Ascherio *et al.*, 1998), the Englyst method for the ATBC study (Larsson *et al.*, 2009), but the method was not reported for NHANES I (Bazzano *et al.*, 2003). Dietary fibre was assessed using FFQs (Oh *et al.*, 2005;Ascherio *et al.*, 1998;Larsson *et al.*, 2009) and single dietary recalls (Bazzano *et al.*, 2003).

Adjustment for appropriate confounders

All studies adjusted for a wide range of covariates including age, smoking, physical activity and gender (in the case of NHANES I) (Bazzano *et al.*, 2003).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.18 Stroke events and dietary fibre/fibre density: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
*13466 (Ascherio *et al.*, 1998) HPFS	USA, No CHD, No T2DM Primarily White, Cancer free	40-75 %M 100	(328) /51529	8 y	FFQ (131)	Dietary Fibre (AOAC method)	Fatal + Non-fatal Events	Stroke, any Medical records/autopsy, Self report	(28.9) vs. (12.4)	g/d	0.7 (0.48, 1.00)		0.028	Age, alcohol, BMI, energy intake, hypercholesterolaemia, hypertension, occupation, parental MI, physical activity, smoking
14011 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(233) /14407	19 y (4)	Dietary recall	Fibre Density (method unclear, likely AOAC method)	Fatal Events	Stroke, any Medical records/ autopsy	Continuous risk estimate	10 g/1735 kcal	1.02 (0.85, 1.24)	0.8		Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, DM, physical activity, saturated fatty acid intake, gender, SBP
*14008 NHANES I			(928) /14407				Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods	Continuous risk estimate	10 g/1735 kcal	0.94 (0.87, 1.02)	0.12		As above
*13317 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Question-naire (276)	Dietary Fibre (Englyst method)	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(35.8) vs. (16.1)	g/d	0.86 (0.47, 1.59)		0.49	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, Magnesium Intake, smoking, group allocation, SBP
*13316 ATBC Study			(383) /29133					Stroke, haemorrhage-Intracerebral Registry data	(35.8) vs. (16.1)	g/d	0.97 (0.61, 1.54)		0.63	As above
*13314 ATBC Study			(2702) /29133					Stroke, ischaemic Registry data	(35.8) vs. (16.1)	g/d	1.01 (0.85, 1.19)		0.83	As above
*13514 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	Dietary Fibre (AOAC method)	Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods	(21) vs. (10)	g/d	0.83 (0.66, 1.04)		0.07	Age, alcohol, aspirin, BMI, carbohydrate intake, energy intake, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, postmenopausal HRT, Vit intake
13517 NHS			(279) /121700					Stroke, haemorrhagic Ascertained using multiple methods	(21) vs. (10)	g/d	0.84 (0.54, 1.3)		0.34	As above
13516 NHS			(515) /121700					Stroke, ischaemic Ascertained using multiple methods	(21) vs. (10)	g/d	0.78 (0.56, 1.09)		0.09	As above

*This result was used in the meta-analysis of dietary fibre and stroke events

Total dietary fibre and CVD summary

Meta-analysis: Dietary fibre and incident CVD events

Data were extracted from 14 publications presenting results from 11 cohort studies for dietary fibre (g/day) and CVD (Laaksonen *et al.*, 2005;Oh *et al.*, 2005;Bazzano *et al.*, 2003;Mozaffarian *et al.*, 2003;Knekt *et al.*, 1994;Liu *et al.*, 2002;Appleby *et al.*, 1999;Wolk *et al.*, 1999;Ascherio *et al.*, 1998;Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Fehily *et al.*, 1993;Streppel *et al.*, 2008;Larsson *et al.*, 2009).

The Finnish Mobile Clinic Health Surveys study was excluded because it did not present any measure of variation, such as confidence intervals, standard errors or standard deviations (Knekt *et al.*, 1994). Both the Caerphilly Study and Kuopio Ischaemic Heart Disease Risk Factor Study were also excluded from meta-analyses because they did not present results adjusted for any confounders (Fehily *et al.*, 1993;Laaksonen *et al.*, 2005).

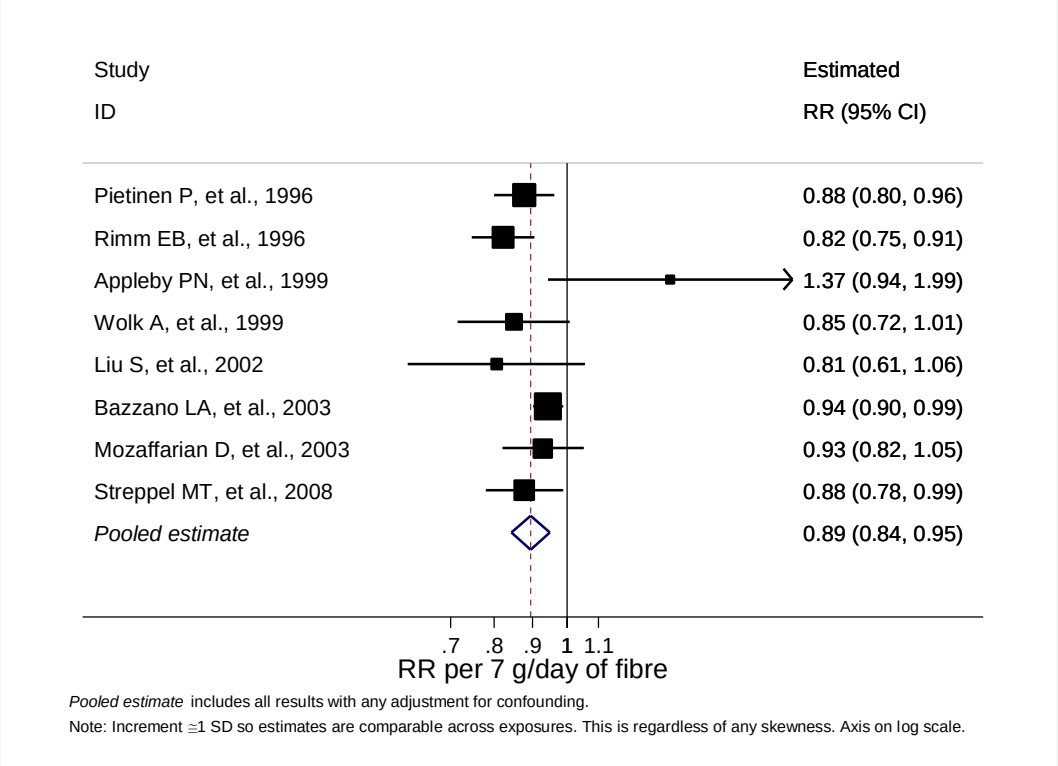
For two studies, intake of fibre was assumed to follow a normal distribution with mean and standard deviation quoted in or derived from the papers, so that median intakes for each category could be estimated for the estimation of a dose-response slope (Appleby *et al.*, 1999;Mozaffarian *et al.*, 2003). One publication from the Oxford Vegetarian Study (Appleby *et al.*, 1999) reported dietary fibre intake split into thirds, with mean (SD) intake of 42.4 (8.4) g/day. If the tertiles are at 33% and 67%, then the category medians were taken as the being at 16.7%, 50%, and 83.3% through the normal distribution with the same mean and SD, i.e. 34.3, 42.4, and 50.5 g/day respectively. The same method was used for the Cardiovascular Health Study (Mozaffarian *et al.*, 2003).

Most studies presented results separately for CHD and stroke, so separate meta-analyses were performed for each. Only two studies presented results for total CVD (Bazzano *et al.*, 2003;Liu *et al.*, 2002), and both of these also provided results for at least one of CHD and stroke.

Relative risks are presented for each 7g/day increase, equivalent to approximately one standard deviation, in fibre intake in the UK. The approximate mean population intake is estimated as 19g/day. These estimates are based on NDNS data (Bates *et al.*, 2009) multiplied by 1.33 (to convert from Englyst to AOAC values).

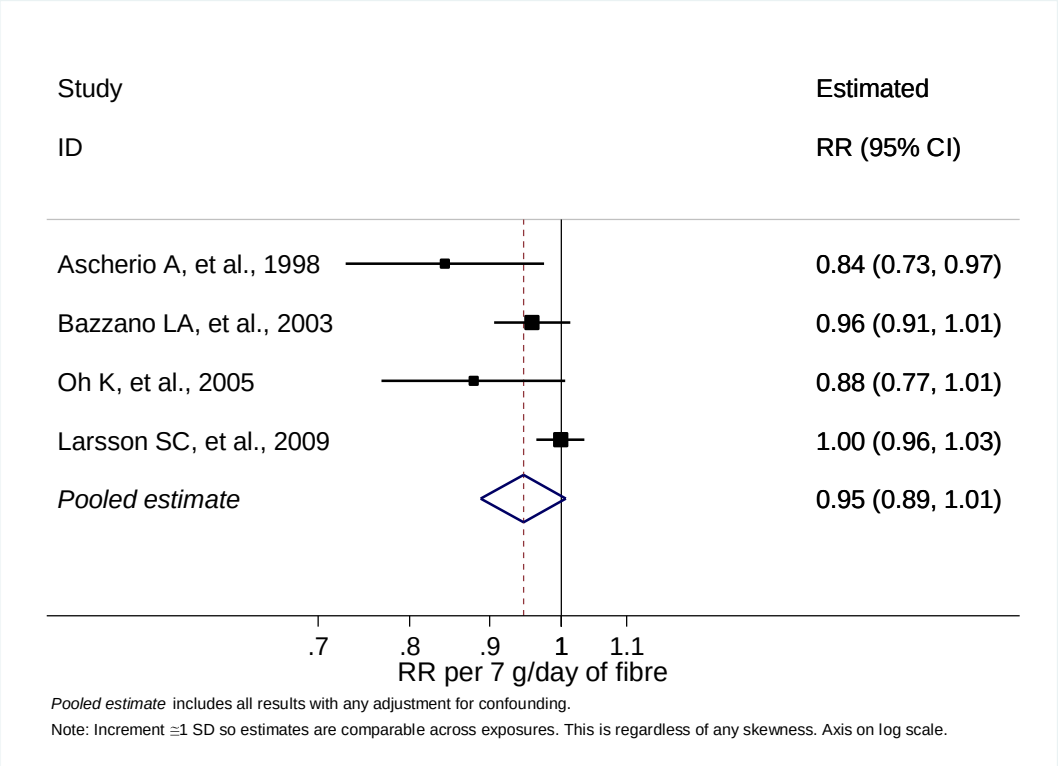
For CHD, the pooled estimate of relative risk was 0.89 (95% CI: 0.84 to 0.95) per 7 g/day of fibre ($p<0.001$).

Figure 1.2 Forest plot for total dietary fibre and CHD events



For stroke, the pooled estimate of relative risk was 0.95 (95% CI: 0.89 to 1.01) per 7 g/day of fibre (p=0.08).

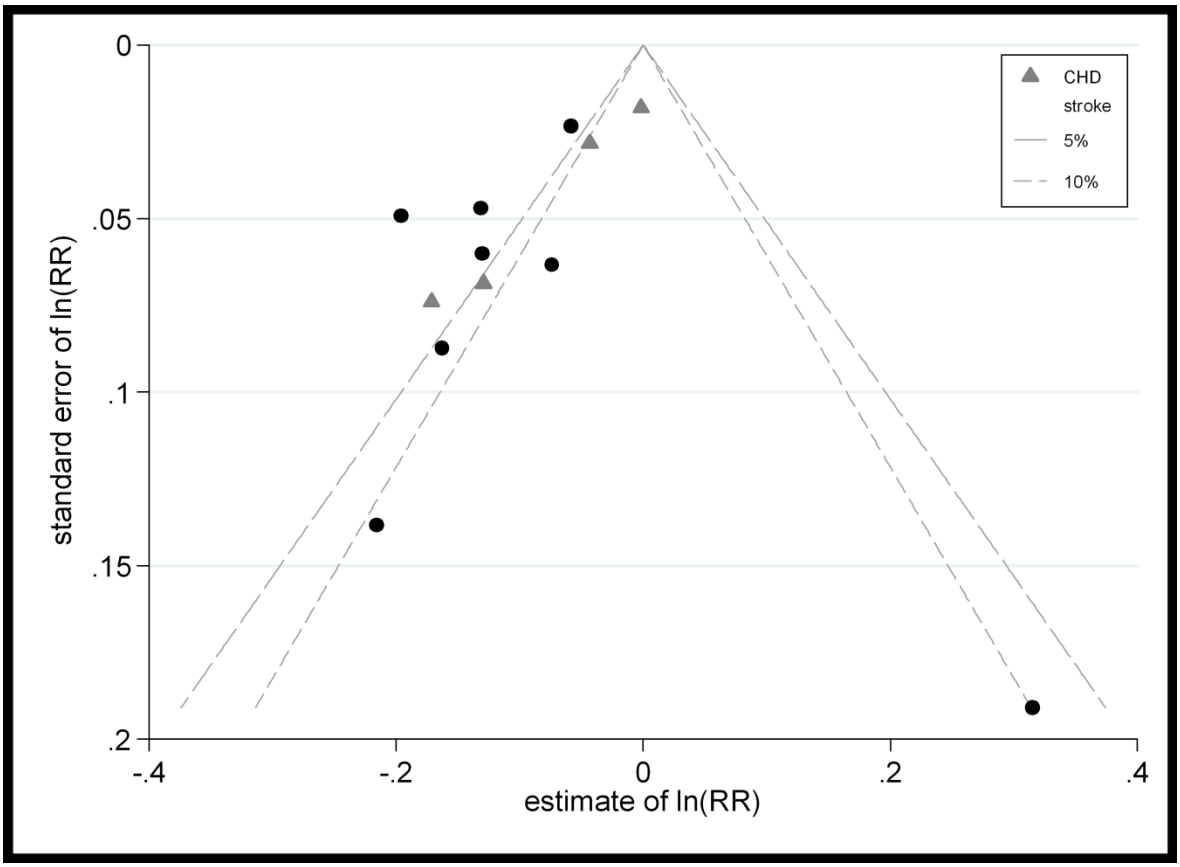
Figure 1.3 Forest plot for total dietary fibre and stroke events



There was moderate heterogeneity between the cohort studies for CHD (I^2=49%, 95% CI: 0% to 73%, Q=13.7, df=7, p=0.06), and moderate heterogeneity between the cohort studies for stroke (I^2=64%, 95% CI: 0% to 88%, Q=8.3, df=3, p=0.04).

Small-study effects (e.g. publication bias) were explored through a contour-enhanced funnel plot. There was considerable evidence of a small-study effect, and with non-significant results largely excluded, this possibly indicates the presence of publication bias for both CHD and stroke. A roughly symmetrical funnel plot would indicate an absence of publication bias (see http://www.cochrane-net.org/openlearning/html/mod15-3.htm for guidance on interpretation of funnel plots).

Figure 1.4 Contour-enhanced funnel plot for publications presenting CHD/Stroke outcomes and total dietary fibre



There were sufficient studies to explore the sources of heterogeneity by subgroup analysis and meta-regression for the CHD outcome, but not for stroke (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 1.19 Subgroup analyses of fibre and incidence of CHD. Relative risks are per 7 g/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.86 (0.81, 0.91)	0%	3	.6	.08
	Mixed	0.96 (0.87, 1.06)	48%	3	.1	
	Female	0.84 (0.72, 0.97)	0%	2	.7	
method used to assess fibre	AOAC	0.88 (0.81, 0.96)	61%	4	.05	
	not AOAC	1.05 (0.69, 1.62)	81%	2	.02	.5
includes non-fatal events	yes	0.92 (0.80, 1.06)	62%	3	.07	
	no	0.89 (0.83, 0.96)	50%	5	.09	.8
length of follow-up	<10 years	0.86 (0.82, 0.92)	0%	4	.4	
	>=10 years	0.93 (0.84, 1.02)	53%	4	.09	.7
geographic location	Americas	0.89 (0.83, 0.96)	50%	5	.09	
	EU	0.92 (0.80, 1.06)	62%	3	.07	
	Other			0		.8
adjusted for age	yes	0.89 (0.84, 0.95)	49%	8	.06	
	no			0		
adjusted for alcohol	yes	0.89 (0.85, 0.93)	34%	7	.2	
	no	1.37 (0.94, 1.99)		1		.07
adjusted for anthropometry	yes	0.88 (0.83, 0.93)	44%	6	.1	
	no	1.08 (0.75, 1.57)	73%	2	.05	.2
adjusted for energy intake	yes	0.87 (0.82, 0.91)	0%	6	.7	
	no	1.08 (0.76, 1.54)	73%	2	.05	.04
adjusted for family history	yes	0.83 (0.76, 0.90)	0%	3	.9	
	no	0.92 (0.87, 0.98)	43%	5	.1	.06
adjusted for physical activity	yes	0.89 (0.84, 0.94)	43%	6	.1	
	no	1.06 (0.69, 1.63)	80%	2	.03	.6
adjusted for gender	yes	0.89 (0.84, 0.95)	49%	8	.06	
	no			0		
adjusted for smoking	yes	0.89 (0.84, 0.95)	49%	8	.06	
	no			0		
adjusted for age & smoking	yes	0.89 (0.84, 0.95)	49%	8	.06	
	no			0		

* P for heterogeneity within each subgroup

** P for heterogeneity between each subgroup

Soluble and insoluble fibre and CVD

Total CVD and soluble and insoluble fibre

Summary of cohort results

Data on soluble and insoluble dietary fibre and risk of total CVD were reported by NHANES I and The Women's Health Study (Bazzano *et al.*, 2003;Liu *et al.*, 2002). Both tended to report reduced risk with increasing consumption. In the NHANES I cohort the continuous estimate of risk for any incident CVD event per 5 gram/1735 kcal/day increment of water-soluble dietary fibre was 0.94 (95% CI, 0.9-0.99; p =0.01 for trend) (Bazzano *et al.*, 2003). However, the estimate of risk for fatal CVD events was closer to one and not statistically significant. No equivalent risk estimates in association with insoluble dietary fibre were reported for this cohort. The Women's Health Study reported data on both soluble and insoluble dietary fibre consumption. Compared to the lowest quantile of soluble fibre consumption, the risk of fatal and non-fatal CVD events in the highest quantile was 0.9 (95% CI, 0.68, 1.21; p =0.5 for trend). For insoluble fibre, the equivalent risk estimate was 0.78 (95% CI, 0.57, 1.06; p =0.09 for trend).

Exposure definition and assessment

The NHANES I cohort study assessed intakes of dietary fibre using 24 hour recall data (Bazzano *et al.*, 2003) and The Women's Health Study reported soluble and insoluble dietary fibre intakes (AOAC) as assessed by FFQ as grams per day (Liu *et al.*, 2002). However, the method of assessing fibre intake in the NHANES I cohort was not reported.

Adjustment for appropriate confounders

Both studies appear to be appropriately adjusted for important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.20 Total CVD and soluble and insoluble fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) /Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
14030 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(1198) /14407	19 y (4)	Dietary recall	Soluble fibre (method unclear, likely AOAC)	Fatal Events	Total CVD Medical records/ autopsy	Continuous risk estimate	5g/ 1735 kcal	0.98 (0.93, 1.04)	0.48		Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, DM, physical activity, saturated fatty acid intake, gender, SBP
14029 NHANES I			(3762) /14407				Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	Continuous risk estimate	5g/ 1735 kcal	0.94 (0.9, 0.99)	0.01		As above
13561 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(570) /39876	6 y	FFQ (131)	Soluble fibre (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	(8.6) vs. (3.7)	g/d	0.9 (0.68, 1.21)		0.5	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
13562 The Women's Health Study			(570) /39876			Insoluble fibre (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	(21.8) vs. (9.5)	g/d	0.78 (0.57, 1.06)		0.09	As above

Coronary events and soluble and insoluble fibre

Summary of cohort results

Four studies provided some evidence of reduced risk for fatal, non-fatal or combined coronary events with greater intake of soluble fibre: ATBC Study, NHANES I, HPFS and The Women's Health Study (Pietinen *et al.*, 1996;Bazzano *et al.*, 2003;Rimm *et al.*, 1996;Liu *et al.*, 2002). This association was statistically significant in both the ATBC study and NHANES I study but not in the HPFS or the Women's Health Study.

Three studies reported insoluble fibre and coronary events, the ATBC Study, HPFS and the Women's Health Study (Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Liu *et al.*, 2002). Some evidence of reduced risk for fatal, non-fatal or combined coronary events with greater intake of insoluble fibre was seen in all three cohorts. The association was statistically significant in the ATBC study for fatal CHD, highest vs. lowest intake, RR: 0.75 (95% CI 0.58, 0.98) (Pietinen *et al.*, 1996) and per 10g/d increase in HPFS RR: 0.75 (95%CI 0.59, 0.94) (Rimm *et al.*, 1996).

Exposure definition and assessment

Fibre intakes were assessed using a single 24hour recall in NHANES I (Bazzano *et al.*, 2003), with fairly long FFQs being used in the Women's Health Study and HPFS (Liu *et al.*, 2002;Rimm *et al.*, 1996) and with a combination of a long FFQ and questionnaire in the ATBC study. The ATBC study provided information relating both to insoluble fibre and also insoluble non-cellulosic polysaccharides as well as soluble fibre (Pietinen *et al.*, 1996).

Fibre was calculated using the Englyst method in the Finnish ATBC study, using the AOAC methods in the Women's Health Study and HPFS and was not reported for the NHANES I study.

Adjustment for appropriate confounders

Appropriate adjustments were made by all studies including age, anthropometry and also energy intake in the Women's Health and ATBC studies (Liu *et al.*, 2002;Pietinen *et al.*, 1996;Rimm *et al.*, 1996).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.21 Coronary events and soluble and insoluble fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
14028 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(668) /14407	19 y (4)	Dietary recall	Soluble fibre density (method unclear, likely AOAC)	Fatal Events	CHD events Medical records/ autopsy	Continuous risk estimate	5 g /1735 kcal	0.91 (0.83, 0.99)	0.03		Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, DM, physical activity, saturated fatty acid intake, gender, SBP
**14025 NHANES I							Fatal + Non-fatal Events	CHD events Ascertained using multiple methods	Continuous risk estimate	5 g /1735 kcal	0.92 (0.87, 0.97)	0.004		As above
**13567 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(177) /39876	6 y	FFQ (131)	Soluble fibre (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods	(8.6) vs. (3.7)	g/d	0.83 (0.47, 1.48)		0.4	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
*13568 The Women's Health Study						Insoluble fibre (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods	(21.8) vs. (9.5)	g/d	0.74 (0.42, 1.3)		0.12	As above
**13388 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Questionnaire (276)	Soluble fibre (based on Englyst method)	Fatal Events	CHD events Registry data	(7.4) vs. (3.7)	g/d	0.68 (0.5, 0.92)		0.003	Age, alcohol, Beta-carotene, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP, Vit C, Vit E
13379 ATBC Study			(1399) /29133				Fatal + Non-fatal Events	Fatal CHD, MI Registry data	(7.4) vs. (3.7)	g/d	0.83 (0.68, 1.01)		0.05	As above
13380 ATBC Study			(1399) /29133			Insoluble fibre (based on Englyst method)	Fatal + Non-fatal Events	Fatal CHD, MI Registry data	(27.7) vs. (12.2)	g/d	0.87 (0.73, 1.04)		0.13	As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
13381 ATBC Study			(1399) /29133			Insoluble non cellulosic polysaccharides (based on Englyst method)	Fatal + Non-fatal Events	Fatal CHD, MI Registry data	(15.9) vs. (6.8)	g/d	0.86 (0.72, 1.03)		0.13	As above
*13389 ATBC Study			(635) /29133			Insoluble fibre (based on Englyst method)	Fatal Events	CHD events Registry data	(27.7) vs. (12.2)	g/d	0.75 (0.58, 0.98)		0.01	As above
**17623 (Rimm *et al.*, 1996) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(740) /51529	6 y	FFQ (131)	Soluble fibre (AOAC method)	Fatal + Non-fatal Events	MI and fatal CHD Medical records/ autopsy, Registry data, Self report	Continuous risk estimate	10g/d	1.07 (0.57, 2.02)			Sat fat, vit E, age, BMI, smoking, alcohol, physical activity, hypertension, hypercholesterolaemia, familial MI, profession, insoluble fibre
*17624 HPFS						Insoluble fibre (AOAC methods)				10 g/d	0.75 (0.59, 0.94)			As above but adjustment for soluble instead of insoluble fibre

*This result was used in the meta-analysis of insoluble fibre and CHD events

**This result was used in the meta-analysis of soluble fibre and CHD events

Stroke events and soluble and insoluble fibre

Summary of cohort results

Data were identified from two studies: the ATBC study (Larsson *et al.*, 2009) and NHANES I (Bazzano *et al.*, 2003). These studies provided evidence concerning the association between soluble and insoluble dietary fibre and fatal and non-fatal stroke – (total stroke, ischaemic, haemorrhagic, haemorrhagic - subarachnoid and haemorrhage – intracerebral). In both studies all relative risks were close to 1 with no significant tests for trend reported for either soluble or insoluble fibre, indicating no evidence of an association.

Exposure definition and assessment

The ATBC study (Larsson *et al.*, 2009) reported soluble fibre and insoluble fibre intake as grams per day. These were assessed using a 276-item FFQ and fibre was estimated using the Englyst method. NHANES I (Bazzano *et al.*, 2003) reported soluble fibre intake as grams per 1,735 kcal which was assessed using a single dietary recall, but the method used for fibre estimates was not provided.

Adjustment for appropriate confounders

Both studies adjusted for a wide range of covariates including age, smoking, physical activity, health outcomes and gender (in the case of NHANES I) (Bazzano *et al.*, 2003).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.22 Stroke events and soluble and insoluble fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
14019 (Bazzano *et al.*, 2003) NHANES I	USA, No CVD	25-74 %M 38.3	(233) /14407	19 y (4)	Dietary recall	Soluble fibre (method unclear, likely AOAC)	Fatal Events	Stroke, any Medical records/ autopsy	Continuous risk estimate	5 g/1735 kcal	1.03 (0.83, 1.28)	0.78		Age, alcohol, BMI, dietary cholesterol, smoking, education, ethnicity, DM, physical activity, saturated fatty acid intake, gender, SBP
14018 NHANES I			(928) /14407				Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods	Continuous risk estimate	5 g/1735 kcal	0.95 (0.88, 1.03)	0.18		As above
13320 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Question-naire (276)	Soluble fibre (Englyst method)	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(7.7) vs. (3.8)	g/d	0.95 (0.51, 1.79)		0.86	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, Magnesium Intake, smoking, group allocation, SBP
13319 ATBC Study			(383) /29133			Soluble fibre (Englyst method)		Stroke, haemorrhage-Intracerebral Registry data	(7.7) vs. (3.8)	g/d	0.99 (0.62, 1.59)		0.6	As above
13318 ATBC Study			(2700) /29133			Soluble fibre (Englyst method)		Stroke, ischaemic Registry data	(7.7) vs. (3.8)	g/d	0.86 (0.73, 1.02)		0.17	As above
13323 ATBC Study			(196) /29133			Insoluble fibre (Englyst method)		Stroke, haemorrhage-Subarachnoid Registry data	(28.3) vs. (12.2)	g/d	0.89 (0.49, 1.64)		0.58	As above
13322 ATBC Study			(383) /29133			Insoluble fibre (Englyst method)		Stroke, haemorrhage-Intracerebral Registry data	(28.3) vs. (12.2)	g/d	0.88 (0.56, 1.39)		0.43	As above
13321 ATBC Study			(2702) /29133			Insoluble fibre (Englyst method)		Stroke, ischaemic Registry data	(28.3) vs. (12.2)	g/d	1.03 (0.87, 1.21)		0.61	As above

Soluble and insoluble fibre and CVD summary

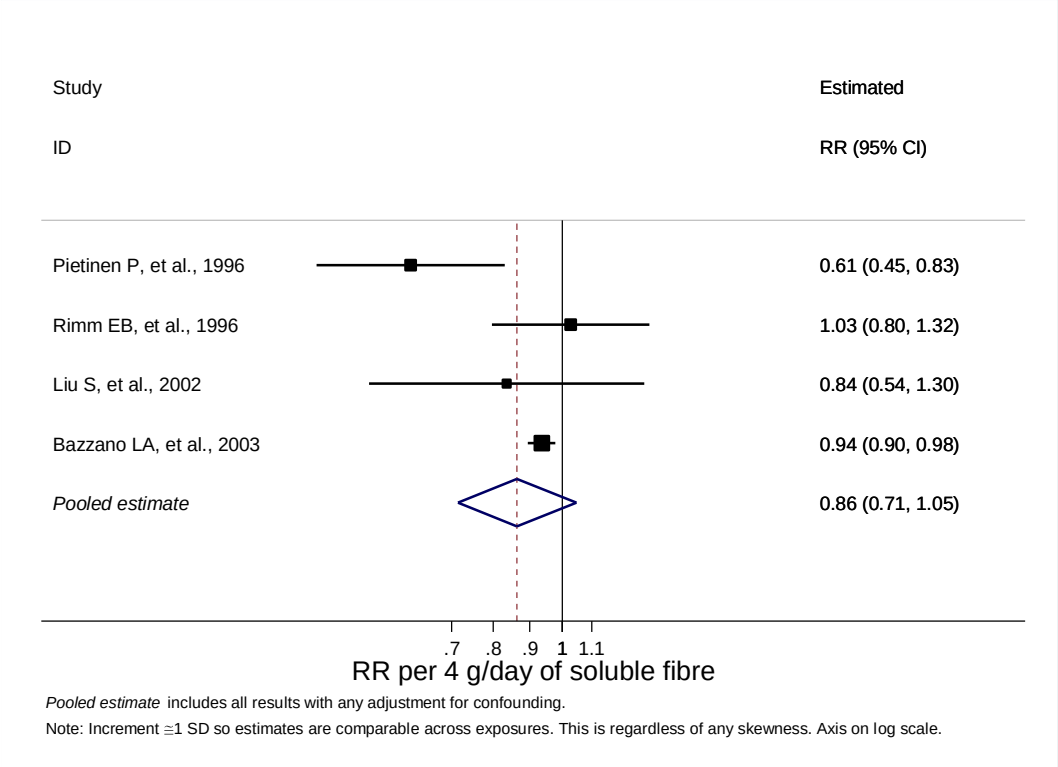
Meta-analysis: Soluble fibre and incident CVD events

Data were identified from five publications presenting results from four cohort studies: The Women's Health Study; NHANES I, ATBC and the HPFS (Liu *et al.*, 2002;Pietinen *et al.*, 1996;Larsson *et al.*, 2009;Rimm *et al.*, 1996). There were sufficient studies presenting results for CHD on its own, to conduct a meta-analysis of this focussed outcome rather than having to combine with stroke events. Two papers presented results from the same cohort (Larsson *et al.*, 2009;Pietinen *et al.*, 1996). The later paper (Larsson *et al.*, 2009) was excluded because it only presented results for stroke. All remaining papers were included in the meta-analysis.

Relative risks are presented for each 4g/day increase, equivalent to approximately one standard deviation, in soluble fibre intake. The approximate mean population intake is 4g/day as based on UK data from NDNS (Bates *et al.*, 2009).

The pooled estimate of relative risk of CHD was 0.86 (95% CI: 0.71 to 1.05) per 4 g/day of soluble fibre (p=0.1).

Figure 1.5 Forest plot for soluble fibre and CHD events



There was moderate excess heterogeneity between the cohort studies (I^2=63%, 95% CI: 0% to 88%, Q=8.1, df=3, p=0.04), but not enough studies to explore sources of heterogeneity through subgroup analysis or meta-regression. There were insufficient studies to explore small-study

effects such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

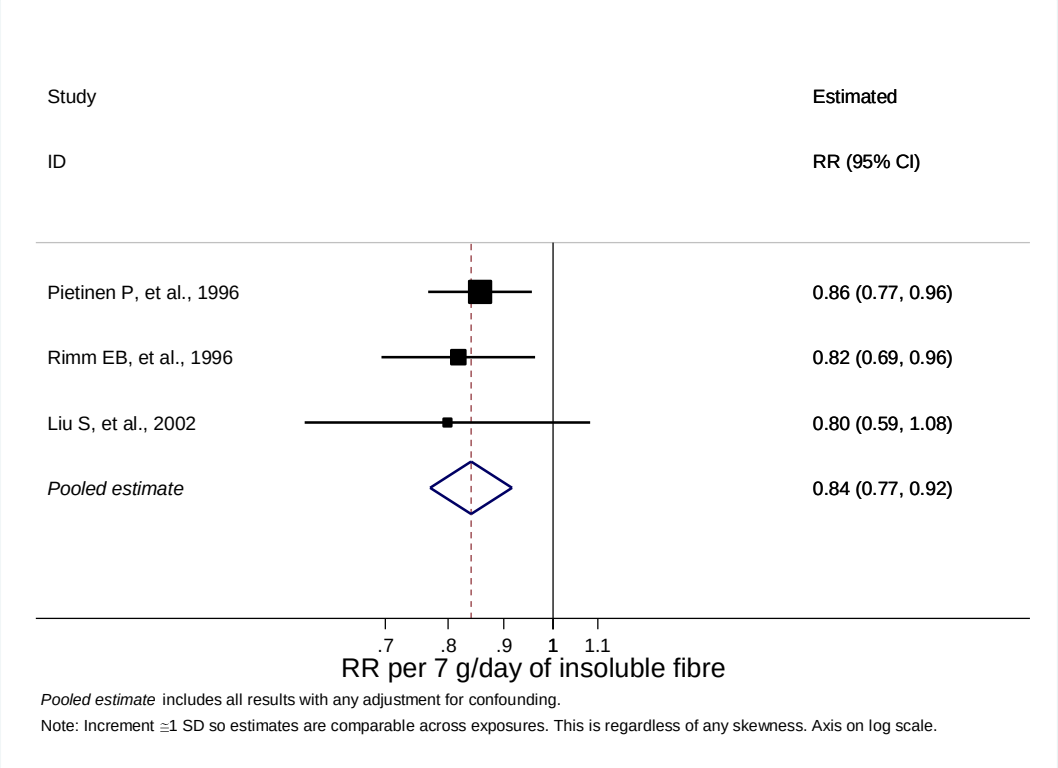
Meta-analysis: Insoluble fibre and incident CVD events

Data were identified from four publications presenting results from three cohort studies: The Women's Health Study, HPFS and ATBC (Liu *et al.*, 2002;Pietinen *et al.*, 1996;Larsson *et al.*, 2009;Rimm *et al.*, 1996). There were sufficient studies presenting results for CHD on its own, to conduct a meta-analysis of this focussed outcome rather than having to combine with stroke events. Two papers presented results from the ATBC study (Larsson *et al.*, 2009;Pietinen *et al.*, 1996). The later paper (Larsson *et al.*, 2009) was excluded because it only presented results for stroke. All remaining papers were included in the meta-analysis.

Relative risks are presented for each 7g/day increase, equivalent to approximately one standard deviation, in insoluble fibre intake. The approximate mean population intake is 15g/day as based on UK data from NDNS for non-starch polysaccharides multiplied by 1.33 to convert to AOAC fibre (Bates *et al.*, 2009).

The pooled estimate of relative risk of CHD was 0.84 (95% CI: 0.77 to 0.92) per 7 g/day of insoluble fibre (p<0.001).

Figure 1.6 Forest plot for insoluble fibre and CHD events



There was no excess heterogeneity between the cohort studies (I^2=0%, 95% CI: 0% to 37%, Q=0.3, df=2, p=0.8), and not enough studies to explore any subgroup analysis or meta-regression. There were insufficient studies to explore small-study effects such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Food sources of dietary fibre and CVD

The following section includes cohort studies which report fibre from cereal foods, fruit, vegetables, potatoes and legumes. These results refer to fibre contained within and not fibre extracted from food sources. Interpretation of these results should therefore be considered in the context of whole food consumption and not necessarily fibre extracted from these foods.

Fibre in cereals and CVD

Total CVD and fibre in cereals

Summary of cohort results

One cohort study provided data. In the Women's Health Study no association with risk of CVD events was observed when comparing high consumers of cereal fibre to the lowest consumers (Liu *et al.*, 2002).

This study reported dietary fibre (AOAC) from cereals as assessed by FFQ in grams per day (Liu *et al.*, 2002) although a list of foods contributing cereal fibre was not reported (Liu *et al.*, 2002). The result was appropriately adjusted for important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.23 Total CVD and fibre in cereals: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) /Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13527 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(570) /39876	6 y	FFQ (131)	Fibre contained within cereals (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	(6.5) vs. (3)	g/d	1.11 (0.84, 1.46)	0.38	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT

Coronary events and fibre in cereal foods

Summary of cohort results

Eight studies presented data on cereal fibre intake and coronary events: the ATBC Study, Blue Mountains Eye Study, Zutphen Elderly Study, Cardiovascular Health Study, HPFS, The Women's Health Study, NHS, and the Caerphilly Study (Pietinen *et al.*, 1996;Kaushik *et al.*, 2009;Streppel *et al.*, 2008;Mozaffarian *et al.*, 2003;Rimm *et al.*, 1996;Liu *et al.*, 2002;Wolk *et al.*, 1999;Fehily *et al.*, 1993).

Risk data were identified from seven studies and, in all but the Blue Mountains Eye study, the direction of association indicated reduced risk with greater intake of fibre from cereal foods, with this association being statistically significant in the ATBC study, the NHS and the HPFS (Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Wolk *et al.*, 1999). In the ATBC cohort, the relative risk for fatal CHD was 0.74 (95% CI: 0.57, 0.96) for high vs. low intake (Pietinen *et al.*, 1996). The HPFS found that the relative risk for fatal and non-fatal MI was 0.71 (95% CI: 0.55, 0.91) per 10g increase in fibre from cereal foods (Rimm *et al.*, 1996). In women from the NHS, the relative risk for fatal and non-fatal CHD was 0.63 (95% CI: 0.49, 0.81; $p<0.001$) for each 5g increase in daily cereal fibre consumption (Wolk *et al.*, 1999). Other statistically significant negative associations (lower risk of coronary events with greater intake of cereal fibre) were seen in subgroups of non-smokers, in those with BMI<25kg/m^2 and subgroups of fatty acid intake levels. This negative association (lower risk with greater intake) was different in subgroups of women who were younger or older than 60 years of age in the NHS (Wolk *et al.*, 1999). An association with borderline statistical significance was also seen in a subgroup of non-diabetic participants in the Cardiovascular Health Study, and indicated lower risk with greater consumption, the relative risk for fatal and non-fatal CHD was 0.85 (95% CI: 0.73, 1.0) for the 80^{th} vs. 20^{th} centile of cereal fibre intake (Mozaffarian *et al.*, 2003).

The Caerphilly Study in Welsh men reported very similar intakes of cereal fibre in cases and non-cases at baseline (7.3 vs. 7.9 g/d), but no statistical comparison of these groups was reported (Fehily *et al.*, 1993).

Exposure definition and assessment

Intake of fibre in cereal foods was assessed with a dietary history in the Zutphen Elderly Study and, in the Caerphilly Study, was assessed with a semi-quantitative FFQ, which had been validated for portion size against seven-day food diaries completed by a 30% sample of the cohort (Fehily *et al.*, 1993). The rest of the studies used FFQs ranging in number of items from 99 in the Cardiovascular Health Study to 276 in the ATBC study.

In the NHS, cereal fibre intake was assessed using a measure of cumulative average intake from questionnaires which were sent at two-year intervals (Wolk *et al.*, 1999). All other studies assessed cereal fibre intake at baseline only.

Studies carried out in the USA have generated values for fibre in cereals using AOAC fibre analysis methods. The other studies have either not reported the method of cereal fibre assessment or have reported that the Englyst method was used.

Studies differed with regard to foods included in 'cereals'. Three cohorts were unclear or simply did not report which foods were classified as cereal foods (Pietinen *et al.*, 1996;Fehily *et al.*, 1993;Kaushik *et al.*, 2009). Those that did specify cereal food items tended to include cold breakfast cereal (Rimm *et al.*, 1996;Liu *et al.*, 2002;Wolk *et al.*, 1999;Mozaffarian *et al.*, 2003) and different varieties of bread.

Adjustment for appropriate confounders

The studies had all adjusted for appropriate confounders including age, nutrients and/or energy intake and most included adjustments for socioeconomic status and anthropometry.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Evidence from COMA reports – Fibre from foods and coronary events

One cohort study from the COMA reports presented data on sources of dietary fibre and coronary events (Morris *et al.*, 1977). This study reported cases of coronary heart disease in association with mean intakes of fibre from cereals as well as fibre from fruit, vegetables, pulses and nuts. There was no association between coronary heart disease and fibre derived from fruit, vegetables, pulses and nuts, yet there was evidence of a relationship with fibre from cereals. A lower intake of fibre from cereals was reported in cases compared to non-cases, but statistical significance values were not stated. After adjustments were made for age, occupation and length of follow-up, cases had "a mean intake of 2.42g of cereal fibre per 1,000 kcal" whereas non-cases had an average intake of 2.84g (Morris *et al.*, 1977). This difference was statistically significant ($p<0.005$).

Table 1.24 Coronary events and sources of fibre in cereals: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
14310 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Fibre contained within cereals (not reported, likely Southgate method)	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/ autopsy, Self report			g/d		Cases: (n: 70) 7.3 (4.6) Non-cases: (n: 1686) 7.9 (4.6)		
13351 (Kaushik *et al.*, 2009) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	>49 (65) %M 44	(Case numbers not reported) /3654	13 y	FFQ (145)	Fibre contained within cereals AOAC method (Energy adjusted cereal fibre)	Fatal Events	CHD events Registry data		(3) vs. (11)	g/d	0.94 (0.73, 1.22)		0.65	Age, BMI, DBP, education,MI, stroke, DM, self-rated health status, gender, hypertension medication smoking, SBP
*13564 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(177) /39876	6 y	FFQ (131)	Fibre contained within cereals (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods		(6.5) vs. (3)	g/d	0.91 (0.56, 1.47)		0.74	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hyper-cholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
*14132 (Mozaffarian *et al.*, 2003) Cardiovascular Health Study	USA, Primarily White, Age >65y, No CHD	65- %M 38.8	(811) /5201	8.6 y	FFQ (99)	Fibre contained within cereals (AOAC method)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy		>6.3 vs. <1.7	g/d	0.79 (0.62, 0.99)		0.02	Age, alcohol, cereal fibre, education, fibre from fruit, fibre from veg, DM, physical activity, gender, smoking
14137 Cardiovascular Health Study			(204) /5201						Age 65-69y	80th vs. 20th Centile	g/d	0.82 (0.67, 1.01)			As above
14138 Cardiovascular Health Study			(255) /5201						Age 70-74y	As above	g/d	0.89 (0.75, 1.06)			As above
14139 Cardiovascular Health Study			(352) /5201						Age >75y	As above	g/d	0.87 (0.73, 1.04)			As above
14140 Cardiovascular Health Study			(434) /5201						Women	As above	g/d	0.89 (0.74, 1.06)			As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
14141 Cardiovascular Health Study			(377) /5201						Men	As above	g/d	0.83 (0.68, 1.02)			As above
14142 Cardiovascular Health Study			(575) /5201						No T2DM	As above	g/d	0.85 (0.73, 1.0)			As above
*13393 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Question naire (276)	Fibre contained within cereals (Englyst method)	Fatal Events	CHD events Registry data		(26.3) vs. (8.8)	g/d	0.74 (0.57, 0.96)		0.01	Age, alcohol, Beta-carotene, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP, Vit C, Vit E
13384 ATBC Study			(1399) /29133				Fatal + Non-fatal Events	Fatal CHD, MI Registry data		(26.3) vs. (8.8)	g/d	0.91 (0.77, 1.09)		0.18	As above
*13483 (Rimm *et al.*, 1996) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(740) /51529	6 y	FFQ (131)	Fibre contained within cereals (AOAC method)	Fatal + Non-fatal Events	MI Medical records/ autopsy, Registry data, Self report		Continuous risk estimate	10 g/d	0.71 (0.55, 0.91)			Age, alcohol, BMI, saturated fatty acid intake, family history of MI, Hyper-cholesterolaemia, occupation, physical activity, hypertension, smoking, Vit E
*13616 (Streppel *et al.*, 2008) Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	Fibre contained within cereals AOAC method (Energy adjusted, fibre contained within bread and other cereal products - recent intake)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.84 (0.64, 1.1)			TFA, alcohol, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class
13417 Zutphen Elderly Study						Fibre contained within cereals AOAC method (Intake in middle age, Energy adjusted fibre from bread and other cereal products)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.86 (0.64, 1.15)			As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
*13629 (Wolk *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM, Not hyperlipidaemic/ hypercholest-erolaemic	30-55 %M 0	(591) /121700	10 y (20)	FFQ (116)	Fibre contained within cereals (Long-term intake over 6 years. AOAC method)	Fatal + Non-fatal Events	Non-fatal MI, fatal CHD Registry data, Medical records/ autopsy, Confirmed self reports		Continuous risk estimate	5 g/d	0.63 (0.49, 0.81)		<0.001	Age, alcohol, aspirin, Beta-carotene, BMI, carbohydrate intake, saturated fatty acid intake, energy intake, fruit fibre, veg fibre, folate, hypertension, magnesium Intake, menopausal status, parental MI, period of exposure, physical activity, smoking, post-menopausal HRT, Vit B6 intake, Vit C
NHS 13636			(289) /121700						Age <60	Continuous risk estimate	5 g/d	0.63 (0.44, 0.9)		0.01	As above
NHS 13637			(302) /121700						Age >60	Continuous risk estimate	5 g/d	0.76 (0.57, 0.99)		0.05	As above
NHS 13638			(319) /121700						Never or former smoker	Continuous risk estimate	5 g/d	0.59 (0.43, 0.79)		<0.001	As above
NHS 13639			(272) /121700						Smokers	Continuous risk estimate	5 g/d	0.87 (0.63, 1.2)		0.39	As above
NHS 13640			(249) /121700						BMI <25	Continuous risk estimate	5 g/d	0.58 (0.4, 0.82)		0.003	As above
NHS 13641			(278) /121700						BMI >25	Continuous risk estimate	5 g/d	0.85 (0.62, 1.17)		0.31	As above
NHS 13642			(177) /121700						Lowest tertile of SFA	Continuous risk estimate	5 g/d	0.62 (0.44, 0.88)		0.007	As above
NHS 13643			(194) /121700						Middle tertile of SFA	Continuous risk estimate	5 g/d	0.79 (0.54, 1.15)		0.21	As above
NHS 13644			(220) /121700						Highest tertile of SFA	Continuous risk estimate	5 g/d	0.68 (0.43, 1.07)		0.1	As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13645 NHS			(189) /121700						Lowest tertile of TFA	Continuous risk estimate	5 g/d	0.69 (0.49, 0.97)		0.03	As above
13646 NHS			(211) /121700						Middle tertile of TFA	Continuous risk estimate	5 g/d	0.77 (0.53, 1.12)		0.18	As above
13647 NHS			(191) /121700						Highest tertile of TFA	Continuous risk estimate	5 g/d	0.57 (0.35, 0.92)		0.02	As above

*This result was used in the meta-analysis of fibre in cereals and CHD events

Stroke events and fibre in cereals

Summary of cohort results

Data were identified from three studies conducted in Finland, the USA and Australia: the ATBC study (Larsson *et al.*, 2009), the NHS (Oh *et al.*, 2005), and the Blue Mountains Eye study (Kaushik *et al.*, 2009). These studies provided evidence concerning the association between fibre contained within cereals and fatal and non-fatal stroke (total stroke, ischaemic, haemorrhagic, haemorrhagic - subarachnoid and haemorrhage – intracerebral). The Blue Mountains Eye study (Kaushik *et al.*, 2009) showed a significantly increased risk of any stroke in individuals with the lowest intakes of fibre (<3g/d) in cereals, with a significant p for trend. Similarly the NHS (Oh *et al.*, 2005) showed a decreased risk with increasing fibre from cereals for both any stroke (44% reduction) and haemorrhagic stroke (49% reduction) each with a significant p for trend. The NHS showed no association between fibre from cereals and ischaemic stroke. Results from the ATBC study (Larsson *et al.*, 2009) showed no association for either haemorrhagic or ischaemic stroke and fibre from cereals.

Exposure definition and assessment

For all three studies, fibre in cereals was assessed using FFQs. The ATBC study (Larsson *et al.*, 2009) reported fibre contained within cereals as measured by the Englyst method, the NHS (Oh *et al.*, 2005) used the AOAC method and the Blue Mountains Eye study (Kaushik *et al.*, 2009) presented energy adjusted cereal fibre consumption (AOAC). These three cohorts did not specify food items included in their 'cereal' classification (Larsson *et al.*, 2009;Kaushik *et al.*, 2009;Oh *et al.*, 2005).

Adjustment for appropriate confounders

All studies adjusted for a wide range of covariates including age, smoking and gender (in the case of the Blue Mountains Eye study) (Kaushik *et al.*, 2009).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.25 Stroke events and fibre in cereals: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
*13332 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Questionnaire (276)	Fibre contained within cereals (Englyst method)	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(27.5) vs. (8.9)	g/d	0.86 (0.5, 1.46)	0.6	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, magnesium Intake, smoking, group allocation, SBP
*13331 ATBC Study			(383) /29133					Stroke, haemorrhage-Intracerebral Registry data	(27.5) vs. (8.9)	g/d	0.94 (0.63, 1.42)	0.71	As above
*13330 ATBC Study			(2702) /29133					Stroke, ischaemic Registry data	(27.5) vs. (8.9)	g/d	1.06 (0.91, 1.23)	0.25	As above
*13350 (Kaushik *et al.*, 2009) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(95) /3654	13 y	FFQ (145)	Fibre contained within cereals AOAC method (Energy adjusted cereal fibre consumption)	Fatal Events	Stroke, any Registry data	(3) vs. (11)	g/d	2.13 (1.19, 3.8)	0.02	Age, BMI, DBP, education,MI, stroke, DM, self-rated health status, gender, smoking, SBP, hypertension medication
*13518 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	Fibre contained within cereals (AOAC method)	Fatal + Non-fatal Events	Stroke, any Multiple methods	(5.7) vs. (1.4)	g/d	0.66 (0.52, 0.83)	0.001	Age, alcohol, aspirin, BMI, carbohydrate intake, energy intake, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, postmenopausal HRT, Vit intake
13520 NHS			(279) /121700					Stroke, haemorrhagic Ascertained using multiple methods	(5.7) vs. (1.4)	g/d	0.51 (0.33, 0.78)	0.01	As above
13519 NHS			(515) /121700					Stroke, ischaemic Ascertained using multiple methods	(5.7) vs. (1.4)	g/d	0.8 (0.57, 1.12)	0.23	As above

*This result was used in the meta-analysis of fibre consumed in cereals and stroke events

Fibre contained in cereal foods and CVD summary

Meta-analysis: Fibre contained in cereals and incident CVD events

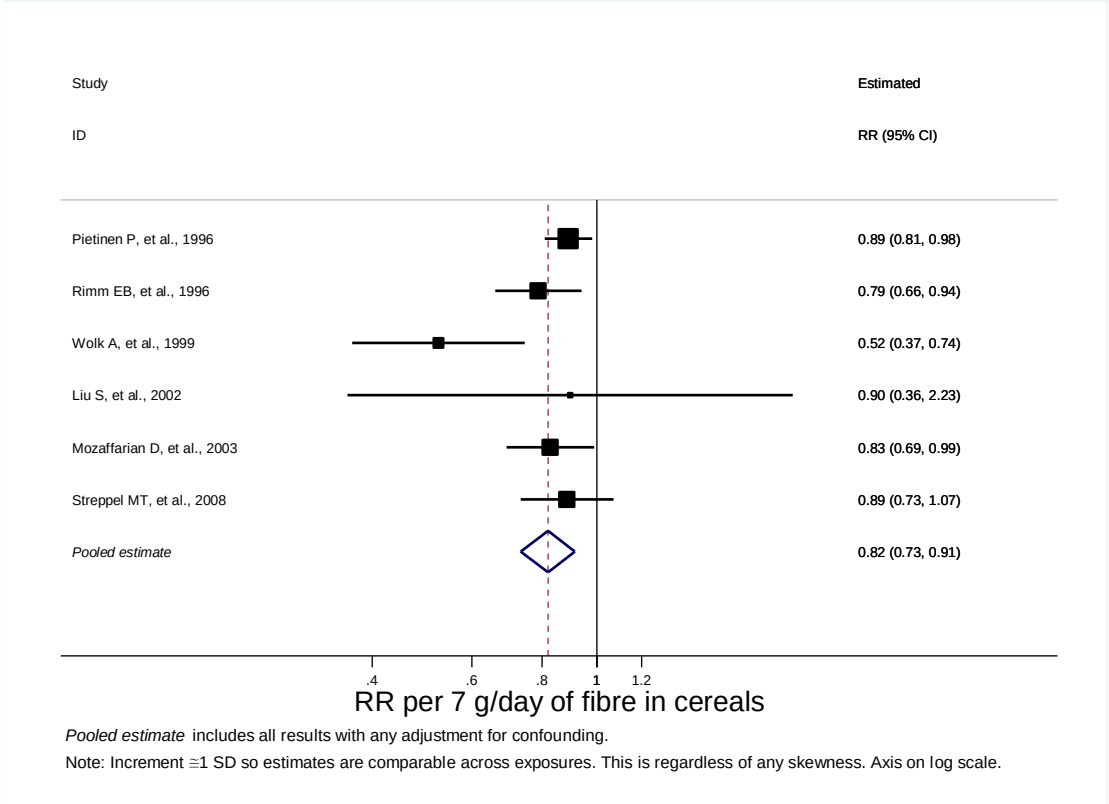
Data were extracted from 9 publications presenting results from 7 cohort studies (Oh *et al.*, 2005;Kaushik *et al.*, 2009;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Streppel *et al.*, 2008;Larsson *et al.*, 2009). All these studies were included in the meta-analysis. One further study, The Caerphilly Study (Fehily *et al.*, 1993) was not included because it did not present results adjusted for any confounders.

Most studies presented results separately for CHD and stroke, so separate meta-analyses were performed for each. Only one study presented results for total CVD (Liu *et al.*, 2002), and this study also presented results for CHD, so was still included in that meta-analysis. Only the stroke results could be included for another study (Kaushik *et al.*, 2009) because the data presented were insufficient to derive a dose-response trend to include in the CHD meta-analysis. For one study, to permit the results to be included in the meta-analysis, we assumed that the median intake for the lowest category was half the upper limit of the lowest category, and the median of the highest category was 1.5 times the lower limit of the highest category (Mozaffarian *et al.*, 2003).

Relative risks are presented for each 7g/day increase, equivalent to approximately one standard deviation, in intake of fibre within cereals. The approximate mean population intake is 12g/day as based on UK data from the National Diet and Nutrition Survey (Bates *et al.*, 2009).

For CHD, the pooled estimate of relative risk was 0.82 (95% CI: 0.73 to 0.91) per 7 g/day of fibre contained within cereal ($p<0.001$).

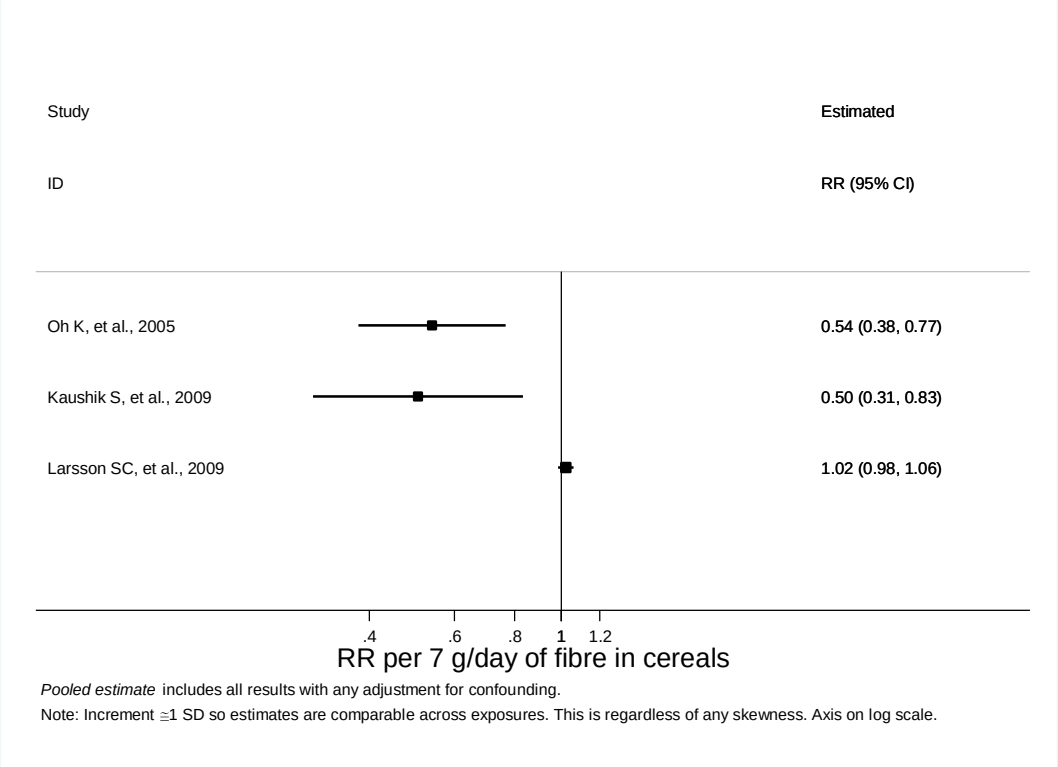
Figure 1.7 Forest plot for fibre in cereal foods and CHD events



Pooled estimate includes all results with any adjustment for confounding.

Note: Increment ≅1 SD so estimates are comparable across exposures. This is regardless of any skewness. Axis on log scale.

Figure 1.8 Forest plot for fibre in cereal foods and stroke events



There was some heterogeneity between the cohort studies for CHD (I^2=45%, 95% CI: 0% to 78%, Q=9.1, df=5, p=0.1), but substantial heterogeneity between the cohort studies for stroke (I^2=90%, 95% CI: 73% to 96%, Q=19.2, df=2, p<0.001), implying that the pooled estimate for stroke is unreliable. This was therefore not included on the plot.

The stroke results were strongly dependent on results from the ATBC Study (Larsson *et al.*, 2009). This study had much larger numbers of stroke cases, with associated narrower confidence intervals and greater weight in the meta-analysis. With this study, the confidence interval was wide, without this study, the negative association between cereal fibre and stroke (lower risk of stroke with greater intake of cereal fibre) was much stronger than the CHD results and heterogeneity improved substantially. Larsson *et al* was the only stroke study not using the AOAC definition of fibre.

There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

There were sufficient studies to further explore the sources heterogeneity by subgroup analysis and meta-regression for the CHD outcome, but not for stroke (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis for CHD.

Table 1.26 Subgroup analyses of fibre in cereal and incidence of CHD. Relative risks are per 7 g/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.87 (0.80, 0.94)	0%	3	.5	.2
	Mixed	0.83 (0.69, 0.99)		1		
	Female	0.58 (0.38, 0.87)	15%	2	.3	
method used to assess fibre	AOAC	0.83 (0.73, 0.95)	0%	3	.7	
	not AOAC	0.89 (0.81, 0.98)		1		.5
includes non-fatal events	yes	0.89 (0.81, 0.97)	0%	2	1	
	no	0.75 (0.62, 0.90)	44%	4	.1	.2
length of follow-up	<10 years	0.86 (0.79, 0.93)	0%	4	.7	
	>=10 years	0.70 (0.42, 1.16)	85%	2	.01	.7
geographic location	Americas	0.75 (0.62, 0.90)	44%	4	.1	
	EU	0.89 (0.81, 0.97)	0%	2	1	
	Other			0		.4
adjusted for age	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		
adjusted for alcohol	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		
adjusted for anthropometry	yes	0.81 (0.70, 0.93)	56%	5	.06	
	no	0.83 (0.69, 0.99)		1		.9
adjusted for energy intake	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		
adjusted for family history	yes	0.69 (0.50, 0.95)	54%	3	.1	
	no	0.88 (0.81, 0.95)	0%	3	.8	.1
adjusted for physical activity	yes	0.80 (0.69, 0.92)	55%	5	.07	
	no	0.89 (0.73, 1.07)		1		.6
adjusted for gender	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		
adjusted for smoking	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		
adjusted for age & smoking	yes	0.82 (0.73, 0.91)	45%	6	.1	
	no			0		

* P for heterogeneity within each subgroup

** P for heterogeneity between each subgroup

Fibre in fruit and CVD

Total CVD and fibre in fruit

Summary of cohort results

One cohort study, the Women's Health Study, provided data on fibre in fruit and risk of total CVD events (Liu *et al.*, 2002). There was some evidence of a reduction in risk associated with increasing intake of fibre contained within fruit. Compared to the lowest quintile of fruit fibre consumption, the risk of CVD events in the highest quintile was 0.82 (95% CI, 0.61, 1.09; p trend=0.09).

The Women's Health Study reported dietary fibre (AOAC) from fruits as assessed by FFQ and this analysis appears to be appropriately adjusted for important potential confounders (Liu *et al.*, 2002).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.27 Total cardiovascular disease and fibre in fruit

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13560 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(570) /39876	6 y	FFQ (131)	Fibre contained within fruit (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	(6) vs. (2.5)	g/d	0.82 (0.61, 1.09)	0.09	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT

Coronary events and fibre in fruit

Summary of cohort results

The Caerphilly Study presented data on combined fruit and vegetable fibre intake and fatal and non-fatal IHD, and reported that cases consumed 7.8g/d at study baseline compared to the 8.4g/d mean consumption in the rest of the cohort (Fehily *et al.*, 1993).

Six studies presented data on intake of fibre within fruit: ATBC Study, Zutphen Elderly Study, Cardiovascular Health Study, HPFS, The Women's Health Study, and the NHS (Pietinen *et al.*, 1996;Streppel *et al.*, 2008;Mozaffarian *et al.*, 2003;Rimm *et al.*, 1996;Liu *et al.*, 2002;Wolk *et al.*, 1999).

For coronary events and fruit fibre intake, most studies reported risk estimates close to 1 (indicating no evidence of an association), and none reported any statistically significant associations.

Exposure definition and assessment

Fruit fibre intakes were assessed with a dietary history in the Zutphen Elderly Study and, in the Caerphilly Study, they were assessed with a semi-quantitative FFQ, which had been validated for portion size against seven-day food diaries completed by a 30% sample of the cohort (Fehily *et al.*, 1993). The rest of the studies used FFQs ranging in number of items from 99 in the Cardiovascular Health Study to 276 in the ATBC study.

In the NHS, fruit fibre intake was assessed using a measure of cumulative average intake from questionnaires which were sent at two-year intervals (Wolk *et al.*, 1999).

All studies calculated fibre using AOAC methods except the ATBC study (Englyst) (Pietinen *et al.*, 1996) and the Caerphilly study (method not reported, likely Southgate) (Fehily *et al.*, 1993).

Adjustment for appropriate confounders

The studies reporting risk estimates had all adjusted for appropriate confounders including age, and nutrients and/or energy intake and most included adjustments for socioeconomic status and anthropometry.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.28 Coronary events and fibre in fruit: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
14311 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Fibre contained within fruit and vegetables (not reported, likely Southgate method)	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/ autopsy, Self report			g/d		Cases: (n: 70) 7.8 g/d (2.3) Non-cases: (n: 1686) 8.4 g/d (2.7)			
*13566 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(177) /39876	6 y	FFQ (131)	Fibre contained within fruit (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods		(6) vs. (2.5)	g/d	1.11 (0.62, 1.96)			0.63	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholest-erolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
*14133 (Mozaffarian *et al.*, 2003) Cardiovascular Health Study	USA, Primarily White, Age >65y, No CHD	65- %M 38.8	(811) /5201	8.6 y	FFQ (99)	Fibre contained within fruit (AOAC method)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy		>7.5 vs. <2.8	g/d	0.99 (0.78, 1.25)			0.98	Age, alcohol, cereal fibre, education, fibre from veg, DM, smoking, physical activity, gender, smoking
14144 Cardiovascular Health Study			(204) /5201						Age 65-69y	80th vs. 20th Centile		0.92 (0.75, 1.13)				As above
14145 Cardiovascular Health Study			(255) /5201						Age 70-74y	80th vs. 20th Centile		1.04 (0.89, 1.23)				As above
14146 Cardiovascular Health Study			(352) /5201						Age >75y	80th vs. 20th Centile		1 (0.85, 1.19)				As above
14147 Cardiovascular Health Study			(434) /5201						Women	80th vs. 20th Centile		1.04 (0.87, 1.24)				As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
14148 Cardiovascular Health Study			(377) /5201						Men	80th vs. 20th Centile		0.94 (0.77, 1.16)				As above
14149 Cardiovascular Health Study			(575) /5201						No diabetics	80th vs. 20th Centile		0.99 (0.85, 1.16)				As above
*13395 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Question naire (276)	Fibre contained within fruit (Englyst method)	Fatal Events	CHD events Registry data		(5.3) vs. (0.7)	g/d	1.16 (0.8, 1.67)			0.77	Age, alcohol, Beta-carotene, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP, Vit C, Vit E
13386 ATBC Study			(1399) /29133				Fatal + Non-fatal Events	Fatal CHD, MI Registry data		(5.3) vs. (0.7)	g/d	0.99 (0.78, 1.27)			0.57	As above
*13479 (Rimm *et al.*, 1996) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(740) /51529	6 y	FFQ (131)	Fibre contained within fruit (AOAC method)	Fatal + Non-fatal Events	MI Medical records/ autopsy, Registry data, Self report		Continuous risk estimate	10 g/d	0.79 (0.6, 1.05)				Age, alcohol, BMI, saturated fatty acid intake, family history of MI, hyper-cholesterolaemia, occupation, physical activity, hypertension, smoking, Vit E
*13620 (Streppel *et al.*, 2008) Zutphen Elderly Study						Fibre contained within fruit AOAC method (Energy adjusted - *recent* intake. Calculated using time-specific food-composition tables)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	1.13 (0.75, 1.7)				TFA, alcohol, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
13423 Zutphen Elderly Study						Fibre contained within fruit AOAC method (Energy adjusted *long term* intake in middle age. Calculated using time-specific food-composition tables).	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	1.01 (0.43, 2.36)				As above
*13631 (Wolk *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM, Not hyperlipid-aemic/ hyper-cholesterol-aemic	30-55 %M 0	(591) / 121700	10 y (20)	FFQ (116)	Fibre contained within fruit (Long-term intake over 6 years. AOAC method)	Fatal + Non-fatal Events	Non-fatal MI, fatal CHD Registry data, Medical records/ autopsy, Confirmed self reports		Continuous risk estimate	5 g/d	0.93 (0.74, 1.16)		0.51		Age, alcohol, aspirin, Beta-carotene, BMI, carbohydrate intake, saturated fatty acid intake, energy intake, cereal fibre, veg fibre, folate, hypertension, magnesium Intake, menopausal status, parental MI, Period of exposure, physical activity, smoking, postmenopausal HRT, Vit B6 intake, Vit C

*This result was used in the meta-analysis of fibre consumed within fruit and CHD events

Stroke events and fibre in fruit

Summary of cohort results

Data were identified from two studies: the ATBC study (Larsson *et al.*, 2009) and the NHS (Oh *et al.*, 2005). These studies provided evidence concerning the association between fibre contained within fruit and fatal and non-fatal stroke (all types). Neither study showed a significant association between fibre contained within fruit and stroke.

Exposure definition and assessment

Both studies assessed fibre contained within fruit using a FFQ. The ATBC study (Larsson *et al.*, 2009) estimated fibre by the Englyst method, while the NHS (Oh *et al.*, 2005) used the AOAC method.

Adjustment for appropriate confounders

Both studies adjusted for a wide range of covariates including age, smoking and various health measures.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.29 Stroke events and fibre in fruit: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13326 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Questionnaire (276)	Fibre contained within *fruit* (Englyst method)	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(6.2) vs. (0.7)	g/d	1.28 (0.8, 2.06)	0.14	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, magnesium Intake, smoking, group allocation, SBP
13325 ATBC Study			(383) /29133					Stroke, haemorrhage-Intracerebral Registry data	(6.2) vs. (0.7)	g/d	0.88 (0.61, 1.26)	0.44	As above
13324 ATBC Study			(2702) /29133					Stroke, ischaemic Registry data	(6.2) vs. (0.7)	g/d	0.91 (0.8, 1.04)	0.83	As above
13524 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	Fibre contained within *fruit* (AOAC method)	Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods	(7.3) vs. (1.3)	g/d	0.87 (0.7, 1.09)	0.28	Age, alcohol, aspirin, BMI, carbohydrate intake, energy intake, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, postmenopausal HRT, Vit intake
13526 NHS			(279) /121700					Stroke, haemorrhagic Ascertained using multiple methods	(7.3) vs. (1.3)	g/d	0.86 (0.57, 1.29)	0.64	As above
13525 NHS			(515) /121700					Stroke, ischaemic Ascertained using multiple methods	(7.3) vs. (1.3)	g/d	0.87 (0.63, 1.21)	0.22	As above

Fibre in fruit and CVD summary

Meta-analysis: Fibre in fruit and incident CVD events

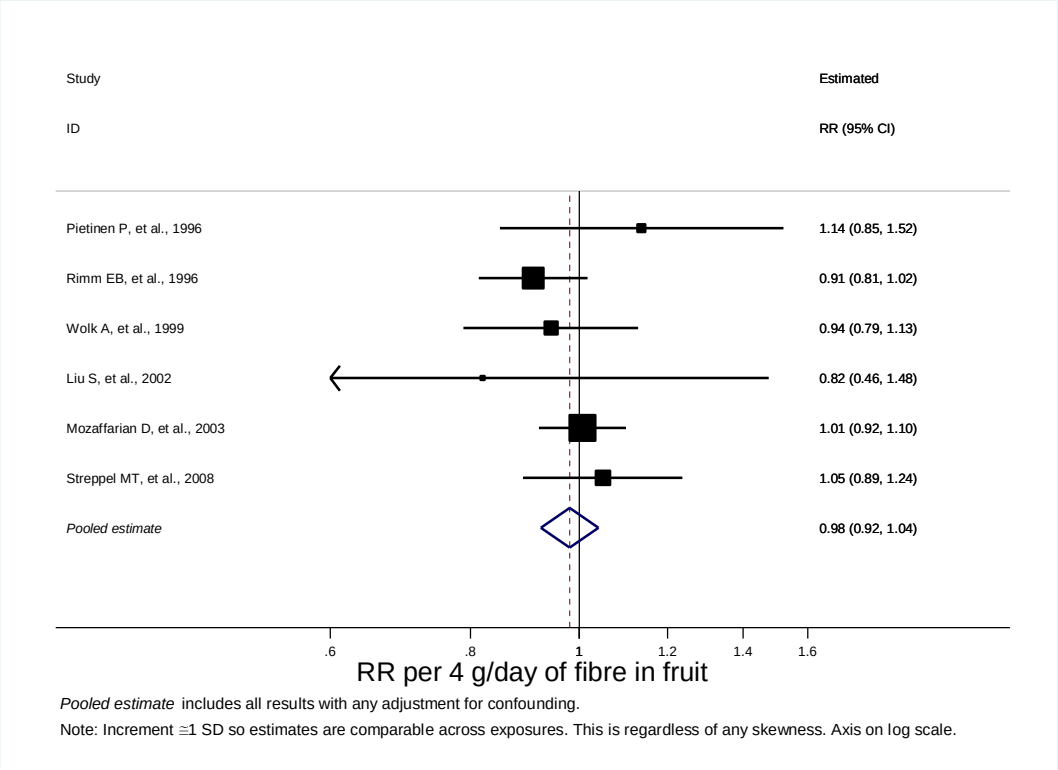
Risk estimates were provided in 8 publications presenting results from 6 cohort studies: NHS, the Cardiovascular Health Study, the Women's' Health Study, HPFS, ATBC and the Zutphen Elderly Study (Oh *et al.*, 2005;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Streppel *et al.*, 2008;Larsson *et al.*, 2009). All studies were included in the meta-analysis.

Most studies presented results separately for CHD and stroke, allowing focussed meta-analysis for the CHD outcome, rather than having to combine the two outcomes. However, only two studies reported stroke outcomes (Oh *et al.*, 2005;Larsson *et al.*, 2009), so no meta-analysis could be conducted independently for stroke. For one study, to permit the results to be included in the meta-analysis, we assumed that the median intake for the lowest category was half the upper limit of the lowest category, and the median of the highest category was 1.5 times the lower limit of the highest category (Mozaffarian *et al.*, 2003).

Relative risks are presented for each 4g/day increase, equivalent to approximately one standard deviation, in intake of fibre within fruit. The approximate mean population intake is 2g/day. These values are based on UK data from NDNS (Bates *et al.*, 2009) and European data from the ATBC study (Pietinen *et al.*, 1996;Larsson *et al.*, 2009) and the Zutphen Elderly Study (Streppel *et al.*, 2008).

For CHD, the pooled estimate of relative risk was 0.98 (95% CI: 0.92 to 1.04) per 4g/day of fibre contained within fruit (p=0.5).

Figure 1.9 Forest plot for fibre in fruit and CHD events



There was no excess heterogeneity between the cohort studies for CHD (I^2=0%, 95% CI: 0% to 70%, Q=4.3, df=5, p=0.5). There were sufficient studies to further explore sources heterogeneity by subgroup analysis and meta-regression for the CHD outcome, but not for stroke (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis for CHD. There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

Table 1.30 Subgroup analyses of fibre in fruit and incidence of CHD. Relative risks are per 4 g/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.99 (0.87, 1.12)	39%	3	.2	.8
	Mixed	1.01 (0.92, 1.10)		1		
	Female	0.93 (0.79, 1.11)	0%	2	.7	
method used to assess fibre	AOAC	0.95 (0.86, 1.06)	11%	3	.3	
	not AOAC	1.14 (0.85, 1.52)		1		.4
includes non-fatal events	yes	1.07 (0.93, 1.23)	0%	2	.6	
	no	0.96 (0.90, 1.03)	0%	4	.5	.3
length of follow-up	<10 years	0.97 (0.90, 1.05)	11%	4	.3	
	>=10 years	1.00 (0.89, 1.13)	0%	2	.4	.4
geographic location	Americas	0.96 (0.90, 1.03)	0%	4	.5	
	EU	1.07 (0.93, 1.23)	0%	2	.6	
	Other			0		.3
adjusted for age	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		
adjusted for alcohol	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		
adjusted for anthropometry	yes	0.96 (0.89, 1.04)	0%	5	.5	
	no	1.01 (0.92, 1.10)		1		.6
adjusted for energy intake	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		
adjusted for family history	yes	0.92 (0.83, 1.01)	0%	3	.9	
	no	1.02 (0.95, 1.11)	0%	3	.7	.1
adjusted for physical activity	yes	0.97 (0.91, 1.03)	0%	5	.5	
	no	1.05 (0.89, 1.24)		1		.4
adjusted for gender	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		
adjusted for smoking	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		
adjusted for age & smoking	yes	0.98 (0.92, 1.04)	0%	6	.5	
	no			0		

* P for heterogeneity within each subgroup

** P for heterogeneity between each subgroup

Fibre in vegetables and CVD

Total CVD and fibre in vegetables

Summary of cohort results

One cohort study, the Women's Health Study provided data on vegetable fibre and risk of total CVD events. No significant association was observed (Liu *et al.*, 2002).

This study used a FFQ to assess diet and used estimates for fibre calculated using the AOAC method. It was not reported whether potatoes were included in the category of vegetables. The result appears to be appropriately adjusted for important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.31 Total cardiovascular disease and fibre in vegetables

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	RR (CI)	p trend	Adjustments
13559 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(570) /39876	6 y	FFQ (131)	Fibre contained within vegetables (AOAC method)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods	(8) vs. (5.9) g/d	0.96 (0.72, 1.28)	0.78	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT

Coronary events and fibre in vegetables (and potatoes)

Summary of cohort results

The Caerphilly Study presented data on combined fruit and vegetable fibre intake and fatal and non-fatal IHD, and reported that cases consumed 7.8g/d compared to the 8.4g/d mean consumption in the rest of the cohort (Fehily *et al.*, 1993).

Six other studies presented data on vegetable fibre intake: ATBC Study, Zutphen Elderly Study, Cardiovascular Health Study, HPFS, The Women's Health Study, and the NHS (Pietinen *et al.*, 1996;Streppel *et al.*, 2008;Mozaffarian *et al.*, 2003;Rimm *et al.*, 1996;Liu *et al.*, 2002;Wolk *et al.*, 1999).

Most risk estimates for coronary events and vegetable fibre intake were close to 1 (indicating no evidence of an association), and none reported any statistically significant associations between intake of vegetable fibre and risk of coronary events. The exception to this was the HPFS which reported a result of borderline statistical significance, for fatal and non-fatal MI RR 0.78 (95% CI: 0.61, 1.0) for each 10g increase in daily vegetable fibre consumption (Rimm *et al.*, 1996).

Potato fibre was only reported in the Zutphen Elderly study which considered both long term and more recent intake over the 40 year follow up period. No significant association was observed in this cohort with respect to coronary events and potato fibre intake (Streppel *et al.*, 2008).

Exposure definition and assessment

Vegetable fibre intakes were assessed with a dietary history in the Zutphen Elderly Study and with semi-quantitative FFQ in the Caerphilly Study (Fehily *et al.*, 1993). The rest of the studies used FFQs ranging in number of items from 99 in the Cardiovascular Health Study to 276 in the ATBC study.

In the NHS, vegetable fibre intake was assessed using a measure of cumulative average intake from questionnaires which were sent at two-year intervals (Wolk *et al.*, 1999). All other studies, except the Zutphen elderly study, only assessed fibre contained within vegetables at baseline. Most studies did not report whether potatoes were included in the vegetable category, with the exception being the Zutphen Elderly Study, in which potatoes were considered as a separate category (Streppel *et al.*, 2008).

Studies carried out in the USA and the Zutphen study used AOAC methods to calculate fibre intakes (Liu *et al.*, 2002;Mozaffarian *et al.*, 2003;Rimm *et al.*, 1996;Streppel *et al.*, 2008;Wolk *et al.*, 1999), the Englyst method was used for estimates of fibre in the ATBC study (Pietinen *et al.*, 1996) and the method used was likely Southgate for the Caerphilly study (Fehily *et al.*, 1993).

Adjustment for appropriate confounders

The studies reporting risk estimates had all adjusted for appropriate confounders including age, and nutrients and/or energy intake and most included adjustments for socioeconomic status and anthropometry.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.32 Coronary events and fibre in vegetables and potatoes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
14311 (Fehily *et al.*, 1993) The Caerphilly Study	Wales, Primarily White, No CHD	45-59 %M 100	(70) /2512	5 y (0.3)	FFQ / Diary	Fibre contained within ***fruit and vegetables*** (fibre method not reported, likely Southgate method)	Fatal + Non-fatal Events	Ischaemic heart disease Medical records/ autopsy, Self report			g/d		Cases: (n: 70) 7.8 g/d (2.3) Non-cases: (n: 1686) 8.4 g/d (2.7)			
*13565 (Liu *et al.*, 2002) The Women's Health Study	USA, Primarily White, Health professionals, No cancer, No Stroke, No CHD	(54) %M 0	(177) /39876	6 y	FFQ (131)	Fibre contained within vegetables (AOAC method)	Fatal + Non-fatal Events	MI Ascertained using multiple methods		(8) vs. (5.9)	g/d	0.89 (0.52, 1.53)			0.87	Age, alcohol, BMI, energy intake, family history of MI, fat intake, folate, DM, hypercholesterolaemia, hypertension, physical activity, protein intake, smoking, group allocation, supplements, postmenopausal HRT
*14134 (Mozaffarian *et al.*, 2003) Cardiovascular Health Study	USA, Primarily White, Age >65y, No CHD	65- %M 38.8	(811) /5201	8.6 y	FFQ (99)	Fibre contained within vegetables (AOAC method)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy		>9.2 vs. <4.2	g/d	1.08 (0.86, 1.36)			0.95	Age, alcohol, cereal fibre, education, fibre from fruit, DM, smoking, physical activity, gender, smoking
14150 Cardiovascular Health Study			(204) /5201						Age 65-69y	80th vs. 20th Centile		0.9 (0.76, 1.04)				As above
14151 Cardiovascular Health Study			(255) /5201						Age 70-74y	80th vs. 20th Centile		1.04 (0.9, 1.19)				As above
14152 Cardiovascular Health Study			(352) /5201						Age >75y	80th vs. 20th Centile		1.09 (0.95, 1.25)				As above
14153 Cardiovascular Health Study			(434) /5201						Women	80th vs. 20th Centile		1.08 (0.92, 1.27)				As above
14154 Cardiovascular Health Study			(377) /5201						Men	80th vs. 20th Centile		0.96 (0.82, 1.14)				As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
14283 Cardiovascular Health Study			(575) /5201						No diabetics	80th vs. 20th Centile		1.05 (0.92, 1.2)				As above
*13394 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Question-naire (276)	Fibre contained within vegetables (based on Englyst method)	Fatal Events	CHD events Registry data		(7.1) vs. (2.9)	g/d	0.88 (0.66, 1.19)			0.08	Age, alcohol, Beta-carotene, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP, Vit C, Vit E
13385 ATBC Study			(1399) /29133				Fatal + Non-fatal Events	Fatal CHD, MI Registry data		(7.1) vs. (2.9)	g/d	0.94 (0.77, 1.14)			0.15	As above
*13482 (Rimm *et al.*, 1996) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(740) /51529	6 y	FFQ (131)	Fibre contained within vegetables (AOAC method)	Fatal + Non-fatal Events	MI Medical records/ autopsy, Registry data, Self report		Continuous risk estimate	10 g/d	0.78 (0.61, 1)				Age, alcohol, BMI, saturated fatty acid intake, family history of MI, hypercholesterolaemia, occupation, physical activity, hypertension, smoking, Vit E
*13619 (Streppel *et al.*, 2008) Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	Fibre contained within vegetables AOAC method (Energy adjusted **recent** intake. Calculated using time-specific food-composition tables)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.88 (0.48, 1.65)				TFA, alcohol, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class
13422 Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	As above but long term intake (not recent intake)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	1 (0.36, 2.77)				TFA, BMI, smoking, cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class, alcohol
*13630 (Wolk *et al.*, 1999) NHS	USA, Primarily White,	30-55 %M 0	(591) / 121700	10 y (20)	FFQ (116)	Fibre contained within vegetables (Long-term intake	Fatal + Non-fatal	Non-fatal MI, fatal CHD		Continuous risk estimate	5 g/d	1.06 (0.84, 1.32)		0.63		Age, alcohol, aspirin, Beta-carotene, BMI, carbohydrate intake,

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	p trend	Adjustments
	Cancer free, No CHD, No T2DM, Not hyperlipid-aemic/ hyper-cholesterol-aemic					over 6 years. AOAC method)	Events	Registry data, Medical records/ autopsy, Confirmed self reports								saturated fatty acid intake,energy intake, fruit fibre, cereal fibre, folate, hypertension, magnesium Intake, menopausal status, parental MI, Period of exposure, physical activity, smoking, postmenopausal HRT, Vit B6 intake, Vit C
13617 (Streppel *et al.*, 2008) Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	Fibre contained within ***potatoes*** AOAC method (Energy adjusted *recent* intake. Calculated using time-specific food-composition tables).	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.71 (0.48, 1.06)				TFA, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class, alcohol
13418 Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	As above but long term intake (not recent intake)	Fatal Events	CHD events Ascertained using multiple methods		Continuous risk estimate	10 g/d	0.94 (0.62, 1.45)				TFA, BMI, smoking, Cis-PUFA, energy intake, fish, prescribed diet, saturated fatty acid intake,SES/class, alcohol

*This result was used in the meta-analysis of fibre within vegetables and CHD events

Stroke events and fibre in vegetables

Summary of cohort results

Data were identified from two studies for stroke outcomes and vegetable fibre: the ATBC study (Larsson *et al.*, 2009) and the NHS (Oh *et al.*, 2005). The ATBC study (Larsson *et al.*, 2009) showed a significantly decreased risk (14%) of ischaemic stroke with increasing fibre contained within vegetables with a significant p for trend (p=0.001). Risk estimates for other types of stroke were less than one, but not statistically significant. No statistically significant associations were observed in the Nurses' Health Study for any type of stroke event.

Exposure definition and assessment

Both studies assessed fibre contained within vegetables using a FFQ but the ATBC used values derived using Englyst methods and AOAC methods were used to calculate values for the NHS (Larsson *et al.*, 2009;Oh *et al.*, 2005). Neither study reported whether potatoes were included in the category of vegetables.

Adjustment for appropriate confounders

Both studies adjusted for a wide range of covariates including age, smoking and various health measures.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.33 Stroke events and fibre in vegetables: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13329 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Questionnaire (276)	Fibre contained within *vegetables* (Englyst method)	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(7.1) vs. (2.9)	g/d	0.63 (0.43, 1.07)	0.06	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, magnesium Intake, smoking, group allocation, SBP
13327 ATBC Study			(383) /29133					Stroke, haemorrhage-Intracerebral Registry data	(7.1) vs. (2.9)	g/d	0.81 (0.57, 1.14)	0.62	As above
13328 ATBC Study			(2702) /29133					Stroke, ischaemic Registry data	(7.1) vs. (2.9)	g/d	0.86 (0.76, 0.99)	0.001	As above
13521 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	Fibre contained within *vegetables* (AOAC method)	Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods	(8.5) vs. (2.9)	g/d	0.92 (0.74, 1.14)	0.14	Age, alcohol, aspirin, BMI, carbohydrate intake, energy intake, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, postmenopausal HRT, Vit intake
13523 NHS			(279) /121700					Stroke, haemorrhagic Ascertained using multiple methods	(8.5) vs. (2.9)	g/d	0.76 (0.51, 1.13)	0.18	As above
13522 NHS			(515) /121700					Stroke, ischaemic Ascertained using multiple methods	(8.5) vs. (2.9)	g/d	1.01 (0.74, 1.38)	0.48	As above

Fibre in vegetables and CVD summary

Meta-analysis: Fibre in vegetables and incident CVD events

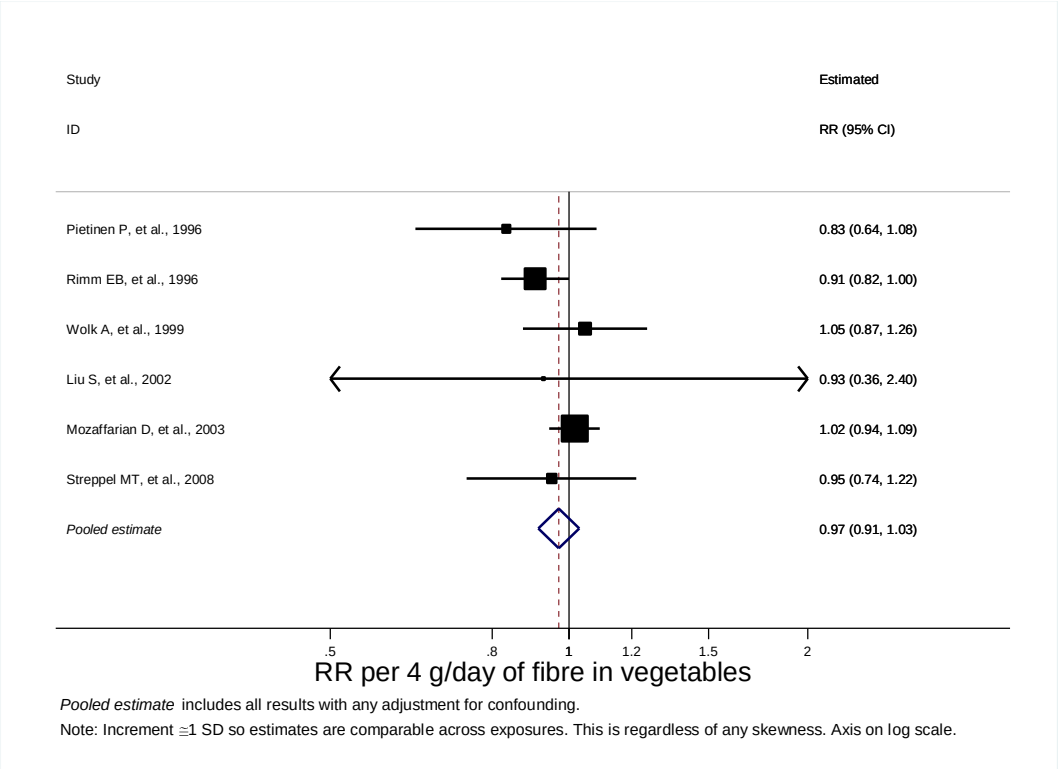
Risk estimates were provided in 8 publications presenting results from 6 cohort studies: NHS, the Cardiovascular Health Study, the Women's' Health Study, HPFS, ATBC and the Zutphen Elderly Study (Oh *et al.*, 2005;Mozaffarian *et al.*, 2003;Liu *et al.*, 2002;Wolk *et al.*, 1999;Pietinen *et al.*, 1996;Rimm *et al.*, 1996;Streppel *et al.*, 2008;Larsson *et al.*, 2009). All studies were included in the meta-analysis.

Most studies presented results separately for CHD and stroke, so a focussed meta-analysis was performed for CHD. However, there were too few studies reporting stroke to provide a separate meta-analysis of this outcome. For one study, to allow the results to be included in the meta-analysis, we assumed that the median intake for the lowest category was half the upper limit of the lowest category, and the median of the highest category was 1.5 times the lower limit of the highest category (Mozaffarian *et al.*, 2003).

Relative risks are presented for each 4g/day increase, equivalent to approximately one standard deviation, in intake of fibre within vegetables. The approximate mean population intake is 4g/day. These values are based on UK data from NDNS (Bates *et al.*, 2009) and European data from the ATBC study (Pietinen *et al.*, 1996;Larsson *et al.*, 2009) and the Zutphen Elderly Study (Streppel *et al.*, 2008).

For CHD, the pooled estimate of relative risk was 0.97 (95% CI: 0.91 to 1.03) per 4 g/day of fibre contained within vegetables (p=0.3).

Figure 1.10 Forest plot for fibre in vegetables and CHD events



There was no excess heterogeneity between the cohort studies for CHD (I^2=7%, 95% CI: 0% to 76%, Q=5.4, df=5, p=0.4). There were sufficient studies to further explore sources of heterogeneity by subgroup analysis and meta-regression for the CHD outcome, but not for stroke (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis for CHD. There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

Table 1.34 Subgroup analyses of fibre in vegetables and incidence of CHD. Relative risks are per 4 g/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.90 (0.83, 0.98)	0%	3	.8	.2
	Mixed	1.02 (0.94, 1.09)		1		
	Female	1.04 (0.87, 1.25)	0%	2	.8	
method used to assess fibre	AOAC	0.91 (0.83, 1.00)	0%	3	.9	
	not AOAC	0.83 (0.64, 1.08)		1		.6
includes non-fatal events	yes	0.89 (0.75, 1.07)	0%	2	.5	
	no	0.98 (0.91, 1.05)	23%	4	.3	.4
length of follow-up	<10 years	0.95 (0.87, 1.04)	36%	4	.2	
	>=10 years	1.01 (0.88, 1.17)	0%	2	.5	.9
geographic location	Americas	0.98 (0.91, 1.05)	23%	4	.3	
	EU	0.89 (0.75, 1.07)	0%	2	.5	
	Other			0		.3
adjusted for age	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		
adjusted for alcohol	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		
adjusted for anthropometry	yes	0.93 (0.86, 1.00)	0%	5	.6	
	no	1.02 (0.94, 1.09)		1		.2
adjusted for energy intake	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		
adjusted for family history	yes	0.94 (0.86, 1.02)	0%	3	.4	
	no	0.99 (0.91, 1.08)	9%	3	.3	.8
adjusted for physical activity	yes	0.97 (0.90, 1.04)	25%	5	.3	
	no	0.95 (0.74, 1.22)		1		.9
adjusted for gender	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		
adjusted for smoking	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		
adjusted for age & smoking	yes	0.97 (0.91, 1.03)	7%	6	.4	
	no			0		

* P for heterogeneity within each subgroup

** P for heterogeneity between each subgroup

Fibre in legumes and CVD

Coronary events and fibre in legumes

Summary of cohort results

The Zutphen Elderly study provided some evidence of risk reduction for fatal CHD with increasing legume fibre intake, although none of the results were statistically significant (Streppel *et al.*, 2008).

Dietary histories were taken and these captured intakes over the six to 12 months prior to assessment. Assessment of intakes was split by period of exposure to explore intake during middle-age and more recent intake in later life. AOAC values were used to estimate fibre intake for this cohort. Appropriate adjustments were made for these results and no adjustment for age was used because the exposures were grouped by age category (middle-aged consumption and recent intake).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.35 Coronary events and fibre in legumes: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Adjustments
13421 (Streppel *et al.*, 2008) Zutphen Elderly Study	The Netherlands	(49) %M 100	(348) /1373	40 y (0.2)	Dietary history	Fibre contained within legumes AOAC method (Energy adjusted *long term* intake in middle age. Calculated using time-specific food-composition tables).	Fatal Events	CHD events Ascertained using multiple methods	Continuous risk estimate	10 g/d	0.52 (0.25, 1.09)	TFA, alcohol, BMI, Cis-PUFA, energy intake, fish, smoking, prescribed diet, saturated fatty acid intake,SES/class
13618						Fibre contained within legumes AOAC method (Energy adjusted *recent* intake. Calculated using time-specific food-composition tables).	Fatal Events	CHD events Ascertained using multiple methods	Continuous risk estimate	10 g/d	0.64 (0.34, 1.2)	As above

Nutrient-based dietary patterns and CVD

Total CVD and nutrient-based dietary patterns

Summary of cohort results

Two cohort studies provided observational data on the impact of replacing carbohydrate as an energy source with other nutrients on risk of total CVD events. The Swedish Women's Lifestyle and Health Study explored the association between long term replacement of carbohydrate sources of energy with protein and risk of total CVD events (Lagiou *et al.*, 2007). For each two-unit increase in low carbohydrate, high protein additive score, the risk of CVD mortality increased by 15% (95% CI 1, 28%). Increased protein and decreased carbohydrate were equally unfavourable for CVD mortality in this study. Higher risk estimates associated with increasing score were observed in women aged more than 40 years at baseline. A similar approach was followed in the Greek arm of EPIC (Trichopoulou *et al.*, 2007), in which a low carbohydrate/high protein score was derived and related to risk of total CVD events. In this study, for each two-unit increment in score, the risk of CVD deaths increased by 9% (95% CI 1, 17%). Both studies therefore provide some evidence that risk of CVD is elevated in women habitually consuming diets lower in carbohydrate, but higher in protein.

Exposure definition and assessment

In both cohort studies, using FFQ-derived dietary data, a low carbohydrate/high protein additive score (LC/HP) was generated for each participant such that a subject with LC/HP score 2 was one with very high consumption of carbohydrates and very low consumption of protein, whereas a subject with score 20 was one with very low consumption of carbohydrates and very high consumption of protein.

Adjustment for appropriate confounders

Both cohort studies adjusted for age, smoking and physical activity, although only EPIC Greece also adjusted for education as a marker of socioeconomic status.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.36 Total CVD and nutrient-based dietary patterns: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Adjustments
16984 (Lagiou *et al.*, 2007) The Women's Lifestyle and Health Cohort Study	Sweden, White	30-49 %M 0	(75) /42237	12 y (~0)	FFQ (80)	Low carbohydrate diet score (Low carbohydrate - high protein additive score (low score=high CHO/low protein). Range = 1-20)	Fatal Events	Total CVD Registry data		Continuous risk estimate	2 units	1.15 (1.01, 1.28)	Age, alcohol, BMI, family history of DM, HRT, physical activity, smoking
17568 The Women's Lifestyle and Health Cohort Study			(19) /42237						Age <40	Continuous risk estimate	2 units	0.98 (0.77, 1.23)	Age, alcohol, BMI, family history of DM, HRT, physical activity, smoking
17569 The Women's Lifestyle and Health Cohort Study			(56) /42237						Age >40	Continuous risk estimate	2 units	1.21 (1.04, 1.39)	Age, alcohol, BMI, family history of DM, HRT, physical activity, smoking
13723 (Trichopoulou *et al.*, 2007) EPIC Greece	Greece, Cancer free, No CHD, No T2DM	20-86 %M 41	(197) /28572	4.9 y (5)	FFQ (150)	Protein replacing carbohydrate (Ratio of descending decile of carbohydrate divided by ascending decile of protein creating LC/HP score)	Fatal Events	Total CVD Registry data		Continuous risk estimate	2 units/d	1.09 (1.01, 1.17)	Age, alcohol, BMI, smoking, education, energy intake, physical activity, Gender

Coronary events and nutrient-based dietary patterns

Summary of cohort results

Three publications from the NHS and the Iowa Women's Health Study provided observational data on the impact of replacing carbohydrate as an energy source with fat or protein on risk of coronary heart disease (Halton *et al.*, 2006;Hu *et al.*, 1999;Kelemen *et al.*, 2005). Both cohort studies used a somewhat different method of generating a dietary profile for each participant that reflected the extent to which dietary carbohydrate was replaced by either protein, fat (degree of saturation) or both nutrients and whether the origin of these nutrients was from vegetable or animal sources. The objective of these studies, however, was to explore whether, when freely consumed, the effects of low carbohydrate high fat/protein diets as typically administered in weight-loss intervention trials are associated with risk of coronary heart disease in prospective cohort studies.

The US Nurses' Health Study provided risk estimates for coronary heart disease events (fatal and non-fatal combined) after 14 and after 20 years of follow-up (Halton *et al.*, 2006;Hu *et al.*, 1999) in association with the replacement of dietary carbohydrate with either an isoenergetic amount of protein, or a combination of fat and protein. After 14 years follow-up, there was a 30% reduction in risk of CHD in women in the highest decile of protein replacing carbohydrate, compared to the lowest decile. After 20 years of follow-up, risk estimates were all less than one when comparing the decile with the lowest carbohydrate intake against the decile with the highest intake and with increasing replacement of dietary carbohydrate with vegetable sources of fat and protein, the test for trend was statistically significant (the relative risk on the basis of the percentage of energy from intake of carbohydrates, vegetable protein, and vegetable fat was 0.70 (95% CI 0.56, 0.88; p for trend=0.002). Similarly, in the Iowa Women's Health Study (Kelemen *et al.*, 2005), CHD mortality was not associated with substituting an isoenergetic quantity of total protein for the same amount of energy from carbohydrate, although there was some evidence of decreased risk when carbohydrate was substituted with protein from vegetable sources. Data from these studies suggest that diets lower in carbohydrate and higher in protein and fat are not associated with increased risk of coronary heart disease in women.

One further cohort study conducted in Denmark reported on the association between dietary fat, fat type and risk of coronary heart disease in the MONICA I and III cohorts (Jakobsen *et al.*, 2004) and is included here since the data are analysed such that for each 5% increment in fat intake, there is a corresponding energy decrement in dietary carbohydrate. Correspondingly, the authors comment that 'in the models used, total energy and protein intake were fixed. Differences in intake of energy from fat thus reflected complementary differences in intake of energy from carbohydrates'. There was no association between total fat intake and risk of coronary heart disease in men or women as a whole, but there was an elevation in risk with increasing intake of fat in women older than 60 years (RR per 5% energy 1.74 (95% CI 1.15, 2.64)). This elevation in risk might potentially be attributable to increasing fat consumption, or decreasing carbohydrate intake.

Collectively, these studies provide contradictory evidence concerning the impact on CHD risk of consuming low carbohydrate/higher fat/protein diets as assessed by FFQ. Speculatively, differences in the nature of carbohydrate consumed as reflected by national or cultural dietary patterns may be influential. Elevations in risk with lower carbohydrate intakes are observed in European, but not US cohort studies.

Exposure definition and assessment

In both the NHS and Iowa Women's Health Study, using FFQ-derived dietary data, a low carbohydrate/high protein additive score (LC/HP) was generated for each participant such that a subject with LC/HP score of 2 was one with very high consumption of carbohydrates and very low consumption of protein, whereas a subject with score 20 was one with very low consumption of carbohydrates and very high consumption of protein.

Adjustment for appropriate confounders

All cohort studies adjusted for age, smoking and physical activity and other important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.37 Coronary events and nutrient-based dietary patterns: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
17435 (Halton *et al.*, 2006) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM, Not hyperlipidaemic/ hypercholesterolaemic	30-55 %M 0	(1994) /82802	20 y	FFQ (122)	Low carbohydrate diet score (Low carbohydrate-diet score based on total carbohydrate, total fat and total protein (low score=high carb) units)	Fatal + Non-fatal Events	Coronary heart disease death, Nonfatal MI Ascertained using multiple methods		(26) vs. (5)	units	0.94 (0.76, 1.18)	0.19	Age, alcohol, aspirin, BMI, HRT, hypercholesterol-aemia, hypertension, parental CHD, physical activity, smoking, supplements
17563 NHS						Low carbohydrate diet score (Low carbohydrate-diet score based on total carbohydrate, ***vegetable*** fat and ***vegetable*** protein (low score=high carb) units)	Fatal + Non-fatal Events	Coronary heart disease death, Nonfatal MI Ascertained using multiple methods		(21.8) vs. (8)	units	0.7 (0.56, 0.88)	0.002	As above
17562 NHS						Low carbohydrate diet score (Low carbohydrate-diet score based on total carbohydrate, ***animal*** fat and ***animal*** protein (low score=high carb) units)	Fatal + Non-fatal Events	Coronary heart disease death, Nonfatal MI Ascertained using multiple methods		(27) vs. (4.5)	units	0.94 (0.74, 1.19)	0.52	As above
13589 (Hu *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM, Not hyperlipidaemic/ hypercholesterolaemic	30-55 %M 0	(939) /121700	14 y	FFQ (61)	Protein replacing carbohydrate (Protein intake substituted for isoenergetic amount carbohydrate)	Fatal + Non-fatal Events	Fatal ischaemic heart disease, Nonfatal MI Medical records/ autopsy		(24) vs. (14.7)	% Energy	0.72 (0.57, 0.91)		Physical activity, age, alcohol, aspirin, BMI, fibre, dietary cholesterol, energy intake, hypertension,MI, menopausal status, smoking, supplements
13969 (Jakobsen *et al.*,	Denmark, Primarily	30-71	(228) /3959	16 y	Diary + interview	CHO replaced by **monounsaturated** fat	Fatal + Non-fatal	CHD events	Men	Continuous risk	5% Energy	0.8 (0.55, 1.15)		alcohol, BMI, dietary cholesterol, Fibre,

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
2004) MONICA I & III Danish Cohorts	White, No CHD, No T2DM	%M 70					Events	Registry data		estimate				education, protein intake, family history of MI, physical activity, PUFA, saturated fatty acid intake, smoking, SBP
13980 MONICA I & III Danish Cohorts			(98) /3959						Women			1.01 (0.56, 1.83)		As above
13986 MONICA I & III Danish Cohorts			(not reported) /3959						Women, Age <60			2.56 (1.15, 5.73)		As above
13987 MONICA I & III Danish Cohorts			(not reported) /3959						Women, >60y			0.75 (0.4, 1.41)		As above
13988 MONICA I & III Danish Cohorts			(not reported) /3959						Men, Age <60			1.37 (0.78, 2.4)		As above
13989 MONICA I & III Danish Cohorts			(not reported) /3959						Men, >60y			0.85 (0.57, 1.28)		As above
13970 MONICA I & III Danish Cohorts	Denmark, Primarily White, No CHD, No T2DM	30-71 %M 70	(98) /3959			CHO replaced by **polyunsaturated** fats	Fatal + Non-fatal Events	CHD events Registry data	Women	Continuous risk estimate	5% Energy	0.89 (0.5, 1.57)		As above
13971 MONICA I & III Danish Cohorts			(228) /3959						Men			0.8 (0.55, 1.15)		As above
13990 MONICA I & III Danish Cohorts			(not reported) /3959						Women, Age <60			0.66 (0.19, 2.35)		As above
13991 MONICA I & III Danish Cohorts			(not reported) /3959						Women, >60y			0.94 (0.51, 1.74)		As above
13992 MONICA I & III Danish Cohorts			(not reported) /3959						Men, Age <60			1.06 (0.56, 1.99)		As above
13993 MONICA I & III Danish Cohorts			(S not reported) /3959						Men, >60y			0.72 (0.47, 1.1)		As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13967 (Jakobsen *et al.*, 2004) MONICA I & III Danish Cohorts	Denmark, Primarily White, No CHD, No T2DM	30-71 %M 70	(98) /3959	16 y	Diary + interview	CHO replaced by **saturated** fat	Fatal + Non-fatal Events	CHD events Registry data	Women	Continuous risk estimate	5% Energy	1.36 (0.98, 1.88)		As above
13968 MONICA I & III Danish Cohorts			(228) /3959						Men			1.03 (0.78, 1.37)		As above
13976 MONICA I & III Danish Cohorts			(not reported) /3959						Women, Age <60			2.68 (1.4, 5.12)		As above
13977 MONICA I & III Danish Cohorts			(not reported) /3959						Women, >60y			1.22 (0.86, 1.71)		As above
13978 MONICA I & III Danish Cohorts			(not reported) /3959						Men, Age <60			1.29 (0.87, 1.91)		As above
13979 MONICA I & III Danish Cohorts			(Subgroup cases not reported) /3959						Men, >60y			0.94 (0.7, 1.28)		As above
13964 (Jakobsen *et al.*, 2004) MONICA I & III Danish Cohorts	Denmark, Primarily White, No CHD, No T2DM	30-71 %M 70	(98) /3959	16 y	Diary + interview	CHO replaced by **total fat**	Fatal + Non-fatal Events	CHD events Registry data	Women	Continuous risk estimate	5% Energy	1.12 (0.93, 1.36)		As above
13966 MONICA I & III Danish Cohorts			(228) /3959						Men			0.98 (0.87, 1.1)		As above
13972 MONICA I & III Danish Cohorts			(not reported) /3959						Women, Age <60			1.74 (1.15, 2.64)		As above
13973 MONICA I & III Danish Cohorts			(not reported) /3959						Women, >60y			1.05 (0.86, 1.28)		As above
13974 MONICA I & III Danish Cohorts			(not reported) /3959						Men, Age <60			1.15 (0.93, 1.41)		As above

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13975 MONICA I & III Danish Cohorts			(not reported) /3959						Men, >60y			0.93 (0.81, 1.06)		As above
13735 (Kelemen *et al.*, 2005) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal	55-69 (61) %M 0	(739) /41836	16.4 y	FFQ (127)	Animal protein/ CHO substitution (Animal protein substituted for an isoenergetic amount of carbohydrate)	Fatal Events	CHD events Registry data		(17.5) vs. (8.9)	% Energy	0.88 (0.42, 1.86)	0.29	Age, alcohol, BMI, dietary Met, education, dietary cholesterol, MUFA, PUFA, saturated fatty acid intake, energy from TFA, energy intake, family history of cancer, Fibre, hypertension, HRT, physical activity, smoking, Vegetable protein, Vit intake
13734 Iowa Women's Health Study						Vegetable protein substituted for carbohydrate (Vegetable protein substituted for an isoenergetic amount of carbohydrate)	Fatal Events	CHD events Registry data		(17.5) vs. (8.9)	% Energy	0.70 (0.49, 0.99)	0.2	Age, alcohol, animal protein, BMI, Dietary Met, education, dietary cholesterol, MUFA, PUFA, saturated fatty acid intake,energy from TFA, energy intake, family history of cancer, Fibre, hypertension, HRT, physical activity, smoking, Vit intake
13727 Iowa Women's Health Study						Protein replacing carbohydrate (Protein intake substituted for isoenergetic amount carbohydrate)	Fatal Events	CHD events Registry data		(22) vs. (14.1)	% Energy	0.84 (0.39, 1.79)	0.62	Age, alcohol, BMI, Dietary Met, education, dietary cholesterol, MUFA, PUFA, saturated fatty acid intake, energy from TFA, energy intake, family history of cancer, Fibre, hypertension, HRT, physical activity, smoking, Vit intake

Carbohydrate-rich foods and CVD

The following sections concern foods which are rich sources of dietary carbohydrates. Studies included in this section report the following exposures: total cereal foods, other cereals and cereal foods such as bread and breakfast cereals, legumes, potatoes, sugar-rich foods, starchy foods and sweetened beverages.

Total cereals and cereal-based foods and CVD

Total CVD and total cereals and cereal-based foods

Summary of cohort results

Data were identified from four studies: the ATTICA Study, EPIC Potsdam, The Norwegian County Study and the Physicians' Health Study. These studies provided evidence concerning the association between consumption of total cereals, breakfast cereals and wholegrain bread and risk of cardiovascular disease. The ATTICA study reported similar mean age-adjusted consumption of total cereals in cases and non-cases (Panagiotakos *et al.*, 2009). The Physicians' Health Study (Liu *et al.*, 2003) provided risk estimates for breakfast cereals and CVD, indicating lower risk with greater consumption of high fibre and total breakfast cereal types. No association was observed in this study with refined grain breakfast cereals. Evidence concerning the association between a wholegrain bread score, wholegrain bread and CVD risk was reported by the Norwegian County Study and EPIC Potsdam respectively (Jacobs, Jr. *et al.*, 2001;Drogan *et al.*, 2007). The former reported a 23% reduction in risk when comparing the highest vs. lowest intake category of wholegrain bread, with a significant test for trend across categories. This indicates evidence of reduced risk with increasing consumption of wholegrain bread. In the EPIC Potsdam study, both fatal and non-fatal cases of CVD reported a lower mean consumption of wholegrain bread compared with the other members of the cohort at baseline (Drogan *et al.*, 2007).

Exposure definition and assessment

The four cohort studies reported data on total cereals and cereal-based food groups, including breakfast cereals and wholegrain bread. The ATTICA study reported total cereal intakes using a 156-item FFQ but did not specify the food items included within 'cereal foods' (Panagiotakos *et al.*, 2009). The Physicians' Health Study (Liu *et al.*, 2003) estimated intake of total, high fibre and refined grain breakfast cereals and CVD using a 61-item FFQ. Data on wholegrain bread consumption was reported by FFQ as grams or slices per day by the EPIC cohort and by the Norwegian County Study respectively (Jacobs, Jr. *et al.*, 2001;Drogan *et al.*, 2007).

Adjustment for appropriate confounders

The EPIC Potsdam cohort and the ATTICA study provided unadjusted or age-adjusted mean consumption estimates in cases and other cohort members only. The Physicians' Health Study and the Norwegian study adjusted for an appropriate range of covariates, including age, gender and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.38 Total CVD and total cereals and cereal-based foods: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13451 (Drogan *et al.*, 2007) EPIC Potsdam	Germany No history of MI/ Stroke	35-65 (50) %M 40	(68) /27548	6.4 y (5)	FFQ (148)	Wholegrain bread	Fatal Events	MI/ Stroke, any Medical records/ death certificate		g/d		Cases: (n=68) 33.9 g/d (51.9) Non-cases: (n=25859) 45.5g/d (54.6)		
14717 EPIC Potsdam			(311) /27548				Non-fatal Events	MI/ Stroke, any Medical records		g/d		Cases: (n=311) 39.1g/d (55) Non-cases: (n=25859) 45.5g/d (54.6)		
14171 (Jacobs, Jr. *et al.*, 2001) Norwegian County Study	Norway, No CHD, No hypertension, No T2DM	35-56 %M 50	(758) /47114	17 y	FFQ (66)	Wholegrain bread (score formed as the product of slices/day* proportion of wholegrain flour)	Fatal Events	Total CVD Medical records/ autopsy	2.25-5.4 vs. 0.05-0.6	Score units	0.77 (0.6, 0.98)		0.016	Age, BMI, dietary cholesterol, Cod liver oil, energy intake, physical activity, saturated fatty acid intake, gender, smoking, SBP, Vit intake
13109 (Liu *et al.*, 2003) PHS I	USA, No CVD, Cancer free	40-84 (54) %M 100	(1381) /104353	5.5 y	FFQ (61)	Breakfast cereals, high fibre (>25% wholegrain or bran by weight)	Fatal Events	Total CVD Registry data	≥1 serv/day vs. Rarely	serv/d	0.8 (0.66, 0.97)		0.008	Age, alcohol, BMI, DM, hypercholesterolaemia, hypertension, physical activity, smoking, supplements
13113 PHS I						Breakfast cereals, low fibre (Refined-grain breakfast cereals)	Fatal Events	Total CVD Registry data	≥1 serv/day vs. Rarely	serv/d	1.04 (0.84, 1.27)		0.37	As above
13125 PHS I						Breakfast cereals, unspecified (total breakfast cereals)	Fatal Events	Total CVD Registry data	≥1 serv/day vs. Rarely	serv/d	0.87 (0.74, 1.03)		0.08	As above
14024 (Panagiotakos *et al.*, 2009) ATTICA study	Greece, No CHD	(45) %M 49.8	(170) /3042	5 y (31)	FFQ (156)	Cereals, total	Fatal + Non-fatal Events	Total CVD Medical records/ autopsy		serv/wk		Cases: (n=170) 49 (11) Non-cases: (n=1826) 52 (12)		Age

Coronary events and total cereals and cereal-based foods

N.B. Text and tables concerning coronary events and bread or breakfast cereal have been separated from total or other cereal results to make interpretation simpler (sections below).

Summary of cohort results

Data were identified from five studies: the Finnish Mobile Clinic Health Surveys study (Knekt *et al.*, 1994), the ATBC study (Pietinen *et al.*, 1996), the Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998), the NHS study (Liu *et al.*, 1999) and the HPFS study (Jensen *et al.*, 2004). These studies provide evidence concerning the association between consumption of total cereals, and specific cereals such as popcorn, brown rice, wheat germ, rye and other cereals, and risk of fatal or combined fatal and non-fatal coronary events. The Finnish Mobile Clinic Health Survey study (Knekt *et al.*, 1994) reported similar mean age-adjusted consumption of total cereals in cases and non-cases for men and women separately. The ATBC study (Pietinen *et al.*, 1996) reported similar risk estimates for highest quintile of total cereal intake compared with lowest quintile of intake.

The remaining results provided risk estimates for individual cereal types. The NHS study (Liu *et al.*, 1999) and the HPFS study (Jensen *et al.*, 2004) provided separate risk estimates for bran and wheat germ. Both studies indicated evidence of decreased risk for combined fatal and non-fatal coronary events with increasing bran intake. The results for wheat germ were inconsistent with an estimated risk close to 1 for the HPFS study but considerably less than 1 for the NHS study. The NHS study also reported risk estimates for popcorn, brown rice and other cereals (e.g. bulgar and couscous). None of the provided risk estimates for these specific cereals were significantly different from 1 (no evidence of an association). The Iowa Women's Health Study (Jacobs, Jr. *et al.*, 1998) provided risk estimates for crackers (which included refined and wholegrain types) which were also close to 1, indicating no significant association.

Exposure definition and assessment

The five cohort studies reported data on total cereals and cereal-based food groups, including bran, wheat germ, popcorn, brown rice, rye and other cereals such as couscous. The Finnish Mobile Clinic Health Surveys (Knekt *et al.*, 1994) reported total cereal intakes using a dietary history. The ATBC Study (Pietinen *et al.*, 1996) estimated intake of total cereal and rye products using a 276-item FFQ. The Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998) estimated intake of unspecified cereals using a 127-item FFQ. The NHS study (Liu *et al.*, 1999) estimated bran, wheat germ, popcorn, brown rice and other cereals using a 126-item FFQ and the HPFS study estimated added bran and added germ using a 131-item FFQ. Knekt *et al.* (Knekt *et al.*, 1994) and Pietinen *et al.* (Pietinen *et al.*, 1996) did not report which foods were classified in 'cereal foods'. Jacobs *et al.* (Jacobs, Jr. *et al.*, 1998), however, included unspecified grain crackers within the cereals category, although no further information was provided in this paper.

Adjustment for appropriate confounders

The Finnish Mobile Clinic Health Surveys cohort provided age-adjusted mean consumption estimates in cases and other cohort members. The remaining studies adjusted for an appropriate range of covariates, including age, gender, smoking and alcohol.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.39 Coronary events and total cereals and cereal-grain foods: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13745 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	Crackers (Unspecified grain type)	Fatal Events	Ischaemic heart disease Registry data		5.5-42 vs. 0	serv/ wk	0.81 (0.57, 1.14)		0.19	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio
13446 (Jensen *et al.*, 2004) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(1818) /51529	14 y	FFQ (131)	Added Bran (wheat, corn, oat and rice bran, added to foods during cooking or by participants)	Fatal + Non-fatal Events	CHD events Medical testing, Registry data, Self report		>6.85 (11.1) vs. (0)	g/d	0.7 (0.6, 0.82)		<0.001	Added germ intake, Age, alcohol, energy intake, family history of MI, fat intake, fish, Fruit, physical activity, smoking, veg, Vit E, Wholegrain
13449 HPFS						Added Germ (added wheat germ, added to foods either during cooking or by participants)	Fatal + Non-fatal Events	CHD events Medical testing, Registry data, Self report		>0.33 (0.83) vs. 0 (0)	g/d	0.95 (0.83, 1.09)		0.43	Added bran intake, Age, alcohol, energy intake, family history of MI, fat intake, fish, Fruit, physical activity, smoking, veg, Vit E, Wholegrain
13137 (Knekt *et al.*, 1994) Finnish Mobile Clinic Health Surveys	Finland, No CHD	30-69 %M 53	(186) /5133	14 y (9)	Dietary history	Cereals, total	Fatal Events	CHD events Registry data	Men		g/d		Cases: (n: 186) 339g/d Non-cases: (n: 2264) 334g/d		Age
13138 Finnish Mobile Clinic Health Surveys			(58) /5133						Women		g/d		Cases: (n: 58) 207g/d Non-cases: (n: 2183) 240g/d		Age
14056 (Liu *et al.*, 1999) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(761) /121700	10 y	FFQ (126)	Cereals-Other grain (e.g., bulgar, kasha, and couscous)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy		<1 (0.07) vs. Almost never (0)	serv/ wk	0.79 (0.57, 1.08)		0.16	alcohol, aspirin, BMI, energy intake, hypercholesterolaemia, hypertension, menopausal status, parental MI, protein intake, smoking, physical activity, Vit intake

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
14055 NHS						Bran				5-6 (1) vs. Almost never (0)	serv/ wk	0.63 (0.42, 0.95)			As above
14054 NHS						Wheat germ				5-6 (0.93) vs. Almost never (0)	serv/ wk	0.41 (0.15, 1.1)		0.01	As above
14051 NHS						Popcorn				1 (1) vs. Almost never (0)	serv/ d	0.92 (0.45, 1.87)		0.27	As above
14053 NHS						Brown rice				5-6 (0.79) vs. Almost never (0)	serv/ wk	0.45 (0.06, 3.2)			As above
13399 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Question-naire (276)	Non-rye cereals, total	Fatal Events	CHD events Registry data		(214.5) vs. (47)	g/d	1.05 (0.79, 1.4)		0.83	Age, alcohol, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity, smoking, group allocation, SBP
13398 ATBC Study						Rye and rye products (total)	Fatal Events	CHD events Registry data		(172.2) vs. (16)	g/d	0.75 (0.58, 0.98)		0.02	As above

Coronary events and bread

Summary of cohort results

Data were identified from five studies: the Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998), the Adventist Health study (Fraser *et al.*, 1992), the Norwegian County study (Jacobs, Jr. *et al.*, 2001), the Health Food Shoppers Study (Key *et al.*, 1996) and the NHS (Liu *et al.*, 1999). These studies provide evidence of the association between consumption of different types of bread and risk of fatal or combined fatal and non-fatal coronary events.

The Iowa Women's study (Jacobs, Jr. *et al.*, 1998) reported a risk estimate for white bread comparing the highest quintile of intake with the lowest intake. There was no association with fatal ischaemic heart disease. All other studies reported risk estimates for wholegrain bread.

Higher wholegrain bread intake was generally associated with lower risk estimates for coronary events. Two studies (Jacobs, Jr. *et al.*, 1998;Jacobs, Jr. *et al.*, 2001) reported significantly lower risk of fatal events with greater wholegrain bread intake and increasing wholegrain bread score, while three studies (Fraser *et al.*, 1992;Key *et al.*, 1996;Liu *et al.*, 1999) reported non-significant, but negative associations with greater wholegrain bread intake for fatal or combined fatal and non-fatal events. The Adventist Health study (Fraser *et al.*, 1992) also provided a risk estimate for non-fatal events only and provided evidence of a lower risk of coronary events with greater intake of wholegrain bread.

Collectively, these cohort studies provide evidence of a reduction in risk of coronary events with increasing consumption of wholegrain or whole-wheat breads.

Exposure definition and assessment

Four cohort studies estimated wholegrain bread intake with FFQs ranging in number of items from 65 to 127 (Jacobs, Jr. *et al.*, 1998;Fraser *et al.*, 1992;Jacobs, Jr. *et al.*, 2001;Key *et al.*, 1996;Liu *et al.*, 1999) whereas Key *et al.* (Key *et al.*, 1996) used a short dietary questionnaire to determine intakes of 'wholemeal bread'.

Adjustment for appropriate confounders

All the studies adjusted for an appropriate range of covariates, including age, gender and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.40 Coronary events and bread: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
14313 (Fraser *et al.*, 1992) Adventist Health Study	USA, Primarily White, No CHD, No T2DM	25-(52) %M 37.4	(260) /59081	6 y	FFQ (65)	Bread: Whole-wheat consumers vs. White consumers	Fatal Events	CHD events Medical records/ autopsy	Whole-wheat vs. White (reference)		0.82 (0.55, 1.21)		NS	Age, Weight, hypertension, physical activity, gender, smoking
14312 Adventist Health Study			(134) /59081				Non-fatal Events	MI Confirmed self report	Whole-wheat vs. White (reference)		0.45 (0.28, 0.71)		<0.01	As above
13741 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	White bread (including pita bread)	Fatal Events	Ischaemic heart disease Registry data	7-42 vs. 0	serv/wk	1.24 (0.94, 1.64)		0.13	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio
13737 Iowa Women's Health Study						Wholegrain bread (Dark bread)	Fatal Events	Ischaemic heart disease Registry data	17.5-42 vs. 0-0.5	serv/wk	0.67 (0.49, 0.91)		0.23	As above
14170 (Jacobs, Jr. *et al.*, 2001) Norwegian County Study	Norway, No CHD, No hypertension, No T2DM	35-56 %M 50	(553) /47114	17 y	FFQ (66)	Wholegrain bread (score formed as the product of slices/day*proportion of wholegrain flour)	Fatal Events	CHD events Medical records/ autopsy	2.25-5.4 vs. 0.05-0.6	Score units	0.76 (0.56, 1.02)		0.04	Age, BMI, dietary cholesterol, Cod liver oil, energy intake, physical activity, saturated fatty acid intake, gender, smoking, SBP, Vit intake
13135 (Key *et al.*, 1996) Health Food Shoppers Study	United Kingdom, Primarily White	16-79 (46) %M 40	(250) /11140	16.8 y (4.7)	Short question-naire	Wholegrain bread (Wholemeal bread consumed daily)	Fatal Events	Ischaemic heart disease Registry data	Daily vs. <daily		0.85 (0.68, 1.06)	NS		Age, gender, smoking
14049 (Liu *et al.*, 1999) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(761) /121700	10 y	FFQ (126)	Wholegrain bread	Fatal + Non-fatal Events	CHD events Medical records/ autopsy	1 (1.3) vs. Almost never (0)	serv/d	0.98 (0.77, 1.25)		0.43	alcohol, aspirin, BMI, energy intake, hypercholesterolaemia, hypertension, menopausal status, parental MI, protein intake, smoking, physical activity, Vit intake

Coronary events and breakfast cereals

Summary of cohort results

Data were extracted from four studies: the Health Food Shoppers Study (Key *et al.*, 1996), the Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998), the Physicians' Health Study I (PHS) (Liu *et al.*, 2003) and the NHS (Liu *et al.*, 1999). These studies provided evidence concerning the association between consumption of breakfast cereals and risk of fatal ischaemic heart disease or combined fatal and non-fatal CHD events. The Health Food Shoppers' Study (Key *et al.*, 1996) reported risk estimates for 'bran cereals'. The Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998) reported risk estimates for high and low fibre breakfast cereals. The PHS I (Liu *et al.*, 2003) reported risk estimates for high fibre, low fibre and unspecified breakfast cereals and the NHS (Liu *et al.*, 1999) reported risk estimates for high fibre and oatmeal breakfast cereals.

Three out of the four studies reported a decreased risk of fatal coronary events with increased consumption of high fibre breakfast cereals and in two studies (Liu *et al.*, 2003;Liu *et al.*, 1999) this decrease was statistically significant. The Health Food Shoppers Study (Key *et al.*, 1996) reported no association. The results provide some evidence of reduced risk of fatal events in individuals with greater high fibre breakfast cereal consumption.

No association of risk of fatal coronary events with low fibre breakfast cereal consumption was reported by the two studies providing risk estimates for this type of breakfast cereal (Jacobs, Jr. *et al.*, 1998;Liu *et al.*, 2003). No association between fatal and non-fatal events and oatmeal consumption was reported by the NHS (Liu *et al.*, 1999). The PHS I (Liu *et al.*, 2003) reported a lower risk estimate for unspecified cereals although this was not statistically significant.

Exposure definition and assessment

Three out four cohort studies estimated breakfast cereal intake with FFQs ranging from 65 to 127 items (Key *et al.*, 1996;Jacobs, Jr. *et al.*, 1998;Liu *et al.*, 1999;Liu *et al.*, 2003). Key *et al*. (Key *et al.*, 1996) used a short dietary questionnaire to determine intakes of 'bran cereals'.

Adjustment for appropriate confounders

The Health Food Shoppers' Study was adjusted for age, gender and smoking (Key *et al.*, 1996) but the Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998), the PHS I (Liu *et al.*, 2003) and the NHS (Liu *et al.*, 1999) provided risk estimates adjusted for additional covariates.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.41 Coronary events and breakfast cereals: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
*13738 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	Breakfast cereals, high fibre (>25% wholegrain or bran content by weight)	Fatal Events	Ischaemic heart disease Registry data	5.5-7 vs. 0	serv/wk	0.77 (0.56, 1.04)		0.23	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio
13742 Iowa Women's Health Study						Breakfast cereals, low fibre			5.5-7 vs. 0	serv/wk	1.45 (0.99, 2.13)		0.14	As above
13431 (Key *et al.*, 1996) Health Food Shoppers Study	United Kingdom, Primarily White	16-79 (46) %M 40	(250) /11140	16.8 y (4.7)	Short question-naire	Breakfast cereals (bran cereals daily)	Fatal Events	Ischaemic heart disease Registry data	Daily vs. <daily		0.99 (0.79, 1.25)	NS		Age, gender, smoking
*13111 (Liu *et al.*, 2003) PHS I	USA, No CVD, Cancer free	40-84 (54) %M 100	(488) /104353	5.5 y	FFQ (61)	Breakfast cereals, high fibre (>25% wholegrain or bran by weight)	Fatal Events	MI Registry data	≥1 vs. Rarely	serv/d	0.71 (0.51, 0.98)		0.01	Age, alcohol, BMI, DM, hypercholesterolaemia, hypertension, physical activity, smoking, supplements
13114 PHS I						Breakfast cereals, low fibre (Refined-grain breakfast cereals)			≥1 vs. Rarely	serv/d	0.96 (0.68, 1.36)		0.97	As above
13127 PHS I						Breakfast cereals, unspecified (total breakfast cereals)			≥1 vs. Rarely	serv/d	0.76 (0.54, 0.94)		0.14	As above
*14050 (Liu *et al.*, 1999) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(761) /121700	10 y	FFQ (126)	Breakfast cereals, high fibre (>25% wholegrain or bran content by weight)	Fatal + Non-fatal Events	CHD events Medical records/ autopsy	1 (0.93) vs. Almost never (0)	serv/d	0.76 (0.57, 1)		0.007	alcohol, aspirin, BMI, energy intake, hypercholesterolaemia, hypertension, menopausal status, parental MI, protein intake, smoking, physical activity, Vit intake
14052 NHS						Oatmeal (Cooked)			1 (1) vs. Almost never (0)	serv/d	1.1 (0.45, 2.68)		0.68	As above

*This result was used in the meta-analysis of high-fibre breakfast cereals and CHD events

Stroke events and total cereals and cereal-based foods

Summary of cohort results

Data were extracted from four studies: the ATBC study (Larsson *et al.*, 2009), the Health Food Shoppers Study (Key *et al.*, 1996), the PHS I (Liu *et al.*, 2003) and the NHS (Liu *et al.*, 2000a). These studies provided evidence concerning the association between total cereals, breakfast cereals and wholegrain bread and fatal and non-fatal stroke. There was one significant association across increasing intakes (trend) for total cereals and haemorrhagic (intracerebral) stroke in the ATBC study (Larsson *et al.*, 2009). No other significant associations between total cereals, breakfast cereals or wholegrain bread and stroke were reported in any of these studies.

Exposure definition and assessment

Three of the studies assessed total cereals, breakfast cereals and wholegrain bread using a FFQ. The FFQ used in the PHS I (Liu *et al.*, 2003) only had 61 items but this should be sufficient for measuring breakfast cereals. The exposures were reported in grams per day (Larsson *et al.*, 2009) or servings per day (Liu *et al.*, 2003).

One publication from the NHS (Liu *et al.*, 2000a) reported data on total cereal consumption, which included whole grain foods such as “dark bread, popcorn, cooked oatmeal, whole grain breakfast cereal (25% + whole grain/ bran content by weight), wheat germ, brown rice, bran, bulgur, kasha and couscous”. Refined grains were also specified as cereals, according to the authors (Liu *et al.*, 2000a), and namely consisted of “sweet rolls and cakes/ desserts, white bread, pasta, English muffins, muffins or biscuits, refined grain breakfast cereal, white rice, pancakes or waffles and pizza”. One cohort did not report which foods were classified as cereal foods (Larsson *et al.*, 2009). Key *et al*. (Key *et al.*, 1996) used a short dietary questionnaire to determine intakes of ‘bran cereals’ and ‘wholmeal bread’.

Adjustment for appropriate confounders

The Health Food Shoppers Study adjusted for age, gender and smoking. The other studies adjusted for an appropriate range of covariates including age, smoking and alcohol intake.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments

Table 1.42 Stroke events and total cereals and cereal-based foods: cohort studies adults

13433 (Key *et al.*, 1996) Health Food Shoppers Study	United Kingdom, Primarily White	16-79 (46) %M 40	(147) /11140	16.8 y (4.7)	Short question naire	Breakfast cereals, (high fibre bran cereals daily)	Fatal Events	Cerebrovascular disease Registry data	Daily vs. <daily		0.93 (0.65, 1.34)	NS		Age, gender, smoking
13432 Health Food Shoppers Study						Wholegrain bread (Wholemeal bread consumed daily)	Fatal Events	Cerebrovascular disease Registry data	Daily vs. <daily		1.08 (0.75, 1.54)	NS		Age, gender, smoking
13335 (Larsson *et al.*, 2009) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(196) /29133	13.6 y	FFQ / Question -naire (276)	Cereals, total	Fatal + Non-fatal Events	Stroke, haemorrhage-Subarachnoid Registry data	(327.4) vs. (116.4)	g/d	1 (0.54, 1.84)		0.91	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, folate, HDL-C, CHD, DM, physical activity, magnesium Intake, smoking, group allocation, SBP
13334 ATBC Study			(383) /29133					Stroke, haemorrhage-Intracerebral Registry data	(327.4) vs. (116.4)	g/d	0.64 (0.41, 1.01)		0.04	Age, alcohol, BMI, dietary cholesterol, DBP, energy intake, HDL-C, CHD, DM, physical activity, smoking, group allocation, SBP
13333 ATBC Study			(2702) /29133					Stroke, ischaemic Registry data	(327.4) vs. (116.4)	g/d	0.87 (0.74, 1.03)		0.08	As above
13652 (Liu *et al.*, 2000a) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(352) /121700	12 y	FFQ (126)	Cereals-Total Grains (whole and refined)	Fatal + Non-fatal Events	Stroke, ischaemic Confirmed self reports, Medical records/autopsy, Registry data	Q5 vs. Q1		0.79 (0.54, 1.18)		0.16	Age, alcohol, aspirin, BMI, saturated fatty acid intake, energy from TFA, energy intake, family history of MI, high TC, hypertension, menopausal status, physical activity, smoking, Vit intake
13112 (Liu *et al.*, 2003) PHS I	USA, No CVD, Cancer free	40-84 (54) %M 100	(146) /104353	5.5 y	FFQ (61)	Breakfast cereals, high fibre (>25% wholegrain or bran by weight)	Fatal Events	Stroke, any Registry data	≥1 vs. Rarely	serv/ d	1.41 (0.85, 2.34)		0.18	Age, alcohol, BMI, DM, hypercholesterolaemia, hypertension, physical activity, smoking, supplements
13124 PHS I						Breakfast cereals, low fibre (Refined-grain breakfast cereals)	Fatal Events	Stroke, any Registry data	≥1 vs. Rarely	serv/ d	1.22 (0.71, 2.11)		0.87	As above
13128 PHS I						Breakfast cereals, unspecified (total breakfast cereals)	Fatal Events	Stroke, any Registry data	≥1 vs. Rarely	serv/ d	1.54 (0.94, 2.52)		0.2	As above

Summary of total cereals and cereal-based foods and CVD

Meta-analysis: Total cereals and incident CVD events

Data were extracted from 5 publications presenting results from 4 cohort studies: the ATTCIA Study, the Finnish Mobile Health Clinic Surveys, the NHS and the ATBC study (Panagiotakos *et al.*, 2009;Knekt *et al.*, 1994;Liu *et al.*, 2000a;Pietinen *et al.*, 1996;Larsson *et al.*, 2009). Of these, one publication (Knekt *et al.*, 1994) contained insufficient information to estimate a dose-response trend for inclusion in meta-analysis. One publication (Pietinen *et al.*, 1996) was an early analysis of CHD data from the same study as a later publication that focussed on stroke (Larsson *et al.*, 2009). These studies could not be combined into an overall CVD outcome because of the different lengths of follow-up. Another study only presented results combined into overall CVD (Panagiotakos *et al.*, 2009). This left too few studies reporting the same outcome to provide a meta-analysis, either CHD or stroke, or any CVD combined.

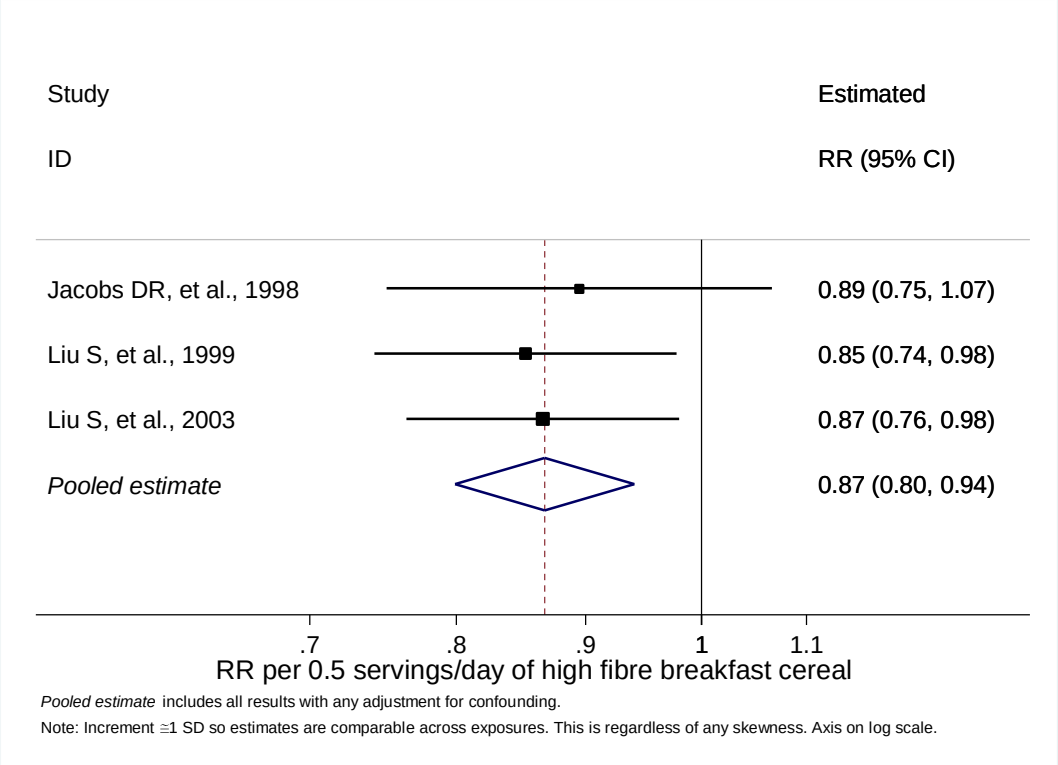
Meta-analysis: High fibre breakfast cereals and incident CVD events

Data were extracted from 5 publications presenting results from 4 cohort studies: NHS (Liu *et al.*, 1999), PHS I (Liu *et al.*, 2003), Health Food Shoppers Study (Key *et al.*, 1996) and Iowa Women's Health Study (Jacobs, Jr. *et al.*, 1998). One paper from the NHS was a later analysis of (Liu *et al.*, 2003), but it presented insufficient information for inclusion in meta-analysis (Djousse *et al.*, 2009). One study could not be included because the exposure was dichotomised, so could not provide a dose-response trend (Key *et al.*, 1996). Only one study reported on stroke events (Liu *et al.*, 2003), so the meta-analysis focussed on the CHD outcome, and included 3 papers (Jacobs, Jr. *et al.*, 1998;Liu *et al.*, 1999;Liu *et al.*, 2003). For one study, to allow the results to be included in the meta-analysis, we assumed that the median intake for the “rarely” category was approximately zero, and the median of the highest category was 1.5 times the lower limit of the highest category (Liu *et al.*, 2003). Each study in the meta-analysis defined high-fibre breakfast cereal as >25% fibre, so there is reasonable similarity in methods.

Relative risks are presented for each 0.5 servings/day increase, equivalent to approximately one standard deviation, in high fibre breakfast cereals intake. The approximate mean population intake is 0.5 servings/day. These values are based on UK data from NDNS (Bates *et al.*, 2009). However, it should be noted that studies providing data for the meta-analysis were all conducted in the USA.

The pooled estimate of relative risk was 0.87 (95% CI: 0.80 to 0.94) per half serving of high-fibre breakfast cereals per day (p=0.001).

Figure 1.11 Forest plot for high fibre breakfast cereals and CHD events



There was no excess heterogeneity between the cohort studies (I^2=0%, 95% CI: 0% to 0%, Q=0.2, df=2, p=0.9).

There were insufficient studies to explore small-study effects, such as publication bias, through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

There were insufficient studies to explore the sources of heterogeneity by stratified forest plots, subgroup analyses or meta-regression.

Meta-analysis: Wholegrain bread and incident CVD events

Data were extracted from 6 publications presenting results from the following 6 cohort studies: EPIC Potsdam, the Iowa Women's Health Study, the Adventist Health Study, the Norwegian County Study, the NHS and the Health Food Shoppers Study (Drogan *et al.*, 2007;Liu *et al.*, 1999;Jacobs, Jr. *et al.*, 2001;Jacobs, Jr. *et al.*, 1998;Key *et al.*, 1996;Fraser *et al.*, 1992). One study could not be included because the exposure was dichotomised, so could not provide a dose-response trend (Key *et al.*, 1996). Another study was excluded because levels of exposure were not in terms of amounts or frequencies, but type of bread (Fraser *et al.*, 1992). Similarly, the exposure provided in the Norwegian County Study was a score that represented wholegrain bread (slices of bread multiplied by the wholegrain content) rather than slices of wholegrain bread per day (Jacobs, Jr. *et al.*, 2001). One study only presented unadjusted results for wholegrain bread (Drogan *et al.*, 2007) and was therefore excluded. This left only 2 studies remaining that provided results for CHD in the same format and so a meta-analysis was not possible.

Legumes (non-soy) and CVD

Total CVD and non-soy legumes

Summary of cohort results

Data on the association between total CVD and consumption of legumes (excluding soy) were provided by 4 papers reporting on five cohort studies: NHS and HPFS combined, NHANES I, the Japanese Collaborative Cohort Study and the ATTICA study (Joshipura *et al.*, 2009;Nagura *et al.*, 2009;Panagiotakos *et al.*, 2009;Bazzano *et al.*, 2001). Data from the NHS and HPFS were pooled in one publication to provide one estimate of risk (Joshipura *et al.*, 2009). The US and Greek cohort studies tended to show no clear direction of association, with risk estimates close to one, and wide confidence intervals. However, there was some evidence of reduced risk with increasing consumption of legumes in the Japan Collaborative Cohort Study, with a 16% (95% CI 0.74, 0.95) reduction in risk of CVD for participants in the highest category of consumption (4.5 times per week) compared to the lowest consumers (0.8 times per week) with a significant test for trend (p=0.01).

Exposure definition and assessment

All cohorts reported consumption data of total legumes excluding soy beans expressed either as servings per day/week or weekly frequency of consumption. Consumption estimates were mainly achieved through use of FFQs, with the number of items on the Japan Collaborative Cohort Study FFQ being particularly limited (n=33).

Adjustment for appropriate confounders

All cohorts were adjusted for important confounders including age, gender, smoking, anthropometry and physical activity.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.43 Total CVD non-soy legumes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
*14345 (Bazzano *et al.*, 2001) NHANES I	USA, No CHD	25-74 %M 38	(3680) /9632	19 y (4)	FFQ + recall	Beans/ Legumes (Frequency of intake)	Fatal + Non-fatal Events	Total CVD Ascertained using multiple methods		>4 vs. 0-0.9	times/wk	0.91 (0.82, 1.01)	0.06	Age, alcohol, BMI, BP, smoking, education, energy intake, ethnicity, family history of DM, Fruit and veg, meat, physical activity, plasma TC, saturated fatty acid intake, Gender
14679 (Joshipura *et al.*, 2009) NHS & HPFS	USA, No CHD	30-75 (60) %M 36	(Total cohort cases 3892) /173229	15 y	FFQ (126)	Beans/ legumes	Fatal + Non-fatal Events	Coronary heart disease & ischaemic stroke Medical records/ autopsy	Low CHO (<40%)	Continuous risk estimate	1 serving/d	1.69 (0.66, 4.32)		Age, alcohol, aspirin, BMI, energy intake, DM, hypercholesterolaemia, hypertension, HRT, menopausal status, parental MI, physical activity, smoking, Vit intake, wholegrain
14684 NHS & HPFS			(Subgroup cases not reported) /173229						Moderate CHO (>40-55%)	Continuous risk estimate	1 serving/d	0.96 (0.63, 1.44)		As above
14685 NHS & HPFS			(Subgroup cases not reported) /173229						High CHO (>55%)	Continuous risk estimate	1 serving/d	1.01 (0.67, 1.53)		As above
13408 (Nagura *et al.*, 2009) Japan Collaborative Cohort Study	Japan, Cancer free, No CHD	40-79 %M 42.4	(738) /59485	12.7 y (16.45)	FFQ (33)	Beans/ Legumes (excluding soy)	Fatal Events	Other CVD (not CHD/Stroke) Registry data		(4.5) vs. (0.8)	times/wk	0.79 (0.64, 0.98)	0.097	Age, alcohol, BMI, education, dietary cholesterol, saturated fatty acid intake, DM, hypertension, hours of sleep, hours of walking, n-3 FA intake, perceived stress, gender, smoking, Na+
*13409 Japan Collaborative Cohort Study			(2981) /59485					Total CVD Registry data		(4.5) vs. (0.8)	times/wk	0.84 (0.74, 0.95)	0.01	As above
14031 (Panagiotakos *et al.*, 2009) ATTICA study	Greece, No CHD	(45) %M 49.8	(170) /3042	5 y (31)	FFQ (156)	Beans/ legumes	Fatal + Non-fatal Events	Total CVD Medical records/ autopsy		Continuous risk estimate	1 unit	1.08 (0.87, 1.36)		Age, BMI, CRP, education, family history of CHD, hypercholesterolaemia, hypertension, physical activity, DM, gender, smoking

*This result was used in the meta-analysis of legumes and any CVD event

Coronary events and non-soy legumes

Summary of cohort results

Data were extracted from three studies: the Adventist Health study (Fraser *et al.*, 1992), the Japan Collaborative Cohort Study (Nagura *et al.*, 2009) and NHANES I (Bazzano *et al.*, 2001). These studies provided evidence concerning the association between consumption of legumes (non soy) and risk of fatal or non-fatal CHD events. All studies provided risk estimates: one study provided estimates for fatal and non-fatal events reported separately (Fraser *et al.*, 1992), one reported a risk estimate for fatal events (Nagura *et al.*, 2009) and one reported a risk estimate for fatal and non-fatal events combined (Bazzano *et al.*, 2001).

The risk estimates from the Japan Collaborative Cohort Study and NHANES I indicated a 20% reduction in risk of fatal heart events in the highest legume consumers, although this was only statistically significant in the NHANES I cohort (Bazzano *et al.*, 2001). The risk estimates reported by the Adventist Health study did not indicate risk reduction with increased consumption of legumes.

Exposure definition and assessment

The three cohort studies reported data on legumes, including beans and peas. The Adventist Health study (Fraser *et al.*, 1992) estimated intake of legumes using a 65-item FFQ. The Japan Collaborative Cohort study (Nagura *et al.*, 2009) estimated intake of legumes using a 33-item FFQ and NHANES I (Bazzano *et al.*, 2001) estimated intake of legumes using a FFQ and recall.

Adjustment for appropriate confounders

All studies provided age, weight, gender and smoking adjusted risk estimates.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.44 Coronary events and non-soy legumes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
14344 (Bazzano *et al.*, 2001) NHANES I	USA, No CHD	25-74 %M 38	(1802) /9632	19 y (4)	FFQ + recall	Beans-Legumes (Frequency of legume intake)	Fatal + Non-fatal Events	CHD events Ascertained using multiple methods	>4 vs. 0-0.9	times/wk	0.79 (0.69, 0.91)	0.003	Age, alcohol, BMI, BP, smoking, education, energy intake, ethnicity, family history of DM, Fruit and veg, meat, physical activity, plasma TC, saturated fatty acid intake, gender
*14315 (Fraser *et al.*, 1992) Adventist Health Study	USA, Primarily White, No CHD, No T2DM	25-(52) %M 37.4	(260) /59081	6 y	FFQ (65)	Beans-Legumes, Beans and peas	Fatal Events	CHD events Medical records/ autopsy	>3 vs. <0.9	serv/wk	1.26 (0.9, 1.78)	NS	Age, weight, hypertension, physical activity, gender, smoking
*14314 Adventist Health Study			(134) /59081				Non-fatal Events	MI Confirmed self report	>3 vs. <0.9	serv/wk	1.16 (0.72, 1.85)	NS	As above
13407 (Nagura *et al.*, 2009) Japan Collaborative Cohort Study	Japan, Cancer free, No CHD	40-79 %M 42.4	(452) /59485	12.7 y (16.45)	FFQ (33)	Beans-Legumes (excluding soy)	Fatal Events	CHD events Registry data	(4.5) vs. (0.8)	times/wk	0.8 (0.61, 1.05)	0.124	Age, alcohol, BMI, education, dietary cholesterol, saturated fatty acid intake,DM, hypertension, hours of sleep, hours of walking, n-3 FA intake, perceived stress, gender, smoking, Na+

*This result was used in the meta-analysis of legumes and any CVD event

Stroke events and non-soy legumes

Summary of cohort results

Data were extracted from three cohorts reported in two papers: the Japan Collaborative Cohort Study (Nagura *et al.*, 2009) and the HPFS and NHS (Joshipura *et al.*, 1999). These studies provided evidence concerning the association between bean/legume consumption and fatal and non-fatal stroke (total stroke, ischaemic and haemorrhagic). None of the studies reported any statistically significant associations between bean/legume consumption and risk of stroke.

Exposure definition and assessment

All of the studies assessed bean/legume consumption using a FFQ. The FFQ used in the Japan Collaborative Cohort Study (Nagura *et al.*, 2009) had only 33 items but did contain a question on boiled beans. The exposure was reported in servings per day (Joshipura *et al.*, 1999) or times per week (Nagura *et al.*, 2009).

Adjustment for appropriate confounders

All studies adjusted for an appropriate range of covariates including age, alcohol, BMI and smoking. The Japan Collaborative Cohort Study (Nagura *et al.*, 2009) also adjusted for gender.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.45 Stroke events and non-soy legumes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
*14285 (Joshipura *et al.*, 1999) HPFS	USA, Cancer free, No CHD, No T2DM	40-75 %M 100	(204) /51529	8 y	FFQ (131)	Beans/Legumes	Fatal + Non-fatal Events	Stroke, ischaemic Medical records/ autopsy	Continuous risk estimate	1 serving/d	0.71 (0.33, 1.52)		Age, alcohol, aspirin, BMI, energy intake, family history of MI, hypercholesterolaemia, hypertension, physical activity, smoking, assessment period, Vit intake
*14349 (Joshipura *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM	30-55 %M 0	(366) /121700	14 y	FFQ (116)	Beans/Legumes	Fatal + Non-fatal Events	Stroke, ischaemic Medical records/ autopsy	Continuous risk estimate	1 serving/d	1.65 (0.81, 3.4)		Age, alcohol, aspirin, BMI, energy intake, family history of MI, HRT, hypercholesterolaemia, hypertension, physical activity, smoking, assessment period, Vit intake
13404 (Nagura *et al.*, 2009) Japan Collaborative Cohort Study	Japan, Cancer free, No CHD	40-79 %M 42.4	(1053) /59485	12.7 y (16.45)	FFQ (33)	Beans/Legumes	Fatal Events	Stroke, any Registry data	(4.5) vs. (0.8)	times/wk	0.9 (0.75, 1.08)	0.188	Age, alcohol, BMI, education, dietary cholesterol, saturated fatty acid intake,DM, hypertension, hours of sleep, hours of walking, n-3 FA intake, perceived stress, gender, smoking, Na+
13405 Japan Collaborative Cohort Study			(393) /59485					Stroke, haemorrhagic Registry data	(4.5) vs. (0.8)	times/wk	1.03 (0.77, 1.4)	0.857	As above
13406 Japan Collaborative Cohort Study			(362) /59485					Stroke, ischaemic Registry data	(4.5) vs. (0.8)	times/wk	0.88 (0.64, 1.19)	0.389	As above

*This result was used in the meta-analysis of legumes and any CVD event

Summary on non-soy legumes and CVD

Meta-analysis: Legumes and incident CVD events

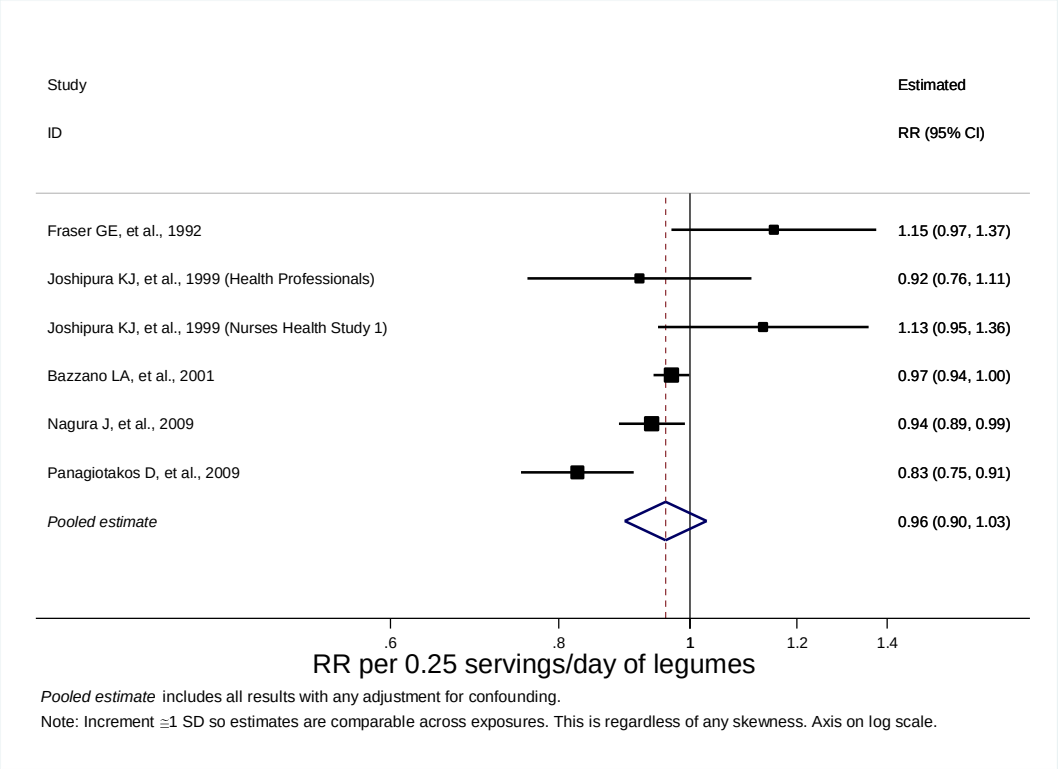
Data were extracted from 6 publications presenting results from the following 7 cohort studies: Japan Collaborative Cohort Study, ATTICA, NHS, HPFS, NHANES I and the Adventist Health Study (Nagura *et al.*, 2009;Panagiotakos *et al.*, 2009;Bazzano *et al.*, 2001;Joshipura *et al.*, 1999;Joshipura *et al.*, 2009;Fraser *et al.*, 1992). One paper presented results from two separate cohorts, and was included as two entries in the meta-analysis (Joshipura *et al.*, 1999). Another paper presented more up-to-date information than this (Joshipura *et al.*, 2009), but stratified by percentage of energy from carbohydrate intake. Because the sizes of those strata were not presented, the earlier results were used in this meta-analysis.

All remaining publications contributed information to the dose-response meta-analysis. The Adventist Health Study presented results for two outcome subgroups (definite fatal and non-fatal events) which were first combined into one estimate for total events before combining with the other studies (Fraser *et al.*, 1992). For this study we also used the midpoint of each exposure category because the median or mean were not available, and assumed the midpoint of the upper category was 1.5 times its lower limit.

There were insufficient studies presenting results for CHD and stroke to present separate meta-analysis for these outcomes, so all CVD outcomes were combined in one meta-analysis. The pooled estimate of relative risk from the cohort studies was 0.96 (95% CI: 0.90 to 1.03) per quarter of a serving of beans or legumes per day (p=0.04).

Relative risks are presented for each 0.25 servings/day increase, equivalent to approximately one standard deviation, in beans and legumes intake. The approximate mean population intake is 0.25 servings/day. These values are based on UK data from NDNS (Bates *et al.*, 2009).

Figure 1.13 Forest plot for legumes and total CVD events



There was considerable heterogeneity between the cohort studies (I^2=73%, 95% CI: 37% to 88%, Q=18.3, df=5, p=0.003), meaning that the result needs to be interpreted with caution. Panagiotakos *et al* had a strong influence on the estimate, and almost doubled the heterogeneity, but this study was only adjusted for age. When this study was excluded, the relative risk was 0.98 (95% CI: 0.93 to 1.04) with I^2=53%.

There were sufficient studies to further explore sources heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups, and heterogeneity generally remained high within each subgroup. There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

Table 1.46 Subgroup analyses of legume intake and incidence of any CVD. Relative risks are per 0.25 servings/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.92 (0.76, 1.11)		1		.6
	Mixed	0.95 (0.87, 1.02)	80%	4	.002	
	Female	1.13 (0.95, 1.36)		1		
includes non-fatal events	yes	0.94 (0.89, 0.99)		1		
	no	0.98 (0.88, 1.09)	77%	5	.001	.8
length of follow-up	<10 years	0.95 (0.77, 1.16)	82%	3	.004	
	>=10 years	0.97 (0.92, 1.02)	52%	3	.1	.7
geographic location	Americas	1.02 (0.92, 1.13)	56%	4	.08	
	EU	0.83 (0.75, 0.91)		1		
	Other	0.94 (0.89, 0.99)		1		.1
adjusted for age	yes	0.96 (0.90, 1.03)	73%	6	.003	
	no			0		
adjusted for alcohol	yes	0.96 (0.92, 1.01)	32%	4	.2	
	no	0.97 (0.70, 1.34)	91%	2	<0.001	.8
adjusted for anthropometry	yes	0.98 (0.93, 1.04)	52%	5	.08	
	no	0.83 (0.75, 0.91)		1		.1
adjusted for energy intake	yes	0.96 (0.92, 1.01)	32%	4	.2	
	no	0.97 (0.70, 1.34)	91%	2	<0.001	.8
adjusted for family history	yes	0.99 (0.90, 1.08)	38%	3	.2	
	no	0.95 (0.82, 1.09)	83%	3	.003	.6
adjusted for physical activity	yes	0.98 (0.93, 1.04)	52%	5	.08	
	no	0.83 (0.75, 0.91)		1		.1
adjusted for gender	yes	0.98 (0.93, 1.04)	52%	5	.08	
	no	0.83 (0.75, 0.91)		1		.1
adjusted for smoking	yes	0.98 (0.93, 1.04)	52%	5	.08	
	no	0.83 (0.75, 0.91)		1		.1
adjusted for age & smoking	yes	0.98 (0.93, 1.04)	52%	5	.08	
	no	0.83 (0.75, 0.91)		1		.1

* P for heterogeneity within each subgroup/ ** P for heterogeneity between each subgroup

Potatoes and CVD

Although potatoes are vegetables, nutritionally they are classified as a source of starch and data for potato consumption are presented here (and not other vegetables) since potatoes are more commonly seen as a source of carbohydrate in the UK.

Total CVD and potatoes

Summary of cohort results

Data on the association between total CVD and consumption of potatoes were provided by three cohort studies conducted in the USA and Greece (Joshipura *et al.*, 2009;Panagiotakos *et al.*, 2009). Data from the Nurses' Health Study and the Health Professionals Follow-up Study were pooled and reported in one publication to provide one estimate of risk (Joshipura *et al.*, 2009). The pooled Nurses' Health Study and the Health Professionals Follow-up Study reported an increased risk of fatal and non-fatal CVD events with increasing consumption of potatoes, although the strength and statistical significance of these associations varied by total carbohydrate consumption subgroup (tending to increase in higher carbohydrate consumers).

The ATTICA study reported a higher age-adjusted frequency of potato consumption in cases of CVD than the other members of the cohort (Panagiotakos *et al.*, 2009). Collectively these studies provide some evidence of increased risk of CVD with increasing intake of potatoes.

Exposure definition and assessment

Potato consumption was reported as either servings per day or an estimate of frequency of consumption derived in both studies from extensive FFQs.

Adjustment for appropriate confounders

The ATTICA study provided age-adjusted estimates of consumption frequency only, but the other cohorts were adjusted for most important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.47 Total CVD and potatoes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p	Adjustments
14686 (Joshipura *et al.*, 2009) NHS & HPFS	USA, No CHD	30-75 (60) %M 36	(Subgroup cases not reported; total cohort cases 3892) /173229	15 y	FFQ (126)	Potatoes	Fatal + Non-fatal Events	Coronary heart disease & ischaemic stroke Medical records/ autopsy	Low CHO (<40%)	Continuous risk estimate	1 serving /d	1.15 (0.87, 1.52)			Age, alcohol, aspirin, BMI, energy intake, DM, hypercholesterolaemia, hypertension, HRT, menopausal status, parental MI, physical activity, smoking, Vit intake, wholegrain
14687 NHS & HPFS			(Subgroup cases not reported; total cohort cases 3892) /173229						Moderate CHO (>40-55%)	Continuous risk estimate	1 serving /d	1.17 (0.94, 1.46)		<0.05	As above
14688 NHS & HPFS			(Subgroup cases not reported; total cohort cases 3892) /173229						High CHO (>55%)	Continuous risk estimate	1 serving /d	1.26 (0.93, 1.69)			As above
14023 (Panagiotakos *et al.*, 2009) ATTICA study	Greece, No CHD	(45) %M 49.8	(170) /3042	5 y (31)	FFQ (156)	Potatoes	Fatal + Non-fatal Events	Total CVD Medical records/ autopsy			Serv /wk		Cases: (n=170) 13.2 (3) Non-cases: (n=1826) 11.6 (4)		Age

Coronary events and potatoes

Summary of cohort results

Data were extracted from two studies: the Finnish Mobile Clinic Health Surveys study (Knekt *et al.*, 1994) and the ATBC study (Pietinen *et al.*, 1996). These studies provided evidence concerning the association between consumption of potatoes and risk of fatal CHD events. The Finnish Mobile Clinic Health Surveys study reported results for men and women separately. Results from the Finnish Mobile Clinic Health Surveys indicated that there was no association between potato consumption and fatal coronary events for men or women. Data from the ATBC study indicates a significantly reduced risk of fatal coronary events in the highest potato consumers (287g/d) compared with the lowest consumers (<95g/d). There were too few studies to undertake a meta-analysis.

Exposure definition and assessment

The Finnish Mobile Clinic Health Surveys estimated intake of potatoes using a dietary history and the ATBC study estimated intake of potatoes using a 276-item FFQ.

Adjustment for appropriate confounders

The Finnish Mobile Clinic Health Surveys study (Knekt *et al.*, 1994) provided age-adjusted mean consumption estimates in cases and other cohort members only, while the ATBC study (Pietinen *et al.*, 1996) adjusted for an appropriate range of covariates, including age, BMI and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	P trend	Adjustments
13139 (Knekt *et al.*, 1994) Finnish Mobile Clinic Health Surveys	Finland, No CHD	30-69 %M 53	(186) /5133	14 y (9)	Dietary history	Potatoes	Fatal Events	CHD events Registry data	Men		g/d		Cases: (n: 186) 287 Non-cases: (n: 2264) 274		Age
13140 Finnish Mobile Clinic Health Surveys			(58) /5133						Women		g/d		Cases: (n: 58) 186 Non-cases: (n: 2183) 180		Age
*13400 (Pietinen *et al.*, 1996) ATBC Study	Finland, Cancer free, Generally healthy, No CHD, Not Alcoholics, Smokers	50-69 %M 100	(635) /29133	6.1 y	FFQ / Questionnaire (276)	Potatoes	Fatal Events	CHD events Registry data		(286.5) vs. (95.3)	g/d	0.74 (0.57, 0.97)		0.02	Age, alcohol, BMI, DBP, education, saturated fatty acid intake, energy intake, physical activity,

Table 1.48 Coronary events and potatoes: cohort studies in adults

	smoking, group allocation, SBP

*This result was used in the meta-analysis of potatoes and any CVD event

Stroke events and potatoes

Summary of cohort results

Data were extracted from two cohorts: the HPFS (Joshipura *et al.*, 1999) and the NHS (Joshipura *et al.*, 1999) reported in one paper. These studies provided evidence concerning the association between potato consumption and fatal and non-fatal ischaemic stroke. Neither study reported any statistically significant associations between potato consumption and risk of stroke. There were too few studies to undertake a meta-analysis.

Exposure definition and assessment

Both of the studies assessed potato consumption using a FFQ. The FFQ used by HPFS (Joshipura *et al.*, 1999) had 131 items and the FFQ used by the NHS (Joshipura *et al.*, 1999) had 116 items. The exposures were reported in servings per day.

Adjustment for appropriate confounders

Both studies adjusted for an appropriate range of covariates including age, alcohol, BMI and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.49 Stroke events and potatoes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Adjustments
*14287 (Joshipura *et al.*, 1999) HPFS	USA, Cancer free, No CHD, No T2DM	40-75 %M 100	(204) /51529	8 y	FFQ (131)	Potatoes	Fatal + Non-fatal Events	Stroke, ischaemic Medical records/ autopsy	Continuous risk estimate	1 serving/d	1.25 (0.85, 1.83)	Age, alcohol, aspirin, BMI, energy intake, family history of MI, hypercholesterolaemia, hypertension, physical activity, smoking, assessment period, Vit intake
*14350 (Joshipura *et al.*, 1999) NHS	USA, Primarily White, Cancer free, No CHD, No T2DM	30-55 %M 0	(366) /121700	14 y	FFQ (116)	Potatoes	Fatal + Non-fatal Events	Stroke, ischaemic Medical records/ autopsy	Continuous risk estimate	1 serving/d	1.15 (0.69, 1.9)	Age, alcohol, aspirin, BMI, energy intake, family history of MI, hypercholesterolaemia, hypertension, physical activity, smoking, assessment period, Vit intake

*This result was used in the meta-analysis of potatoes and any CVD event

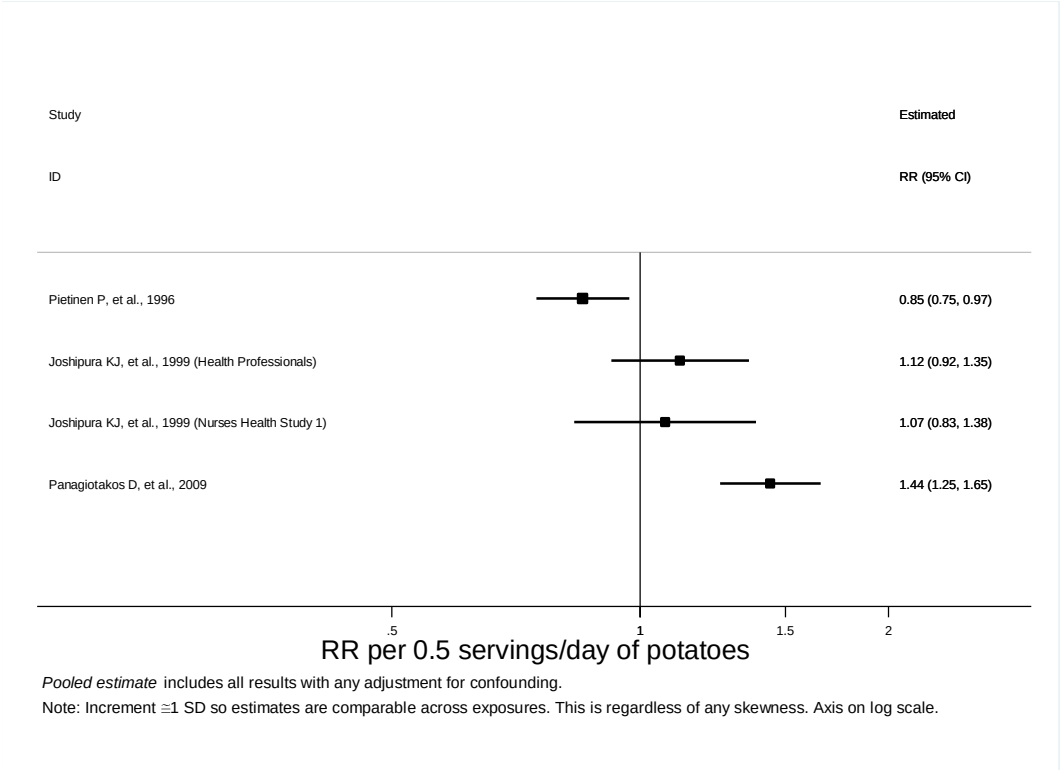
Summary on potatoes and CVD

Meta-analysis: Potatoes and incident CVD events

Data were extracted from 5 publications presenting results from the following 5 cohort studies: ATTICA Study, the Finnish Mobile Health Clinic Surveys, NHS, HPFS and the ATBC study (Panagiotakos *et al.*, 2009;Knekt *et al.*, 1994;Joshipura *et al.*, 1999;Joshipura *et al.*, 2009;Pietinen *et al.*, 1996). Of these, two publications (Knekt *et al.*, 1994;Joshipura *et al.*, 2009) contained insufficient information to estimate a dose-response trend for inclusion in meta-analysis. The remaining studies all contributed towards the meta-analysis. One paper contained information from two US cohorts (Joshipura *et al.*, 1999). To combine studies presenting results in units of grams/day (Pietinen *et al.*, 1996) with those using servings/day or /week (Joshipura *et al.*, 1999;Panagiotakos *et al.*, 2009), we assumed a serving size of 200 grams.

Relative risks are presented for each 0.5 servings/day increase, equivalent to approximately one standard deviation, in potato intake. The approximate mean population intake is 0.5 servings/day. These values are based on UK data from NDNS (Bates *et al.*, 2009).

Figure 1.14 Forest plot for potatoes and CVD events



There was excessive heterogeneity between the cohort studies (I^2=90 %, 95% CI: 76% to 96%, Q=29.1, df=3, p<0.001). Heterogeneity was too high to estimate a meaningful pooled estimate. One of the studies with strong influence on the pooled estimate did not adjust for smoking (Panagiotakos *et al.*, 2009), but when this study was excluded heterogeneity was still high (69%). There were insufficient studies to explore subgroups.

There were insufficient studies to explore small-study effects such as publication bias through funnel plots or hypothesis tests.

Sugar- or starch-rich foods and CVD

Total CVD starchy foods and sweets

Summary of cohort results

The ATTICA study of Greece provided data on the association between added sugars, starchy food consumption and risk of total CVD events (Panagiotakos *et al.*, 2009). Age-adjusted servings per week of added sugars in the form of sweets in cases of CVD were similar to the other members of the cohort. Similarly there was no evidence of an association between consumption of starchy foods and risk of CVD in this cohort.

Exposure definition and assessment

Consumption of sweets and starchy foods was reported as either servings per week and was derived from a 156-item FFQ.

Adjustment for appropriate confounders

The ATTICA study provided age-adjusted estimates of consumption frequency only for sweets, but the model used for starchy foods was adjusted for most important potential confounders.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.50 Total CVD starchy foods and sweets: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	Adjustments
14026 (Panagiotakos *et al.*, 2009) ATTICA study	Greece, No CHD	(45) %M 49.8	(170) /3042	5 y (31)	FFQ (156)	Added sugars-Sweets	Fatal + Non-fatal Events	Total CVD Medical records/ autopsy		serv/wk		Cases: (n=170) 4.5 (2.2) Non-cases: (n=1826) 4.9 (2.3)	Age
14027 ATTICA study						Starchy foods (Cereals, potatoes, bread)	Fatal + Non-fatal Events	Total CVD Medical records/ autopsy	Continuous risk estimate	1 unit	1.02 (0.72, 1.42)		Age, BMI, CRP, education, FH, hypercholesterolemia, hypertension, PHYSICAL ACTIVITY, DM, gender, smoking , CHD

Coronary events and sweet foods

Summary of cohort results

Data were extracted from one study: the Iowa Women's Health Study (Jacobs, Jr. *et al.*, 1998). This study did not report any evidence an association between consumption frequency of 'sweets and desserts' and risk of fatal coronary events in the fully adjusted model.

Exposure definition and assessment

The cohort study provided risk estimates in association with weekly servings of sweets and desserts, which included cookies/biscuits, doughnuts, brownies, sweet rolls, cakes, pastries and pies using a 127 item FFQ.

Adjustment for appropriate confounder

The study adjusted for an appropriate range of covariates, including age, BMI, smoking, physical activity and alcohol.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.51 Coronary events and sweet foods: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13743 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	Added sugars-Sweet snack foods. (Cookies; doughnuts; brownies; sweet roll, coffee cake, other pastry; cake; pie; muffins or biscuits)	Fatal Events	Ischaemic heart disease Registry data	11.5-143 vs. 0-2	serv/wk	0.86 (0.56, 1.31)	0.56	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio

Sweetened beverages and CVD

Coronary events and sweetened beverages

Summary of cohort results

Data were extracted from one study, the NHS (Fung *et al.*, 2009). This study provided evidence concerning the association between consumption of total sugar-sweetened beverages and total sugar and non-calorically- sweetened beverages plus three other drink types, namely; fruit drinks and punch, cola and non-cola carbonated beverages with risk of fatal and non-fatal CHD events. The study provided continuous risk estimates for each additional two servings consumed per day except for the total sugar and artificially sweetened beverage exposure which was reported as highest intake (more than two servings per day) compared with the lowest consumers (<1 serving per day). Regardless of beverage type, increasing consumption was associated with increased risk of fatal or non-fatal coronary events. The study reported 27% to 35% increased risk of fatal or non-fatal CHD events with an increase of two servings of sweetened beverages of any type per day. These increases in risk were statistically significant for four out of the five beverage types.

When assessed separately, non-calorically- sweetened beverages were not associated with coronary events (data not in tables).

Exposure definition and assessment

The cohort estimated intakes of total sugar sweetened beverages, total sugar and non-calorically-sweetened beverages, non-cola carbonated beverages, cola beverages and fruit drinks and punch using a 116-item FFQ.

Adjustment for appropriate confounders

The study provided risk estimates adjusted for an appropriate range of covariates, including age, smoking status, physical activity and alcohol intake. Further adjustment for body mass index, energy intake, and incident diabetes attenuated the associations, but they remained significant (data not shown in tables).

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.52 Coronary events and sweetened beverages: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	p trend	Adjustments
13621 (Fung *et al.*, 2009) NHS	USA, No CHD, No T2DM	30-55 %M 0	(3105) /121700	24 y (5)	FFQ (116)	Total Sugar-sweetened beverages	Fatal + Non-fatal Events	CHD events Confirmed self reports	Continuous risk estimate	2 serv/d	1.28 (1.14, 1.44)	<0.001		Age, alcohol, aspirin, family history of CHD, HEI, high TC, hypertension, menopausal status, physical activity, smoking, postmenopausal HRT
13623 NHS						Full-calorie sugar sweetened beverages (Carbonated non-cola)	Fatal + Non-fatal Events	CHD events Confirmed self reports	Continuous risk estimate	2 serv/d	1.27 (0.87, 1.86)	0.22		
13622 NHS						Full-calorie sugar sweetened beverages (Cola)	Fatal + Non-fatal Events	CHD events Confirmed self reports	Continuous risk estimate	2 serv/d	1.35 (1.15, 1.57)	<0.001		As above
13624 NHS						Full-calorie sugar sweetened beverages (Fruit drinks and punch)	Fatal + Non-fatal Events	CHD events Confirmed self reports	Continuous risk estimate	2 serv/d	1.33 (1.03, 1.71)	0.03		As above
13614 NHS						Total sugar and non-calorically-sweetened beverages	Fatal + Non-fatal Events	CHD events Confirmed self reports	>2 (2.6) vs. <1 (0)	serv/d	1.35 (1.07, 1.69)		<0.001	As above

Carbohydrate form and CVD

The following section focuses on CVD outcomes and carbohydrate form, including studies reporting the following exposures: wholegrain foods, refined grain foods, glycaemic index (GI) and glycaemic load (GL).

Wholegrains and CVD

Total CVD and wholegrains

Summary of cohort results

Three cohort studies, namely the EPIC Potsdam study, Iowa Women's Health Study and the Boston Study of Wholegrains and CVD risk, conducted in North America and Germany provided data on the association between wholegrains and risk of total CVD (Drogan *et al.*, 2007;Sahyoun *et al.*, 2006;Jacobs, Jr. *et al.*, 2007). From these cohorts there is evidence of a consistent decreased risk with increasing consumption of wholegrains. Mean consumption of wholegrains by CVD cases was lower than other members of the EPIC Potsdam cohort, and in the two US cohorts, individuals in the highest frequency intake category experienced a 27% to 52% reduction in risk of CVD compared to individuals in the lowest consumption category.

Exposure definition and assessment

The Iowa Women's Health Study and EPIC Potsdam cohorts used FFQs to assess dietary intake, whereas the Boston Study of Wholegrains and CVD Risk, used three-day food diaries to collect dietary data. In the Boston Study of Wholegrains and CVD Risk, the total number of grain servings recorded was divided into wholegrain servings and refined-grain servings on the basis of the proportion of the grain ingredients in the foods. It is unclear which foods were classified as wholegrain as the paper does not explicitly state the definition for these foods (Sahyoun *et al.*, 2006). The Iowa Women's Health Study classified wholegrain foods as those containing >25% wholegrain or bran by weight (Jacobs, Jr. *et al.*, 2001) and EPIC Potsdam simply reported wholegrain intake as 'grain flakes, grains and muesli'. All three cohorts therefore characterise wholegrain intakes somewhat differently.

Adjustment for appropriate confounders

Unadjusted mean consumption data in cases and non-cases were reported only for EPIC Potsdam, but the other two cohorts adjusted for important confounders including age, smoking, and education.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.53 Total CVD and wholegrains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Mean Exposure (SD)	p trend	Adjustments
13463 (Drogan *et al.*, 2007) EPIC Potsdam	Germany, No history of MI/Stroke	35-65 (50) %M 40	(68) /27548	6.4 y (5)	FFQ (148)	Total wholegrain foods (Grain flakes, grains, muesli)	Fatal Events	MI/ Stroke, any Medical records/ death certificate		g/d		Cases: (n: 68) 2.9 (10.2) Non-cases: (n: 25859) 5.5 (14.7)		
14718 EPIC Potsdam			(311) /27548				Fatal + Non-fatal Events	MI/ Stroke, any Medical records		g/d		Cases: (n: 311) 3.1 (9.7) Non-cases: (n: 25859) 5.5 (14.7)		
*13746 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal, Without colitis, Without liver cirrhosis	55-69 (61) %M 0	(1900) /41836	17 y	FFQ (127)	Wholegrains, non-FDA definition (as described in (Jacobs, Jr. *et al.*, 2007)	Fatal Events	Total CVD Medical records/ autopsy	>19 vs. 0-3.5	serv/wk	0.73 (0.62, 0.86)		0.0001	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, red meat, refined grain, smoking, Vit intake, waist:hip ratio
*14318 (Sahyoun *et al.*, 2006) Boston Study of Wholegrains and CVD Risk	USA, Primarily White, Generally healthy	60- (73) %M 33	(89) /747	15 y	Food diary	Wholegrain: definition unclear (non-FDA definition of wholegrains)	Fatal Events	Total CVD Medical records/ autopsy	>1.95 vs. <0.56	serv/d	0.48 (0.25, 0.96)		0.04	Age, alcohol, BMI, education, energy intake, ethnicity, CHD, marital status, physical activity, saturated fatty acid intake, gender, smoking, statin use, hypertension medication

*This result was used in the meta-analysis of wholegrains and any CVD event

Coronary events and wholegrains

Summary of cohort results

Data were extracted from five papers relating to four cohorts: the Iowa Women's Health study (nine years follow up) (Jacobs, Jr. *et al.*, 1998), the Iowa Women's Health study (17 years follow up) (Jacobs, Jr. *et al.*, 2007), the HPFS (Jensen *et al.*, 2004), the Atherosclerosis Risk in Communities (ARIC) (Steffen *et al.*, 2003) and the NHS (Liu *et al.*, 1999). All studies reported risk estimates for wholegrain consumption and incidence of coronary events (either fatal events only or combined fatal plus non-fatal events).

Results consistently showed evidence of decreased risk of incident coronary events with greater wholegrain consumption in all studies and subgroups, with the exceptions being the 'other wholegrain' consumption in the nine year follow up of the Iowa Women's Health study (Jacobs, Jr. *et al.*, 1998) and a result in those taking no regular physical activity in the NHS (Liu *et al.*, 1999). A significant p for trend value was also reported for four out of the five publications (Jacobs, Jr. *et al.*, 1998;Jacobs, Jr. *et al.*, 2007;Liu *et al.*, 1999).

Exposure definition and assessment

The four cohort studies reported data on wholegrain foods which include wholegrain bread, wholegrain breakfast cereals and oatmeal. All cohorts used FFQs with ARIC having the fewest (66 items) (Steffen *et al.*, 2003) and the rest having around 130 items (Jacobs, Jr. *et al.*, 1998;Jacobs, Jr. *et al.*, 2007); (Jensen *et al.*, 2004); (Liu *et al.*, 1999). Three of the cohorts (Jacobs, Jr. *et al.*, 1998;Jacobs, Jr. *et al.*, 2007;Liu *et al.*, 1999;Steffen *et al.*, 2003) defined wholegrain intake using classifications outlined by Jacobs and colleagues (Jacobs, Jr. *et al.*, 1998). This definition classifies the following foods as wholegrain: 'dark bread', breakfast cereals with ≥25% wholegrain or bran by weight, brown rice, popcorn, wheat germ, bran, cooked oatmeal and other grains including bulgar, kasha and couscous (Jacobs, Jr. *et al.*, 1998).

The American Association of Cereal Chemists International and the American Food and Drug Administration (FDA) defines whole grains as "intact, ground, cracked or flaked fruit of the grain whose principal components, the starchy endosperm, germ and bran, are present in the same relative proportions as they exist in the intact grain" (American Association of Cereal Chemists International, 1999;United States FDA, 2006). This approach therefore includes all foods with more than 51% whole-grain content. One study (HPFS) applied the (FDA) definition for wholegrains (Jensen *et al.*, 2004).

While it is recommended that Americans eat at least three portions (around 85g) of whole grains per day, the UK does not currently have any specific recommendations other than the recommendation “to choose whole-grain varieties whenever you can” (USDA, 2010;Food Standards Agency, 2010).

Adjustment for appropriate confounders

All five publications provided risk estimates adjusted for an appropriate range of covariates, including age, gender and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.54 Coronary events and wholegrains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13739 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	Wholegrain: "Other wholegrains" (Brown rice, popcorn, wheat germ, bran, cooked oatmeal, other grains (bulgar, kasha, couscous))	Fatal Events	Ischaemic heart disease Registry data		5.5-91 vs. 0	serv/ wk	1.26 (0.81, 1.95)	0.69	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio
13726 Iowa Women's Health Study						Wholegrain: Jacobs *et al* definition: (Jacobs, Jr. *et al.*, 1998) (Non-FDA definition)	Fatal Events	Ischaemic heart disease Registry data		18.5-84.5 (22.5) vs. 0-3.5 (1.5)	serv/ wk	0.7 (0.5, 0.98)	0.018	As above
*13747 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal	55-69 (61) %M 0	(1034) /41836	17 y	FFQ (127)	Wholegrains, non-FDA definition (as described in (Jacobs, Jr. *et al.*, 2007)	Fatal Events	CHD events Medical records/ autopsy		>19 vs. 0-3.5	serv/ wk	0.72 (0.57, 0.9)	0.002	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, red meat, refined grain, smoking, Vit intake, waist:hip ratio
**13435 (Jensen *et al.*, 2004) HPFS	USA, Primarily White, Cancer free, No CHD, No T2DM	40-75 %M 100	(1818) /51529	14 y	FFQ (131)	Wholegrain, FDA definition (foods contain wholegrain components –bran, germ, endosperm in the same proportion as naturally in intact grains)	Fatal + Non-fatal Events	CHD events Medical testing, Registry data, Self report		(42.4) vs. (3.5)	g/d	0.82 (0.7, 0.96)	0.29	Age, alcohol, BMI, dietary Met, education, dietary cholesterol, MUFA, PUFA, saturated fatty acid intake, Energy from TFA, energy intake, family history of cancer, fibre, hypertension, HRT, physical activity, smoking, vegetable protein, Vit intake
*14041 (Liu *et al.*, 1999) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(761) /121700	10 y	FFQ (126)	Total wholegrain foods, Jacobs *et al* definition (Jacobs, Jr. *et al.*, 1998) (Dark bread, wholegrain breakfast cereal,	Fatal + Non-fatal Events	Fatal CHD events + non-fatal MI Medical records/ autopsy		1.77-17.86 vs. 0-0.26	serv /d	0.75 (0.59, 0.95)	0.01	Age, alcohol, aspirin, BMI, energy intake, hypercholesterolaemia, hypertension, menopausal status, MUFA, parental MI, PUFA, protein intake,

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
						popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (e.g., bulgar, kasha, and couscous))								saturated fatty acid intake, smoking, TFA, physical activity, Vit intake
14042 NHS			(184) /121700						Never or former smoker	1.77-17.86 vs. 0-0.26		0.49 (0.3, 0.79)	0.003	As above
14043 NHS			(632) /121700						No Hypercholest-erolaemia	1.77-17.86 vs. 0-0.26		0.72 (0.54, 0.91)	0.01	As above
14044 NHS			(392) /121700						No Supplement Use	1.77-17.86 vs. 0-0.26		0.73 (0.52, 1.02)	0.05	As above
14045 NHS			(398) /121700						No Vit E Supplement Use	1.77-17.86 vs. 0-0.26		0.83 (0.6, 1.15)	0.32	As above
14046 NHS			(264) /121700						Alcohol Non-drinkers	1.77-17.86 vs. 0-0.26		0.72 (0.49, 1.06)	0.07	As above
14047 NHS			(439) /121700						No vigorous PA	1.77-17.86 vs. 0-0.26		0.74 (0.54, 1.02)	0.11	As above
14048 NHS			(432) /121700						Not HRT users	1.77-17.86 vs. 0-0.26		0.75 (0.54, 1.04)	0.02	As above
**13285 (Steffen *et al.*, 2003) ARIC Study	USA, Multi-ethnic	45-64 (54) %M 44	(535) /15792	11 y (2)	FFQ (66)	Total wholegrain foods (dark bread and whole-grain cold breakfast cereal with >25% whole grain or bran by weight). FFQ items classified as wholegrain using Jacobs et al definition (Jacobs, Jr. *et al.*, 1998)	Fatal and non fatal	Coronary artery disease (MI, CAD death, coronary revascular-isation) Medical records/ autopsy		(3) vs. (0.1)	serv/ d	0.72 (0.53, 0.97)	0.05	Age, alcohol, BMI, education, energy intake, ethnicity, smoking, physical activity, gender, smoking, SBP, hypertension medication, postmenopausal HRT, waist:hip ratio, HDL, LDL

*This result was used in the meta-analysis of wholegrains and CHD events

**This result was used in the meta-analysis of wholegrains and CHD events and wholegrains and any CVD event

Stroke events and wholegrains

Summary of cohort results

Data were extracted from three studies: the Iowa Women's Health Study (Jacobs, Jr. *et al.*, 2007), the ARIC Study (Steffen *et al.*, 2003) and the NHS (Liu *et al.*, 2000a). These studies provided evidence concerning the association between consumption of wholegrains and fatal and non-fatal stroke including any stroke, nonhaemorrhagic/ischaemic and haemorrhagic stroke. In each cohort, risk estimates tended to be lower with increasing wholegrain consumption. However, these risk estimates were not significantly lower in either the Iowa Women's Health Study (Jacobs, Jr. *et al.*, 2007) or the ARIC study (Steffen *et al.*, 2003). The Nurses' Health Study (Liu *et al.*, 2000a) reported a significantly reduced risk of ischaemic stroke with wholegrain consumption for the whole cohort and in 'never or former smokers'. The risk was reduced by 31% and 50% respectively. Additionally, there was a p for trend of 0.006 in the 'never or former smokers' subgroup. This significant association was not seen in the 'alcohol non-drinkers', 'no vigorous physical activity' or the 'not HRT users' (not hormone replacement therapy users) subgroups.

Exposure definition and assessment

The three studies all assessed wholegrain consumption using FFQs with between 66 and 127 items. The FFQ used by ARIC (Steffen *et al.*, 2003) had only 66 items which calls into question the validity of the estimate of wholegrain intake. All three cohorts classified wholegrain foods using the Jacobs *et al*. definition which includes 'dark bread', breakfast cereals with ≥25% wholegrain or bran by weight, brown rice, popcorn, wheat germ, bran, cooked oatmeal and other grains including bulgar, kasha and couscous (Jacobs, Jr. *et al.*, 1998).

Adjustment for appropriate confounders

All three studies adjusted for an appropriate range of covariates including age, alcohol, BMI and smoking. The ARIC study (Steffen *et al.*, 2003) also adjusted for gender.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments

Table 1.55 Stroke events and wholegrains: cohort studies in adults

*13748 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal	55-69 (61) %M 0	(414) /41836	17 y	FFQ (127)	Wholegrain, non-FDA definition (Jacobs, Jr. *et al.*, 1998)	Fatal Events	Stroke, any Medical records/ autopsy		>19 vs. 0-3.5	serv/wk	0.85 (0.6, 1.21)	0.52	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, Red meat, refined grain, smoking, Vit intake, waist:hip ratio
13750 Iowa Women's Health Study			(251) /41836					Nonhaemorrhagic stroke		>19 vs. 0-3.5	serv/wk	0.88 (0.57, 1.36)	0.94	As above
13749 Iowa Women's Health Study			(113) /41836					Stroke, haemorrhagic		>19 vs. 0-3.5	serv/wk	1.28 (0.64, 2.56)	0.93	As above
**13650 (Liu *et al.*, 2000a) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(352) /121700	12 y	FFQ (126)	Wholegrain, Jacobs *et al* definition (Jacobs, Jr. *et al.*, 1998) (non-FDA definition) (dark bread, wholegrain breakfast cereal (with >25% wholegrain or bran), popcorn, cooked oatmeal, wheat germ, brown rice, bran and other grains (bulgur, kasha and couscous))	Fatal + Non-fatal Events	Stroke, ischaemic Confirmed self reports, Medical records/autopsy, Registry data		1.77-17.86 vs. 0-0.26		0.69 (0.5, 0.98)	0.08	Age, alcohol, aspirin, BMI, saturated fatty acid intake, energy from TFA, energy intake, family history of MI, high TC, hypertension, menopausal status, physical activity, smoking, Vit intake
13653 NHS			(238) /121700						Never or former smoker	1.77-17.86 vs. 0-0.26		0.5 (0.34, 0.76)	0.006	As above except smoking
13654 NHS			(94) /121700						Alcohol Non-drinkers	1.77-17.86 vs. 0-0.26		0.72 (0.39, 1.36)	0.22	As first except alcohol
13655 NHS			(201) /121700						No vigorous PA	1.77-17.86 vs. 0-0.26		0.73 (0.48, 1.11)	0.08	As first except physical activity
13656 NHS			(249) /121700						Not HRT users	1.77-17.86 vs. 0-0.26		0.69 (0.46, 1.05)	0.05	As first except menopausal status
**13289 (Steffen *et al.*, 2003) ARIC Study	USA, Multi-ethnic	45-64 (54) %M 44	(214) /15792	11 y (2)	FFQ (66)	Total wholegrain foods (dark bread and whole-grain cold breakfast cereal with >25% whole grain or bran by weight). FFQ items classified as wholegrain using Jacobs *et al* definition (Jacobs, Jr. *et al.*, 1998)	Non-fatal Events	Stroke, ischaemic Medical records/ autopsy		(3) vs. (0.1)	serv/d	0.75 (0.46, 1.22)	0.15	Age, alcohol, BMI, education, energy intake, ethnicity, smoking, physical activity, gender, smoking, SBP, hypertension medication, postmenopausal HRT, waist:hip ratio

*This result was used in the meta-analysis of wholegrains and stroke events

**This result was used in the meta-analysis of wholegrains and stroke events and wholegrains and any CVD event

Summary on wholegrains and CVD

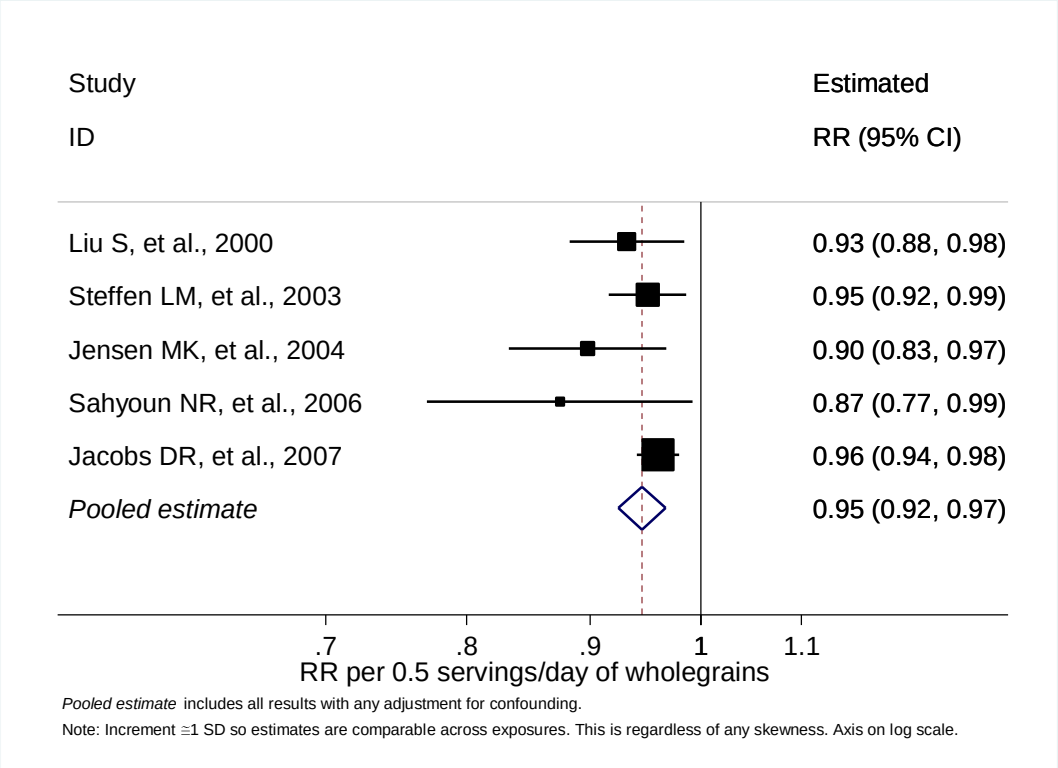
Meta-analysis: Wholegrains and incident CVD events

Data were extracted from 8 publications presenting results from 6 cohort studies (Drogan *et al.*, 2007;Jacobs, Jr. *et al.*, 2007;Sahyoun *et al.*, 2006;Liu *et al.*, 1999;Jensen *et al.*, 2004;Steffen *et al.*, 2003;Liu *et al.*, 2000a;Jacobs, Jr. *et al.*, 1998;Nettleton *et al.*, 2008). Of these, one publication (Liu *et al.*, 1999) was an early analysis of data from the Nurses' Health Study I data, presented more fully in a later publication (Liu *et al.*, 2000a). Another publication (Jacobs, Jr. *et al.*, 1998) was an early analysis of data from the Iowa Women's Health Study presented more fully in a later publication (Jacobs, Jr. *et al.*, 2007). One study had to be excluded because, whilst results for different sources of wholegrains were presented, no overall result could be estimated (Drogan *et al.*, 2007). The remaining studies all contributed towards the meta-analysis. For one study, intake of whole grains was assumed to follow a normal distribution with mean and standard deviation quoted in the paper, so that median intakes for each category could be estimated (Liu *et al.*, 2000a). For two studies we assumed that the median intake for the highest category was 1.5 times the lower limit of the highest category (Jacobs, Jr. *et al.*, 2007;Sahyoun *et al.*, 2006). So that one study could be included in the meta-analysis (Jensen *et al.*, 2004), an average serving size of 40 grams was assumed.

Relative risks are presented for each 0.5 servings/day increase, equivalent to approximately one standard deviation, in wholegrain intake. The approximate mean population intake is estimated at 0.5 servings/day based on published data (Lang *et al.*, 2003).

The pooled estimate of relative risk from the cohort studies was 0.95 (95% CI: 0.92 to 0.97) per half serving of wholegrains per day ($p<0.001$).

Figure 1.15 Forest plot for wholegrains and total CVD events



There was little heterogeneity between the cohort studies (I^2=25%, 95% CI: 0% to 70%, Q=5.3, df=4, p=0.3). There were sufficient studies to investigate sources of heterogeneity through subgroup analysis and meta-regression:

Table 1.56 Subgroup analyses of wholegrain intake and incidence of any CVD. Relative risks are per 0.5 servings/day.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	0.90 (0.83, 0.97)		1		.5
	Mixed	0.93 (0.87, 1.00)	35%	2	.2	
	Female	0.96 (0.94, 0.97)	0%	2	.3	
definition of wholegrain	FDA	0.90 (0.83, 0.97)		1		
	Jacobs	0.96 (0.94, 0.97)	0%	3	.6	
	not stated	0.87 (0.77, 0.99)		1		.3
includes non-fatal events	yes	0.94 (0.86, 1.01)	51%	2	.2	
	no	0.94 (0.91, 0.96)	0%	3	.4	.4
length of follow-up	<10 years			0		
	>=10 years	0.95 (0.92, 0.97)	25%	5	.3	.7
geographic location	Americas	0.95 (0.92, 0.97)	25%	5	.3	
	EU			0		
	Other			0		
adjusted for age	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no			0		
adjusted for alcohol	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no		25%	0		
adjusted for anthropometry	yes	0.95 (0.94, 0.97)	0%	4	.4	
	no	0.90 (0.83, 0.97)		1		.2
adjusted for energy intake	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no			0		
adjusted for family history	yes	0.92 (0.88, 0.96)	0%	2	.4	
	no	0.96 (0.94, 0.97)	8%	3	.3	.2
adjusted for physical activity	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no			0		
adjusted for gender	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no			0		
adjusted for smoking	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no		25%	0		
adjusted for age & smoking	yes	0.95 (0.92, 0.97)	25%	5	.3	
	no		25%	0		

* P for heterogeneity within each subgroup

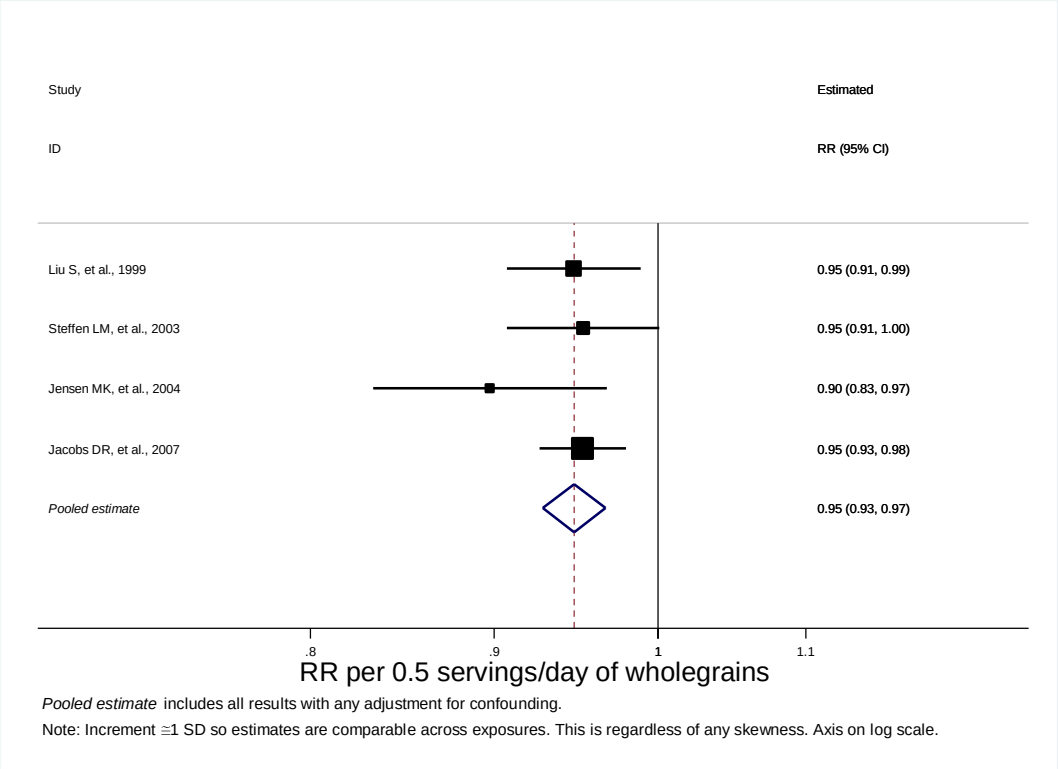
** P for heterogeneity between each subgroup

The results for the individual sources of wholegrains from Drogan *et al* (Drogan *et al.*, 2007), which could not be included, were in broad agreement with those from this meta-analysis.

There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

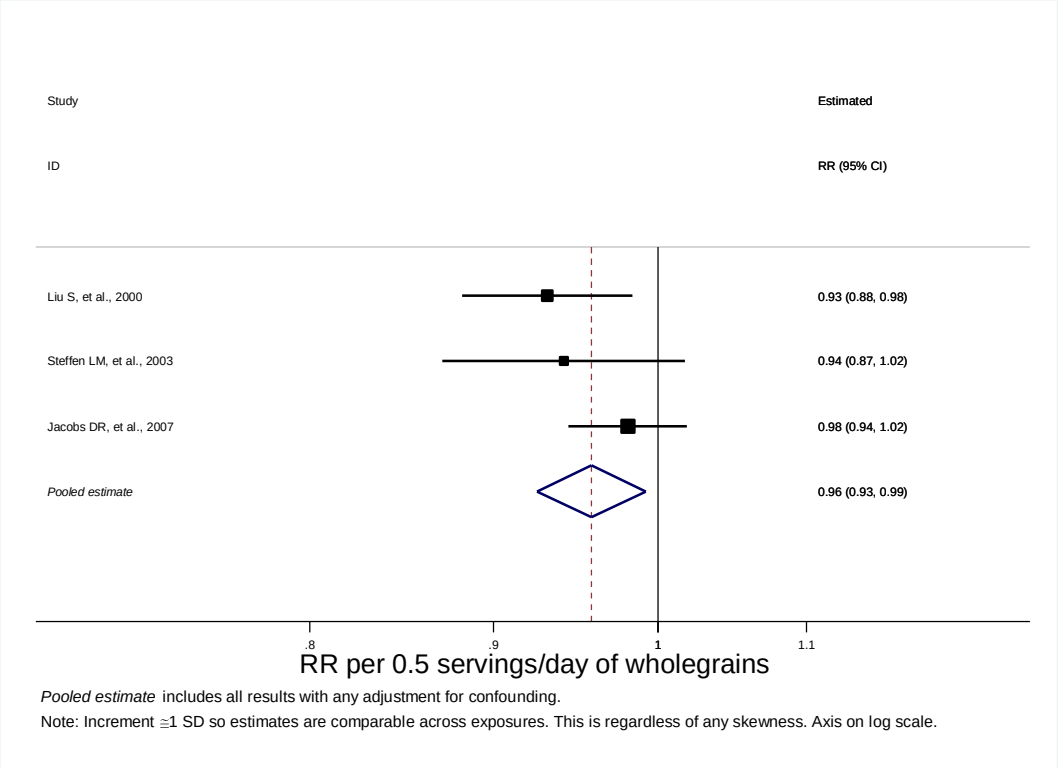
When results were explored by outcome type (CHD / stroke), results for both outcomes were very similar. For CHD, the pooled estimate was 0.95 (95% CI: 0.93 to 0.97) per half serving of wholegrains per day (p<0.001), with no excess heterogeneity (I^2=0%):

Figure 1.16 Forest plot for wholegrains and CHD events



For stroke, the pooled estimate was 0.96 (95% CI: 0.93 to 0.99) per half serving of wholegrains per day (p=0.02), with little excess heterogeneity (I^2=24%):

Figure 1.17 Forest plot for wholegrains and stroke events



There were too few studies to explore heterogeneity within each outcome type.

Refined grains and CVD

Total CVD and refined grains

Summary of cohort results

Two cohort studies from the US provided data on the association between refined grains and risk of total CVD (Sahyoun *et al.*, 2006;Jacobs, Jr. *et al.*, 2007). In both the Boston Study of Wholegrains and CVD Risk and the Iowa Women's Health Study, there was no evidence of an association between refined grain consumption and risk of CVD mortality.

Exposure definition and assessment

The Iowa Women's Health Study used a FFQ to assess dietary intake, whereas the Boston Study of Wholegrains and CVD Risk, being smaller, was able to use three-day food diaries to collect dietary data. In the Boston Study of Wholegrains and CVD Risk the total number of grain servings recorded was divided into wholegrain servings and refined-grain servings on the basis of the proportion of the grain ingredients in the foods that were wholegrain and refined grain. The gram amount of each food consumed was then added for wholegrain and refined grain separately.

Adjustment for appropriate confounders

Both cohorts adjusted for important confounders including age, BMI, smoking, and education.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.57 Total CVD and refined grains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
*13751 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal, Without colitis, Without liver cirrhosis	55-69 (61) %M 0	(1900) /41836	17 y	FFQ (127)	Refined grains	Fatal Events	Total CVD Medical records/ autopsy	>22.5 vs. 0-5.75	serv/wk	0.94 (0.78, 1.12)	0.33	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, red meat, smoking, Vit intake, waist:hip ratio, wholegrain
17575 (Sahyoun *et al.*, 2006) Boston Study of Wholegrains and CVD Risk	USA, Primarily White, Generally healthy	60- (73) %M 33	(89) /747	15 y	Food diary	Refined grains	Fatal Events	Total CVD Medical records/ autopsy	>1.95 vs. <0.56	serv/d	No association	0.41	Age, alcohol, BMI, education, energy intake, ethnicity, CHD, marital status, physical activity, saturated fatty acid intake, gender, smoking, statin use, hypertension medication

*This result was used in the meta-analysis of refined grains and any CVD event

Coronary events and refined grains

Summary of cohort results

Data were extracted from two publications, reporting on one cohort, the Iowa Women's Health Study at nine years (Jacobs, Jr. *et al.*, 1998) and 17 years follow up (Jacobs, Jr. *et al.*, 2007). These publications provided evidence concerning the association between consumption of refined grains and risk of fatal CHD and fatal IHD, comparing groups with highest and lowest intake. The risk estimates were close to 1 indicating no evidence of an association with refined grain consumption and fatal CHD or fatal IHD.

Exposure definition and assessment

The Iowa Women's Health Study reported data on refined grains including white rice, pasta, pizza, bread and rolls, using a 127-item FFQ.

Adjustment for appropriate confounders

An appropriate range of covariates, including age, smoking and BMI, were used.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.58 Coronary events and refined grains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13740 (Jacobs, Jr. *et al.*, 1998) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, No CHD, Post-menopausal	55-69 (61) %M 0	(438) /41836	9 y	FFQ (127)	Refined grains (white bread; refined-grain breakfast cereals; and other refined grains – English muffins, bagels, or rolls; pancakes or waffles; white rice; pasta; pizza)	Fatal Events	Ischaemic heart disease Registry data	23-155.5 vs. 0-6	serv/wk	1.12 (0.77, 1.62)	0.57	Age, alcohol, BMI, education, energy intake, fish, Fruit and veg, DM, HRT, hypertension, marital status, meat, oral contraceptive pill, smoking, physical activity, sugar intake, supplements, waist:hip ratio
13744 Iowa Women's Health Study						Other refined grains (English muffins, bagels, or rolls; pancakes or waffles; white rice; pasta; pizza)	Fatal Events	Ischaemic heart disease Registry data	5.5-50 vs. 0-1.5	serv/wk	0.79 (0.52, 1.21)	0.29	As above
13752 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal, Without colitis, Without liver cirrhosis	55-69 (61) %M 0	(2934) /41836	17 y	FFQ (127)	Refined grains	Fatal Events	CHD events Medical records/ autopsy	>22.5 vs. 0-5.75	serv/wk	0.89 (0.7, 1.14)	0.22	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, red meat, smoking, Vit intake, waist:hip ratio, wholegrain
*13290 (Steffen *et al.*, 2003) ARIC Study	USA, Multi-ethnic	45-64 (54) %M 44	(535) /15792	11 y (2)	FFQ (66)	Refined-grains (cold breakfast cereal with <25% wholegrain content, white bread, bagels, donuts, pastry, muffins, biscuits, cookies, cake, brownies, pasta and rice)	Fatal and non fatal	Coronary artery disease (MI, CAD death, coronary revascularisation) Medical records/ autopsy	(5.0) vs. (0.5)	serv/d	1.17 (0.82, 1.66)	0.11	Age, alcohol, BMI, education, energy intake, ethnicity, smoking, physical activity, gender, smoking, SBP, hypertension medication, postmenopausal HRT, waist:hip ratio, HDL, LDL

*This result was used in the meta-analysis of refined grains and any CVD event

Stroke events and refined grains

Summary of cohort results

Data were extracted from three studies: the Iowa Women's Health Study (Jacobs, Jr. *et al.*, 2007), the ARIC Study (Steffen *et al.*, 2003) and the NHS (Liu *et al.*, 2000a). These studies provided evidence concerning the association between consumption of refined grains and fatal and non-fatal stroke including any stroke, nonhaemorrhagic/ischaemic and haemorrhagic stroke. The direction of association was inconsistent for these analyses and there were no significant p values for trend reported.

Exposure definition and assessment

The three studies all used FFQs to assess refined grain consumption. The FFQs used had between 66 and 127 items. The FFQ used by ARIC (Steffen *et al.*, 2003) had only 66 items which calls into question the validity of the estimate of intake of refined grains. The exposures were reported in servings per day or servings per week.

Adjustment for appropriate confounders

All three studies adjusted for an appropriate range of covariates including age, alcohol, BMI and smoking. The ARIC study (Steffen *et al.*, 2003) also adjusted for gender.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.59 Stroke events and refined grains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13753 (Jacobs, Jr. *et al.*, 2007) Iowa Women's Health Study	USA, Primarily White, Cancer free, No CHD, No T2DM, Post-menopausal, Without colitis, Without liver cirrhosis	55-69 (61) %M 0	(414) /41836	17 y	FFQ (127)	Refined grains	Fatal Events	Stroke, any Medical records/ autopsy	>22.5 vs. 0-5.75	serv/wk	1.3 (0.88, 1.91)	0.24	Age, alcohol, BMI, coffee, education, energy intake, oestrogen use, fish, fruit and veg, physical activity, red meat, smoking, Vit intake, waist:hip ratio, wholegrain
13755 Iowa Women's Health Study			(251) /41836					Nonhaemorrhagic stroke Medical records/ autopsy	>22.5 vs. 0-5.75	serv/wk	1.19 (0.72, 1.97)	0.4	As above
13754 Iowa Women's Health Study			(113) /41836					Stroke, haemorrhagic Medical records/ autopsy	>22.5 vs. 0-5.75	serv/wk	1.1 (0.54, 2.23)	0.87	As above
*13651 (Liu *et al.*, 2000a) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(352) /121700	12 y	FFQ (126)	Refined grains (sweet rolls, cakes, desserts, white bread, pasta, English muffins, muffins or biscuits. Refined grain breakfast cereal, white rice, pancakes or waffles and pizza)	Fatal + Non-fatal Events	Stroke, ischaemic Confirmed self reports, Medical records/autopsy, Registry data	Q5 vs. Q1		0.97 (0.67, 1.42)	0.58	Age, alcohol, aspirin, BMI, saturated fatty acid intake, energy from TFA, energy intake, family history of MI, high TC, hypertension, menopausal status, physical activity, smoking, Vit intake
*13291 (Steffen *et al.*, 2003) ARIC Study	USA, Multi-ethnic	45-64 (54) %M 44	(214) /15792	11 y (2)	FFQ (66)	Refined-grains (cold breakfast cereal with <25% wholegrain content, white bread, bagels, donuts, pastry, muffins, biscuits, cookies, cake, brownies, pasta and rice)	Non-fatal Events	Stroke, ischaemic Medical records/ autopsy	(5) vs. (0.5)	serv/d	0.82 (0.48, 1.4)	0.16	Age, alcohol, BMI, education, energy intake, ethnicity, smoking, physical activity, gender, smoking, SBP, hypertension medication, postmenopausal HRT, waist:hip ratio

*This result was used in the meta-analysis of refined grains and any CVD event

Summary of refined grains and CVD

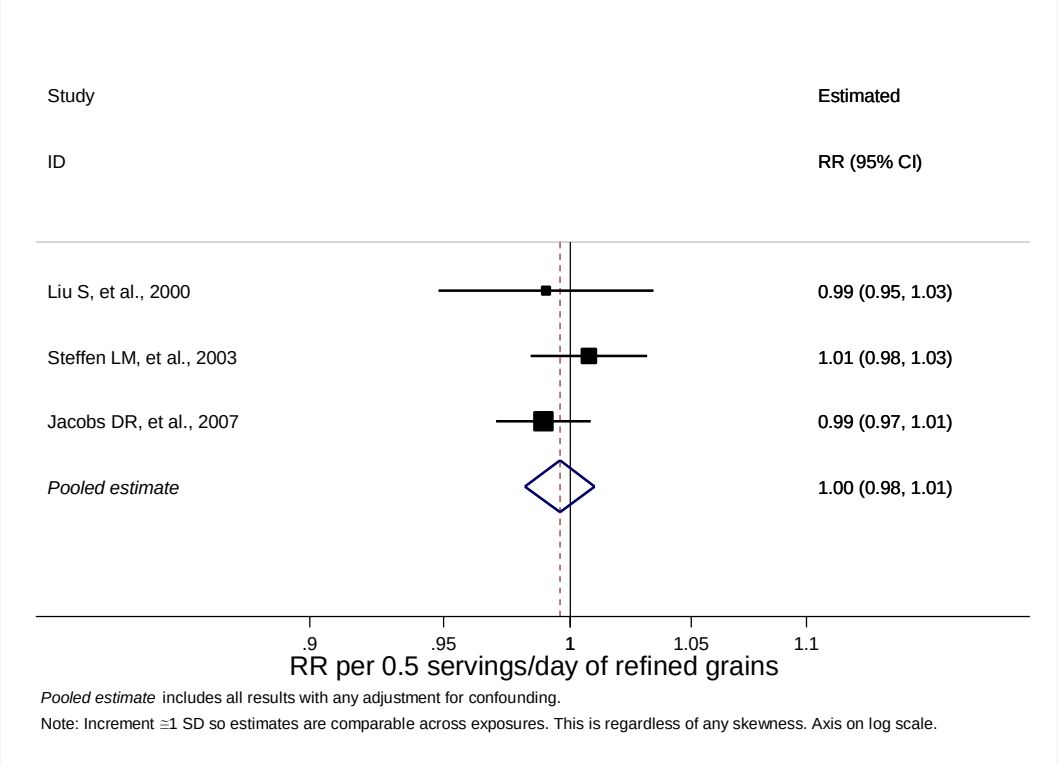
Meta analysis: Refined grains and incident CVD events

Data were extracted from 5 publications presenting results from the following 4 cohort studies: the Iowa Women's Health Study, NHS, ARIC and the Boston Study of Wholegrains and CVD risk (Sahyoun *et al.*, 2006). Of these, one publication (Jacobs, Jr. *et al.*, 1998) was an early analysis of data presented more fully in a later publication (Jacobs, Jr. *et al.*, 2007). The remaining studies all contributed towards the meta-analysis. For one study, intake of refined grains was assumed to follow a normal distribution with mean and standard deviation quoted in the paper, so that median intakes for each category could be estimated (Liu *et al.*, 2000a). For one study we assumed that the median intake for the highest category was 1.5 times the lower limit of the highest category (Jacobs, Jr. *et al.*, 2007).

Relative risks are presented for each 0.5 servings/day increase, equivalent to approximately one standard deviation, in refined grains intake. The approximate mean population intake is 0.5 servings/day as based on published data (Lang *et al.*, 2003).

The pooled estimate of relative risk from the cohort studies was 1.00 (95% CI: 0.98 to 1.01) per half serving of refined grains per day (p=0.5).

Figure 1.18 Forest plot for refined grains and total CVD events



There was no excess heterogeneity between the cohort studies (I^2=0%, 95% CI: 0% to 86%, Q=1.5, df=2, p=0.5). There were insufficient studies to explore stroke and CHD results separately. There were insufficient studies to explore the sources of heterogeneity by subgroup analysis and meta-regression. There were insufficient studies to explore small-study effects such as publication

bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Glycaemic index and CVD

The glycaemic index (GI) is a relative measure of the plasma glucose response induced by a specific food, as compared to the response induced by the same amount of carbohydrate from a reference source, such as white bread or pure glucose (Liu *et al.*, 2000b).

All studies used previously published glycaemic index values, from a variety of sources. Many studies described the need to adapt or use averaged values, though only one reported the extent of this (11.1% of values used) (Kaushik *et al.*, 2009). For the majority, the reference food used to calculate GI values was not listed, but four sources selected values which used white bread (Van Dam *et al.*, 2000;Levitan *et al.*, 2007;Oh *et al.*, 2005), and others used glucose as a reference.

Most studies used a similar method to calculate dietary GI and GL: namely, summing the products of the GI for each food multiplied by its carbohydrate content per serving multiplied by the average number of servings of that food per day (to give dietary GL), then dividing by the average daily carbohydrate intake to give dietary GI:

Dietary GI = {∑[(servings of food per day) x (CHO content) x GI)]}/total CHO (Meyer *et al.*, 2000).

Three studies, however, calculated dietary GI by summing the products of each food's GI multiplied by its % contribution to total carbohydrate intake (Barclay *et al.*, 2007;Kaushik *et al.*, 2009;Van Dam *et al.*, 2000). The glycaemic index (and thus also GL) is determined not only by the nature of the carbohydrate component of a food or diet, but also by the types and amounts of protein, fat and dietary fibre, as well food processing and storage (Venn and Green, 2007). Unless tightly controlled in an experimental situation, in most cases high and low GI/GL diets differ in many ways other than the carbohydrate fraction, including dietary fibre content, energy density and sensory quality.

Total CVD and glycaemic index

Summary of cohort results

One Swedish cohort study provided data on the association between total CVD and glycaemic index (GI) (Levitan *et al.*, 2007). In the Cohort of Swedish Men publication, dietary GI was not associated with cardiovascular mortality.

Exposure definition and assessment

Dietary GI was estimated from a 96-item FFQ administered once at study baseline and the result from this study was appropriately adjusted.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.60 Total CVD and glycaemic index: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Assessment/ Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	RR (CI)	p trend	Adjustments
*14097 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(785) /48850	5 y (0)	96-item FFQ GI	Fatal Events	Total CVD Registry data	(82.9) vs. (73) units/day	1.09 (0.88, 1.36)	0.46	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, energy intake, family history of HTN, family history of MI, marital status, physical activity, PUFA, SFA

*This result was used in the meta-analysis of glycaemic index and any CVD event

Coronary events and glycaemic index

Summary of cohort results

Data were extracted from five studies: the Blue Mountains Eye study (Kaushik *et al.*, 2009), the Prospect-EPIC Utrecht study (Beulens *et al.*, 2007), the NHS (Liu *et al.*, 2000b), the Cohort of Swedish Men study (Levitan *et al.*, 2007) and the Zutphen Elderly study (Van Dam *et al.*, 2000). Prospect-EPIC Utrecht reported results for the total sample and two subgroups, namely those with a BMI of less than 25 and those with a BMI of more than 25. The Blue Mountains Eye study reported results for high versus low glycaemic index and also the rest of the group vs. lowest GI tertile and highest cereal fibre. These studies provided evidence concerning the association between glycaemic index and fatal incident coronary events. All the studies provided risk estimates comparing highest and lowest groups (quintiles or quartiles) of glycaemic index measured as a score or in units with the risk of fatal or combined fatal and non-fatal CHD events.

Three out of the five studies reported increased risk of fatal or non-fatal coronary events for all participants with greater levels of dietary GI, with risk estimates in the region of 1.31 to 1.91 (Kaushik *et al.*, 2009;Liu *et al.*, 2000b;Beulens *et al.*, 2007). The Prospect-EPIC Utrecht study subgroups reported similar increases in risk of 31% to 36%. Two studies (Levitan *et al.*, 2007;Van Dam *et al.*, 2000) reported risk estimates close to 1 and therefore no evidence of an association between GI and fatal and fatal or non-fatal CHD events.

Exposure definition and assessment

Four cohorts estimated GI using FFQ data; The Blue Mountains Eye study (Kaushik *et al.*, 2009), Prospect-EPIC Utrecht study (Beulens *et al.*, 2007), the NHS (Liu *et al.*, 2000b) and the Cohort of Swedish Men (Levitan *et al.*, 2007). The Zutphen Elderly study (Van Dam *et al.*, 2000) estimated glycaemic index using a dietary history.

Adjustment for appropriate confounders

All studies provided risk estimates adjusted for an appropriate range of covariates, including age, BMI, gender (where relevant) and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.61 Coronary events and glycaemic index: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
**13475 (Beulens *et al.*, 2007) Prospect-EPIC Utrecht	The Netherlands, No CHD, No T2DM	49-70 %M 0	(556) /17357	9 y (10)	FFQ (178)	GI	Fatal + Non-fatal Events	CHD events Registry data		Q4 vs. Q1		1.33 (1.07, 1.67)	0.02	Age, alcohol, BMI, smoking, physical activity, hypercholesterolaemia, hypertension, menopausal status, nutrient intake, oral contraceptive pill, SBP
13490 Prospect-EPIC Utrecht			(cases not reported;) /17357						BMI <25	Q4 vs. Q1		1.36 (0.97, 1.92)	0.19	As above
13491 Prospect-EPIC Utrecht			(cases not reported;) /17357						BMI >25	Q4 vs. Q1		1.31 (0.97, 1.76)	0.06	As above
**13349 (Kaushik *et al.*, 2009) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49-(65) %M 44	(95) /3654	13 y	FFQ (145)	GI (Energy adjusted)	Fatal Events	CHD events Registry data		(60.6) vs. (52.4)	Units	1.91 (1.01, 3.47)	0.04	Age, BMI, DBP, education,MI, stroke, DM, self-rated health status, gender, smoking, SBP, hypertension medication
13353 Blue Mountains Eye Study			(Cases not reported) /3654			GI and cereal fibre composite score	Fatal Events	CHD events Registry data		Rest of group vs. Lowest GI tertile and highest cereal fibre		1.03 (0.74, 1.45)		As above
14689 (Liu *et al.*, 2000b) NHS	USA, No T2DM, Without angina or heart attack	38-63 %M 0	(761) /75521	10 y (2)	FFQ (126)	GI (Energy adjusted score)	Fatal + Non-fatal Events	Fatal CHD + non-fatal MI Medical records/ autopsy		Q5 vs. Q1	score	1.31 (1.02, 1.68)		Age, alcohol, aspirin, BMI, energy intake, Fibre, folate, hypercholesterolaemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements, Vit E
*14087 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(1324) /48850	5 y (0)	FFQ (96)	GI	Fatal Events	MI Registry data		(82.9) vs. (73)	units/d	0.99 (0.84, 1.17)	0.93	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, energy intake, family history of HTN, family history of MI, marital status, physical activity, PUFA, SFA
**13919 (Van Dam *et al.*, 2000) Zutphen Elderly Study	The Netherlands, No CHD, No T2DM	64-84 %M 100	(94) /646	10 y (0.15)	Dietary history	GI (Energy adjusted)	Fatal + Non-fatal Events	Coronary heart disease death, Nonfatal MI Ascertained using multiple methods		(85) vs. (77)		1.11 (0.66, 1.87)	0.7	Age, alcohol, BMI, carbohydrate intake, energy intake, physical activity, PUFA, prescribed diet, saturated fatty acid intake, smoking

*This result was used in the meta-analysis of GI and CHD events/ **This result was used in the meta-analysis of GI and CHD events plus any CVD event

Stroke events and glycaemic index

Summary of cohort results

Data were extracted from three studies: the Cohort of Swedish Men (Levitan *et al.*, 2007), the Blue Mountains Eye Study (Kaushik *et al.*, 2009) and the NHS (Oh *et al.*, 2005). These studies provided evidence concerning the association between the glycaemic index of the diet and fatal and non-fatal stroke including any stroke, ischaemic and haemorrhagic stroke. The Blue Mountains Eye Study (Kaushik *et al.*, 2009) showed a significantly increased risk (91%) for any stroke when comparing a high GI diet to a low GI diet. All other relative risk scores were closer to 1 and non-significant with no significant p values for trend reported.

Exposure definition and assessment

The three studies all used FFQs to assess the glycaemic index of the diet. The FFQs used had 96 (Levitan *et al.*, 2007), 116 (Oh *et al.*, 2005) and 145 (Kaushik *et al.*, 2009) items.

Adjustment for appropriate confounders

The Cohort of Swedish Men (Levitan *et al.*, 2007) adjusted for a number of appropriate covariates including age, BMI and smoking. The other two studies adjusted for these factors and a number of other health-related variables.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.62 Stroke events and glycaemic index: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
13352 (Kaushik *et al.*, 2009) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49-(65) %M 44	(95) /3654	13 y	FFQ (145)	GI and cereal fibre composite score	Fatal Events	Stroke, any Registry data		Rest of group vs. Lowest GI tertile and highest cereal fibre		1.83 (0.83, 4.02)		Age, BMI, DBP, education,MI, stroke, DM, self-rated health status, gender, smoking, SBP, hypertension medication
**13348 Blue Mountains Eye Study						GI (Energy adjusted)	Fatal Events	Stroke, any Registry data		(60.6) vs. (52.4)	Units	1.91 (1.01, 3.47)	0.04	As above
14088 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(692) /48850	5 y (0)	FFQ (96)	GI	Fatal Events	Stroke, ischaemic Registry data		(82.9) vs. (73)	units/d	1.09 (0.85, 1.38)	0.67	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, SFA energy intake, family history of HTN, family history of MI, PUFA, marital status, physical activity,
*14089 Cohort of Swedish Men			(165) /48850					Stroke, haemorrhagic		(82.9) vs. (73)	units/d	1.19 (0.77, 1.83)	0.49	Age, BMI, cereal fibre, smoking, education, energy intake, family history of HTN, PA
**13440 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	GI	Fatal + Non-fatal Events	Stroke, any Ascertained using multiple methods		(80.3) vs. (68)	Units	0.98 (0.8, 1.2)	0.98	Age, alcohol, aspirin, BMI, energy intake, energy from cereal fibre, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, Vit intake postmenopausal HRT,
13501 NHS			(528)						BMI <25	Q5 vs. Q1		0.9 (0.67, 1.18)	0.37	As above
13502 NHS			(492)						BMI >25	Q5 vs. Q1		1.12 (0.83, 1.52)	0.26	As above
13442 NHS			(279)					Stroke, haemorrhagic		(80.3) vs. (68)	Units	1.06 (0.73, 1.53)	0.87	As above
13505 NHS			(178)						BMI <25	Q5 vs. Q1		0.98 (0.64, 1.51)	0.87	As above
13506 NHS			(101)						BMI >25	Q5 vs. Q1		1.27 (0.62, 2.6)	0.54	As above
13441 NHS			(515)					Stroke, ischaemic		(80.3) vs. (68)	Units	1.05 (0.78, 1.4)	0.62	As above
13503 NHS			(259)						BMI <25	Q5 vs. Q1		0.84 (0.56, 1.26)	0.42	As above
13504 NHS			(256)						BMI >25	Q5 vs. Q1		1.39 (0.91, 2.12)	0.09	As above

*This result was used in the meta-analysis of glycaemic index and stroke events

**This result was used in the meta-analysis of glycaemic index and stroke events plus any CVD event

Summary of glycaemic index and CVD

Meta-analysis: Glycaemic index and incident CVD events

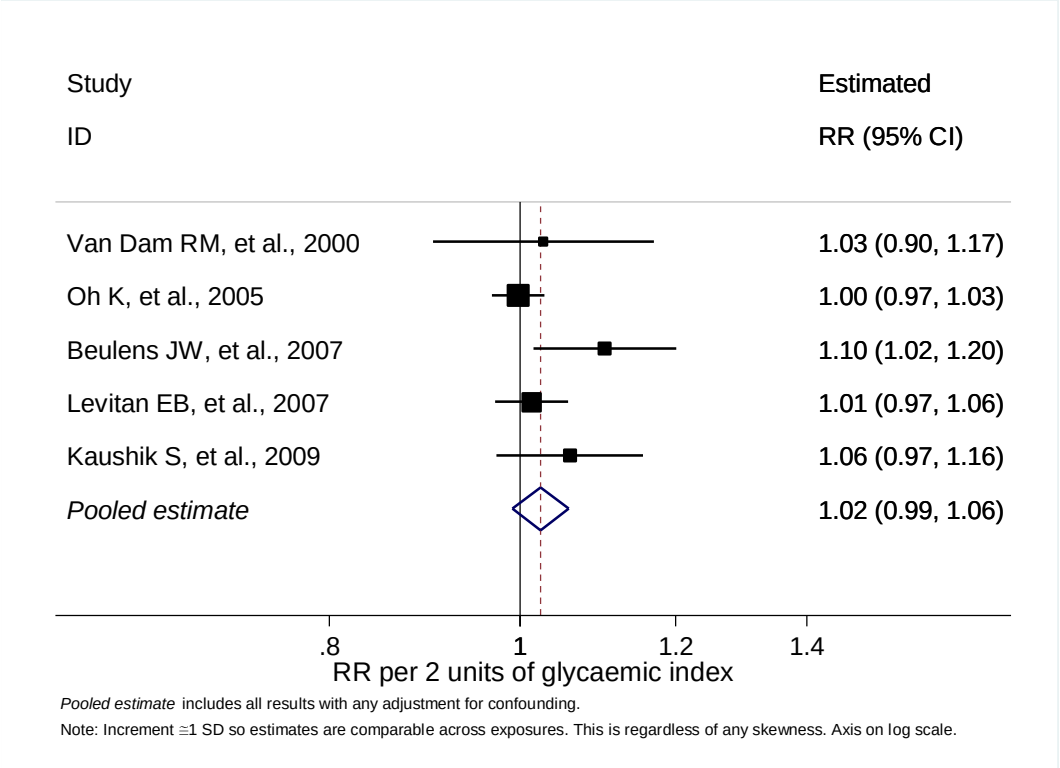
Data were extracted from 6 publications presenting results from 5 cohort studies, namely EPIC-Potsdam Utrecht, the NHS, the Cohort of Swedish Men, the Blue Mountains Eye Study and the Zutphen Elderly Study (Beulens *et al.*, 2007;Levitan *et al.*, 2007;Oh *et al.*, 2005;Kaushik *et al.*, 2009;Liu *et al.*, 2000b;Van Dam *et al.*, 2000). Of these, 1 publication (Liu *et al.*, 2000b) was an early analysis of data presented more fully in a later publication (Oh *et al.*, 2005). All remaining publications contributed information to the dose-response meta-analysis.

For one paper (Kaushik *et al.*, 2009), the CHD and stroke events were first combined before they could be included in the analysis of any CVD. For Beulens *et al.* (Beulens *et al.*, 2007), the quartile mean score of glycaemic load divided by the total carbohydrates in grams, was used as an estimate of the mean glycaemic index in each category.

Combining all studies reporting any CVD outcome in one meta-analysis, the pooled estimate of relative risk from the cohort studies was 1.02 (95% CI: 0.99 to 1.06) per 2 units of glycaemic index (p=0.07).

Relative risks are presented for every 2 GI unit increment (equivalent to approximately one standard deviation) in glycaemic index. The approximate mean UK population dietary GI value is 55 GI units. These figures are based on published UK and European data from the EPIC study (van Bakel *et al.*, 2009).

Figure 1.19 Forest plot for glycaemic index and total CVD events



There was little heterogeneity between the cohort studies (I^2=34%, 95% CI: 0% to 75%, Q=6.1, df=4, p=0.2). There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression for all CVD outcomes combined, but not for CHD or stroke (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 1.63 Subgroup analyses of glycaemic index and incidence of any CVD. Relative risks are per 2 GI units.

Subgroup	subgroup	RR (95% CI)	I^2	n	P_{het} *	P_{het} **
subjects' gender	Male	1.02 (0.98, 1.06)	0%	2	.8	.9
	Mixed	1.06 (0.97, 1.16)		1		
	Female	1.04 (0.94, 1.15)	80%	2	.03	
standard used to derive GI values	glucose	1.08 (1.02, 1.15)	0%	2	.5	
	white bread	1.00 (0.98, 1.03)	0%	3	.8	
	not stated			0		.1
median glycaemic index	<=60	1.08 (1.02, 1.15)	0%	2	.5	.1
	>60	1.00 (0.98, 1.03)	0%	3	.8	
includes non-fatal events	yes	1.02 (0.98, 1.06)	0%	2	.4	
	no	1.04 (0.97, 1.11)	60%	3	.08	1
length of follow-up	<10 years	1.05 (0.97, 1.14)	68%	2	.07	
	>=10 years	1.01 (0.98, 1.04)	0%	3	.4	.6
geographic location	Americas	1.00 (0.97, 1.03)		1		
	EU	1.04 (0.99, 1.10)	37%	3	.2	
	Other	1.06 (0.97, 1.16)		1		.9
adjusted for age	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		
adjusted for alcohol	yes	1.02 (0.98, 1.06)	40%	4	.2	
	no	1.06 (0.97, 1.16)		1		.5
adjusted for anthropometry	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		
adjusted for energy intake	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		
adjusted for family history	yes	1.00 (0.98, 1.03)	0%	2	.6	
	no	1.07 (1.02, 1.13)	0%	3	.6	.1
adjusted for physical activity	yes	1.02 (0.98, 1.06)	40%	4	.2	
	no	1.06 (0.97, 1.16)		1		.5
adjusted for gender	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		
adjusted for smoking	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		
adjusted for age & smoking	yes	1.02 (0.99, 1.06)	34%	5	.2	
	no			0		

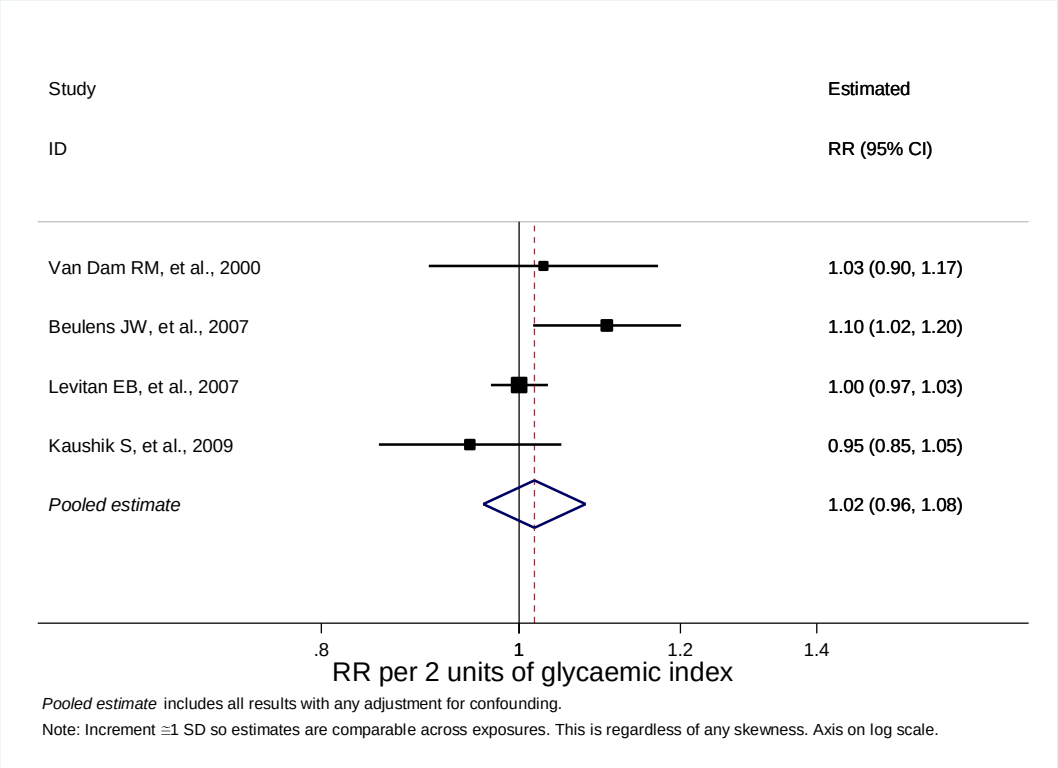
* P for heterogeneity within each subgroup

** P for heterogeneity between each subgroup

There were too few studies to explore any small study effects (such as publication bias) using funnel plots.

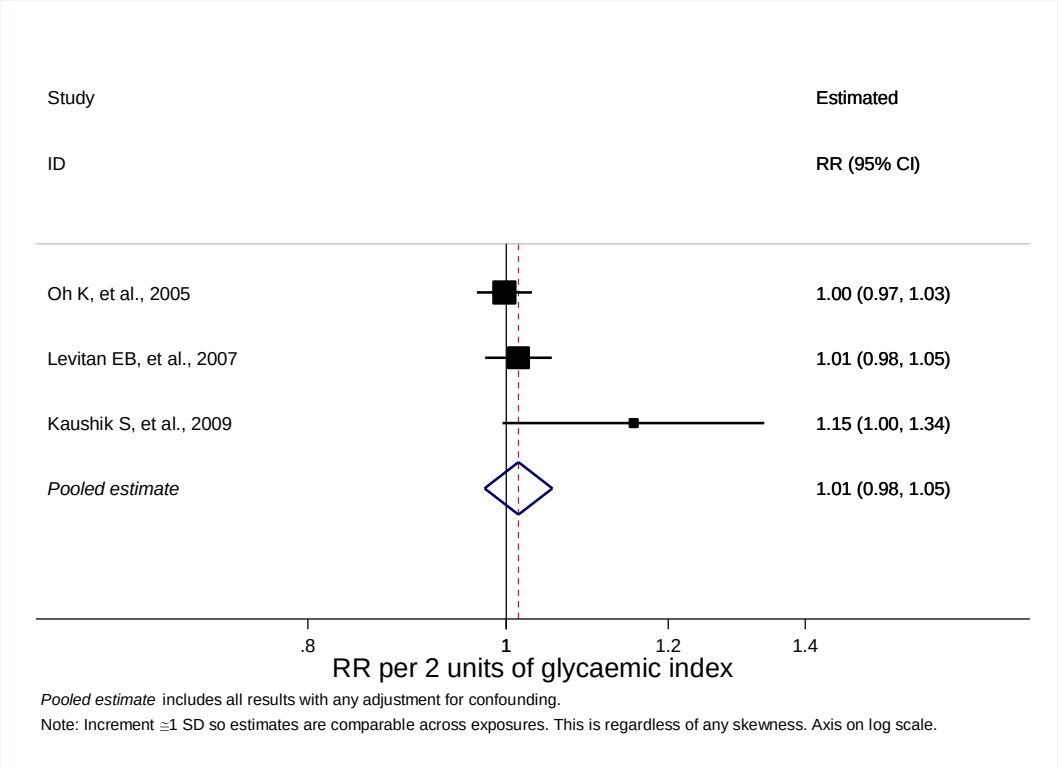
There was no evidence of any association between glycaemic index and CHD, with RR=1.02 per 2 units of glycaemic index for CHD (95% CI: 0.96 to 1.08), but heterogeneity did not improve by stratifying on outcome (I^2=53%). Levitan *et al* had a strong influence on the CHD outcome, but only presented results for MI (Levitan *et al.*, 2007). This may be one possible source of the heterogeneity within the CHD analysis.

Figure 1.20 Forest plot for glycaemic index and CHD events



There was no evidence of any association with stroke, (RR=1.01 per 2 GI units, 95% CI: 0.98 to 1.05, I^2=46%).

Figure 1.21 Forest plot for glycaemic index and stroke events



There were insufficient studies to explore these disease-specific analyses further.

Glycaemic load and CVD

The glycaemic load (GL) is the product of a specific food's GI and its carbohydrate content (Liu *et al.*, 2000b), therefore taking into account both the quality and quantity of carbohydrate consumed. This may be interpreted as a measure of diet-induced insulin demand (Stevens *et al.*, 2002).

Total CVD and glycaemic load

Summary of cohort results

One Swedish cohort study provided data on the association between total CVD and glycaemic load (Levitan *et al.*, 2007). In the Cohort of Swedish Men study, dietary GL was not associated with cardiovascular mortality.

Dietary GL was estimated from a 96-item FFQ administered once at study baseline and the result was appropriately adjusted.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.64 Total CVD and glycaemic load: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Assessment/ Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Contrast (mean)	RR (CI)	p trend	Adjustments
*14112 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(785) /48850	5 y (0)	96-item FFQ GL	Fatal Events	Total CVD Registry data	(250) vs. (180) units/day	1.13 (0.81, 1.56)	0.39	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, energy intake, family history of HTN, family history of MI, marital status, physical activity, PUFA, SFA

*This result was used in the meta-analysis of glycaemic load and any CVD event

Coronary events and glycaemic load

Summary of cohort results

Data were extracted from four papers presenting results from three cohort studies: the Cohort of Swedish Men (Levitan *et al.*, 2007), Prospect-EPIC Utrecht study (Beulens *et al.*, 2007) and two references from the NHS, one with a follow up of 10 years (Liu *et al.*, 2000b) and one of 20 years (Halton *et al.*, 2006). These studies provided evidence concerning the association between glycaemic load and fatal and non-fatal coronary events including myocardial infarction, unspecified coronary heart disease events and coronary heart disease death. Glycaemic load was either reported simply as glycaemic load or energy adjusted glycaemic load. All results from the Prospect-EPIC Utrecht study (Beulens *et al.*, 2007) and the NHS (Liu *et al.*, 2000b;Halton *et al.*, 2006) show an increase risk of coronary heart disease events with increasing glycaemic load, with four out of six results showing a significantly increased risk of between 47% (Beulens *et al.*, 2007) and 98% (Liu *et al.*, 2000b). Additionally, all four of these results have a significant p for trend. The two remaining results from these studies showing non-significant increased risks are in subgroups of people with a healthy BMI (Liu *et al.*, 2000b;Beulens *et al.*, 2007). The Cohort of Swedish Men (Levitan *et al.*, 2007) showed no association between glycaemic load and fatal myocardial infarction.

Exposure definition and assessment

All studies used FFQs to assess the glycaemic load of the diet with 96 (Levitan *et al.*, 2007), 122 (Halton *et al.*, 2006), 126 (Liu *et al.*, 2000b) and 178 (Beulens *et al.*, 2007) items.

Adjustment for appropriate confounders

All four references adjust for an appropriate range of covariates including age, BMI and smoking.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.65 Coronary events and glycaemic load: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
**13467 (Beulens *et al.*, 2007) Prospect-EPIC Utrecht	The Netherlands, No CHD, No T2DM	49-70 %M 0	(556) /17357	9 y (10)	FFQ (178)	GL	Fatal + Non-fatal Events	CHD events Registry data		(121.8) vs. (78.5)	score	1.47 (1.04, 2.09)	0.03	Age, alcohol, BMI, smoking, physical activity, hypercholesterolaemia, hypertension, menopausal status, nutrient intake, oral contraceptive pill, SBP
13487 Prospect-EPIC Utrecht			(Subgroup cases not reported;) /17357						BMI <25	(121.8) vs. (78.5)	score	1.14 (0.67, 1.93)	0.43	As above
13489 Prospect-EPIC Utrecht			(Subgroup cases not reported;) /17357						BMI >25	(121.8) vs. (78.5)	score	1.78 (1.11, 2.85)	0.04	As above
17565 (Halton *et al.*, 2006) NHS	USA, Primarily White, No T2DM, No CVD	30-55 %M 0	(1994) /82802	20 y	FFQ (122)	GL	Fatal + Non-fatal Events	Coronary heart disease death, Nonfatal MI Ascertained using multiple methods		Q10 vs. Q1	units	1.9 (1.15, 3.15)	0.003	Age, alcohol, aspirin, BMI, cereal fibre, fat intake, HRT, hypercholesterol-aemia, hypertension, parental CHD, physical activity, protein intake, smoking, supplements
*14102 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(1324) /48850	5 y (0)	FFQ (96)	GL	Fatal Events	MI Registry data		(250) vs. (180)	units/d	1.04 (0.8, 1.34)	0.65	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, energy intake, family history of HTN, family history of MI, marital status, physical activity, PUFA, SFA
*14629 (Liu *et al.*, 2000b) NHS	USA, No T2DM, Without angina or heart attack	38-63 %M 0	(761) /75521	10 y (2)	FFQ (126)	GL (Energy adjusted score)	Fatal + Non-fatal Events	Fatal CHD + Non-fatal MI Medical records/ autopsy		(206) vs. (117)	score	1.98 (1.41, 2.77)	0.0001	Age, alcohol, aspirin, BMI, energy intake, fat intake, Fibre, folate, Hypercholesterol-aemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements, Vit E

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14683 NHS							Fatal + Non-fatal Events	CHD events Medical records/ autopsy	BMI <23	Q3 vs. Q1	Score	1.11 (0.74, 1.66)		Age, alcohol, aspirin, BMI, energy intake, Fibre, folate, hypercholesterolaemia, hypertension, menopausal status, physical activity, parental CHD, protein intake, smoking, supplements, Vit E

*This result was used in the meta-analysis of glycaemic load and any CHD events

**This result was used in the meta-analysis of glycaemic load and any CHD event plus any CVD event

Stroke events and glycaemic load

Summary of cohort results

Data were extracted from two studies: the Cohort of Swedish Men (Levitan *et al.*, 2007) and the NHS (Oh *et al.*, 2005). These studies provided evidence concerning the association between glycaemic load and fatal and non-fatal stroke including any stroke, ischaemic and haemorrhagic stroke. The Cohort of Swedish Men (Levitan *et al.*, 2007) showed no association between glycaemic load and fatal haemorrhagic or ischaemic stroke. The NHS (Oh *et al.*, 2005) showed a 61% increased risk of any stroke when high glycaemic load was compared to low glycaemic load in participants with a BMI greater than 25kg/m^2. There was also a significant p for trend for this association. This association was not seen in the subgroup of participants with a BMI below 25. Additionally there was no significant association between glycaemic load and any, haemorrhagic or ischaemic stroke when the whole cohort was analysed or with haemorrhagic and ischaemic stroke in the BMI<25 and BMI>25 subgroups.

Exposure definition and assessment

Both studies used FFQs to assess the glycaemic load of the diet with 96 (Levitan *et al.*, 2007) and 116 (Oh *et al.*, 2005) items.

Adjustment for appropriate confounders

The Cohort of Swedish Men (Levitan *et al.*, 2007) adjusted for a number of appropriate factors including age, BMI and smoking. The NHS (Oh *et al.*, 2005) adjusted for these covariates and a number of other health-related variables.

Please interpret observational data with caution: With observational studies there is substantial potential for biases.

Table 1.66 Stroke events and glycaemic load: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess-ment	Exposure	Fatal / Non-fatal Events	Outcome/ Assessment Details	Subgroup Detail	Contrast (mean)	Units	RR (CI)	p trend	Adjustments
14111 (Levitan *et al.*, 2007) Cohort of Swedish Men	Sweden, Cancer free, No CHD, No T2DM	45-79 %M 100	(165) /48850	5 y (0)	FFQ (96)	GL	Fatal Events	Stroke, haemorrhagic Registry data		(250) vs. (180)	units	1.44 (0.91, 2.27)	0.047	Age, BMI, cereal fibre, smoking, education, energy intake, family history of HTN, PA
14103 Cohort of Swedish Men			(692) /48850					Stroke, ischaemic Registry data		(250) vs. (180)	units	1.05 (0.74, 1.49)	0.76	Age, alcohol, aspirin, BMI, carbohydrate intake, cereal fibre, smoking, education, energy intake, family history of HTN, family history of MI, marital status, physical activity, PUFA, saturated fatty acid intake
*13443 (Oh *et al.*, 2005) NHS	USA, Primarily White, No CHD, No T2DM	30-55 %M 0	(1020) /121700	18 y	FFQ (116)	GL	Fatal + Non-fatal Events	Stroke, any Multiple methods		(166.8) vs. (96.4)	Units	1.23 (0.98, 1.53)	0.08	Age, alcohol, aspirin, BMI, energy intake, energy from cereal fibre, family history of DM, family history of hypertriglycerideaemia, family history of HTN, family history of MI, menopausal status, physical activity, smoking, postmenopausal HRT, Vit intake
13507 NHS			(528)						BMI <25	Q5 vs. Q1		1.03 (0.76, 1.38)	0.93	As above
13508 NHS			(492)						BMI >25	Q5 vs. Q1		1.61 (1.15, 2.27)	0.01	As above
13445 NHS			(279)					Stroke, haemorrhagic Ascertained using multiple methods		(166.8) vs. (96.4)	Units	1.23 (0.81, 1.89)	0.31	As above
13511 NHS			(178)						BMI <25	Q5 vs. Q1		1.07 (0.64, 1.81)	0.81	As above
13512 NHS			(101)						BMI >25	Q5 vs. Q1		1.69 (0.81, 3.56)	0.13	As above
13444 NHS			(515)					Stroke, ischaemic Ascertained using multiple methods		(166.8) vs. (96.4)	Units	1.23 (0.98, 1.53)	0.87	As above
13509 NHS			(259)						BMI <25	Q5 vs. Q1		0.88 (0.57, 1.36)	0.42	As above
13510 NHS			(256)						BMI >25	Q5 vs. Q1		1.56 (0.96, 2.54)	0.11	As above

*This result was used in the meta-analysis of glycaemic load and any CVD event

Summary of glycaemic load and CVD

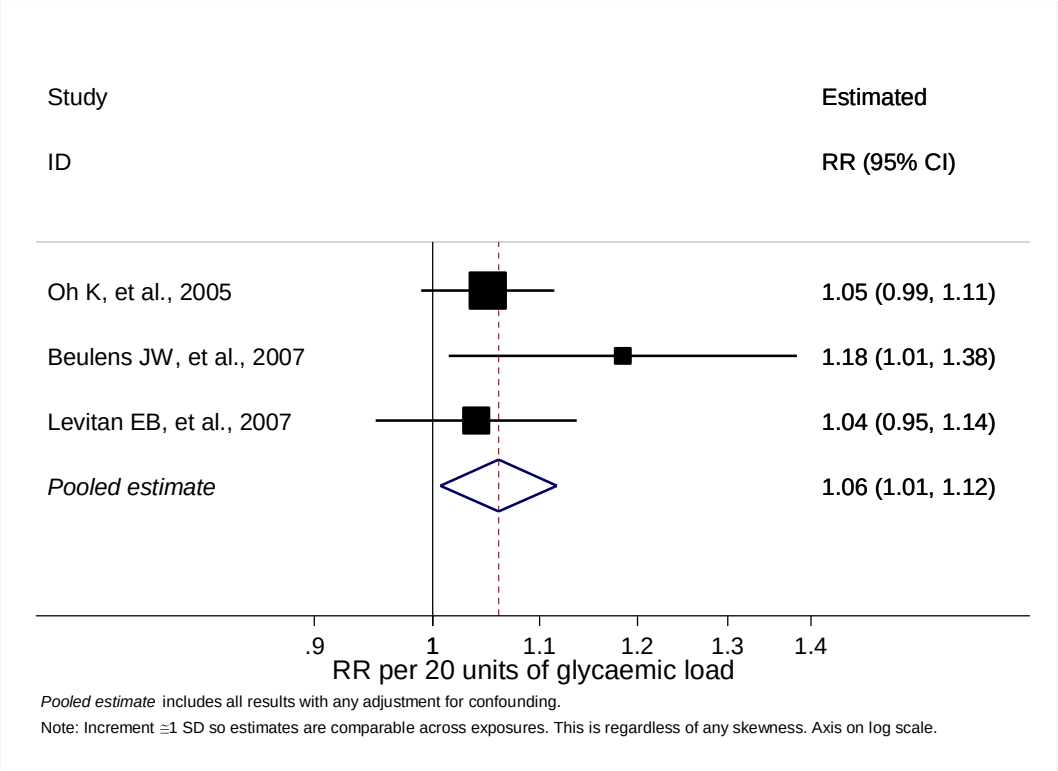
Meta analysis: Glycaemic load and incident CVD events

Data were extracted from 5 publications presenting results from 3 cohort studies conducted in the USA, Sweden and the Netherlands (Beulens *et al.*, 2007;Levitan *et al.*, 2007;Halton *et al.*, 2006;Oh *et al.*, 2005;Liu *et al.*, 2000b). Of these, one publication from the NHS (Liu *et al.*, 2000b) was an early analysis (10 year follow-up) of data presented more fully in a later publication (18 year follow-up) (Oh *et al.*, 2005). Another publication from the NHS was a later analysis of data presented in that publication (20 year follow-up), but did not include enough detail for inclusion in dose-response meta-analysis (Halton *et al.*, 2006), so the middle publication (18 year follow-up) was used (Oh *et al.*, 2005). All remaining publications, those from the NHS (Oh *et al.*, 2005), Prospect-EPIC Utrecht (Beulens *et al.*, 2007) and the Cohort of Swedish Men (Levitan *et al.*, 2007), contributed information to the dose-response meta-analysis.

Combining all studies reporting any CVD outcomes in one meta-analysis, the pooled estimate of relative risk from the cohort studies was 1.06 (95% CI: 1.01 to 1.12) per 20 units of GL (p=0.03).

Relative risks are presented for every 20 GL unit increase, equivalent to approximately one standard deviation, in glycaemic load. The approximate population mean GL is 120 units. These figures are based on published UK and European data from the EPIC study (van Bakel *et al.*, 2009).

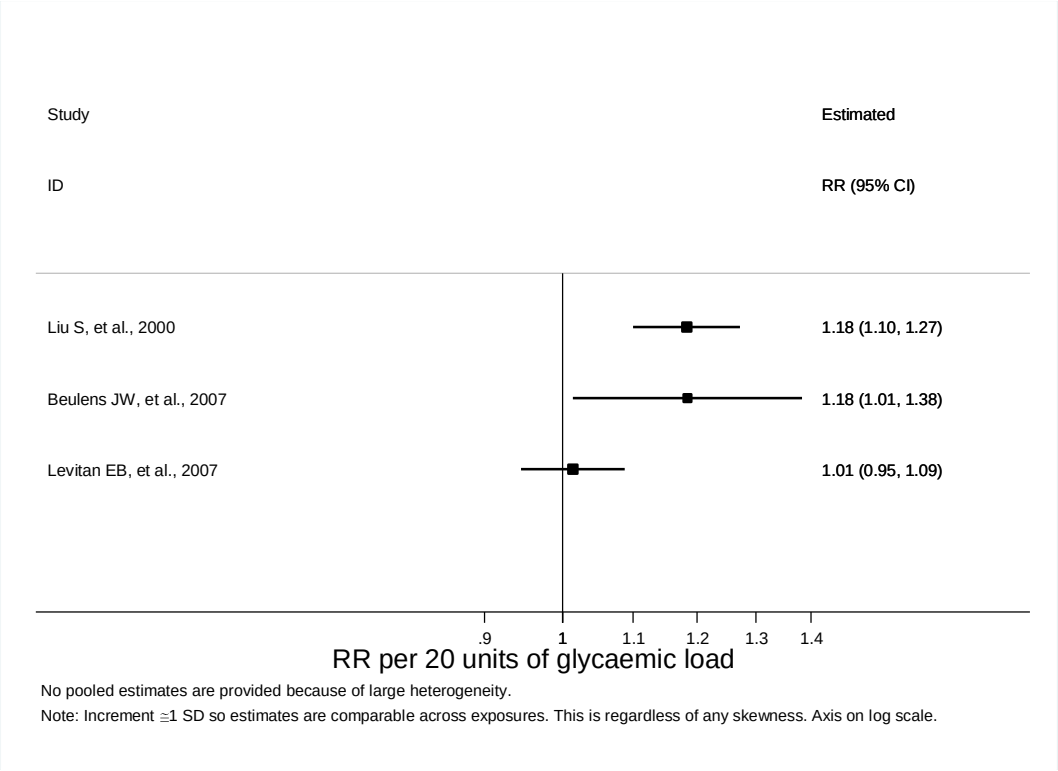
Figure 1.22 Forest plot for glycaemic load and total CVD events



There was little heterogeneity between the cohort studies (I^2=11%, 95% CI: 0% to 91%, Q=2.2, df=2, p=0.3). There were too few studies to explore sources of heterogeneity using subgroup analysis or meta-regression or to explore any small study effects such as publication bias.

Including CHD and stroke separately, one publication that was excluded earlier to avoid duplication could be included for CHD (Liu *et al.*, 2000b). The pooled estimate of relative risk for CHD from the cohort studies is not presented though, because the substantial heterogeneity makes it unreliable (I^2=80%, 95% CI: 36% to 94%).

Figure 1.23 Forest plot for glycaemic load and CHD events

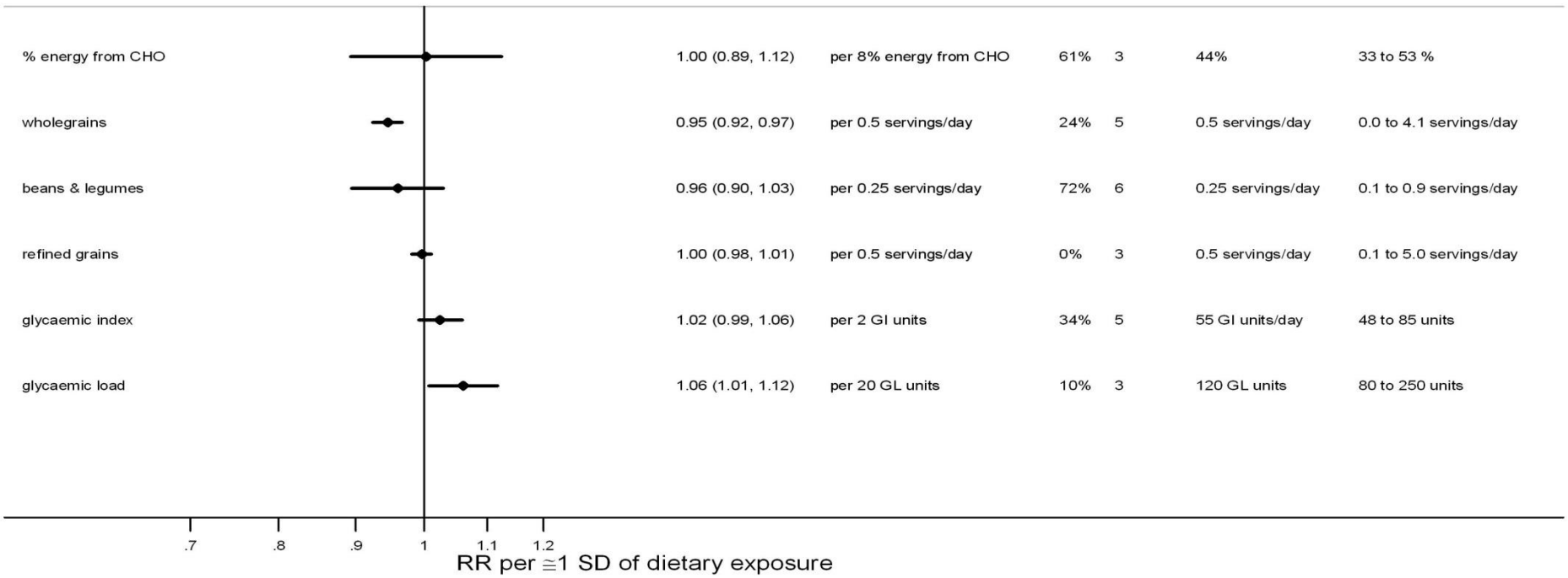


There were insufficient studies of CHD to investigate the potential sources of this heterogeneity using subgroup analysis or meta-regression. However, Levitan *et al*. had a strong influence on the CHD outcome, but only presented results for MI (Levitan *et al.*, 2007). This may be one possible source of the heterogeneity within the CHD analysis.

Pooled estimate plots for CVD

The following section includes all the calculated pooled risk estimates from previous sections. These have been plotted together to give an over-arching picture of the relationship of various carbohydrate exposures for any or total CVD, coronary events and stroke events. Please refer back to previous sections for further detail on each point estimate to aid interpretation of these pooled results. Please also refer back to the methods for justification of the size of increments used, approximating one standard deviation for each exposure, so the point estimates for each exposure are on comparable scales.

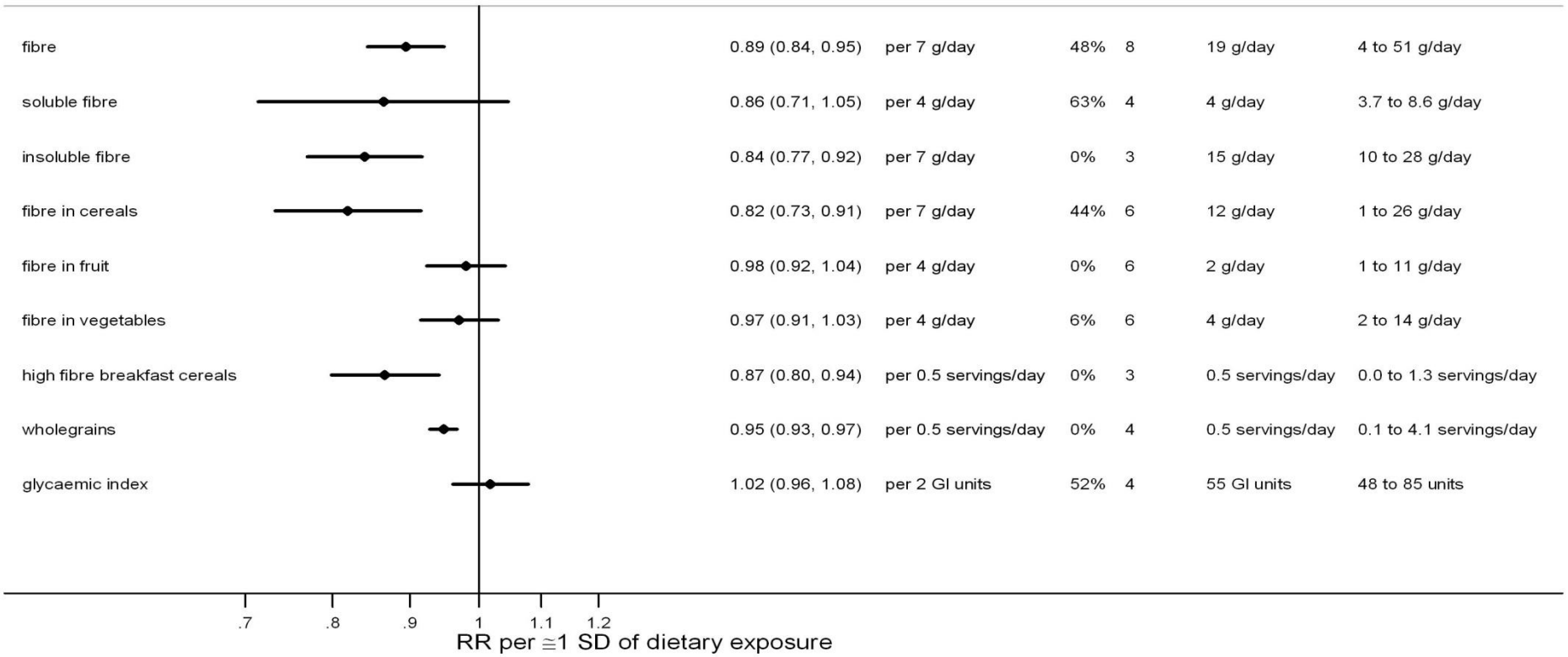
Pooled estimates for any CVD event



Exposure	RR (95% CI)	Increment	I^2	No. of studies	Mean intake in UK	Range of intakes in meta-analysis *
% energy from CHO	1.00 (0.89, 1.12)	per 8% energy from CHO	61%	3	44%	33 to 53 %
wholegrains	0.95 (0.92, 0.97)	per 0.5 servings/day	24%	5	0.5 servings/day	0.0 to 4.1 servings/day
beans & legumes	0.96 (0.90, 1.03)	per 0.25 servings/day	72%	6	0.25 servings/day	0.1 to 0.9 servings/day
refined grains	1.00 (0.98, 1.01)	per 0.5 servings/day	0%	3	0.5 servings/day	0.1 to 5.0 servings/day
glycaemic index	1.02 (0.99, 1.06)	per 2 GI units	34%	5	55 GI units/day	48 to 85 units
glycaemic load	1.06 (1.01, 1.12)	per 20 GL units	10%	3	120 GL units	80 to 250 units

Note: Increments are chosen to approximate 1 standard deviation so that estimates are comparable across exposures. Axis on log scale.
* The reported range of intakes included in meta-analyses is taken to be from the lowest category mean or midpoint up to the highest.

Pooled estimates for coronary events



Exposure	RR (95% CI)	Increment	I^2	No. of studies	Mean intake in UK	Range of intakes in meta-analysis *
fibre	0.89 (0.84, 0.95)	per 7 g/day	48%	8	19 g/day	4 to 51 g/day
soluble fibre	0.86 (0.71, 1.05)	per 4 g/day	63%	4	4 g/day	3.7 to 8.6 g/day
insoluble fibre	0.84 (0.77, 0.92)	per 7 g/day	0%	3	15 g/day	10 to 28 g/day
fibre in cereals	0.82 (0.73, 0.91)	per 7 g/day	44%	6	12 g/day	1 to 26 g/day
fibre in fruit	0.98 (0.92, 1.04)	per 4 g/day	0%	6	2 g/day	1 to 11 g/day
fibre in vegetables	0.97 (0.91, 1.03)	per 4 g/day	6%	6	4 g/day	2 to 14 g/day
high fibre breakfast cereals	0.87 (0.80, 0.94)	per 0.5 servings/day	0%	3	0.5 servings/day	0.0 to 1.3 servings/day
wholegrains	0.95 (0.93, 0.97)	per 0.5 servings/day	0%	4	0.5 servings/day	0.1 to 4.1 servings/day
glycaemic index	1.02 (0.96, 1.08)	per 2 GI units	52%	4	55 GI units	48 to 85 units

Note: Increments are chosen to approximate 1 standard deviation so that estimates are comparable across exposures. Axis on log scale.
* The reported range of intakes included in meta-analyses is taken to be from the lowest category mean or midpoint up to the highest.

Pooled estimates for stroke events

Exposure	RR (95% CI)	Increment	I^2	No. of studies	Mean intake in UK	Range of intakes in meta-analysis *
fibre	0.95 (0.89, **1.01)**	per 7 g/day	63%	4	19 g/day	10 to 36 g/day
wholegrains	0.96 (0.93, 0.99)	per 0.5 servings/day	23%	3	0.5 servings/day	0.0 to 4.1 servings/day
glycaemic index	1.01 (0.98, 1.05)	per 2 GI units	46%	3	55 GI units	52 to 83 units

Note: Increments are chosen to approximate 1 standard deviation so that estimates are comparable across exposures. Axis on log scale.
* The reported range of intakes included in meta-analyses is taken to be from the lowest category mean or midpoint up to the highest.

References

Allender, S., Scarborough, P., Peto, V., Rayner, M., Leal, J., Luengo-Fernandez, R, and Gray, A. European Cardiovascular Disease Statistics 2008. 2008. Brussels, European Heart Network.

American Association of Cereal Chemists International. AACC members agree on definition of whole grain. 1999. 11-9-2011.

American Heart Association. American Heart Association. Cardiovascular Disease Statistics online. 2011. 5-5-2011.

Appleby PN, Thorogood M, Mann JI, Key TJ (1999) The Oxford Vegetarian Study: an overview. *Am J Clin Nutr* **70** (3:Suppl): Suppl-531S

Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC (1998) Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* **98** (12): 1198-1204

Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC (2007) Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. *Diabetes Care* **30** (11): 2811-2813

Bates, B., Lennox, A, and Swan, G. National Diet and Nutrition Survey: Headline results from Year 1 of the rolling programme. [Online]. 2009. 21-2-2011.

Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK (2001) Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. *Arch Intern Med* **161** (21): 2573-2578

Bazzano LA, He J, Ogden LG, Loria CM, Whelton PK, National Health and Nutrition Examination Survey (2003) Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Intern Med* **163** (16): 1897-1904

Bennett K, Kabir Z, Unal B, Shelley E, Critchley J, Perry I, Feely J, Capewell S (2006) Explaining the recent decrease in coronary heart disease mortality rates in Ireland, 1985-2000. *J Epidemiol Community Health* **60** (4): 322-327, doi:60/4/322 [pii];10.1136/jech.2005.038638 [doi]

Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT (2007) High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. *J Am Coll Cardiol* **50** (1): 14-21

Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S (2009) Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J* **30** (9): 1046-1056, doi:ehn554 [pii];10.1093/eurheartj/ehn554 [doi]

Bonow ROM, Mann DLMF, Zipes DPM, Libby PM (2011) *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Elsevier - Health Sciences Division:

Brainin M, Heiss WD (2009) *Textbook of Stroke Medicine*. Cambridge University Press: Cambridge, United Kingdom

British Heart Foundation. www.heartstats.org. 2010. 20-1-2010.

British Nutrition Foundation (1990) *Complex carbohydrates in foods: report of the British Nutrition Foundation's Task Force.* Chapman and Hall: London

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM (1989) Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* **2** (8666): 757-761, doi:S0140-6736(89)90828-3 [pii]

Capewell, S., Allender, S., Critchley, J., Lloyd-Williams, F., O'Flaherty, M., Rayner, M., and Scarborough, P. Modelling the UK burden of Cardiovascular Disease to 2020. 2008. London, British Heart Foundation.

Capewell S, Morrison CE, McMurray JJ (1999) Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart* **81** (4): 380-386

Committee on Medical Aspects of Food Policy (1989) *Dietary Sugars and Human Disease*. London, HMSO

Committee on Medical Aspects of Food Policy (1991) *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. HMSO: London

Committee on Medical Aspects of Food Policy (1994) *Nutritional aspects of cardiovascular disease*. HMSO: London

Department of Health (2000) *National Service Framework for Coronary Heart Disease*. The Stationary Office: London

Department of Health Coronary Heart Disease Policy Team (2008) *Coronary Heart Disease National Service Framework. Building for the future. Progress report 2007*. HMSO: London

Djousse L, Driver JA, Gaziano JM (2009) Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA* **302** (4): 394-400

Drogan D, Hoffmann K, Schulz M, Bergmann MM, Boeing H, Weikert C (2007) A food pattern predicting prospective weight change is associated with risk of fatal but not with nonfatal cardiovascular disease. *J Nutr* **137** (8): 1961-1967

Esrey KL, Joseph L, Grover SA (1996) Relationship between dietary intake and coronary heart disease mortality: lipid research clinics prevalence follow-up study. *J Clin Epidemiol* **49** (2): 211-216

Farchi G, Fidanza F, Grossi P, Lancia A, Mariotti S, Menotti A (1995) Relationship between eating patterns meeting recommendations and subsequent mortality in 20 years. *Eur J Clin Nutr* **49** (6): 408-419

Fehily AM, Yarnell JW, Butland BK (1987) Diet and ischaemic heart disease in the Caerphilly Study. *Hum Nutr Appl Nutr* **41** (5): 319-326

Fehily AM, Yarnell JW, Sweetnam PM, Elwood PC (1993) Diet and incident ischaemic heart disease: the Caerphilly Study. *Br J Nutr* **69** (2): 303-314

Food Standards Agency. Eat well. Be well. Heping you make healthier choices [accessed September 2011]. 27-9-2010.

Fraser GE, Sabate J, Beeson WL, Strahan TM (1992) A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* **152** (7): 1416-1424

Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB (2009) Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr* **89** (4): 1037-1042

Gale CP, Cattle BA, Moore J, Dawe H, Greenwood DC, West RM (2011a) Impact of missing data on standardised mortality ratios for acute myocardial infarction: evidence from the Myocardial Ischaemia National Audit Project (MINAP) 2004-7. *Heart*, doi:hrt.2010.204883 [pii];10.1136/hrt.2010.204883 [doi]

Gale CP, Cattle BA, Woolston A, Baxter P, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KAA, West RM (2011b) Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003 - 2010. *Eur Heart J*

Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB (2006) Low-carbohydrate-diet score and the risk of coronary heart disease in women. *New England Journal of Medicine* **355** (19): 1991-2002

Howard BV, Van HL, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM (2006) Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* **295** (6): 655-666

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Speizer FE, Hennekens CH, Willett WC (1999) Dietary protein and risk of ischemic heart disease in women. *Am J Clin Nutr* **70** (2): 221-227

Jacobs DR, Jr., Andersen LF, Blomhoff R (2007) Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women's Health Study. *Am J Clin Nutr* **85** (6): 1606-1614

Jacobs DR, Jr., Meyer HE, Solvoll K (2001) Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr* **55** (2): 137-143

Jacobs DR, Jr., Meyer KA, Kushi LH, Folsom AR (1998) Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr* **68** (2): 248-257

Jakobsen MU, Overvad K, Dyerberg J, Schroll M, Heitmann BL (2004) Dietary fat and risk of coronary heart disease: possible effect modification by gender and age. *Am J Epidemiol* **160** (2): 141-149

Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Gronbaek M, Rimm EB (2004) Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* **80** (6): 1492-1499

Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC (1999) Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* **282** (13): 1233-1239

Joshipura KJ, Hung HC, Li TY, Hu FB, Rimm EB, Stampfer MJ, Colditz G, Willett WC (2009) Intakes of fruits, vegetables and carbohydrate and the risk of CVD. *Public Health Nutr* **12** (1): 115-121

Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P (2009) Glycemic index, retinal vascular caliber, and stroke mortality. *Stroke* **40** (1): 206-212

Kelemen LE, Kushi LH, Jacobs DR, Jr., Cerhan JR (2005) Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol* **161** (3): 239-249

Key TJ, Thorogood M, Appleby PN, Burr ML (1996) Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. *British Medical Journal* **313** (7060): 775-779

Keys A (1971) Sucrose in the diet and coronary heart disease. *Atherosclerosis* **14** (2): 193-202

Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A (1994) Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol* **139** (12): 1180-1189

Kromhout D, Bosschieter EB, de Lezenne CC (1982) Dietary fibre and 10-year mortality from coronary heart disease, cancer, and all causes. The Zutphen study. *Lancet* **2** (8297): 518-522

Kushi LH, Lew RA, Stare FJ, Ellison CR, el LM, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, . (1985) Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. *N Engl J Med* **312** (13): 811-818, doi:10.1056/NEJM198503283121302 [doi]

Laaksonen DE, Nyyssonen K, Niskanen L, Rissanen TH, Salonen JT (2005) Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. *Arch Intern Med* **165** (2): 193-199

Laatikainen T, Critchley J, Vartiainen E, Salomaa V, Ketonen M, Capewell S (2005) Explaining the decline in coronary heart disease mortality in Finland between 1982 and 1997. *Am J Epidemiol* **162** (8): 764-773, doi:kwi274 [pii];10.1093/aje/kwi274 [doi]

Lagiou P, Sandin S, Weiderpass E, Lagiou A, Mucci L, Trichopoulos D, Adami HO (2007) Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J Intern Med* **261** (4): 366-374

Lang R, Thane CW, Bolton-Smith C, Jebb SA (2003) Consumption of whole-grain foods by British adults: findings from further analysis of two national dietary surveys. *Public Health Nutr* **6** (5): 479-484, doi:10.1079/PHN2002453 [doi];S136898000300065X [pii]

Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J (2009) Dietary fiber and fiber-rich food intake in relation to risk of stroke in male smokers. *Eur J Clin Nutr* **63** (8): 1016-1024

Levitan EB, Mittleman MA, Hakansson N, Wolk A (2007) Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. *Am J Clin Nutr* **85** (6): 1521-1526

Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE (2002) A prospective study of dietary fiber intake and risk of cardiovascular disease among women. *J Am Coll Cardiol* **39** (1): 49-56

Liu S, Manson JE, Stampfer MJ, Rexrode KM, Hu FB, Rimm EB, Willett WC (2000a) Whole grain consumption and risk of ischemic stroke in women: A prospective study. *JAMA* **284** (12): 1534-1540

Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC (1999) Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr* **70** (3): 412-419

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE (2000b) A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* **71** (6): 1455-1461

Liu S, Sesso HD, Manson JE, Willett WC, Buring JE (2003) Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr* **77** (3): 594-599

McGandy RB, Hegsted DM, Stare FJ (1967a) Dietary fats, carbohydrates and atherosclerotic vascular disease. *N Engl J Med* **277** (4): 186-192, doi:10.1056/NEJM196707272770405 [doi]

McGandy RB, Hegsted DM, Stare FJ (1967b) Dietary fats, carbohydrates and atherosclerotic vascular disease. *N Engl J Med* **277** (5): 245-247

Meyer KA, Kushi LH, Jacobs DR, Jr., Slavin J, Sellers TA, Folsom AR (2000) Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* **71** (4): 921-930

Morris JN, Marr JW, Clayton DG (1977) Diet and heart: a postscript. *Br Med J* **2** (6098): 1307-1314

Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS (2003) Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA* **289** (13): 1659-1666

Nagura J, Iso H, Watanabe Y, Maruyama K, Date C, Toyoshima H, Yamamoto A, Kikuchi S, Koizumi A, Kondo T, Wada Y, Inaba Y, Tamakoshi A, JACC Study Group (2009) Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Br J Nutr* **102** (2): 285-292

Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR (2008) Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc* **108** (11): 1881-1887

Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC (2005) Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol* **161** (2): 161-169

Panagiotakos D, Pitsavos C, Chrysohoou C, Palliou K, Lentzas I, Skoumas I, Stefanadis C (2009) Dietary patterns and 5-year incidence of cardiovascular disease: a multivariate analysis of the ATTICA study. *Nutrition Metabolism & Cardiovascular Diseases* **19** (4): 253-263

Park HA, Lee JS, Kuller LH (2006) Relationship between premenopausal dietary intake and postmenopausal subclinical atherosclerosis. *Atherosclerosis* **186** (2): 420-427

Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J (1996) Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* **94** (11): 2720-2727

Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, Robinson E, Wareham NJ (2002) Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. *Am J Clin Nutr* **75** (1): 11-20

Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC (1996) Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* **275** (6): 447-451

Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM (2006) Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr* **83** (1): 124-131

Scarborough, P, Bhatnagar, P., Wickramasinghe, K., Smolina, K., Mitchell, C., and Rayner, M. Coronary heart disease statistics 2010 edition. British Heart Foundation: London. 2010.

Scarborough, P., Allender, S., Peto, V., and Rayner, M. Regional and social differences in Coronary Heart Disease 2008. British Heart Foundation Health Promotion Research Group. Department of Public Health, University of Oxford. 1-76. 2008.

Shah M, Baxter JE, McGovern PG, Garg A (1996) Nutrient and food intake in obese women on a low-fat or low-calorie diet. *Am J Health Promot* **10** (3): 179-182

Shah M, Mcgovern P, French S, Baxter J (1994) Comparison of A Low-Fat, Ad-Libitum Complex-Carbohydrate Diet with A Low-Energy Diet in Moderately Obese Women. *Am J Clin Nutr* **59** (5): 980-984

Shammas NW (2007) Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vasc Health Risk Manag* **3** (2): 229-234

Southgate DAT (1969) Determination of carbohydrates in foods. II.Unavailable carbohydrates. *J Sci Food Agric* **20** 331-335

Steffen LM, Jacobs DR, Jr., Stevens J, Shahar E, Carithers T, Folsom AR (2003) Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* **78** (3): 383-390

Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D (2002) Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The ARIC study. *Diabetes Care* **25** (10): 1715-1721

Streppel MT, Ocke MC, Boshuizen HC, Kok FJ, Kromhout D (2008) Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study. *Am J Clin Nutr* **88** (4): 1119-1125

Todd S, Woodward M, Tunstall-Pedoe H, Bolton-Smith C (1999) Dietary antioxidant vitamins and fiber in the etiology of cardiovascular disease and all-causes mortality: results from the Scottish Heart Health Study. *Am J Epidemiol* **150** (10): 1073-1080

Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D (2007) Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur J Clin Nutr* **61** (5): 575-581

Unal B, Critchley JA, Capewell S (2004) Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* **109** (9): 1101-1107, doi:10.1161/01.CIR.0000118498.35499.B2 [doi];01.CIR.0000118498.35499.B2 [pii]

Unal B, Critchley JA, Capewell S (2005) Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. *BMJ* **331** (7517): 614, doi:bmj.38561.633345.8F [pii];10.1136/bmj.38561.633345.8F [doi]

United States FDA. FDA provides guidance on "Whole Grain" for manufacturers [accessed September 2001]. 2006.

USDA. Dietary Guidelines for Americans;2010. 2010.

van Bakel MM, Slimani N, Feskens EJ, Du H, Beulens JW, van der Schouw YT, Brighenti F, Halkjaer J, Cust AE, Ferrari P, Brand-Miller J, Bueno-de-Mesquita HB, Peeters P, Ardanaz E, Dorronsoro M, Crowe FL, Bingham S, Rohrmann S, Boeing H, Johansson I, Manjer J, Tjonneland A, Overvad K, Lund E, Skeie G, Mattiello A, Salvini S, Clavel-Chapelon F, Kaaks R (2009) Methodological challenges in the application of the glycemic index in epidemiological studies using data from the European Prospective Investigation into Cancer and Nutrition. *J Nutr* **139** (3): 568-575, doi:jn.108.097121 [pii];10.3945/jn.108.097121 [doi]

Van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D (2000) Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: the Zutphen Elderly Study. *Eur J Clin Nutr* **54** (9): 726-731

Venn BJ, Green TJ (2007) Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. *Eur J Clin Nutr* **61 Suppl 1** S122-S131, doi:1602942 [pii];10.1038/sj.ejcn.1602942 [doi]

Walker AR (1971) Sugar intake and coronary heart disease. *Atherosclerosis* **14** (2): 137-152

Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC (1999) Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* **281** (21): 1998-2004

World Health Organisation (2003) *Joint WHO/FAO Expert Consultation. Diet, nutrition and the prevention of chronic diseases*. WHO: Geneva

World Health Organization. http://www.who.int/countries/gbr/en/ Accessed July 2008. 2008.

Yano K, Rhoads GG, Kagan A, Tillotson J (1978) Dietary intake and the risk of coronary heart disease in Japanese men living in Hawaii. *Am J Clin Nutr* **31** (7): 1270-1279

Yudkin J (1957) Diet and coronary thrombosis hypothesis and fact. *Lancet* **273** (6987): 155-162

Yudkin J (1964) Dietary fat and dietary sugar in relation to ischaemic heart-disease and diabetes. *Lancet* **2** (7349): 4-5

Yudkin J (1971) Sugar consumption and myocardial infarction. *Lancet* **1** (7693): 296-297

Yudkin J, Morland J (1967) Sugar intake and myocardial infarction. *Am J Clin Nutr* **20** (5): 503-506