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Evaluation of the evidence between consumption of refined grains and health outcomes

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Abstract
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Keywords
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PW was solely responsible for design of the study, literature search and preparation of the manuscript.

Abstract

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Sponsorship: Go Grains Health & Nutrition Ltd is a membership-based organisation that links the Australian grains industry value chain from grain growers to food manufacturers, providing scientifically based information about the role of grains and legumes in health and nutrition, to develop educational resources to support health promotion and education.
Go Grains Health & Nutrition Ltd commissioned a nutrition academic from the University of Wollongong to conduct an independent literature review. The author, acts as a paid scientific advisor to Go Grains, but confirms the sponsor had no role in writing this review.

INTRODUCTION

Cereal grains are staple foods providing an important source of essential micro- and macro-nutrients, and form part of the dietary patterns recommended throughout the world. Dietary guidelines generally distinguish plain cereal products (part of the core food groups that should form the foundation of a healthy diet) from cereal-based products with significant amounts of added fat and sugar, such as cakes, pizza or pastries [1].

Walker [2], Burkitt [3], Cleave [4] and Trowell [5] pioneered the concept that highly-refined foods contribute to Western diseases and this spurred several decades of research interest in the dietary fibre content of the diet. More recently attention has turned to wholegrain foods, recognising that not only their fibre content, but also other properties related to their provision of resistant starch, vitamins, minerals, phytoestrogens and antioxidants, may protect against chronic disease. Over the last two decades, research into the benefits of wholegrain cereal foods has strengthened [6-8]. In particular this has been demonstrated in relation to reduced risks of coronary heart disease [9-11], becoming overweight [12-14], diabetes [15] and certain cancers [16-18].

The 2010 US Dietary Guidelines include the advice to consume at least half of all grains as wholegrains (which in a 2000 calorie diet equates to three or more ounce-equivalents of wholegrain products per day) [19]. They also advise people to "limit the consumption of foods that contain refined grains, especially grain foods that contain added fats, added sugars, and sodium". The 2007 revision of the Canada's Food Guide also included the recommendation to make at least half of your grain products whole grain each day [20], and there has been a recent recommendation for 4 servings of whole grain per day in Denmark [21].

However, despite these guidelines, the actual consumption of wholegrain foods is very low. There are substantial barriers to increasing consumption of wholegrain foods, including traditional preferences for refined products, limited availability in supermarkets and unfamiliarity with cooking techniques [22]. Cross-country studies in

Europe have reported that consumers expect wholegrain products to be healthier, but also believe that they will be less pleasant to eat [23]. In the UK, wholegrain consumption has been reported to have decreased since 1986 to just 14g per day in 2000-2001, and 29% of adults report consuming no wholegrain foods [24]. In the US it is estimated that less than 15% of total grain consumption is wholegrain and only 6-8% of adults meet the target of three servings per day [25-27]. In Australia the last National Nutrition Survey estimated that the average adult daily intakes were 83g of wholegrain cereals and grains and 188g of refined cereals and grains – so that almost 70% of grain foods were refined [28].

Given these low levels of wholegrain consumption, many reviews of the relationship of dietary patterns to disease prevention have made recommendations to reduce refined grain consumption and increase consumption of wholegrains [29, 30]. However rarely do such recommendations give specific guidance about what level of refined grains can be safely included in a healthy diet. It is unlikely that advice to entirely exclude popular foods like white bread, rice or pasta from the diet would be acceptable to most consumers, nor that this is necessary.

The purpose of this review was to evaluate the evidence between consumption of refined grains and health outcomes and, if possible, answer the question: "What proportion of refined grains can be consumed in a healthy diet?"

METHODS

A search for original studies and reviews was carried out in the following databases: Scopus (which includes Medline and Science Direct) and PubMed in the period 2000-2010. The following search terms were used: *refined grain, refined cereal, refined starch, refined carbohydrate*. Studies were limited to those published in English and conducted in humans. The references in retrieved papers were also examined individually to supplement the electronic search.

For the purposes of the review, whenever possible, studies were chosen which reported results for core refined foods, not cereal-based foods with large levels of added fat, sugar or sodium. Examples of such core refined grain foods inlcude: *Breads (*eg*,* white bread, bagels, crumpets, tortillas); *Breakfast cereals* (eg, low fibrecereals and those containing <25% wholegrain); *Refined cereal grains* (eg, white rice, polenta, semolina, couscous); *Pasta and noodles* based on white wheat or rice flour (ie not wholemeal varieties). Foods that were excluded were refined cereal-based foods with large levels of added fat, sugar, or sodium (eg, cakes, pastries, cookies, doughnuts, pizza) and whole-grain and high-fiber cereal foods.

In some of the studies selected for inclusion desserts or other high fat/high sugar foods had been included in the refined grain category, but the results did not suggest adverse health outcomes.

A total of 396 articles were identified from the initial search and their abstracts reviewed. Of these only 96 were directly relevant to the topic. The others were excluded because they did not report outcomes related to refined grains (255), were conducted in animals or patients with established disease conditions (39), were editorial or commentaries without original data (4), or were duplicates of other articles (2). Hand searching of bibliographies added a further 39 references to make a total of 135 articles for review.

The types of articles were: studies of dietary patterns of clusters (38); cross-sectional studies of foods and health relationships (20), case-control studies (13), prospective longitudinal studies (31), randomised controlled trials (9) and reviews and meta-analyses (24).

Articles were reviewed to rate the study quality, using the methods of the American Dietetic Association Evidence Analysis Manual [31]. The ADA system results in three categories of rating: Positive, Neutral, or Negative. All the retrieved articles judged relevant to be included in this review were of Positive or Neutral quality.

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RESULTS

1) Studies of dietary patterns

In the literature search, a total of 38 studies were identified that reported the impact of food patterns with different levels of refined grain foods. These covered a range of different health outcomes, including: total mortality [32, 33]; obesity and metabolic syndrome [34-49]; diabetes [50-55]; cardiovascular disease [56-59]; cancer [60-68]; pulmonary disease [69]; depression and anxiety [70].

In addition one meta-analysis of prospective studies related to the prevention of type 2 diabetes has been published [29]. This meta-analysis of 10 dietary pattern studies concluded that those most consistently associated with the prevention of type 2 diabetes were characterised by high consumption of fruit and vegetables, whole grains, fish and poultry, and by decreased consumption of red meat, processed foods, sugar sweetened beverages, and starchy foods.

However, such studies are only of limited use in attempting to define the level of refined grains that can be incorporated into a healthy diet, for several reasons:

1) A single pattern that is called a “high refined grain pattern” by the authors often contain mixtures of “core” low fat grain foods and also “non-core” refined grain foods which may high in added fat, sugar or sodium (eg, pizza, doughnuts, cakes, and biscuits) as well as other non-cereal high carbohydrate foods (eg, soft drinks, potatoes, confectionery)
2) Refined grain foods may appear in several patterns at different levels of consumption
3) The term “Western diet” has been used in a number of publications examining disease risk, but the grain foods contained in this pattern varies considerably between studies
4) In some pattern studies, core refined grain foods are split between different dietary patterns
5) It is rarely possible to relate results of dietary pattern studies to actual intakes of specific foods.

For all the reasons given above, it is difficult to use the results from dietary pattern studies to draw conclusions about the how particular levels of refined grain foods might impact health outcomes. Better data is available from studies that have looked specifically at the consumption of individual foods.

2) Cross-sectional studies

Eighteen cross-sectional studies were identified that reported the association of consumption of refined grain foods with a range of health outcomes, although most only report risk of obesity or metabolic syndrome. Of these, five found no relationship [71 72-75], three reported some protective effects [76-78], and ten reported a positive association between refined grain food and adverse health status [79-88]. Although cross-sectional studies do not have a high level of explanatory power in nutrition studies [89], the results are briefly summarised below for the purpose of providing a complete picture of the evidence.

Studies showing lack of relationship or protection

Most of the studies that reported no relationship were those examining measures of obesity, body fat distribution, or markers of the metabolic syndrome. In four cross-sectional surveys of 24600 subjects in Finland, bread consumption (which is predominantly wholegrain - 60% rye and 40% wheat bread - in that country [90]) was either not associated (in men) or inversely associated (in women, OR=0.94) with obesity (BMI>30)[77]. In Brazil, a survey of 48470 households found no significant relationship between the prevalence of obesity and any of the following foods: rice, bread, biscuits, pasta, white flour [71]. In contrast, consumption of sugar, soft drinks and ready-to-eat meals were significantly correlated. In a representative cross-sectional sample of 39640 Portuguese adults, the odds ratios of obesity for bread were 0.91 for men and 0.85 for women (neither statistically significant) [76]. For “other starchy food” (pasta, rice and potatoes), consumption was significantly protective for women (OR=0.65) but not for men (OR=0.92)

In the US, an ancillary analysis from a 3-year trial of vitamin K supplementation with 434 adults found that refined grain consumption was not associated with BMI, % body fat or trunk fat mass [72]. Two reports from the Framingham Offspring Cohort have studied refined grain foods. The first study of 2941 subjects found no association with body mass index (BMI), waist-to-hip ratio (WHR), waist circumference (WC) , blood pressure (BP), lipids, insulin or glucose, with refined grain servings up to a median intake of 38 per week in the highest quintile (= 5.5 servings/d) [73]. The second study with 2834 subjects examined insulin resistance and presence of the metabolic syndrome [74]. The metabolic syndrome was not associated with refined grain intake. Similar findings were reported amongst 1516 participants in the Baltimore Longitudinal Study of Aging [75]. There was no relationship with BMI, weight, WC, overweight (BMI>25), cholesterol, fasting glucose, or hypertension up to a median refined grain intake of 103g/d in the highest quintile.

Lastly, a study of prostate cancer rates in 71 countries found that apparent consumption of up to 1800 calories per day from cereal grains (rice, wheat and maize) correlated strongly with decreasing prostate cancer mortality [78].

Studies showing increased risk

In a subsample of healthy adult participants from the Framingham Heart Study, visceral adipose tissue (VAT) was positively associated at high intakes of refined grains, although the lowest VAT was recorded with 2 servings of refined grains and 3 servings of wholegrains per day. In contrast, waist circumference and subcutaneous adipose tissue were not significantly associated with refined grain intakes up to 4 servings per day in the highest quintile [79].

In a small convenience sample of 159 US college students, participants were grouped by BMI category and the intakes of whole and total cereal grains compared by analysis of variance [80]. Total grain intakes were similar in normal and obese subjects (around 5.5 servings/d) but a significantly higher percentage were wholegrain in the normal weight group (14.8%) compared to obese participants (5.9%). However, even for the normal weight subjects, 85% of total grain foods were from refined grains.

In a cross-sectional sample of 827 adults in Tehran mean refined grain consumption was 201g/d, ranging up to 362g/d in the highest quartile, and the associations with health states have been reported in two publications [81, 82]. Obesity and diabetes were not associated with refined grain intake, but the highest quartile of consumption was significantly associated hypercholesterolemia (OR=1.23), hypertriglyceridemia (OR=1.14), hypertension (OR=1.69), hypertriglyceridemic waist (OR=2.1) and metabolic syndrome (OR=2.25). At the level of consumption in the second quartile (156g/d) these associations did not appear to be statistically significant. In a second Iranian survey of 2000 adolescents, there was a reported significant linear association between BMI and the frequency of consumption of rice, bread, pasta, fast foods and fat/salty snacks [83]. The mean frequency of intake (times/week) of subjects who were not overweight (with a BMI <85th percentile) were: bread (10.8), rice (6.8), pasta (2.1).

Two studies from India also report adverse associations of high intakes of refined grain (primarily white rice) with higher waist circumference (WC), blood pressure (BP), fasting blood glucose, serum triglyceride, low HDL cholesterol, insulin resistance and diabetes prevalence [84, 85]. However the intakes of cooked rice were very high, ranging from 218g/d in the lowest to 584g/d in the highest quartiles, which are two to three times higher than typical intakes in Western countries.

From North America, three studies provide some evidence of increased risk with refined grains. Data from 1088 participants in the Insulin Resistance Atherosclerosis Study was used to examine cross-sectional relationships between grains and three inflammatory proteins in plasma (PAI-1, CRP and fibrinogen) [86]. Refined grain intake was positively related to PAI-1, indicating it could have pro-inflammatory effects, but was not related to the other two markers.

A study in Boston of 535 adults with a mean age of 72 years used a 3-day diet record to estimate grain intake and measured a range of metabolic risk factors [87]. No significant association were found between intakes of refined grains and all cause or

CVD mortality. Those in the highest quartile of intake (6.1 servings per day) had significantly higher risk of metabolic syndrome (OR=2.16), but in the second quartile (median of 2.9 servings/d) there was no significant difference.

Many of these cross-sectional studies have limitations based on lack of detail about the foods included within the refined grain category, and all suffer from the general problem that such studies cannot explore the temporal relation between consumption and health endpoints to infer causation. Furthermore five of the ten studies showing some adverse associations were conducted in non-Western countries with significantly different food patterns from those in the US, UK or Australia. Overall, however, from these studies, there is no strong evidence that consumption of a moderate intake of up to three servings of refined grains per day is incompatible with a healthy diet.

3) Case-control studies

There were 13 case-control studies: 10 for various cancers and 3 for ischemic heart disease, summarised in Table 1.

In 2001, a review of case-control studies of diet and cancer risk in Italy suggested that refined grain intake was associated with increased risk of stomach, colorectal, breast, upper-digestive and thyroid cancers [91]. Since then ten more case-control studies on cancer risk have been published, seven of which found a significant increase in risk at the highest level of refined grain consumption (for renal, upper-digestive, stomach and colorectal cancer), while two examining pancreatic cancer and one on colorectal adenomas found no relationship. Of those showing increased risk, two for colorectal cancer only found this at the highest intake – not at the third quartile [92, 93] and the third such study did not present results for levels below the highest quartile [94].

Two case-control studies of risk of cardiovascular disease have reported no association with refined grain intake [95, 96] while one Chinese study found an

increased risk of stroke at very high levels of cooked white rice - above 1100g per week [97]. Overall, therefore, there is a lack or consistency in the case-control data about cancer that makes it difficult to draw clear conclusions. Some of the increased risks are only present at the very highest levels of intake, which is still consistent with safe intakes at lower levels. The small number of case-control studies on ischemic heart disease risk do not suggest any significant risk with moderate refined grain consumption, but better data is available from the larger number of prospective cohort studies reported in the next section.

4) Prospective cohort studies

Longitudinal cohort studies provide some of the strongest evidence on which recommendations for dietary intakes can be based. Table 2 summarises 31 recent studies that have examined refined grain intake and health outcomes.

Only five studies reported an association with adverse health outcomes. Two of these studies used definitions of refined grains that included high fat cereal-based foods such as pizza, cakes and biscuits [98, 99]; one analysed refined grain food plus potatoes [100], one did not define the foods included but focused on energy density (a quality associated with greater consumption of non-core refined grains) [101], one found an effect for women but not men [102], and one stated a conclusion without providing any detailed results [99], so caution is required when interpreting these results.

The great majority (26/31) of the longitudinal studies found no association or a protective effect for cardiovascular disease [103-111], type 2 diabetes or metabolic syndrome [112-117], various cancers [118-121], weight gain [122-124], all-cause mortality [125, 126], inflammatory disease [127], and periodontitis [128]. The data on CVD is consistent with a recent meta-analysis of cohort studies which concluded that while wholegrains were consistently protective, there was no evidence of differences in risk of CVD events when comparing groups with high vs low refined grain intake [11].

5) Intervention studies

While results from case-control and cohort studies can be powerful, they can only indicate associations between diets and health outcomes, rather than provide evidence of causal relationships. High consumption of refined grain foods may be markers of less healthy lifestyle practices, such as lower physical activity, smoking, and higher fat and alcohol intakes. Good quality epidemiological studies attempt to control for such factors, but they cannot reliably predict outcomes when diet patterns are changed, and randomised controlled trials are therefore even better evidence of the effect of diet components. Regrettably there are very few diet intervention trials that are available to consider, and most are limited by small numbers of participants and short follow-up periods.

A total of nine relevant studies were identified [129-137]. None was designed to examine the effects of different levels of refined grain intakes specifically; most were attempting to increase wholegrain intake [129-131, 134-137] or lower the GI of diets [132, 133], using refined grain foods as controls. Table 3 summarises these studies, which largely focused on cardiovascular and metabolic risk outcomes. Only one reported the energy provided by the refined grain intake in the study [133]; others reported frequency of intake.

Six of the nine studies reported no significant differences between diets high in refined versus wholegrain cereal intakes [130, 133-137]. One of these papers reported plasma antioxidant status (with the ORAC method) rather than more direct measures of health status[131]. Since the antioxidant content of wholegrains has been postulated to be one of the mechanisms by which they reduce cardiovascular disease risk, the lack of difference found when comparing refined and wholegrain diets suggests that having some grains in the refined form will not adversely affect antioxidant status. One reported superior reductions in % abdominal fat reduction with a wholegrain hypocaloric diet intervention, but there were still improvements to a lesser extent with the refined grain diet as well [131]. Similarly, in the large New Zealand study, waist circumference was reduced to a greater extent on the wholegrain diet, but also reduced with the control diet, with increased consumption

of refined cereals [137]. One small study suggested a breakfast including refined grain rice/corn cereal improves satiety in overweight women, but there were no measures of food intake [132], and the results contradict similar studies in the past [138]. Lastly, the Iranian study [129], reported better weight outcomes with the wholegrain interventions compared to refined grains, but the wholegrain diets were combined with energy reduction, while the controls with a higher content of refined grains did not attempt to alter the energy content, so it is not possible to draw any clear conclusions.

Most of these few studies do not show any difference in health outcomes when refined grains are compared to wholegrains, which can be interpreted to support a conclusion that some core refined grain foods can be included in a diet without increased risk to health.

6) Reviews and Meta-analyses

Almost all of the identified reviews were primarily concerned with the health benefits of wholegrains or low GI diets, and none specifically reviewed the levels of refined grain consumption in relation to health outcomes.

Three reviews looked at the question of weight control. Van Dam and Seidell's non-systematic review examined the general issue of carbohydrate intake and obesity and concluded that wholegrain cereals, vegetables, legumes and fruits seem the most appropriate source of dietary carbohydrate, but did not report any studies of refined grain intake [14]. Gaesser's systematic review looked at carbohydrate quality in relation to body mass index and concluded that while wholegrain intake was generally inversely associated with BMI, refined grain intake is not consistently linked to higher BMI [12]. This is consistent with the conclusion of the systematic review of Williams et al, which reported no clear association of refined grains with BMI [13]. They noted there were three cohort studies reporting that higher intakes of refined grains were associated with increases in waist circumference and BMI in women, but the weight changes, although statistically significant, were relatively

411 minor in absolute terms: <0.7kg over a 12 year period. Liu has suggested that large
412 and long-term intervention trials are needed to assess the effects of wholegrain
413 versus refined grains on weight loss and maintenance [30].
414
415 Four systematic reviews have examined risk of cardiovascular disease. In 2002
416 Truswell concluded there was no clear association between total cereal consumption
417 and CHD [139]. Anderson's review and meta-analysis showed a significant risk
418 reduction of 29% with the highest wholegrain intake, but cereal fibre was not
419 associated, suggesting other components of the grain may be protective [9]. That
420 review did not make any conclusions about refined grain specifically. Flight and
421 Clifton's review in 2006 also concluded that wholegrains are clearly protective in
422 relation to CHD but that data on refined grains is not consistent [10]. The most recent
423 meta-analysis published in 2008 did specifically report on refined grains and
424 concluded there was no evidence of increased or decreased risk for cardiovascular
425 events when comparing high versus low refined grain intake; OR(CI)=1.07(0.94-1.22)
426 [11].
427
428 Five recent reviews have summarised studies relating refined grain intake to risk of
429 cancer. La Vecchia's non-systematic summary of a series of case-control studies in
430 Italy concluded that refined grain consumption was associated with a moderate
431 increase in risk of five cancers (stomach, colorectal, breast, upper-digestive and
432 thyroid cancers), but not at 15 other sites [91]. Later systematic [140] and non-systematic
433 reviews [141, 142] of pharyngeal and other oral cancer risks have also suggested
434 inconsistent results in relation to refined grains. In 2007, the World Cancer Research
435 Fund's systematic review of Food, Physical Activity and the Prevention of Cancer
436 concluded that there was too little evidence about the relationship of cereals and
437 grains to draw any conclusions about cancer risk [143].
438
439 Finally, in relation to prevention of diabetes, most reviews have recommended
440 changes to lower glycemic index diets, rather than specifically focusing on refined
441 grains [30, 53, 144-146]. One editorial hypothesised that the very high intakes of refined

white rice found in China (6 servings per day) and India (8.5 servings per day) may explain the high levels of diabetes in those populations [147].

DISCUSSION

This review has focused on health outcome studies and did not consider the nutritional adequacy of diets with different levels of refined grain intake. However, diet modeling for the latest revision of the Australian dietary guidelines showed that diets including one-third of grains foods as refined was compatible with the nutritional adequacy of the total diet [28] and the US Dietary Guidelines also showed nutritional adequacy was achievable with half of grain foods as refined [19]. The great majority (45/61) of the case-control, cohort, intervention studies and reviews summarised here found no clear association between refined grain intake and adverse health outcomes. However in 16 studies there was an increase in health risk at the highest level of consumption. In some of these cases the highest quantile of intake was often extremely high compared to typical Western intakes (eg, rice intakes in India and China) and does not provide useful guidance as to the risk at lower intakes. More importantly in 7/16 studies showing increased risk, the definition of refined grain foods included high-fat or sugar-added products like pizza or cakes, so it is not possible to draw conclusions from those results about the effect of core refined grains alone.

Table 4 summarises nine studies which reported increased health risk at the highest intakes of refined grains but also provided sufficient information to allow calculation of the lower levels of intake at which there was no increase in risk. These data can provide guidance as to what level could be recommended in a healthy diet.

It should be noted that these studies relate to only a few specific health outcomes; none look at total morbidity or mortality. Most of the studies present results as amounts or numbers of servings per day. The reported frequencies range from 2.4-5.9 servings per day, with a mean of 4 refined grain servings per day. However it is difficult to relate these to total grain intakes. Only two of the studies specified the

highest *proportion* of all grains that could be refined without increased risk, and these ranged from 57-67% [93, 110].

Table 5 summarises the evidence base, using the format of guidelines from the Australian National Health and Medical Research Council for the evaluation of evidence [89]. It should be noted that the dietary pattern studies were not considered in establishing this summary, since few of these studies reported the amount of refined grains in the different dietary patterns. Cross-sectional studies are still listed in the table, but they provide only low-level supportive evidence rather than being the primary justification for the final evidence statement.

CONCLUSION

Most of the dietary guidance to reduce refined grains is based primarily on the evidence supporting increased wholegrain consumption, rather than particular concerns about risks of refined grains per se. The protective effects of wholegrains are well established, and in order to promote increased consumption there has to be a decrease in the refined grain food alternatives. However this is difficult to achieve. Even in the best large intervention trials, with high levels of education and support - eg, the 18-month trial in New Zealand [137] – compliance with increased wholegrain targets was relatively poor.

The totality of evidence shows that consumption of up to 50% of all grain foods as refined grain foods (without significant added fat, sugar or sodium) is not associated with any increased disease risk. Nonetheless, eating more wholegrain foods remains an important health recommendation, and most consumers will need to reduce their current refined grain consumption to no more than one-third to one-half of all grains in order to meet the targets for wholegrain foods. It needs to be noted that this conclusion about refined grains only applies to core refined grain cereal foods. In all communications with the public the importance of limiting cereal-based foods that are high in added fat, sugar and sodium still needs to be emphasised.

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Table 1. Case-control studies investigating the association of refined grain intakes and health risk

Author ***Quality rating***	***Subjects***	***Food intake method***	***Foods defined as refined grain***	***Servings consumed***	***Odds ratios highest vs lowest (95% CI)***
Increased risk					
Levi et al (2000) [148] Positive quality	297 cases upper digestive tract cancer 349 controls Switzerland	79 item FFQ*	White bread, biscuits, pizza, pasta, rice (tertiles)	Q1: <9/week Q2: 9-17/week Q3: >17/week	Oral cavity/Pharynx: 1.9 (1.1-3.5); p<0.05 Oesophagus: 3.7 (1.8-7.9); p<0.01 Larynx: 4.0 (1.3-12.1); p<0.01 Total: 5.7 (2.8-11.4); p<0.01
Lissowska (2004) [149] Positive quality	274 cases stomach cancer 463 controls Poland	118 item FFQ	Non-wholegrain bread, cereal, rice and pasta, sugar, cake, crispbread, shortbread	*Breads, cereals, rice, pasta:* Q1: <17.5/week Q2: 17.5-21.2/week Q3: 21.3-25.2/week Q4: >25.2/week *Refined grains* Q1: <15.4/week Q2: 15.4-25.2/week Q3: 20.3-25.2/week Q4: >25.2/week	Breads, cereals, rice, pasta: 2.4 (1.35-4.25); p<0.001 Refined grains: 1.8 (1.04-3.13); p=0.02
Lucenforte et al (2008) [150] Positive quality	230 cases stomach cancer 547 controls Italy	78 item FFQ	Mostly bread, rice and pasta	Q1: 15.8/week Q3: 24.8/week Q5: 64.3/week	All cereals (mostly refined): 2.07 (1.01-4.24); p=0.03

Author ***Quality rating***	***Subjects***	***Food intake method***	***Foods defined as refined grain***	***Servings consumed***	***Odds ratios highest vs lowest (95% CI)***
Bravi et al (2006) [151] Neutral quality	767 cases renal cell cancer 1534 controls Italy	78 item FFQ	n/a (data presented for bread, or pasta and rice only)	*Bread* Q1: 9.5/week Q3: 14.75/week Q5: >28.5/week *Pasta and rice* Q1: 3.25/week Q3: 5.25/week Q5: >6.5/week	Bread: 1.94 (1.40-2.71); p=0.0002 Pasta and rice: 1.29 (0.95-1.76); p=0.06
Satia-Abouta et al (2004) [92] Positive quality	613 cases colon cancer 996 controls USA	100 item FFQ	Rice or dishes with rice, hamburger, spaghetti, pizza, bread (white, dark and rye), breakfast cereals, noodles, biscuits, muffins, pancakes, waffles, popcorn	*Caucasians* Q1: 9.1/week (116g/day) Q2: 13.3/week (172g/day) Q3: 16.8/week (235g/day) Q4: 23.1/week (319g/day)	*Caucasians* Adjusted for energy: 1.5 (0.9-2.5); p=0.58 Not adjusted for energy: 2.3 (1.5-3.6); p=0.001 (Note: at Q3 OR=1.1 (0.7-1.8) *African- Americans* Both energy-adjusted and not adjusted: 1.2 (0.7-2.1); p=0.74)
Slattery et al (2004) [93] Positive quality	952 cases rectal cancer 1205 controls USA	Diet history	Products consisting primarily of white flour, white rice, and pasta; subdivided into those high in fat (>30%E from fat)	*Low fat/high fat* Q1: <1.5/<0.25/d Q2: 1.6-2.5/0.25-0.5/d Q3: 2.6-3.5/0.51-0.75/d Q4: 3.6-4.5/0.76-1.5/d Q5: >4.5/>1.5/d	Low fat refined grains: 1.42 (1.04-1.92); p=0.05 Note: At Q3, OR=1.01 (0.74-1.40) High fat refined grains: 1.09 (0.78-1.53); p=0.67

Author ***Quality rating***	***Subjects***	***Food intake method***	***Foods defined as refined grain***	***Servings consumed***	***Odds ratios highest vs lowest (95% CI)***
Ravasco et al (2005) [94] Neutral quality	70 cases colorectal cancer 70 controls Portugal	Diet history	n/a (refined cereal products - undefined)	Q1: 6/week Q2: 10/week Q3: 20/week Q4: 30/week	Refined cereal products: 1.79 (1.65-1.78); p=0.003 No results presented for Q2 or Q3.
Liang et al (2010) [97] Positive quality	374 cases ischemic stroke 464 controls China	125 item FFQ	n/a (data presented for cooked rice, congee, rice noodles only)	*White rice (cooked)* Q1: <1100g/weeks Q2: 1100-1449g/week Q3: 1450-2449g/week Q4: ≥2450g/week *Rice noodles (dry wt)* Q1: <50g/week Q2: ≥50g/week	White rice: 2.73 (1.31-5.69); p=0.006 Rice noodles 2.03 (1.40-2.94); p=0.029
No increased risk					
Chan et al (2007) [152] Positive quality	532 cases pancreatic cancer 1701 controls USA	131 item FFQ	White rice, white bread, bagels/English muffins/rolls, muffins/biscuits, pizza, pasta, pancakes, waffles, pretzels	Q1: <1/day Q2: 1/day Q3: 2/day Q4: ≥3/day	Total refined cereals: 0.80 (0.55-1.2); p=0.46) Pasta: 1.3 (0.83-2.1); p=0.67 White bread: 1.1 (0.82-1.4); p=0.86 White rice: 1.2 (0.89-1.7); p=0.24
Rossi et al (2010) [153] Positive quality	326 cases pancreatic cancer 652 controls Italy	78 item FFQ	n/a (data presented for total CHO**, glycemic index and load)	Tertiles: amounts not reported	Total carbohydrates: 0.86 (0.56-1.30); p=0.52 Sugar, candy, honey, jam: 1.88 (1.24-2.86); p=0.004 GI: 1.78 (1.2-2.62); p=0.005 GL: 1.26 (0.83-1.91); p=0.23 Note: bread, pasta and rice contributed 59% of glycemic load

Author ***Quality rating***	***Subjects***	***Food intake method***	***Foods defined as refined grain***	***Servings consumed***	***Odds ratios highest vs lowest (95% CI)***
Senesse et al (2002) [154] Positive quality	362 cases precancerous colorectal adenomas 427 controls France	Food history	n/a (data presented for bread, rice and pasta only)	*Bread (males/females)* Q2: 100/47.4g/d Q3: 151.5/83.6g/d Q4: 202.7/103.0g/d *Pasta (males/females)* Q2: 21.4/10/7g/d Q3: 35.7/22.5g/d Q4: 57.1/39.6g/d *Rice (males/females)* Q2: 7.1/7.1g/d Q3: 17.9/16.1g/d Q4: 32.1/23.6g/d	*Bread* Small adenomas: 2.0 (1.1-3.6); p=0.06 Large adenomas: 2.2 (1.3-3.7); p=0.01 *Note*: not significant at Q3 *Pasta* Small adenomas: 1.7 (0.9-3.0); p=0.06 Large adenomas: 1.3 (0.8-2.2); p=0.5 *Rice* Small adenomas: 1.4 (0.8-2.4); p=0.2 Large adenomas: 0.8 (0.5-1.3); p=0.12
Martinez-Gonzalvez et al (2002) [95] Positive quality	171 cases first acute myocardial infarction 171 controls Spain	136 item FFQ	n/a (data presented for white bread +rice+ pasta	Q1: 84-138g/d Q2: 138-180g/d Q3: 181-252g/d Q4: >252g/d	Bread+rice+pasta: 0.97 (0.36-2.64)
Tavani et al (2003) [96] Positive quality	433 cases first nonfatal acute myocardial infarction 448 controls Italy	78 item FFQ	n/a (data presented for GI, GL, bread, and pasta+rice	Upper tertile limits *Bread* T1: 15.3/week T2: 22.2/ week *Pasta and rice* T1: 4.5/week T2: 6.3/week	Bread: 1.00 (0.70-1.45); p=0.99 Pasta and rice: 1.27 (0.88-1.84); p=0.19 GI: 1.38 (0.95-2.0); p=0.10 GL: 1.08 ((0.73-1.60); p=0.69

* FFQ - food frequency questionnaire; ** CHO - carbohydrate

Table 2. Summary of recent prospective studies examining the effect of refined grain intake on health outcomes

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Increased risk				
Liu et al (2003) [98] Positive quality	74, 091 females in Nurses Health Study USA Cohort followed every two years since 1976, with 126-item FFQ and self-reported weight. Multiple regression analysis of data from 1984-1996	Sweet rolls, cakes, desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereals, white rice, pancakes or waffle, pizza Q1: 0.4 servings/1000kcal/d Q3: 1.05 servings/1000kcal/d Q5: 2.27 servings/1000kcal/d	Weight, BMI, OR of developing BMI≥30	At baseline, mean weight of women in highest quintile of refined grain intake weighed 1.2kg more than those in the lowest quintile (BMI 25.2±5 vs 24.6±4; p<0.001) Over 12 years, higher refined grain consumption was related to greater weight gain 1.65±0.03kg vs 0.99±0.03kg (p<0.001) and risk of becoming obese: OR=1.18 (1.08-1.28); p<0.0001).
Koh-Banerjee et al (2004) [99] Positive quality	27, 082 men aged 40-75 years at baseline in the Health Professionals Follow-Up Study. USA Longitudinal prospective study 1986-1994. Multiple linear regression examined changes in grain intake and weight using self-reported weights and 131-item FFQ administered in 1986, 1990, 1990.	Grain foods with <25% whole-grain content by weight, such as cooked and cold breakfast cereals, dark bread made with wheat flour rather than wholewheat flour, white bread, English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, cookies, doughnuts, brownies, sweet rolls, coffee cake, and pizza	Weight	For every 40g/d increment in whole-grain intake, weight gain was reduced by 0.49kg. Wholegrain foods contributed only 3.3g/d of out of daily total of 27.2g grain foods/day It is stated that refined grain cereals were positively related to long-term weight gain (p for trend < 0.001), but no results data are provided.

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Halkjaer (2004) [102] Positive quality	1200 women and 1236 men aged 30-60y in the MONICA 1 study, recruited 1982-3 and followed up in 1987 and 1993. Denmark. Diet assessed with 26-item FFQ and weight measured. Multiple linear regression examined associations of weight change and intakes of 10 food groups.	n/a Data reported for: Refined bread (white wheat and rye bread) Rice and pasta	BMI and waist circumference	For men, a high intake of refined bread, rice and pasta tended to be associated with a subsequent decrease in WC, but the effects were not statistically significant. For women a high intake of rice and pasta also tended to be associated with decreased WC, but refined bread was significantly associated with increased WC (ß=0.29; p<0.05).
Halkjaer et al (2006) [100] Positive quality	22,570 women and 20,126 men aged 50-64y in the Danish Diet, Cancer and Health Study, Denmark. 5 year follow-up of longitudinal prospective study commenced 1993-97. Linear regression analysis of baseline diet assessed by 192-item FFQ, and self-reported weight and WC.	Refined grain cereals (white bread, white flour, rice, rice flour, potato flour, corn flour, and pasta) and potatoes Median intakes at baseline: Men: 1.26MJ/d Women: 0.90MJ/d	Waist circumference	CHO from refined grains and potatoes was significantly associated with WC increase in women: 0.48 (0.18-1.78) cm; p=0.002 but not men: 0.06 (-0.12-0.25)cm; p=0.49.
Savage et al (2008) [101] Neutral quality	192 white women in a longitudinal study of parental influences on girls' growth and development, USA. Data collected on 4 occasions across 6 year. Mixed model analysis, using dietary data from 24-h recall telephone interviews	Not defined	Energy density (ED) tertiles: T1: <1.5kcal/g T2: 1.5-1.85kcal/g T3: >1.85 kcal/g	ED was positively associated with weight gain over 6 years (6.4kg vs 2.5kg; p<0.001). Women consuming high energy density diets consumed more servings of refined grains (5.0 servings/d) compared to those in the T1 groups (3.9 servings/d); p<0.05.

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
No increased risk				
Jacobs et al (1998) [104] Positive quality	34,492 postmenopausal women aged 55-69y in the Iowa Women's Health Study, USA. Disease outcomes determined by link to State Health registry; diet assessed by 127 item FFQ. Association of grains with ischemic heart disease over 9 years determined by proportional hazards regression analysis.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza. Median and range of intakes (servings/week) Q1: 4.0 (0-6.0 Q2: 8.8 (6.5-9.5) Q3: 12.0 (10.0-14.5) Q4: 18.0 (15.0-22.5) Q5: 30.0 (23.0-155.5)	Death from ischemic heart disease	No significant association of refined grain intake and ischemic heart disease in women. Total refined grain: RR=1.12 (0.77-1.62); p=0.57 White bread: RR=1.24 (0.94-1.64); p=0.13 Refined breakfast cereal: RR=1.45 (0.99-2.13); p=0.14 Other refined grains: RR=0.79 (0.52-1.21); p=0.29
Liu et al (2000) [103] Positive quality	75,521 women aged 38-62y in the Nurses Health Study, USA. Disease outcomes confirmed by review of medical records; diet assessed by 126-item FFQ. Association with ischemic stroke over 12 years determined by multivariate logistic regression.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza. Mean intake 2 servings per day (quintile amounts not reported0	Death from ischemic stroke	There was no significant association between refined grain intake and ischemic stroke; RR=0.97 (0.67-1.42); p=0.58
Liu et al (2003) [109] Positive quality	86,190 men in the Physicians Health Study, USA. Deaths over 5.5y follow-up identified from the National Death Index and confirmed from death certificates; diet assessed by 126-item FFQ. Cox proportional hazards regression analysis used to compute hazard ratios.	Breakfast cereals divided into wholegrain (>25% whole grain or bran content) or refined grain cereals. Q1: 0 servings/week Q2: ≤1 serving/ week Q3: 2-6 servings/week Q4: ≥7 servings/week	Deaths from cardiovascular disease (CVD), myocardial infarction (MI), or stroke.	Consumption of refined grain breakfast cereals was unrelated to risk of CVD, MI or stroke. CVD: HR=1.04 (0.84-1.27); p=0.37 MI: HR=0.96 (0.68-1.36); p=0.97 Stroke: HR=1.22 (0.71-2.11); p=0.87

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Lee et a (2004) [108] Neutral quality	3146 men and women aged 17-35y in the CARDIA longitudinal study, USA. Diet measured at years 0 and 7 with 700-item FFQ. GGT measured at 0 and 10y. Association of GTT and 14 food groups assessed by linear regression.	Not defined. Mean intake 9.7 times/week	Serum gamma-glutamyltransferase (GGT), a predictor of future heart disease	Refined grain intake was not associated with GTT Regression coefficient: -0.009; p=0.498
Erkkila et al (2005) [107] Positive quality	229 women in prospective cohort Estrogen Replacement and Atherosclerosis Trial, USA. Diet assessed with 126-tem FFQ and outcomes measured with quantitative coronary angiography at baseline and 3 years.	White bread or rolls, cold breakfast cereal with <25% wholegrain or bran content, muffins, cakes, cookies, pancakes or waffles, white rice, pasta, pizza. Median intake: 8.5 servings/week	Change in mean minimum coronary artery diameter (MCAD) and percent stenosis	Number of servings of refined grains was not associated with progression of coronary artery atherosclerosis progression. Comparing intakes ≤ median intake vs > median intake, p values for changes in MCAD and % stenosis were 0.44 and 0.32 respectively.
Steffen et al (2005) [106] Neutral quality	4304 men and women aged 8-30 in the CARDIA 15 year longitudinal study, USA. Diet measured at years 0 and 7 with 700-item FFQ; blood pressure measured at 6 clinical exams. Cox proportional hazards regression analysis used to evaluate associations or average food group consumption with 15 year EBP incidence	Refined grains not defined, Q1: <1.8 times/d Q2: 1.8-2.4 times/d Q3: 2.4-3.1 times/d Q4: 3.1-4.3 times/d Q5: >4.3 times/d	Elevated blood pressure (EBP), defined as systolic BP ≥130mm Hg, diastolic BP ≥85mm Hg, or use of hypertensive medication	There was no association between refined grain intake and elevated blood pressure. HR=0.87 (0.68-1.12); p=0.70

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Djousse et al (2007) [105] Neutral quality	21,376 participants in the Physicians Heath Study, USA. Diet assessed with 126-item FFQ and incident heart failure ascertained by annual follow-up questionnaires. Cox proportional hazards regression analysis used to compute hazard ratios.	Breakfast cereals divided into wholegrain (>25% whole grain or bran content) or refined grain cereals. Q1: 0 servings/week Q2: ≤1 serving/ week Q3: 2-6 servings/week Q4: ≥7 servings/week	Incident heart failure	There was no association between refined breakfast cereal intake and incident heart failure. HR=0.83 (0.58-1.18); p=0.70
Wang et al (2007) [110] Positive quality	28,926 women aged ≥45y in the Health Professionals Study, USA. Diet assessed with a 131-item FFQ and hypertension ascertained by self-report. Cox regression analysis used to model relative risk of hypertension over 10y of follow-up	Sweet rolls, cakes, desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereals, white rice, pancakes or waffle, pizza Q1: 0.76 servings/d Q3: 1.85 servings/d Q5: 4.06 servings/d Proportion of refined to total grains: Q1: 90%; Q3: 63%; Q5: 31%	Hypertension	Absolute intake of refined grain intake was not associated with risk of hypertension. RR= 0.97 (0.89-1.06); p=0.80 However, a lower proportion of refined grains was associated with a reduced risk of hypertension, implying a protective effect of wholegrains RR=0.90 (0.84-0.98); p=0.002 <u>Note:</u> The significant reduction began at Q3 (31-43% wholegrains)

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Lutsey et al (2009) [111] Positive quality	37,393 women in the Iowa Women's Health Study, USA. Diet assessed with 127-item FFQ. VTE incidence obtained from Medicare data. Cox regression analysis evaluated relations of 11 food groups to incident VTE over 19 years of follow-up.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza. Median servings/week Q1: 2.5 Q2: 4.5 Q3: 7.0 Q4: 10.5 Q5: 19.0	Incident venous thromboembolism (VTE)	There was no association between refined grain intake and VTE. HR=0.98 (0.84-1.15); p=0.66
Meyer et al (2000) [117] Positive quality	35,988 women aged 55-69y in the Iowa Women's Health Study, USA. Food intake assessed with 127-item FFQ, and diabetes incidence determined in 3 surveys over 6y follow-up. Relative risk calculated with proportional hazards regression of upper and lower intakes.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza Median intakes (servings/week): Q1: 3.5 Q2: 7.5 Q3 11.5 Q4: 15.5 Q5: 29.5	Incident type 2 diabetes	Refined grain intake not associated with incidence of type 2 diabetes in older women. RR= 0.87 (0.70-1.08); p=0.36

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Fung et al (2002) [116] Positive quality	42,898 men aged 40-75y from the Health Professionals Follow-Up Study, USA. Diet assessed with 131-item FFQ. Type 2 diabetes incidence identified by self-report in biennial questionnaires. Pooled logistic regression used to assess association between diet and diabetes risk over 12y of follow-up.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza Median and range of intake: Q1: 0.6 (0-0.9) servings/d Q3: 1.7 (1.4-2.0) servings/d Q5: 4.3 (3.2-21.5) servings/d	Incident type 2 diabetes	Intake of refined grains was not associated with risk of type 2 diabetes in men. RR=1.08 (0.87-1.33); p=0.69
Hodge et al (2004) [115] Positive quality	36,787 men and women in the Melbourne Collaborative Cohort Study, recruited 1990-94 (Australia). Diet variables assessed with 121-item FFQ and tested in logistic regression models.	n/a/ Data reported for all cereals white bread, rice, pasta. *All cereals* Q1: <20 times/week Q4: ≥41 times/week *White bread* Q1: <0.5 times/week Q3: 3.0-6.9 times/week Q4: ≥7 times/week *Rice* Q1: <1.0 times/week Q4: ≥2.5 times/week *Pasta* Q1: <0.5 times/week Q4: ≥3.0 times/week	Incident type 2 diabetes	No significant association with risk of diabetes at the highest consumption of cereals, rice, or pasta, nor for white bread at up to 7 times per week. Odds ratios for highest quartiles of intake: *All cereals:* 1.05 (0.73-1.52); p=0.7 *White bread:* Q4: 1.13 (0.86-1.50) p=0.04 Q3: 0.95 (0.67-1.35) not significant Rice: 0.93 (0.68-1.27); p=0.9 Pasta: 0.86 (0.60-1.23); p=0.6

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Sun et al (2010) [114] Positive quality	197,228 participants from the Health Professionals Follow-Up Study, and the Nurses Health Studies I and II (USA). Cox's proportional hazard regression used to estimate relative risk, using data from 116-item FFQ completed every 4 years from 1986-2002.	Only white rice. Q1: <1 serving/month Q2: 1-3 servings/month Q3: 1 serving/week Q4: 2-4 servings/week Q5: ≥5servings/seek	Incident type 2 diabetes	High intake of white rice associated with higher risk of diabetes. Pooled RR: Q2: 1.10 (0.94-1.08) Q3: 1.04 (0.94-1.08) Q4: 1.11 (1.03-1.20) Q5: 1.17 (1.02-1.36); p<0.001 In contrast high brown rice intake (≥2 servings/week) was associated with a lower risk: RR=0.89 (0.81-0.97); p=0.005.
Nanri et al (2010) [113] Positive quality	25,666 men and 33,622 women aged 45-75y in the Japan Public Health Centre-based Prospective Study (Japan). Diet assessed with 147-item FFQ and diabetes incidence determined by self-report. Odds ratio for type 2 diabetes over the 5 years of follow-up determined by multiple logistic regression analysis.	n/a Rice, bread and noodle intakes reported. Median intakes (men/women): *Rice (g/d)* Q1: 280/165 Q4: 700/560 *Bread (g/d)* Q1: 0/4 Q4: 47/60 *Noodles (g/d)* Q1: 41/225 Q4: 29/177	Incident type 2 diabetes	Bread and noodles intakes were not associated with diabetes risk: *Bread:* Men: OR=0.85 (0.64-1.14); p=0.30 Women: OR=0.99 (0.73-1.34); p=0.87 *Noodles* Men: OR=0.89 (0.68-1.17); p=0.49 Women: OR=1.15 (0.83-1.58); p=0.23 *Rice* There was a significant relationship in women but not men. Men: OR=1.19 (0.85-1.68); p=0.32 Women: OR=1.65 (1.06-2.57); p=0.005 Note: at Q2 (315g/day) for women there was no significant association: OR=1.15(0.85-1.55)

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Lutsey et al (2008) [112] Positive quality	9514 men and women aged 45-64y in the ARIC study, USA. Diet assessed with 66-item FFQ. MetSyn determined at 3-yearly examinations. Cox proportional hazards regression used to measure association with MetSyn risk over 6y follow-up.	Homemade pie, ready-made pie, donuts, pastries, cake or brownies, biscuit or cornbread, white bread, sandwich bread, potato or corn chips, rice, pasta, refined grain cereal Median servings per day: Q1: 0.70 Q3: 1.99 Q5: 4.64	Incident metabolic syndrome	There was no association between consumption of refined grains and incident MetSyn HR=0.89 (0.78-1.01); p=0.15.
Kasum et al (2001) [121] Positive quality	23,104 women aged 55-69y in 1986 in the Iowa Women's Health Study, USA. Diet assessed with 127-item FFQ and occurrence of cancer identified from Iowa Health Registry. Proportional hazards regression analysis used to calculate hazard ratio of cancer risk over 12years.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza Q1: 0-2.5 servings/week Q3: 5.5-8.0 servings/week Q5: 13.5-73.0 servings/week	Incident endometrial cancer	There was no association between refined grain intake and endometrial cancer. HR=1.19 (0.80-1.78); p=0.32
Kasum et al (2002) [120] Positive quality	34,651 postmenopausal women aged 55-69 in 1985 in the Iowa Women's Health Study, USA. Diet assessed with 127-item FFQ and occurrence of cancer identified from Iowa Health Registry. Proportional hazards regression analysis used to calculate hazard ratio of cancer risk over 14y follow-up.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza T1: 0-4.0 servings/week T2: 4.5-9.0 servings/week T3: 9.5-78.0 servings/week	Incident upper aerodigestive cancer	There was no significant association between refined grain intake and upper aerodigestive cancers combined, nor for any individual sites. *All sites combined* HR=1.03 (0.67-1.58); p=0.92 *Oral/pharyngeal:* HR=0.70 (CI not reported) *Esophageal*: HR=0.60 (CI not reported) *Nasopharyngeal*: HR=1.44 (CI not reported) *Laryngeal*: HR=0.77(CI not reported)

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Nicodemus et al (2001) [119] Positive quality	29,110 postmenopausal women aged 55-69 in 1985 in the Iowa Women's Health Study, USA. Diet assessed with 127-item FFQ and occurrence of cancer identified from Iowa Health Registry. Proportional hazards regression analysis used to calculate hazard ratio of cancer risk over 9y follow-up.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza Q1: 0-2.5 servings/week Q3: 5-8 servings/week Q5: 13-78 servings/week	Incident postmenopausal breast cancer	Intakes of refined grain foods was unrelated to postmenopausal breast cancer. RR=1.06 (0.84-1.3); p=0.80
Fung et al (2005) [118] Positive quality	71,058 women in the Nurses Health Study, USA. Diet assessed 6 times with 116-item FFQ and incident breast cancer obtained by self-report in biennial questionnaires. Cox's proportional hazards regression analysis used to assess associations between dietary patterns and risk of breast cancer over 16y	Not stated in paper but assumed to be the same as other reports from the Nurses Health Study, ie: White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza. Low: 1-1.9 servings per day Hi: 4+ servings per day	Incident breast cancer	Intake of refined grain food was unrelated to breast cancer risk: RR=1.10 (0.85-1.43). RR one serving increase = 1.07(0.99-1.17); p=0.09
Schulz et al (2002) [124] Positive quality	11,005 women and 6364 men in the EPIC Potsdam cohort, a large multicentre European cohort study. Two year changes in weight were measured and diet assessed by 148 item FFQ. Differences in mean food group intake across weight changes tested using ANOVA.	n/a The following food groups were reported: *Bread*: bread and rolls (white and wholewheat), croissant, pretzel *Cereals*: pasta, cereals, rice, cornflakes, crisps, muesli *Cakes:* fruitcake, layer cake, biscuits, pancake, cookies	Weight change	Odds ratios for large weight <u>gain</u> in men/women : (none statistically significant) Bread: 1.00 (0.89-1.13)/1.09(0.96-1.24) Cereals: 0.97 (0.68-1.40)/0.93 (0.66-1.31) Cakes: 1.09 (0.95-1.25)/1.04 (0.92-1.18) Odds ratios for large weight <u>losses</u> in men/women: Bread: 1.01 (0.90-1.14)/0.93 (0.83-1.04) NS Cereals: 0.91 (0.63-1.30)/ 1.43 (1.09-1.88); p<0.05)

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Newby et al (2003) [123] Positive quality	1379 healthy children aged 2-5y in North Dakota, USA. The cohort has been followed every two years since 1976 using a validated 84-item FFQ and self-reported weight. Multiple regression analysis estimated association of diet and weight change.	*Bread and grains* food group included rice, spaghetti and sauce, pizza, macaroni and cheese, bread, hot and cold cereals, pancakes, English muffins, biscuits and cornbread.	Annual weight change	There was a 0.16 (0.20-0.12)kg lower weight increase per year with each additional daily serving of breads and grains ($p<0.01$)
Bazzano et al (2005) [122] Neutral quality	17,881 men aged 40-84 recruited in 1982 in the Physicians Health Study, USA. Diet assessed annually with 61-item FFQ for 13 years of follow up. Cox's proportional hazards model used to calculate relative risks.	Breakfast cereals divided into wholegrain (>25% whole grain or bran content) or refined grain cereals. Q1: rarely Q2: 1 serving/week Q3: 2-6 servings/week Q4: ≥1 serving/ day	Body weight gain BMI ≥ 25 RR of weight gain >10kg	Over 8 years, compared to men with the lowest intake of refined grain cereals, men with the highest intake of refined grain breakfast cereals had: Less weight gain (0.94± 0.16 vs 1.46±0.05kg; $p=0.005$ Risk of BMI ≥ 25, RR=0.81(0.64-1.03); $p=0.03$ After 13 years of follow up, men with the highest intake of refined grain breakfast cereals had the lowest risk of more than 10kg weight gain: RR=0.77 (0.56-1.06); $p=0.05$.

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Steffen et al (2003) [126] Positive quality	11,940 men and women aged 45-64y in 1987-9 in the ARIC study, USA. Diet assessed with 61-item FFQ. Total deaths were confirmed by hospital and physician records at 3-yearly examinations. Cox proportional hazards regression used to measure dietary association with death over 11y follow-up.	Cold breakfast cereals containing <25% wholegrain or bran by weight, cooked cereals, white bread, bagels, donuts, pastry, muffins, biscuits, cookies, cakes, brownies, pasta and rice. Q1: 0.5 servings/d Q3: 2.0 servings/d Q5: 5.0 servings/d	All-cause mortality	The risk of all-cause mortality was not associated with consumption of refined grain foods. RR=1.08 (0.83-1.40); p=0.62
Trichopoulou et al (2009) [125] Neutral quality	23,349 men and women in the European Prospective Investigation into Cancer and nutrition (EPIC) – Greek segment. Diet assessed with 150-item FFQ. Associations between dietary variable and mortality derived from Cox regression comparing < or ≥ median intake over 8.5y follow-up.	n/a Only “cereals” (undefined) reported Median intakes and interquartile range: Men: 178 (135-233) g/d Women: 140 (108-176) g/d	Total mortality	High cereal consumption (≥ median) was not significantly related to overall mortality Mortality ratio: 0.989 (0.862-1.133); p=0.869.

Author ***Quality rating***	**Subjects and study design**	**Foods defined as refined grain**	**Outcomes measured**	**Key results**
Buyken et al (2010) [127] Positive quality	1490 postmenopausal women and 1245 men aged ≥49y at baseline (1992-4) in the prospective cohort Blue Mountains Eye Study, Australia. Diet assessed with 145-item FFQ and mortality data obtained from the Australian National Death Index. Cox proportional hazards regression analysis used to assess relation of carbohydrate foods and mean dietary GI with deaths form inflammatory disease and CVD over 13y follow-up.	n/a. Study reported on: *Breads and cereals,* comprising: Breakfast cereals, bread (white or other), pasta and rice And *Foods rich in refined sugars and starches*, comprising: Soft drinks, cordials, sweet biscuits, cakes, buns, scones, pastries, confectionery, sugar, honey, jams and syrup Median tertile intakes not reported	Death from inflammatory diseases and CVD	A higher baseline consumption of breads and cereals was associated with a reduced risk of inflammatory disease-related mortality in women. HR=0.45 (0.26-0.80); p=0.008 There was no association for men (p=0.24) Foods rich in refined sugars and starch were associated with increased risk in women HR=1.93z90.98-3.82); p=0.04, but not in men (p=0.41). There were no associations between refined grain food and CVD risk (data not reported)
Merchant et al (2006) [128] Positive quality	34,160 men aged 40-75y in the Health Professionals Follow-Up Study, USA. Diet assessed with 131-item FFQ. Periodontitis assessed by self report in biennial questionnaires over 12 years. Cox proportional hazard model used to estimate relative risk.	White bread (including pita bread), cold breakfast cereal with <25% wholegrain or bran content), English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, pizza Median intakes (servings/d) Q1: 0.7 Q3: 1.8 Q5: 4.2	Periodontitis	Periodontitis was not associated with refined grain intake. RR=1.04 (0.89-1.23): p=0.37

Table 3. Intervention studies that have examined the effects of different levels of refined grain intake

Author ***Quality rating***	**Subjects**	**Study design**	**Diet**	**Outcomes**	**Key results**
Azadbakht et al (2005) [129] Positive quality	34 men and 82 women (mean age 41.2y; mean BMI 28.9) Iran.	6-month RCT with 2 intervention 500kcal/d hypocaloric diets and one "as usual" control.	All contained total 8 grain servings per day. Refined grain servings/d: DASH – 3.8 Weight reduction – 4.0 Control – 7.1	Weight, WC, HDL cholesterol, TGs, BP	No significant change in any measures in the control group with the highest refined grain intake. Reduced weight (13-16kg) and WC (5-7 cm) in the two intervention diets compared to control ($p<0.04$), but no significant different between two intervention diets in weight or WC changes. Greater reduction in TG, BP and increases in HDL in DASH group vs weight control diet ($p<0.05$)
Andersson et al (2007) [130] Positive quality	22 women and 8 men (mean age 59y; mean BMI 28) Sweden.	Nonblinded crossover randomized trial, with two 6-week periods, separated by 6-8 weeks washout. All cereal foods provided.	7 cereals servings/d of (3 bread slices, 2 crispbread slices, 1 portion muesli, 1 portion pasta) provided – either all wholegrain (WG) or all refined grain. WG period: 162g/d WG Refined grain: 154g/d	Insulin sensitivity, blood glucose, serum insulin, lipids, blood pressure, markers of inflammation (CRP or IL-6)	Substitution of wholegrains for refined grains in the habitual daily diets of healthy moderately overweight adults for 6 weeks did not affect insulin sensitivity or markers of lipid peroxidation or inflammation
Katcher et al (2008) [131] Positive quality	25 men and 25 women with metabolic syndrome and BMI >30 (mean age 56y; mean BMI 36) USA	12-week randomized parallel arm study with participants given advice for a 500kcal/d hypocaloric diet.	Participants given target number of grain servings per day based on energy needs (4-7/d) and assigned to either consume either all or none of grains as WG foods.	Weight, WC, % body fat, fasting glucose and insulin, lipids, BP, and markers of inflammation (CRP, PAQ-1, IL-6, TNF-alpha)	Body weight, WC and % body fat decreased significantly in both groups ($p<0.001$), but there were no significant difference between groups for total weight loss, or lipid or BP changes. The only significant differences between the two diets were: 1) a greater decline in % abdominal fat in the WG group (-2.2 vs -0.9; $p=0.03$), and 2) C-reactive protein decreased 38% in the WG group ($p<0.05$) and remained unchanged in the refined grain group.

Author ***Quality rating***	**Subjects**	**Study design**	**Diet**	**Outcomes**	**Key results**
Burton-Freeman & Keim (2008) [132] Positive quality	25 overweight women (mean age 31y; mean BMI 27) USA.	Two-arm RCT with a low or high GI energy and CHO-matched breakfast meals. Each study preceded by 3-day run in with all breakfast foods provided.	High GI (76.7) meal based on rice/corn cereal, reduced fat milk and fruit yoghurt. Low GI (36.5) meal based on bran cereal, reduced fat milk and yoghurt Whey protein and cream added to equalise fat and protein contents.	Subjective satiety, cholecystokinin, glucose, insulin, TGs and free fatty acids measured at defined intervals for 8h after breakfast meal	The high GI meal resulted in greater satiety overall compared with the low GI meal: High vs Low GI meal results: Hunger: -27.6 vs -22.4 ($p=0.0001$) CCK was greater with high GI meal ($p<0.001$). Plasma glucose, insulin and TG were higher and free fatty acids lower after the high GI meal ($p<0.001$).
Wolever et al (2008) [133] Positive quality	162 men and women with type 2 diabetes managed by diet alone (mean age 60y; BMI: 30-31) Canada	12 month RCT with three arms: • High CHO-High GI • High CHO-Low GI • Low CHO-high MUFA	Proportion of energy from refined grains (breads, cereals, rice, pasta): High GI: 35% Low GI: 26% Low CHO: 0%	Weight, WC, HbA1c, CRP	Body weights and HbA1c did not differ between the diets. Mean CRP with the low GI diet was 30% less than the high GI diet ($p=0.0078$) but the low CHO diet (with lowest refined grain content) was intermediate.
Enright & Slavin (2008) [134] Positive quality	10 men and 10 women (mean age 27y, mean BMI 23.9). USA.	14 day randomized crossover dietary intervention consuming either WG (>51% WG) or refined grain foods provided.	8 grain servings per day (males) or 6 servings/d (females)	Antioxidant measures: ORAC in blood; Isoprostanes and thiabarituric acid reactive substances (TBARS) in urine	No significant differences in any antioxidant measures were found between the refined and wholegrain diets.

Author ***Quality rating***	**Subjects**	**Study design**	**Diet**	**Outcomes**	**Key results**
Giacco et al (2010) [135] Positive quality	12 men and 3 women (mean age 55y, mean BMI 27.4). Italy.	After 2 week run-in. a randomized crossover study with two 3-week interventions of isoenergetic diets including wholemeal or refined wheat foods.	Usual diet with inclusion of wholemeal or refined wheat bread, pasta, rusks and crackers. All food provided to participants Differences in cereal fibre: 23.1 vs 9.8g/d	Weight, BP, plasma glucose, lipids, C-peptide, free fatty acids, leptin, adiponectin, ghrelin, CRP and plasma antioxidants.	There were no differences in weight, blood pressure, or fasting clinical or metabolic parameters. There were also no differences in plasma antioxidant levels between the two diets. Total and LDL cholesterol were lower than run-in values with both diets ($p<0.01$) but with a greater reduction on the WG rather than the refined grain diet ($P=0.04$)
Brownlee et al (2010) [136] Positive quality	316 men and women (mean age 46y, mean BMI 30) consuming <30gWG/d. UK	16-week intervention trial with subjects randomised to: • control (no change) • 60gWG/d 16 weeks • 60gWG/d for 8 weeks followed by 120WG/d for further 8 weeks	Subject provided with WG foods (bread, cereals, rice, snack bars) = 3 slices of bread per day (60g WG)	BMI, WC, % body fat, lipids, glucose and insulin, inflammatory markers (CRP, IL-6, Fibrinogen, PA-1)	Achieved WG intakes: Control: 19g/d Intervention 1: 74g/d Intervention 2: 115g/d Despite good compliance there were no significant differences in any CVD risk markers between groups, possibly because subjects added the WG foods to their diet (and increased energy intakes) rather than substituting for refined grain alternatives.
Venn et al (2010) [137] Positive quality	93 women and 15 men with BMI ≥ 28 (mean age 42; mean BMI 35-36) New Zealand	18-month RCT; control group instructed to follow NZ Heart Foundation guidelines; intervention: additional pulses and WG cereals	Control: at least 6 servings breads and cereals Intervention: at least 2 servings pulses to substitute for cereals and 4 servings breads and cereals to be wholegrain. One serving – one 37g slice bread; 30g cereal.	Weight, BMI, WC, plasma lipids,	Participants only achieved 1.4 servings/d WG in intervention vs 1.1 in control ($p=0.71$) Body weight, BMI, WC and BP in both groups reduced compared to baseline, but differences between the two diet groups were not significant ($p>0.05$), except for WC (2.8cm greater reduction on the WG diet at 18months).

Table 4. Studies allowing assessment of the highest intake of refined grain foods with no increased health risk

Author ***Quality rating***	***Study type***	***Outcomes***	***Highest intake with no increased risk***
Senesse et al (2002) [154]	Case-control	Colorectal adenomas	Bread – Q3: 152g/d; Pasta – Q4: 57g/d Rice – Q4: 32g/d
Satia-Aboutia et al (2004) [92]	Case-control	Colon cancer	Q3: 235 g/d 16.8x/week (= 2.4x/d)
Slattery et al (2004) [93]	Case-control	Rectal cancer	Q4: 4.5x/d (vs total 6.71) = 67% of all grains as refined
Liang et al (2010) [97]	Case-control	Ischemic stroke	Rice – Q1; <1100g/week (= 157g/d)
Hodge et al (2004) [115]	Prospective	Type 2 diabetes	All cereals - Q4: 5.9x/d) Breakfast cereal - Q4: 1x/d Rice- Q4: 2.5x/week White bread – Q3: 6.9x/week Pasta – Q4: 3x/week
Wang et al (2007) [110]	Prospective	Hypertension	Lower risk of HT began when wholegrains >43% of total grains (= 57% of all grains as refined) Refined grains - Q4: 3.1x/d
Savage et al (2008) [101]	Prospective	Weight change	T1: 3.9x/d
Sun et al (2010) [114]	Prospective	Type 2 diabetes	White rice – Q3: 1x/week
Nanri et al (2010) [113]	Prospective	Type 2 diabetes	White rice – Q2: 315g/d Rice noodles – Q4: 177g/d

Table 5. Evidence Summary

What proportion of refined grains can be consumed in a healthy diet?		
Evidence Statement	**Consumption of up to 50% of grains as refined grain foods, without significant added fat, sugar or sodium, is not associated with increased disease risk.**	
Grade	**C**	Body of evidence provides some support but care should be taken in its application
Component	**Rating**	**Notes**
Evidence base	Good	8 Level 1 studies (1 meta-analysis of 3 RCTs; 7 systematic reviews) 9 Level 2 studies (RCTs) 44 Level 3 studies (31 cohort and 13 case-control studies) 18 Level 4 studies (cross-sectional studies)
Consistency	Satisfactory	Evidence is inconsistent but the clear majority find no significant effect on risk
Clinical impact	Moderate	Highest: Stomach cancer RR=2.07 Lowest: Pancreatic cancer RR=0.80
Generalisability	Good	A diverse range of adult populations from different countries were included in the studies
Applicability	Satisfactory	Differences in food products and dietary patterns between countries may limit applicability