



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

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

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40 **observational studies**

41

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

43

44 **Abstract**

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

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54 **Introduction**

55 Whole grains have been defined as “the intact ground, cracked or flaked kernel after the removal of
56 inedible parts such as hull and husk, where the principal anatomical components (the starchy
57 endosperm, germ and bran) are present in the same relative proportions as they exist in the intact
58 kernel and allowing for very small losses during preparation” (Ross et al. 2017). Consumption of
59 whole grain ingredients (hereafter referred to as whole grains) has been associated with several
60 benefits on human health (Calinoiu and Vodnar 2018). For example, epidemiological evidence
61 identifies increased intake of whole grains is associated with decreased mortality from
62 cardiovascular disease (CVD) (Reynolds et al. 2019). In addition, there is significant evidence that a
63 diet high in whole grains is beneficial for the prevention and treatment of type II diabetes mellitus
64 (T2DM) (Della Pepa et al. 2018). Given the metabolic basis of such conditions, high rates of
65 obesity globally (Collaboration 2017), may be a mediating factor for many chronic degenerative
66 non-communicable diseases (Zhu and Sang 2017). Evidence suggests a potential role of whole
67 grains in helping maintaining a healthy body weight and reducing risk of obesity, further
68 reinforcing a role for whole grains in a healthful diet (Koh-Banerjee et al. 2004, Kristensen et al.
69 2012).

70
71 Whole grains are high in dietary fiber, which is overwhelmingly linked with positive health
72 outcomes. However, in addition to fiber, whole grains contain vitamins, minerals, and
73 phytochemicals with antioxidant properties, all of which may contribute to health benefits of whole
74 grains (Zhu and Sang 2017). Somewhat disappointingly, despite all evidence, intake of whole
75 grains globally is lower than general recommendations (Barrett, Amoutzopoulos, et al. 2020,
76 Barrett, Batterham, et al. 2020, Galea et al. 2017, Kissock et al. 2020, Mann et al. 2015, McGill et
77 al. 2015). A recent review of global morbidity and mortality data in 195 countries identified poor
78 whole grain intake secondary only to high sodium intake as a key risk for mortality associated with
79 chronic disease. With respect to morbidity, low whole grain intake was associated with the highest
80 number of disability adjusted life years (Collaborators 2019).

81
82 Therefore, overall, there is general agreement that consumption of whole grains might lead to
83 prevention of several non-communicable diseases (NCDs). Surprisingly, evidence from prospective
84 cohort studies is sometimes mixed, as some individual reports showed no significant or even
85 contrasting results. Thus, the aim of the present study was to systematically review current evidence

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

89

90 **Methods**

91 *Study selection*

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

103

104 *Data extraction*

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

111 *Data evaluation and evidence synthesis*

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

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117 evaluated. Direction and magnitude of the association, heterogeneity (I^2) of results, and
118 subgroup/stratified analyses for potential confounding factors were considered to have indication of
119 level of evidence. Criteria used for evidence categorization were modified from the Joint
120 WHO/FAO Expert Consultation (Degrees of evidence by the Joint WHO/FAO Expert Consultation.
121 http://www.who.int/nutrition/topics/5_population_nutrient/en/#diet5.1.2 Accessed November
122 2015) (Table 1). Briefly, the relation between exposure and outcomes was categorized as following:
123 suggestive/limited/contrasting evidence, when there was availability of solely meta-analyses of
124 case-control studies, limited prospective cohort studies included in meta-analyses ($n < 3$), or evident
125 contrasting results from meta-analyses with the same level of evidence; possible evidence, when
126 there was availability of meta-analyses with lack of information on/significant heterogeneity (I^2
127 $> 50\%$) or identification of potential confounding factors (i.e., different findings in subgroups);
128 probable association, when there was availability of meta-analyses of prospective cohort studies
129 with no heterogeneity, no potential confounding factors identified, and eventual disagreement of
130 results over time reasonably explained (and evidence of dose-response relation further
131 investigated); convincing association, when there was concordance between meta-analyses of RCTs
132 and observational studies. Lack of fulfillment of the previous criteria was considered as insufficient
133 evidence.

134

135 **Results**

136 *Study selection*

137 Of 407 articles identified through the database search, 315 and 39 articles were excluded based on
138 title and abstract evaluation, respectively (Figure 1). Fifty-three articles were further investigated
139 for eligibility. The exclusion list included 31 meta-analyses of RCT ($n = 4$), systematic reviews or
140 narrative reviews without quantitative evaluation of the association between exposure and outcome
141 ($n = 7$), pooled analysis of prospective cohort studies ($n = 2$), and investigation of different
142 exposures ($n = 18$). Additionally, one article was retrieved through hand searching of reference
143 lists. Thus, a total number of 23 studies on whole grain consumption and various health outcomes
144 was selected for evaluation (Anderson et al. 2000, Aune et al. 2012, Aune et al. 2011, Aune et al.
145 2016, Aune et al. 2013, Chen, Tong, et al. 2016, Chen, Huang, et al. 2016, de Munter et al. 2007,
146 Fang et al. 2015, Hajishafiee et al. 2016, Jacobs et al. 1998, Lei et al. 2016, Li et al. 2016, Liu and
147 Lin 2014, Ma et al. 2016, Mellen et al. 2008, Schulze et al. 2007, Schwedhelm et al. 2016, Tang et
148 al. 2015, Wang et al. 2015, Wei et al. 2016, Ye et al. 2012, Zong et al. 2016).

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149

150 *Characteristics of the studies included for evaluation*

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

170

171 *Summary of evidence*

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

178

179 **Discussion**

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

187
188 The level of evidence on the potential protective effect of whole grain consumption on colorectal
189 cancer risk found in our review is in line with the conclusions of the World Cancer Research Fund's
190 (WCRF) 2017 Colorectal report (WCRF/AICR 2018b). Our combined meta-analyses identified a
191 high level of evidence due to consistency of results and no potential confounding factors among the
192 studies investigated. Moreover, separate analyses reviewing the results by cancer site, showed that
193 the evidence of inverse association is only significant for cancer within the colon.

194
195 There are plausible mechanisms operating in humans for a protective role of whole grains in colon
196 cancer. In general, the benefits of whole grains towards cancer risk are thought to be mainly related
197 to the content of fiber, which may reduce the risk through different mechanisms. These include a
198 shorter transit time of the feces, resulting in a lower exposure of colonocytes to carcinogens, the
199 modulation of the composition and function of gut microbiota and the prevention of insulin
200 resistance (Bultman 2017, Slavin 2000). Specifically, dietary fiber may enhance the growth of non-
201 pathogenic gut bacteria (namely lactic acid producing bacteria, such as *Bifidobacterium*) with
202 increased production of lactic acid or short-chain fatty acids (SCFAs), including butyrate, acetate
203 and propionate (Gong et al. 2018). In normal colon cells, butyrate is a growth factor and a nutrient,
204 but it has been hypothesized that it may exert epigenetic effects leading to the hyperacetylation of
205 histones. This subsequently compensates for an imbalance of histone acetylation, which can lead to
206 transcriptional dysregulation and influencing the genes that are involved in the control of cell-cycle
207 progression, differentiation, apoptosis and cancer development (Scharlau et al. 2009). Whole grains
208 are also a rich source of various bioactive compounds, including vitamin E, selenium, copper, zinc,
209 phytoestrogens and phenolic compounds, which may exert beneficial effects above those of cereal
210 fiber (Song et al. 2015, Webb and McCullough 2005). Whole grains may also protect against colon
211 cancer by regulating glycemic response (Sieri et al. 2017). Lastly, an indirect mechanism of

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

215

216 Among other cancer outcomes, we found that whole grains were associated with higher risk of
217 prostate cancer. In the latest WCRF's prostate report (WCRF/AICR 2018c), updated to 2014,
218 cereals (grains) and their products, dietary fiber have been included among dietary exposure with
219 "limited-no evidence" for their effects toward prostate cancer risk. Possible reasons for such
220 contrasting results include a number of limitations or bias in the individual studies included in the
221 meta-analyses. One such limitation is the use of varied and potentially inappropriate definitions of
222 whole grains in certain studies. For example, studies within the meta-analysis of Wang (2015)
223 included work which did not differentiate between whole and refined grains adequately (Lewis et
224 al. 2009) or provided lists of foods contributing to whole grains (Drake et al. 2012, Nimptsch et al.
225 2011) but no set definitions of these foods to provide comparisons to other studies. In addition to
226 these technical difficulties, there has been a change over time of incident cases of prostate cancer
227 due to use of PSA as screening tool, which might have been more common among more health-
228 conscious men consuming higher amount of whole grains (Drake, et al. 2012, Nimptsch, et al.
229 2011). Considering these or other unidentified limitations, further prospective cohort studies
230 accounting for such confounding factors and effect modifiers are warranted in order to collect a
231 stronger rationale to explain this controversial association.

232

233 Consistent with other work, we found a convincing inverse association between whole grain
234 consumption and T2DM. Several international scientific bodies, such as American Diabetes
235 Association and Diabetes UK, recommend inclusion of whole grains within a healthy diet for
236 prevention or management of diabetes. Inclusion of whole grains with an emphasis on a diet with
237 low glycemic load is encouraged (American Diabetes 2018, group 2018). In both prospective
238 studies and RCTs, higher intakes of whole grains or total dietary fiber are associated with reduced
239 incidence and mortality from several NCDs, including T2DM. The dose-response evidence
240 indicating that the relationships could be causal (Reynolds, et al. 2019). For example, in a meta-
241 analysis of RCTs, it emerged that the consumption of whole grains improves acute postprandial
242 glucose and insulin homeostasis compared to similar refined foods in healthy subjects (Marventano
243 et al. 2017). Whole grains products have high concentration of fibers, in particular the insoluble

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244 fraction, while some products derived from barley and oats are also sources of soluble β -glucans.
245 Insoluble dietary fibers have been shown to improved whole-body insulin resistance after short-
246 term and prolonged cereal fiber intake (Weickert and Pfeiffer 2018). The dietary fiber component of
247 whole grains has been shown to result in decreased blood glucose excursions and attenuated insulin
248 responses, resulting in an improved insulin sensitivity (Liese et al. 2003). Specifically, cereal β -
249 glucans show a dose response to attenuate blood glucose excursions (Bao et al. 2014). For all fibers,
250 this may be due to delayed gastric emptying, which slows glucose release in circulation, through a
251 delayed or decreased intestinal absorption (Lattimer and Haub 2010).

252

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

264

265 In our umbrella review we also observed a possible decreased risk of fatal CHD and CVD mortality
266 for higher intake of whole grains. CVD risk in general, including CHD risk, may be significantly
267 influenced by modifying a number of risk factors, such as high blood pressure, elevated blood lipids
268 and excess of body weight, through diet and lifestyle changes (Eckel et al. 2014, Piepoli et al.
269 2016). Once again, the strongest evidence for their potential beneficial effects relies on their content
270 in dietary fiber (Reynolds, et al. 2019). In 2013, the “AHA/ACC Guideline on Lifestyle
271 Management to Reduce Cardiovascular Risk” emphasized the role of whole grain consumption to
272 lower blood pressure and LDL-cholesterol (Eckel, et al. 2014). Similarly, the ESC Guidelines on
273 CVD prevention, encourage intake of whole grain products as one important dietary goal to reduce
274 CVD risk contributing to the suggested fiber intake of 30-45 g per day for CVD prevention (Piepoli,
275 et al. 2016). While the mechanism is not fully elucidated, it has been shown that a high fiber intake

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276 reduces postprandial glucose responses after carbohydrate-rich meals and lowers total cholesterol
277 and LDL-cholesterol levels (Piepoli, et al. 2016). Although is often not possible to distinguish
278 between the effect of the different type of whole grains in the investigated studies, it is known that
279 the intake of barley and oat β -glucan, is effective in reducing LDL-cholesterol and non-HDL-
280 cholesterol, thus contributing in the reduction of CVD risk factors (Ho et al. 2016, Li, et al. 2016,
281 Whitehead et al. 2014). The significant evidence means that in 2010, the European Food Safety
282 Authority (EFSA) concluded that a cause and effect relationship has been established between the
283 consumption of oat β -glucan and lowering of blood LDL-cholesterol concentrations following at
284 least 3 g of oat β -glucan per day (EFSA Panel on Dietetic Products 2010). Cholesterol-lowering
285 effects of oat β -glucan may depend on the increased viscosity in the small intestine that reduces the
286 reabsorption of bile acids, increases the synthesis of bile acids from cholesterol, and reduces
287 circulating LDL-cholesterol concentrations (Henrion et al. 2019). The effect is proportional to
288 viscosity of the β -glucan and this typically decreases with significant processing (Wolever et al.
289 2010), further substantiating the importance of the whole grain rather than refined alternatives of
290 grains. Some clinical studies also reported a potential influence of whole grain in ameliorating
291 blood pressure, but further studies are needed to confirm such effect (Saltzman et al. 2001, Tighe et
292 al. 2010).

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

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

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317

318 **Declaration of interests**

319 The authors declare no conflicts of interest.

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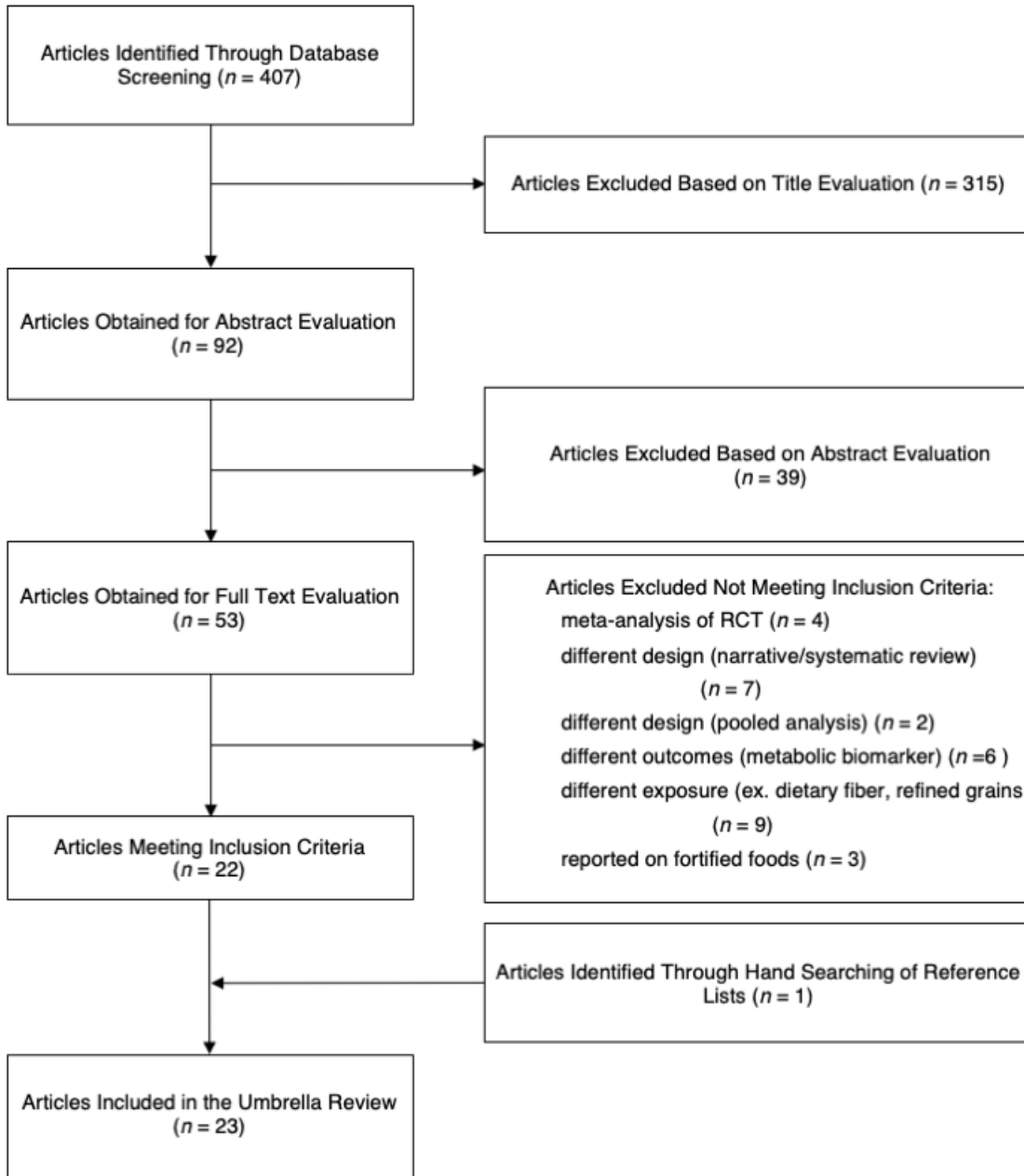
528 Table 1. Level of evidence for the association between dairy (total and individual foods)
529 consumption and health outcomes.

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 declassified 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 declassified as possible].	None.
Possible	Meta-analysis of prospective cohort studies with no heterogeneity and lack of information on potential confounding factors.	<ul style="list-style-type: none"> • 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 declassified as possible].	No association with risk of cancer (rectum), stroke (fatal).
<p>*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</p>		

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532 **Figure legend**

533 Figure 1. Flow chart of study selection.

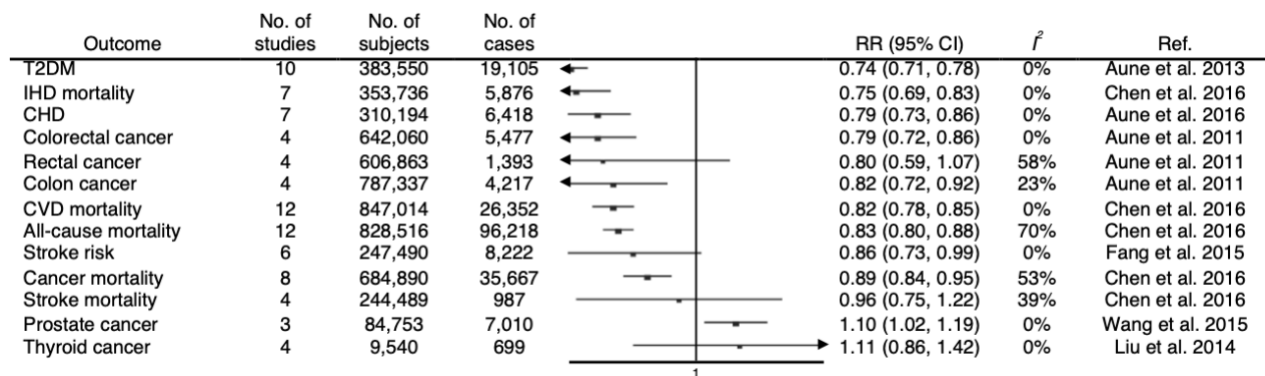


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536 Figure 2. Summary results from meta-analyses of prospective cohort studies on whole grain
 537 consumption on various health outcomes included in umbrella review.



538

539

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540 **Supplementary material**

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

543

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

546

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

550

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

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