POSTPRINT VERSION

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Whole grain consumption and human health: an umbrella review of observational studies

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Keywords: whole grain; fiber; evidence; prospective; cohort; meta-analysis; umbrella review

Abstract

Whole grains have been associated with a number of health benefits. We systematically reviewed existing meta-analyses of observational studies and evaluated the level of evidence for their putative effects based on pre-selected criteria. Of the 23 included studies, we found convincing evidence of an inverse association between whole grain consumption and risk of type-2 diabetes and colorectal cancer; possible evidence of decreased risk of colon cancer and cardiovascular mortality with increased whole grain intake, as well as increased risk of prostate cancer. Limited or insufficient evidence was available for all other outcomes investigated. Overall findings are encouraging for a positive effect of whole grain consumption on certain diseases, especially highly prevalent metabolic diseases, however, uncertainty of some negative associations deserves further attention.

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Introduction

Whole grains have been defined as “the intact ground, cracked or flaked kernel after the removal of inedible parts such as hull and husk, where the principal anatomical components (the starchy endosperm, germ and bran) are present in the same relative proportions as they exist in the intact kernel and allowing for very small losses during preparation” (Ross et al. 2017). Consumption of whole grain ingredients (hereafter referred to as whole grains) has been associated with several benefits on human health (Calinoiu and Vodnar 2018). For example, epidemiological evidence identifies increased intake of whole grains is associated with decreased mortality from cardiovascular disease (CVD) (Reynolds et al. 2019). In addition, there is significant evidence that a diet high in whole grains is beneficial for the prevention and treatment of type II diabetes mellitus (T2DM) (Della Pepa et al. 2018). Given the metabolic basis of such conditions, high rates of obesity globally (Collaboration 2017), may be a mediating factor for many chronic degenerative non-communicable diseases (Zhu and Sang 2017). Evidence suggests a potential role of whole grains in helping maintaining a healthy body weight and reducing risk of obesity, further reinforcing a role for whole grains in a healthful diet (Koh-Banerjee et al. 2004, Kristensen et al. 2012).

Whole grains are high in dietary fiber, which is overwhelmingly linked with positive health outcomes. However, in addition to fiber, whole grains contain vitamins, minerals, and phytochemicals with antioxidant properties, all of which may contribute to health benefits of whole grains (Zhu and Sang 2017). Somewhat disappointingly, despite all evidence, intake of whole grains globally is lower than general recommendations (Barrett, Amoutzopoulos, et al. 2020, Barrett, Batterham, et al. 2020, Galea et al. 2017, Kissock et al. 2020, Mann et al. 2015, McGill et al. 2015). A recent review of global morbidity and mortality data in 195 countries identified poor whole grain intake secondary only to high sodium intake as a key risk for mortality associated with chronic disease. With respect to morbidity, low whole grain intake was associated with the highest number of disability adjusted life years (Collaborators 2019).

Therefore, overall, there is general agreement that consumption of whole grains might lead to prevention of several non-communicable diseases (NCDs). Surprisingly, evidence from prospective cohort studies is sometimes mixed, as some individual reports showed no significant or even contrasting results. Thus, the aim of the present study was to systematically review current evidence

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on whole grain consumption and various health outcomes provided from meta-analyses of observational studies. This may further identify health outcomes associated with whole grain consumption but also inform where research into specific conditions is lacking.

Methods

Study selection

We performed a systematic review of existing meta-analyses of prospective cohort studies on whole grain consumption and various health outcomes in Medline and Embase electronic databases until January 2017. The search strategy included: [(whole grain OR whole grains OR fiber) AND (meta-analysis OR meta-analyzed OR pooled analysis OR systematic review)] with Title/Abstract restriction. Only meta-analyses of prospective cohort studies on whole grain consumption as the variable of exposure were included for evaluation. Meta-analyses of RCTs with outcomes of intermediary biomarkers of disease (i.e., blood lipids, blood pressure, etc.) or intermediary clinical conditions (i.e., variation in body weight/BMI, etc.), and systematic reviews without quantitative evaluation of the association between exposure and outcome were not included for evaluation. Hand searching of reference lists was also undertaken. Any discrepancy on the inclusion/exclusion decision was solved through discussion.

Data extraction

From each meta-analysis included, the following information was extracted: name of the first author and year of publication, outcome, number of studies included in the meta-analysis, study design of included studies (i.e., case-control/cross-sectional and prospective), total number of population, number of cases, type of exposure, measure of exposure [including highest versus lowest (reference) category of exposure or dose-response incremental servings per day (linear)], effect sizes [risk ratio (RR), odds ratio (OR), or hazard ratio (HR)].

Data evaluation and evidence synthesis

Where more than one meta-analysis was conducted on the same outcome, including the same study design, and the same population group, the concordance for the main outcome of interest, including direction and magnitude (overlapping confidence interval) of the association was evaluated. For further analyses, the most recent/exhaustive study was considered. The pooled analyses of the highest versus. the lowest (reference) category of exposure and dose-response analyses were

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evaluated. Direction and magnitude of the association, heterogeneity (I_2) of results, and subgroup/stratified analyses for potential confounding factors were considered to have indication of level of evidence. Criteria used for evidence categorization were modified from the Joint WHO/FAO Expert Consultation (Degrees of evidence by the Joint WHO/FAO Expert Consultation. http://www.who.int/nutrition/topics/5_population_nutrient/en/#diet5.1.2 Accessed Novermber 2015) (Table 1). Briefly, the relation between exposure and outcomes was categorized as following: suggestive/limited/contrasting evidence, when there was availability of solely meta-analyses of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence; possible evidence, when there was availability of meta-analyses with lack of information on/significant heterogeneity (I_2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups); probable association, when there was availability of meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained (and evidence of dose-response relation further investigated); convincing association, when there was concordance between meta-analyses of RCTs and observational studies. Lack of fulfillment of the previous criteria was considered as insufficient evidence.

Results

Study selection

Of 407 articles identified through the database search, 315 and 39 articles were excluded based on title and abstract evaluation, respectively (Figure 1). Fifty-three articles were further investigated for eligibility. The exclusion list included 31 meta-analyses of RCT (n = 4), systematic reviews or narrative reviews without quantitative evaluation of the association between exposure and outcome (n = 7), pooled analysis of prospective cohort studies (n = 2), and investigation of different exposures (n = 18). Additionally, one article was retrieved through hand searching of reference lists. Thus, a total number of 23 studies on whole grain consumption and various health outcomes was selected for evaluation (Anderson et al. 2000, Aune et al. 2012, Aune et al. 2011, Aune et al. 2016, Aune et al. 2013, Chen, Tong, et al. 2016, Chen, Huang, et al. 2016, de Munter et al. 2007, Fang et al. 2015, Hajishafiee et al. 2016, Jacobs et al. 1998, Lei et al. 2016, Li et al. 2016, Liu and Lin 2014, Ma et al. 2016, Mellen et al. 2008, Schulze et al. 2007, Schwedhelm et al. 2016, Tang et al. 2015, Wang et al. 2015, Wei et al. 2016, Ye et al. 2012, Zong et al. 2016).

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Characteristics of the studies included for evaluation

The main characteristics of the studies included for evaluation, including the risk estimates for the highest *versus* the lowest category of whole grain consumption are reported for 13 unique outcomes of seven non-overlapping meta-analyses in Figure 2 and Supplementary Table 1 (Aune, et al. 2011, Aune, et al. 2016, Aune, et al. 2013, Chen, et al. 2016, Fang, et al. 2015, Liu and Lin 2014, Wang, et al. 2015). These included three or more prospective cohort studies and risk estimates for increasing consumption (linear) of whole grains evaluated in four non-overlapping meta-analyses. Studies on T2DM, CVD and coronary heart disease (CHD) risk and mortality, colorectal (more specifically, colon) cancer, and all-cause mortality showed significant decreased risk associated with higher whole grain consumption, with generally no evidence of heterogeneity (except for all-cause and cancer mortality). No significant associations were found for risk of rectal and thyroid cancer, while an increased risk of prostate cancer with no evidence of heterogeneity among studies was reported. These results were mostly consistent when considering a continuous linear increasing intake of whole grains (Supplementary Table 1). When controlling for potential confounding factors, results were relatively consistent, except in relation to CHD and stroke risk, which was observed only among women but not men (Supplementary Table 2). When controlling for stability of findings over time, all previous studies reported consistent results (Supplementary Table 3). Only one study on pancreatic cancer risk (Lei, et al. 2016) was conducted on a limited number of prospective cohort studies (<3) and case-control studies, reporting an inverse association with whole grain consumption with no evidence of heterogeneity.

Summary of evidence

A detailed evaluation of parameters investigated to assess the strength of the evidence on whole grain consumption and various health outcomes is reported in Supplementary Table 4. There is a convincing evidence of an inverse association between whole grain consumption and risk of T2DM and colorectal cancer; possible evidence of decreased risk of colon cancer and CVD and CHD mortality with increased consumption of whole grains; as well as increased risk of prostate cancer. Limited or insufficient evidence has been reported for all other outcomes investigated (Table 1).

Discussion

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In this umbrella review, we investigated the evidence from existing meta-analyses on whole grain consumption and varied health outcomes. Overall, the strongest evidence was a convincing association with decreased risk of colorectal cancer and T2DM with higher compared to lower dietary intake of whole grains. Moreover, a possible decreased risk of colon cancer, fatal CHD and CVD mortality was also observed, together with a possible increased risk of prostate cancer. These latter associations lacked information on potential confounding factors, resulting in a weaker level of evidence compared to colorectal cancer and T2DM.

The level of evidence on the potential protective effect of whole grain consumption on colorectal cancer risk found in our review is in line with the conclusions of the World Cancer Research Fund's (WCRF) 2017 Colorectal report (WCRF/AICR 2018b). Our combined meta-analyses identified a high level of evidence due to consistency of results and no potential confounding factors among the studies investigated. Moreover, separate analyses reviewing the results by cancer site, showed that the evidence of inverse association is only significant for cancer within the colon.

There are plausible mechanisms operating in humans for a protective role of whole grains in colon cancer. In general, the benefits of whole grains towards cancer risk are thought to be mainly related to the content of fiber, which may reduce the risk through different mechanisms. These include a shorter transit time of the feces, resulting in a lower exposure of colonocytes to carcinogens, the modulation of the composition and function of gut microbiota and the prevention of insulin resistance (Bultman 2017, Slavin 2000). Specifically, dietary fiber may enhance the growth of non-pathogenic gut bacteria (namely lactic acid producing bacteria, such as Bifidobacterium) with increased production of lactic acid or short-chain fatty acids (SCFAs), including butyrate, acetate and propionate (Gong et al. 2018). In normal colon cells, butyrate is a growth factor and a nutrient, but it has been hypothesized that it may exert epigenetic effects leading to the hyperacetylation of histones. This subsequently compensates for an imbalance of histone acetylation, which can lead to transcriptional dysregulation and influencing the genes that are involved in the control of cell-cycle progression, differentiation, apoptosis and cancer development (Scharlau et al. 2009). Whole grains are also a rich source of various bioactive compounds, including vitamin E, selenium, copper, zinc, phytoestrogens and phenolic compounds, which may exert beneficial effects above those of cereal fiber (Song et al. 2015, Webb and McCullough 2005). Whole grains may also protect against colon cancer by regulating glycemic response (Sieri et al. 2017). Lastly, an indirect mechanism of

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protection may depend on lower risk of obesity associated with higher consumption of whole grain, which is considered a convincing risk factor for several cancers, including colon cancer (WCRF/AICR 2018a).

Among other cancer outcomes, we found that whole grains were associated with higher risk of prostate cancer. In the latest WCRF's prostate report (WCRF/AICR 2018c), updated to 2014, cereals (grains) and their products, dietary fiber have been included among dietary exposure with "limited-no evidence" for their effects toward prostate cancer risk. Possible reasons for such contrasting results include a number of limitations or bias in the individual studies included in the meta-analyses. One such limitation is the use of varied and potentially inappropriate definitions of whole grains in certain studies. For example, studies within the meta-analysis of Wang (2015) included work which did not differentiate between whole and refined grains adequately (Lewis et al. 2009) or provided lists of foods contributing to whole grains (Drake et al. 2012, Nimptsch et al. 2011) but no set definitions of these foods to provide comparisons to other studies. In addition to these technical difficulties, there has been a change over time of incident cases of prostate cancer due to use of PSA as screening tool, which might have been more common among more health-conscious men consuming higher amount of whole grains (Drake, et al. 2012, Nimptsch, et al. 2011). Considering these or other unidentified limitations, further prospective cohort studies accounting for such confounding factors and effect modifiers are warranted in order to collect a stronger rationale to explain this controversial association.

Consistent with other work, we found a convincing inverse association between whole grain consumption and T2DM. Several international scientific bodies, such as American Diabetes Association and Diabetes UK, recommend inclusion of whole grains within a healthy diet for prevention or management of diabetes. Inclusion of whole grains with an emphasis on a diet with low glycemic load is encouraged (American Diabetes 2018, group 2018). In both prospective studies and RCTs, higher intakes of whole grains or total dietary fiber are associated with reduced incidence and mortality from several NCDs, including T2DM. The dose-response evidence indicating that the relationships could be causal (Reynolds, et al. 2019). For example, in a meta-analysis of RCTs, it emerged that the consumption of whole grains improves acute postprandial glucose and insulin homeostasis compared to similar refined foods in healthy subjects (Marventano et al. 2017). Whole grains products have high concentration of fibers, in particular the insoluble fraction, while some products derived from barley and oats are also sources of soluble β-glucans. Insoluble dietary fibers have been shown to improved whole-body insulin resistance after short-term and prolonged cereal fiber intake (Weickert and Pfeiffer 2018). The dietary fiber component of whole grains has been shown to result in decreased blood glucose excursions and attenuated insulin responses, resulting in an improved insulin sensitivity (Liese et al. 2003). Specifically, cereal β-glucans show a dose response to attenuate blood glucose excursions (Bao et al. 2014). For all fibers, this may be due to delayed gastric emptying, which slows glucose release in circulation, through a delayed or decreased intestinal absorption (Lattimer and Haub 2010).

However, the mechanisms behind insoluble fiber are thought to be more peripheral and not limited to nutrient absorption. For instance, whole grain intake is also associated with lower inflammatory markers in both women and men with T2DM (Qi et al. 2005, Qi et al. 2006). Higher concentrations of pro-inflammatory cytokines, such as C-reactive protein and adiponectin, may increase T2DM risk (Li et al. 2009, Wang et al. 2013). Another possible mechanism for the beneficial effects of whole grains include the fermentation of fiber and resistant starch by microbiota in the large intestine with the production of SCFAs, which have been linked to secretion of gut hormones, glucose and lipid metabolism, therefore with implications for insulin sensitivity and glucose homeostasis (Bach Knudsen 2015). Finally, whole grain consumption has also been considered as a dietary behavior inversely associated with long-term weight gain, which in turn is related to risk of developing insulin resistance and T2DM (Mozaffarian et al. 2011).

In our umbrella review we also observed a possible decreased risk of fatal CHD and CVD mortality for higher intake of whole grains. CVD risk in general, including CHD risk, may be significantly influenced by modifying a number of risk factors, such as high blood pressure, elevated blood lipids and excess of body weight, through diet and lifestyle changes (Eckel et al. 2014, Piepoli et al. 2016). Once again, the strongest evidence for their potential beneficial effects relies on their content in dietary fiber (Reynolds, et al. 2019). In 2013, the “AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk” emphasized the role of whole grain consumption to lower blood pressure and LDL-cholesterol (Eckel, et al. 2014). Similarly, the ESC Guidelines on CVD prevention, encourage intake of whole grain products as one important dietary goal to reduce CVD risk contributing to the suggested fiber intake of 30-45 g per day for CVD prevention (Piepoli, et al. 2016). While the mechanism is not fully elucidated, it has been shown that a high fiber intake

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reduces postprandial glucose responses after carbohydrate-rich meals and lowers total cholesterol and LDL-cholesterol levels (Piepoli, et al. 2016). Although is often not possible to distinguish between the effect of the different type of whole grains in the investigated studies, it is known that the intake of barley and oat β-glucan, is effective in reducing LDL-cholesterol and non-HDL-cholesterol, thus contributing in the reduction of CVD risk factors (Ho et al. 2016, Li, et al. 2016, Whitehead et al. 2014). The significant evidence means that in 2010, the European Food Safety Authority (EFSA) concluded that a cause and effect relationship has been established between the consumption of oat β-glucan and lowering of blood LDL-cholesterol concentrations following at least 3 g of oat β -glucan per day (EFSA Panel on Dietetic Products 2010). Cholesterol-lowering effects of oat β -glucan may depend on the increased viscosity in the small intestine that reduces the reabsorption of bile acids, increases the synthesis of bile acids from cholesterol, and reduces circulating LDL-cholesterol concentrations (Henrion et al. 2019). The effect is proportional to viscosity of the β-glucan and this typically decreases with significant processing (Wolever et al. 2010), further substantiating the importance of the whole grain rather than refined alternatives of grains. Some clinical studies also reported a potential influence of whole grain in ameliorating blood pressure, but further studies are needed to confirm such effect (Saltzman et al. 2001, Tighe et al. 2010).

The present study has some limitations that should be addressed. The results shown in this report share the common issues of the original meta-analyses included through the systematic search, such as (i) lack of homogeneity in measurement methods (for example food frequency questionnaires vs. dietary recalls for collection of dietary data), (ii) disagreement in quantification of a serving of whole grains among studies, (iii) lack of information regarding type of whole grains (i.e. wheat, oat, rye etc. as whole grain ingredients alone or incorporated into grain-based products). Furthermore, whole grain consumption is generally a health-conscious choice, which tends to cluster with lower prevalence of smoking, higher physical activity levels, lower fat and higher fiber intakes (Harland and Garton 2008). Thus, uncontrolled or residual confounding cannot be excluded. Finally, the definition of whole grains or whole grain foods is not univocal, thus the original papers may incur in misclassification and overall heterogeneity of exposure. It has been suggested that for future whole grain studies, grams of whole grain on a dry weight basis must be calculated and that use of whole approximations based on whole grain food definitions or “serves” of whole grains are not suitable (Ross et al. 2015).

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In conclusion, dietary intake of whole grains has been shown to provide substantial benefits toward human health. The findings are quite consistent and there is evidence for assuming causation, at least for colorectal cancer and T2DM, for which we observed a convincing level of evidence. The contributions of whole grains in increasing daily fiber intake seem to be crucial in explaining the biological mechanisms underpinning these associations. Further research where weak associations of whole grain intake with health outcomes are noted, require further investigation and a critical aspect in this work may be careful adherence to recommendations for reporting of whole grain definitions and quantification of intake.

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Declaration of interests

The authors declare no conflicts of interest.

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Table 1. Level of evidence for the association between dairy (total and individual foods) consumption and health outcomes.

Level of evidence*	Criteria§	Whole grains
Convincing	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	Association with decreased risk of cancer (colorectal), T2DM.
Probable	Meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	None.
Possible	Meta-analysis of prospective cohort studies with no heterogeneity and lack of information on potential confounding factors.	• Association with decreased risk of cancer (colon), CHD (fatal), mortality (CVD) • Association with increased risk of cancer (prostate).
Limited	Meta-analysis of prospective cohort studies with presence of significant heterogeneity (I_2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups).	Association with decreased risk of mortality (cancer), CHD (any)#, mortality (all-cause), stroke (total)#
Insufficient	Meta-analysis of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence.	Association with decreased odds of adenoma (colorectal), cancer (pancreas).
No evidence	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	No association with risk of cancer (rectum), stroke (fatal).

*all the associations should be biologically plausible; potential confounding factors should be taken into account.
§ modified from the Joint WHO/FAO Expert Consultation
# presence of potential confounding factors

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Figure legend

Figure 1. Flow chart of study selection.

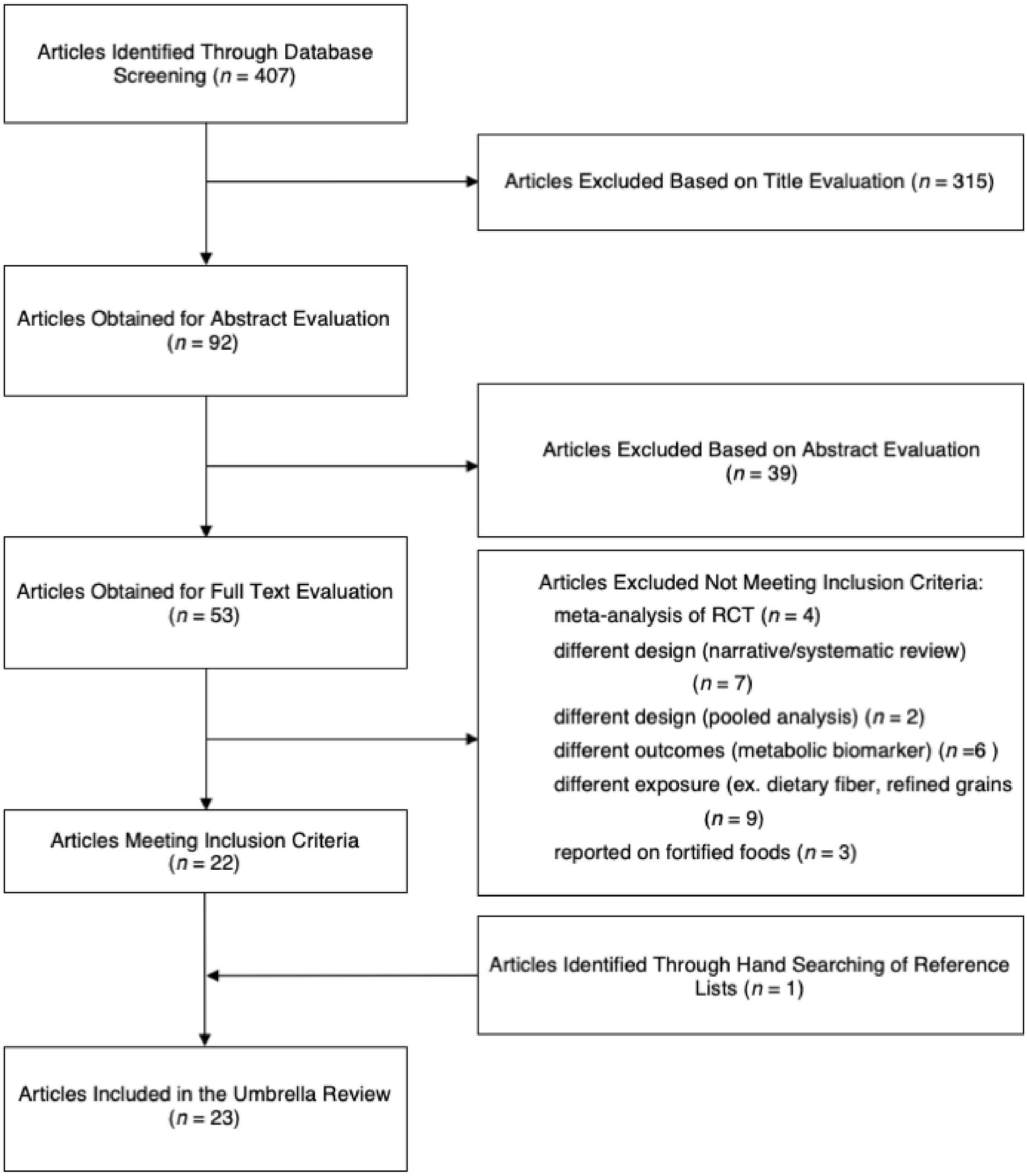

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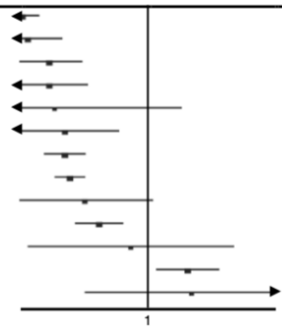
Figure 2. Summary results from meta-analyses of prospective cohort studies on whole grain consumption on various health outcomes included in umbrella review.

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
T2DM	10	383,550	19,105	0.74 (0.71, 0.78)	0%	Aune et al. 2013
IHD mortality	7	353,736	5,876	0.75 (0.69, 0.83)	0%	Chen et al. 2016
CHD	7	310,194	6,418	0.79 (0.73, 0.86)	0%	Aune et al. 2016
Colorectal cancer	4	642,060	5,477	0.79 (0.72, 0.86)	0%	Aune et al. 2011
Rectal cancer	4	606,863	1,393	0.80 (0.59, 1.07)	58%	Aune et al. 2011
Colon cancer	4	787,337	4,217	0.82 (0.72, 0.92)	23%	Aune et al. 2011
CVD mortality	12	847,014	26,352	0.82 (0.78, 0.85)	0%	Chen et al. 2016
All-cause mortality	12	828,516	96,218	0.83 (0.80, 0.88)	70%	Chen et al. 2016
Stroke risk	6	247,490	8,222	0.86 (0.73, 0.99)	0%	Fang et al. 2015
Cancer mortality	8	684,890	35,667	0.89 (0.84, 0.95)	53%	Chen et al. 2016
Stroke mortality	4	244,489	987	0.96 (0.75, 1.22)	39%	Chen et al. 2016
Prostate cancer	3	84,753	7,010	1.10 (1.02, 1.19)	0%	Wang et al. 2015
Thyroid cancer	4	9,540	699	1.11 (0.86, 1.42)	0%	Liu et al. 2014



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Supplementary material

Supplementary Table 1. Summary results from meta-analyses investigating continuous linear exposure to whole grain consumption and health outcomes.

Supplementary Table 2. Significance and direction of results from selected meta-analyses on whole grain consumption and health outcomes.

Supplementary Table 3. Characteristics and main findings of meta-analyses of cohort studies (highest vs. lowest category of exposure) on whole grain consumption on overlapping outcomes over time.

Supplementary Table 4. Variables investigated to address the strength of evidence from selected meta-analyses on whole grain consumption and health outcomes.

POSTPRINT VERSION

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