

The Dietary Inflammatory Index and Human Health: An Umbrella Review of Meta-Analyses of Observational Studies

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Published

2021

Journal Title

Advances in Nutrition

Version

Accepted Manuscript (AM)

DOI

[10.1093/advances/nmab037](https://doi.org/10.1093/advances/nmab037)

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Title: The Dietary Inflammatory Index and Human Health: An Umbrella Review of Meta-analyses of Observational Studies

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Word count: 6961

Number of figures: 2

Number of tables: 1

Running title: DII Umbrella Review

List of abbreviations

AMSTAR - A Measurement Tool to Assess Systematic Reviews

CRP - C-reactive protein

DII[®] - Dietary Inflammatory Index

IL - Interleukin

MMP-9 - matrix metalloproteinase-9

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

sCD40L - soluble CD40 ligand

TNF- α - Tumor necrosis factor- α

1 **Abstract**

2 Numerous observational studies have investigated the role of the Dietary Inflammatory Index
3 (DII®) in chronic disease risk. The aims of this umbrella review and integrated meta-analyses
4 were to systematically synthesize the observational evidence reporting on the associations
5 between the DII and health outcomes based on meta-analyses, and to assess the quality and
6 strength of the evidence for each associated outcome. This umbrella review with integrated
7 meta-analyses investigated the association between the DII and a range of health outcomes
8 based on meta-analyses of observational data. A credibility assessment was conducted for each
9 outcome using the following criteria: statistical heterogeneity, 95% prediction intervals,
10 evidence for small-study effect and/or excess significance bias, as well as effect sizes and P
11 values using calculated random effects meta-analyses. In total, 15 meta-analyses reporting on
12 38 chronic disease-related outcomes were included, incorporating a total population of
13 4,360,111 subjects. Outcomes ($n=38$) were examined through various study designs including
14 case-control ($n=8$), cross-sectional ($n=5$), prospective ($n=5$), and combination ($n=20$) study
15 designs. Adherence to a pro-inflammatory dietary pattern had a significant positive association
16 with 27 (71%) of the included health outcomes (P value <0.05). Using the credibility
17 assessment, Class I (Convincing) evidence was identified for myocardial infarction only, Class
18 II (Highly suggestive) evidence was identified for increased risk of all-cause mortality, overall
19 risk of incident cancer, and risk of incident site-specific cancers (colorectal, pancreatic,
20 respiratory, and oral cancers) with increasing (more pro-inflammatory) DII score. Most
21 outcomes ($n=31$) presented Class III (Suggestive) or lower evidence (Weak or No association).
22 Pro-inflammatory dietary patterns were nominally associated with an increased risk of many
23 chronic disease outcomes. However, the strength of evidence for most outcomes was limited.
24 Further prospective studies are required to improve the precision of the effect size.

25 Keywords: diet, inflammation, dietary inflammatory index, prevention, mental disorders,
26 cancer, cardiovascular disease, non-communicable disorders, medicine.

27

28 **Introduction**

29 Chronic low-grade inflammation is implicated in the pathogenesis of several chronic non-
30 communicable diseases.(1, 2) In particular, chronic systemic inflammation is associated with
31 increased mortality from all causes, as well as with an increased risk of chronic disease
32 including cancer, type 2 diabetes, neurodegenerative diseases, and cardiovascular disease.(3-
33 8) Observational studies suggest that a range of pro-inflammatory markers including
34 interleukin-6 (IL-6), IL-18, matrix metalloproteinase-9 (MMP-9), soluble CD40 ligand
35 (sCD40L), and tumor necrosis factor- α (TNF- α) are prospectively associated with coronary
36 heart disease risk.(9) In addition to physical chronic diseases, inflammation is implicated in
37 range of mental illnesses including depression, schizophrenia, and bipolar disorder.(10-12)
38 Elevated baseline C-reactive protein (CRP) levels predict *de novo* depression.(13) Due to the
39 substantial burden of chronic diseases on mortality and morbidity,(14) studies that seek to
40 understand and address the drivers of inflammation are of substantial scientific value and public
41 health interest.

42 Diet is a key modifiable target for chronic disease risk reduction given that dietary factors
43 remain the primary driver of the global burden of chronic disease.(15, 16) Diet can affect
44 chronic disease risk via multiple mechanisms of action, including modulation of the gut
45 microbiome, oxidative stress, and energy balance.(17, 18) Fundamental to these mechanisms
46 of action is the potential pro- or anti-inflammatory properties of dietary patterns and individual
47 dietary components. Increased adherence to healthy dietary patterns, as well as a higher
48 consumption of nutrient-dense food groups, are associated with reduced inflammatory
49 markers.(19) For example, the Mediterranean dietary pattern – rich in fruits, vegetables, fatty
50 fish, poultry, extra virgin olive oil, and whole grains – is associated with reductions in systemic
51 inflammatory markers such as CRP.(20) Intervention studies support causality: a meta-analysis
52 of randomized controlled trials investigating the effect of a Mediterranean dietary pattern

53 reported significant reductions in CRP and IL-6 as well as increased adiponectin.(21)
54 Furthermore, individual compounds within nutrient-dense foods including omega-3 fatty
55 acids,(22) fiber,(23) and polyphenols(24) have demonstrated anti-inflammatory properties. In
56 contrast, consumption of Western dietary patterns, characterized by low consumption of fruits
57 and vegetables and high consumption of calorie-dense ultra-processed foods, are associated
58 with increased levels of inflammatory markers.(19)

59 The Dietary Inflammatory Index (DII[®]) provides a novel tool to further explore the mechanistic
60 inflammatory contribution of various dietary components.(25) Informed by an *a priori*
61 literature-based method, the DII is based on 45 food parameters including individual nutrients
62 (e.g. omega-3 fatty acids), compounds (e.g. flavonoids), and food items (e.g. garlic, ginger)
63 that were identified within the literature as possessing either anti- or pro-inflammatory
64 properties. The DII has now been validated in 29 studies with a range of inflammatory markers
65 including CRP, IL-6, and TNF- α .(26) A strategic advantage of the DII is that, in contrast to
66 individual dietary compounds, the investigation of dietary patterns acknowledges the food
67 matrix or the complex interactions of nutrients and compounds within foods and dietary
68 patterns.

69 Since the development of the current DII in 2014,(25) over 450 studies have investigated the
70 association between the DII and a diverse range of chronic disease-related outcomes, including
71 all-cause mortality, depression, and intermediate risk factors for chronic disease such as
72 elevated blood pressure or hypertension.(26, 27) Due to the large number and diverse range of
73 studies that have investigated the DII, there are now several meta-analyses that have
74 synthesized these outcomes.(28-36) However, no umbrella review has been conducted to assess
75 the strength of association between the DII and these diverse chronic disease outcomes. The
76 aim of this umbrella review was to aggregate and synthesize the results from meta-analyses of

77 observational studies examining the association between the DII and any available health
78 condition.

79 **Methods**

80 The study was reported in line with the Preferred Reporting Items for Systematic Reviews and
81 Meta-Analyses (PRISMA)(37) guidelines and was prospectively registered in an international
82 registry of systematic reviews (PROSPERO registration no. CRD42020192991).

83 *Literature search and selection criteria*

84 All meta-analyses that examined the association between the DII and all available health
85 outcomes using observational study designs (e.g., cross-sectional, prospective, case-control)
86 were eligible for inclusion. There were no restrictions on the population or age group, with
87 both healthy and clinical populations included. Eligible outcomes included those that were
88 related to physical chronic diseases (e.g., cardiovascular disease, cancer), mental illnesses (e.g.,
89 depression), and intermediate risk factors (e.g., hypertension).

90 Two independent authors (WM & JD) searched MEDLINE (via PubMed), PsycINFO (via
91 Ovid), EMBASE (via Ovid), and the Cochrane databases (via Ovid), from journal inception
92 dates to June 2020. Key search terms were related to the DII (DII OR “dietary inflammatory
93 index” OR “inflammatory diet” OR “anti-inflammatory diet”) and the meta-analysis study
94 design (“meta-analy*” OR metaanaly* OR “meta reg*” OR “metareg*”). Retrieved articles
95 were independently screened in duplicate (WM and JK) to identify studies that potentially met
96 the inclusion criteria. Any disagreement between authors over the eligibility of particular
97 studies was resolved through discussion with a third reviewer (ML). In line with methods used
98 in prior umbrella reviews, (38-40) if two or more meta-analyses were available for the same
99 disease outcome, the most recently updated and/or largest meta-analysis was included.

100 *Data extraction*

101 Duplicate extraction was conducted for data from the included studies for assessment of study
102 quality and evidence synthesis. Data relating to study design, sample size, outcomes, and effect
103 sizes were extracted. Where required, the study author of the original paper was contacted for
104 further information on relevant data that were not reported.

105 ***Data analysis***

106 We reanalyzed each meta-analysis dataset using a random effects model and reported effect
107 sizes (relative risk, odds ratio, and weighted mean differences), with 95% confidence intervals
108 (CI). In line with the methods of prior umbrella reviews,(41) assuming the associations between
109 the DII and health outcomes were linear, the lowest and highest categories - where the highest
110 category indicates a more pro-inflammatory diet - were considered in the overall analyses.
111 Additionally, the 95% prediction intervals were calculated for all random effect sizes, which
112 provide the possible range in which the effect sizes of additional future studies is expected to
113 fall.(42) Statistical heterogeneity between studies was evaluated using the I^2 statistic with a
114 value $\geq 50\%$ indicative of high heterogeneity and values $>75\%$ suggestive of very high
115 heterogeneity. Evidence of a small study effect was defined as a P value <0.10 using Egger's
116 regression asymmetry test(43) and where the effect size of the largest individual study for each
117 meta-analysis was more conservative than that of the overall summary effect for each
118 outcome.(44)

119 We conducted a test for excess significance for all outcomes,(45) which evaluates whether the
120 number of studies with nominally significant results (i.e., P value <0.05) within an included
121 meta-analysis exceeds what would be expected based on the statistical power of the meta-
122 analysis. As described elsewhere, the number of expected significant studies can be compared
123 with the observed number of significant studies through a chi-square-based test.(45) The larger

124 the difference between observed and expected, the higher the degree of excess of significance
125 bias.

126 *Quality assessment of the meta-analyzed studies and evidence grading*

127 The quality of all eligible meta-analyses was assessed using the A Measurement Tool to Assess
128 Systematic Reviews (AMSTAR 2) quality assessment tool.(46) In line with prior umbrella
129 reviews,(41, 47) and as summarized elsewhere,(48, 49) the results of this umbrella review were
130 classified as Convincing, Highly Suggestive, Suggestive, Weak, or No evidence, as defined
131 using the following criteria.

- 132 • Convincing (Class I); where the number of cases is >1000, statistically significant using
133 a P value of $<1 \times 10^{-6}$, $I^2 < 50\%$, 95% prediction interval excludes the null, the largest
134 included individual study has a statistically significant effect ($p \leq 0.05$), no small-study
135 effects, and no excess significance bias
- 136 • Highly suggestive (Class II); where the number of cases is >1000, statistically
137 significant using a P value of $<1 \times 10^{-6}$, the largest included individual study has a
138 statistically significant effect ($p \leq 0.05$), and Class I criteria not met
- 139 • Suggestive (Class III); where the number of cases is >1000, P value of $<1 \times 10^{-3}$, and
140 Class I–II criteria not met
- 141 • Weak (Class IV); statistically significant using a P value of ≤ 0.05 and Class I–III
142 criteria not met
- 143 • No evidence (Class V); no statistical significance using a P value of >0.05

144 **Results**

145 As shown in Figure 1, the systematic search identified 70 deduplicated articles. After applying
146 the inclusion criteria, 15 meta-analyses of 38 distinct outcomes were included for review.(28-
147 36, 50-55)

148 ***Study characteristics***

149 All meta-analyses were published within the last 5 years. The median number of studies
150 included for each outcome was 6 (range: 2–44), the median number of participants was 36,592
151 (range: 1,966–1,299,621), and the median number of cases (i.e., with the outcome of interest)
152 was 2,760 (range: 442–48,345). Outcomes predominantly included a combination of study
153 designs ($n=20$), with the remaining meta-analyses including only case-control ($n=8$), cross-
154 sectional ($n=5$), and prospective ($n=5$) study designs exclusively.

155 As displayed in Table 1, a range of outcomes were included for review: cancer ($n=16$),
156 metabolic risk markers ($n=11$), cardiovascular diseases (CVDs) ($n=6$), all-cause and specific-
157 cause mortality ($n=4$), and depression ($n=1$). The exposure variable for all analyzed outcomes
158 was assessed by comparing the highest versus lowest categories (e.g., quartiles, tertiles) of
159 adherence to a pro-inflammatory diet. Most outcomes ($n=30$) were categorical variables, with
160 the remaining eight outcomes treated as continuous (HbA1c, fasting blood glucose, insulin,
161 HOMA-IR, waist circumference, waist-to-hip ratio, systolic and diastolic blood pressure).(50)

162 ***Study results***

163 Overall, 27 (71%) of the 38 outcomes reported statistically significant effect sizes using a
164 random effects model (P value <0.05), with the following 8 outcomes surviving a more
165 stringent P value ($P <1 \times 10^{-6}$): incidence of myocardial infarction,(34) oral cancer,(28)
166 pharyngeal cancer,(28) respiratory cancer,(28) pancreatic cancer,(29) colorectal cancer,(30)
167 overall cancer,(30) and all-cause mortality.(53) In 27 (71%) meta-analyses, the largest included

168 study was significant (Table 1). There was evidence of a small study effect across 12 (31%)
169 included outcomes (Supplementary Table 1). Heterogeneity was generally high with most
170 outcomes (27 of 38; 71%) displaying an I^2 value $\geq 50\%$. Seven outcomes (incidence of
171 myocardial infarction,(34) ovarian cancer,(32) pharyngeal cancer,(28) respiratory cancer,(28)
172 colorectal cancer,(30) overall cancer,(30) and all-cause mortality(53)) presented 95%
173 prediction intervals excluding the null value. Evidence of excess significance was present for
174 2 outcomes (prostate cancer and stroke) from the 29 outcomes that were able to be assessed.

175 ***Credibility assessment***

176 When the credibility assessment criteria was applied (Figure 2), one outcome presented
177 convincing evidence (Class I): myocardial infarction(34). Six (16%) outcomes presented
178 highly suggestive evidence (Class II: association between higher DII values and increased
179 risk/presence of all-cause mortality,(53) overall cancer,(30) colorectal cancer,(30) pancreatic
180 cancer,(29) respiratory cancers,(28) oral cancer(28)), and 8 (21%) outcomes presented
181 suggestive evidence (Class III: esophageal cancer,(28) lung cancer,(52) breast cancer,(32)
182 ovarian cancer,(32) pharyngeal cancer,(28) depression,(35) HbA1c,(50) waist
183 circumference(51)). Twelve studies presented weak evidence (Class IV) and a further 11
184 presented no significant evidence for an association (P value >0.05 ; Table 1, Supplementary
185 Table 1).

186 ***Quality assessment***

187 The overall quality of included studies was moderate (median score: 16 of 32 using the
188 AMSTAR tool), with limited reporting on a number of quality assessment items including
189 details regarding excluded studies and sources of funding of the included studies
190 (Supplementary Table 2).

191 **Discussion**

192 This is the first umbrella review to provide a comprehensive overview of the observational data
193 assessing associations between the DII and all available health outcomes. This umbrella review
194 comprised 15 meta-analyses of 38 outcomes in a total population of more than 4,360,111
195 participants. A pro-inflammatory dietary pattern was significantly associated with an increased
196 risk for 27 (71%) of the included health outcomes. Convincing (Class I) evidence was presented
197 for myocardial infarction only and Highly suggestive (Class II) evidence was presented for all-
198 cause mortality, overall cancer risk, and a range of site-specific cancers (colorectal cancer,
199 pancreatic cancer, respiratory cancers, oral cancer).

200 A strength of the DII is its focus on dietary assessment that captures the composite effect of
201 multiple dietary components, rather than a single nutrient or individual food item, where it is
202 reductionistic and difficult to discern the effect from other co-occurring bioactive nutrients or
203 their interactions. A further strength relates to the analysis of the association between health
204 outcomes and a dietary pattern based on one consistent method, represented by the DII, as
205 opposed to other dietary patterns (e.g., Mediterranean diet) where there are multiple *post-hoc*
206 and *a priori* methods of assessing a specific dietary pattern, which may reduce precision in the
207 observed effect due to the variation in assessment methods.(56)

208 There are a diverse range of bioactive compounds that may be responsible for the associations
209 between the DII and the included health outcomes of the present review. Examples of dietary
210 components that are incorporated in the DII and have demonstrated anti-inflammatory
211 properties include phytochemicals such as polyphenols, omega-3 fatty acids, and dietary
212 fiber.(57) A higher dietary intake of polyphenols has been associated with reduced
213 inflammatory markers with the proposed pathway via their antioxidant properties.(24) Omega-
214 3 fatty acids have been widely studied for their anti-inflammatory potential and include the
215 modulation of eicosanoid and resolvin synthesis.(58, 59) Anti- and pro-inflammatory effects

216 of dietary compounds also appear to be mediated via the gut microbiome.(60) Intake of dietary
217 fibers, probiotic supplements and fermented foods have been suggested to provide anti-
218 inflammatory properties via the increase in anti-inflammatory short-chain fatty acids and other
219 gut-derived metabolites.(17, 61) In contrast, dietary components common to a Western-style
220 dietary pattern such as trans- and saturated fatty acids may increase inflammation via
221 mechanisms such as toll-like receptor 4 expression and modulation of the gut microbiome.(62,
222 63)

223 Despite the majority ($n=27/38$, 71%) of outcomes showing a significant ($P < 0.05$) positive
224 association with adherence to a pro-inflammatory dietary pattern, only one outcome provided
225 “convincing” (Class I) evidence and most outcomes presented Class III or lower evidence. This
226 was largely attributed to the high level of statistical heterogeneity ($n=27/38$, 71%, with I^2
227 $\geq 50\%$), a 95% prediction interval that included the null ($n=31/38$, 82%), and a P value greater
228 than 10^{-6} ($n=30/38$, 79%).

229 A possible explanation for the low credibility assessment and high levels of heterogeneity in
230 many outcomes may be related to the type of populations included in each meta-analysis. For
231 example, some prior meta-analyses suggested differential associations between the DII and
232 health outcomes between men and women.(29, 34) To illustrate, Shivappa et al.(34) reported
233 that the DII was associated with CVD outcomes in women, but not men. To some extent, these
234 observations may be explained by the limited number of studies that have assessed gender-
235 specific differences. Furthermore, several outcomes had a limited number of included studies
236 (e.g. 13 outcomes (34%) including $n=2-3$ studies per analysis), thus limiting the power to detect
237 a statistical association and, in some circumstances, preventing formal analysis of excess
238 significance. An additional potential source of heterogeneity that is common to nutrition
239 epidemiology relates to the complexity of assessing dietary intake. Variations in the dietary
240 assessment tools used between studies to calculate DII as well as bias common to self-reported

241 measures (e.g. social desirability)(64) may have introduced heterogeneity into the included
242 outcomes.

243 Findings of the current umbrella review need to be interpreted with the following limitations
244 in mind. First, as this study included only outcomes with available meta-analyses, additional
245 outcomes where meta-analyses are currently unavailable could not be considered. For example,
246 the DII has been associated with risk of multiple sclerosis in two prior studies;(65, 66) however,
247 these have not been the subject of any identified meta-analysis at this time. A related limitation
248 of umbrella reviews in general is the use of existing meta-analyses, which are dependent on
249 prior investigators decisions regarding the inclusion of individual studies and the analysis
250 methods used including the type and extent of sensitivity analyses conducted. Second, as this
251 umbrella review included observational data only, limitations common to this approach may
252 also affect the results of this review, such as information bias and residual confounding. This
253 is particularly pertinent to the current review as there were a limited number of meta-analyses
254 that exclusively included prospective study designs, where information bias is reduced. Case-
255 control and cross-sectional study designs were more common than prospective study designs
256 and are associated with a higher potential for information bias and reverse causation. Subgroup
257 analyses of included meta-analyses support this, with cross-sectional and case-control studies
258 generally reporting a larger effect size than prospective studies.(32, 35, 36) Future studies are
259 encouraged to use prospective study designs to reduce the existing bias within the literature.
260 Randomized controlled trials that provide an anti-inflammatory dietary intervention pattern
261 consistent with lower DII scores would provide further evidence of directionality, as well as
262 allowing for cause-effect inferences and reducing possible biases inherent to observational
263 study designs. A related consideration is that poor diet quality is likely to cluster with other
264 adverse health behaviors (e.g. smoking, alcohol consumption, sedentariness) that are also
265 associated with the included chronic diseases outcomes. While many individual studies have

266 adjusted for these risk factors, there is heterogeneity in the quality of the data and methods of
267 adjustment. Consequently, problems with residual effects may persist. Finally, while this
268 review assessed the strength of the evidence for each outcome according to a framework
269 commonly used in umbrella reviews, this approach largely relies on statistical methods to
270 determine evidence strength which does not incorporate other factors such as the rigor of the
271 included study designs, plausible underlying biological mechanisms, and effect sizes.

272 It also should be kept in mind that the literature on the DII is rapidly advancing. According to
273 Clarivate Web of Science® there has been an increase in DII-focused articles of approximately
274 25% per year, on average (i.e., from 2014-2019 by year: 11, 32, 45, 78, 92, 104 articles). This
275 indicates that the evidence will continue to accumulate for outcomes where an insufficient
276 number of articles limited the possibility of meta-analysis. Also, existing topics on which a
277 meta-analysis currently exists may have a sufficient increase in the number of qualifying
278 articles to merit an additional meta-analysis. While expansion of the literature will, no doubt,
279 contribute to the robustness of the evidence, it will be important to monitor other factors,
280 including heterogeneity.

281 Notwithstanding the discussed limitations of the current literature, the evidence identified in
282 this review provides further support for the role of improved diet quality as a protective factor
283 against chronic disease risk and mortality. While this review suggests that higher adherence to
284 an anti-inflammatory dietary pattern may be beneficial, other healthy dietary patterns such as
285 the Mediterranean diet and government dietary guidelines are also strongly associated with an
286 anti-inflammatory score using the DII.(67, 68) These associations provide novel mechanistic
287 evidence regarding the potential anti-inflammatory effect of these dietary patterns. In regard to
288 the public health implications of these results, this suggests that diverse dietary patterns that
289 incorporate factors related to the individual context (e.g., culture, food availability, taste

290 preferences) may be associated with the same decrease in chronic disease risk observed in this
291 review.

292 **Conclusion**

293 In summary, this umbrella review identified pro-inflammatory dietary patterns (reflected by a
294 higher dietary inflammatory index) to be adversely associated with a range of chronic disease-
295 related health outcomes. This provides further evidence for the role of anti-inflammatory
296 dietary patterns in the prevention of chronic diseases, as well as inflammation as a mechanism
297 of action in the genesis of adverse health outcomes. Further prospective evidence is required
298 to explore this association in health outcomes where current studies are limited (e.g.,
299 pancreatic, endometrial, and urological cancers), to address the large degree of heterogeneity,
300 and to explore potential subgroup populations that are particularly susceptible to diet-induced
301 inflammation.

302 **Acknowledgments**

303 All authors have read and approved the final manuscript.

304 **Conflict of interest disclosure**

305 Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a
306 company that has licensed the right to his invention of the dietary inflammatory index (DII®)
307 from the University of South Carolina in order to develop computer and smart phone
308 applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin
309 Shivappa is an employee of CHI. The subject matter of this paper will not have any direct
310 bearing on that work, nor has that activity exerted any influence on this project.

311 **Funding declaration**

312 **WM** is currently funded by an Alfred Deakin Postdoctoral Research Fellowship and a Multiple
313 Sclerosis Research Australia early-career fellowship. Wolfgang has previously received
314 funding from the Cancer Council Queensland and university grants/fellowships from La Trobe
315 University, Deakin University, University of Queensland, and Bond University, received
316 industry funding and has attended events funded by Cobram Estate Pty. Ltd, received travel
317 funding from Nutrition Society of Australia, received consultancy funding from Nutrition
318 Research Australia, and has received speakers honoraria from The Cancer Council Queensland
319 and the Princess Alexandra Research Foundation. **JK** is supported through a Griffith University
320 Postdoctoral Research Fellowship. **MB** is supported by a NHMRC Senior Principal Research
321 Fellowship (1156072). MB has received Grant/Research Support from the NIH, Cooperative
322 Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical
323 Research Foundation, Medical Benefits Fund, National Health and Medical Research Council,
324 Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and
325 Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker

326 for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra
327 Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck,
328 Pfizer and Servier – all unrelated to this work. **EH** is supported by a National Health and
329 Medical Research Council Early Career Fellowship (APP1156909). **MH** is supported by an
330 Australian Rotary Health PhD Scholarship and has received research support from the A2 Milk
331 Company. **SC** is supported by a Deakin University Postgraduate Research (DUPR)
332 Scholarship. **ST** is funded through the Mindgardens Alliance and is a contractor to Nutrition
333 Research Australia. **HA** is supported by Deakin University Postgraduate Industry Research
334 Scholarship. **AO** is supported by a Future Leader Fellowship (#101160) from the Heart
335 Foundation Australia and Wilson Foundation. She has received research funding
336 from National Health & Medical Research Council, Australian Research Council, University
337 of Melbourne, Deakin University, Sanofi, Meat and Livestock Australia and Woolworths
338 Limited and Honoraria from Novartis. The Food & Mood Centre has received funding
339 from the Fernwood Foundation, the A2 Milk Company and Be Fit Foods. **AW** is supported by
340 an NHMRC Boosting Dementia Research Grant (GNT1171313). **AW** has received previous
341 funding from the University of South Australia, the Nutrition Society of Australia and the Pork
342 Cooperative Research Centre, all of which are unrelated to this work. **FJ** has received: (1)
343 competitive Grant/Research support from the Brain and Behaviour Research Institute, the
344 National Health and Medical Research Council (NHMRC), Australian Rotary Health, the
345 Geelong Medical Research Foundation, the Ian Potter Foundation, The University of
346 Melbourne; (2) industry support for research from Meat and Livestock Australia, Woolworths
347 Limited, the A2 Milk Company, Be Fit Foods; (3) philanthropic support from the Fernwood
348 Foundation, Wilson Foundation, the JTM Foundation, the Serp Hills Foundation, the Roberts
349 Family Foundation, the Waterloo Foundation and; (4) travel support and speakers honoraria
350 from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition,

351 Angelini Farmaceutica, Eli Lilly and Metagenics. Felice Jacka has written two books for
352 commercial publication. **ML** is supported by a Deakin University Scholarship and has received
353 research funding support from Be Fit Foods. **LCB** is supported by an NHMRC of Australia
354 Emerging Leadership Investigator Grant (ID: 1172987) and a National Heart Foundation of
355 Australia Post-Doctoral Research Fellowship (ID: 102498). LCB has received project funding
356 from Edith Cowan University and Department of Health Western Australia, and travel support
357 from the Nutrition Society of Australia and The University of Western Australia.

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558 **Figure 1. PRISMA flow chart of study selection**

559 **Figure 2. Credibility Assessment for each included outcome**

560

Table 1. Summary of included health outcomes and their associations with the Dietary Inflammatory Index within the general population

Out- come	Study design include d in MA	Level of compar ison	Studies , <i>n</i>	Particip ants, <i>n</i>	Cases, <i>n</i>	Type of effect size metric	Effect size (95% CI)	95% CI predicti on interval s	<i>P</i>	<i>I</i> ²	Largest study effect size (95% CI)	Publica tion bias	Small- study effect or excess signific ance bias	Eviden ce Class
Mortality														
All- cause mortalit y(53)	Prospec tive	High versus low	12	220,20 6	44,809	RR	1.235 (1.157, 1.318)	1.01, 1.51	2.27x1 0 ⁻¹⁰	71.5%	1.16 (1.1, 1.22)	Yes	Small study effect	II

Cancer Mortality(36)	Prospective	High versus low	11	229,448	9,497	OR	1.229 (1.067, 1.415)	8.30 $\times 10^{-1}$, 1.82	4.27 $\times 10^{-3}$	54.1%	1.33 (1.01, 1.76)	No	Neither	IV
CVD Mortality(34)	Prospective	High versus low	6	93,866	11,094	OR	1.374 (1.114, 1.696)	7.00 $\times 10^{-1}$, 2.70	3.01 $\times 10^{-3}$	77.2%	1.09 (1.01, 1.18)	Yes	Small-study effect	IV
CHD Mortality(34)	Prospective	High versus low	3	31,278	3,686	RR	1.634 (1.012, 2.636)	1.00 $\times 10^{-2}$, 4.34 $\times 10^2$	4.45 $\times 10^{-2}$	76.7%	1.17 (1.05, 1.3)	Yes	Small-study effect	IV
Cancer risk														
Overall cancer(30)	Case-control and Prospective	High versus low	44	1,299,621	48,345	RR	1.599 (1.466, 1.745)	1.01, 2.52	5.08 $\times 10^{-26}$	75.3%	1.4 (1.28, 1.53)	Yes	Small-study effect	II

Colorectal cancer(30)	Case-control and Prospective	High versus low	11	975,683	20,076	RR	1.426 (1.280, 1.589)	1.03, 1.98	1.26x10 ⁻¹⁰	69.1%	1.4 (1.28, 1.53)	No	Small-study effect	II
Prostate cancer(55)	Case-control and Prospective	High versus low	10	52,943	5,326	OR	1.098 (1.035, 1.166)	9.20x10 ⁻¹ , 1.30	1.95x10 ⁻³	72.9%	1.02 (0.99, 1.04)	Yes	Both	IV
Pancreatic cancer(29)	Case-control	High versus low	2	3,551	1,143	RR	2.524 (1.941, 3.281)	Not estimable*	4.73x10 ⁻¹²	0.0%	2.48 (1.5, 4.1)	Not estimable*	No excess significance*	II

Respiratory cancer (pooled)(28)	Case-control	High versus low	18	17,514	4,834	OR	2.274 (1.894, 2.729)	1.24, 4.18	1.13x10 ⁻¹⁸	60.2%	2.08 (1.47, 2.93)	Yes	Small-study effect	II
Esophageal cancer (28)	Case-control	High versus low	5	4,645	1,310	OR	2.530 (1.738, 3.682)	7.50 x10 ⁻¹ , 8.85	1.25x10 ⁻⁶	71.7%	1.71 (1.54, 1.9)	Yes	Small-study effect	III
Laryngeal cancer (28)	Case-control	High versus low	3	2,805	997	OR	2.046 (0.848, 4.934)	0.00, 9.08x10 ⁴	1.11x10 ⁻¹	85.6%	3.3 (2.06, 5.28)	Yes	Neither	V
Oral cancer (28)	Case-control	High versus low	3	4,785	1,366	OR	2.229 (1.735, 2.865)	4.00 x10 ⁻¹ ,	3.72x10 ⁻¹⁰	0.0%	2.08 (1.47, 2.93)	No	Neither	II

								1.13x10 ¹						
Pharyngeal cancer (28)	Case-control	High versus low	7	5,279	1,161	OR	2.019 (1.544, 2.640)	1.17, 3.48	2.81x10 ⁻⁷	20.3%	1.64 (0.93, 2.89)	No	Neither	III
Lung cancer(52)	Prospective	High versus low	3	149,929	2,453	RR	1.304 (1.130, 1.504)	5.20 x10 ⁻¹ , 3.29	2.71x10 ⁻⁴	0.0%	1.28 (1.09, 1.51)	No	Neither	III
Breast cancer(32)	Case-control and Prospective	High versus low	12	347,147	30,052	RR	1.335 (1.142, 1.560)	7.60 x10 ⁻⁰¹ , 2.33	2.79x10 ⁻⁴	89.9%	0.99 (0.91, 1.07)	Yes	Small-study effect	III

Ovarian cancer(32)	Case-control	High versus low	4	7,982	3,104	RR	1.414 (1.214, 1.647)	(1.01, 1.98)	8.57x10 ⁻⁶	0.0%	1.47 (1.07, 2.01)	No	Neither	III
Gastric cancer(31)	Case-control and Prospective	High versus low	3	2,118	700	RR	2.120 (1.411, 3.183)	4.00 x10 ⁻⁰² , 1.17 x10 ²	2.93x10 ⁻⁴	42.7%	1.63 (1.15, 2.29)	Yes	Small-study effect	IV
Endometrial cancer(32)	Case-control	High versus low	2	1,966	751	RR	1.881 (0.803, 4.407)	Not estimable*	1.46x10 ⁻¹	68.6%	1.34 (0.96, 1.87)	Not estimable*	No excess significance*	V
Kidney cancer(33)	Case-control and	High versus low	2	36,118	1,030	RR	1.463 (1.157, 1.850)	Not estimable*	1.49x10 ⁻³	0.0%	1.52 (1.09, 2.13)	Not estimable*	No excess	IV

	Prospective												significance*	
Urothelial cancer(36)	Case-control and Prospective	High versus low	2	42,869	1,069	OR	1.526 (0.972, 2.397)	Not estimable*	6.63x10 ⁻²	65.2%	1.24 (0.9, 1.7)	Not estimable*	No excess significance*	V
Cardiovascular disease risk														
Hypertension(50)	Cross-sectional and Prospective	High versus low	15	71,729	24,648	OR	1.133 (1.013, 1.266)	8.00 x10 ⁻¹ , 1.60	2.81x10 ⁻²	55.6%	1.21 (1.02, 1.43)	No	Neither	IV
Cardiovascular(34)	Cross-sectional and	High versus low	6	57,781	3,022	OR	1.345 (1.110, 1.631)	8.40 x10 ⁻¹ , 2.17	2.52x10 ⁻³	36.3%	2.03 (1.06, 3.89)	No	Neither	IV

	Prospective													
Myocardial Infarction(34)	Case-control and Prospective	High versus low	6	37,065	2,497	RR	1.717 (1.419, 2.077)	1.31, 2.25	2.64x10 ⁻⁸	0.0%	2.28 (1.09, 4.75)	Yes	Neither	I
IHD-CHD Risk(34)	Cross-sectional and Prospective	High versus low	3	23,962	875	RR	1.272 (0.874, 1.853)	2.00 x10 ⁻² , 7.83 x10 ¹	2.09x10 ⁻¹	62.2%	0.96 (0.72, 1.28)	Yes	Small study effect	V
Stroke(34)	Cross-sectional and	High versus low	3	30,408	569	RR	1.099 (0.605, 1.999)	0.00, 8.61 x10 ²	7.56x10 ⁻¹	65.5%	1.56 (1.21, 2.01)	No	Excess significance	V

	Prospective													
Angina (34)	Cross-sectional and Prospective	High versus low	2	23,436	442	RR	0.793 (0.561, 1.120)	Not estimable*	1.88x10 ⁻¹	0.0%	0.83 (0.54, 1.28)	Not estimable*	No excess significance*	V
Mental health risk														
Depression (35)	Cross-sectional and Prospective	High versus low	15	55,490	4,884	OR	1.441 (1.225, 1.695)	(0.87 x10 ⁻¹ , 2.40)	1.02x10 ⁻⁶	58.8%	1.46 (1.1, 1.94)	No	Neither	III
Metabolic risk markers														

Metabolic syndrome(54)	Case-control and Prospective	High versus low	5	15,161	2,242	RR	1.006 (0.816, 1.242)	5.80 $\times 10^{-1}$, 1.74	9.53 $\times 10^{-1}$	32.6%	0.86 (0.6, 1.23)	No	Neither	V
HbA1c(50)	Cross-sectional	Continuous	3	23,138	-	WMD	0.615 (0.266, 0.965)	-3.66, 4.89	5.60 $\times 10^{-4}$	87.5%	0.4 (0.34, 0.46)	No	No Small study effect*	III
Fasting Blood Glucose(50)	Case-control and Prospective	Continuous	15	93,739	-	WMD	1.083 (0.100, 2.065)	-2.38, 4.54	3.08 $\times 10^{-2}$	89.0%	3.7 (0.04, 5.36)	No	No Small study effect*	IV

Insulin(50)	Cross-sectional	Continuous	6	38,359	-	WMD	0.829 (0.169, 1.488)	-1.27, 2.93	1.38x10 ⁻²	86.5%	2.47 (1.64, 3.3)	No	No Small study effect*	IV
HOMA-IR(50)	Cross-sectional	Continuous	7	41,645	-	WMD	0.191 (0.021, 0.362)	-3.90 x10 ⁻⁰¹ , 7.70 x10 ⁻⁰¹	2.80x10 ⁻²	93.2%	0.88 (0.67, 1.09)	No	No Small study effect*	IV
Hyperglycemia (50)	Cross-sectional	High versus low	11	30,424	4,883	OR	1.130 (0.948, 1.347)	6.70 x10 ⁻⁰¹ , 1.91	1.73x10 ⁻¹	60.7%	1.09 (0.83, 1.44)	Yes	Small-study effect	V
Central Obesity (51)	Cross-sectional	High versus low	13	25,435	5,121	OR	1.162 (0.945, 1.429)	6.00 x10 ⁻⁰¹ , 2.24	1.54x10 ⁻¹	65.4%	1.35 (0.94, 1.94)	No	Small-study effect	V

Waist circumference(51)	Case-control and Prospective	Continuous	25	78,828	-	WMD	1.782 (0.722, 2.842)	-3.00, 6.56	9.82x10 ⁻⁴	100.0%	3.7 (2.81, 4.59)	No	Neither	III
Waist to Hip ratio(51)	Case-control and Prospective	Continuous	11	16,685	-	WMD	-0.005 (-0.039, 0.029)	-1.10 x10 ⁻⁰¹ , 1.00 x10 ⁻⁰¹	7.59x10 ⁻¹	87.1%	0.0 (-.01, .01)	No	No Small study effect*	V
Systolic Blood Pressure(50)	Case-control, Cohort, and Prospective	Continuous	15	87,202	-	WMD	1.230 (0.283, 2.177)	-2.29, 4.76	1.09x10 ⁻²	91.5%	5.4 (4.52, 6.28)	No	No Small study effect*	IV

Diastolic Blood Pressure(50)	Case-control and Prospective	Continuous	12	79,871	-	WMD	0.009 (-0.686, 0.703)	-2.40, 2.42	9.81x10 ⁻¹	91.6%	1.7 (0.99, 2.41)	No	No Small study effect *	V
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Legend

- * Either tests for small study effect, excess significance, or both, could not be conducted due to small sample size of included studies.
- Evidence class criteria—class I (convincing): statistical significance at $P < 10^{-6}$, >1000 cases (or >20,000 participants for continuous outcomes), the largest component study reported a significant effect ($P < 0.05$); the 95% prediction interval excluded the null, no large heterogeneity ($I^2 < 50\%$), no evidence of small-study effects ($P > 0.10$) and excess significance bias ($P > 0.10$); class II (highly suggestive): significance at $P < 10^{-6}$, >1000 cases (or >20,000 participants for continuous outcomes), the largest component study reported a significant effect ($P \leq 0.05$); class III (suggestive): statistical significance at $P < 10^{-3}$, >1000 cases (or >20,000 participants for continuous outcomes); and class IV (weak): the remaining significant associations at $P < 0.05$.

