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

Authors: Wolfgang Marx[1^], Nicola Veronese[2], Jaimon T. Kelly[3, 4], Lee Smith[5], Meghan Hockey[1], Sam Collins[1], Gina L. Trakman [6], Erin Hoare[1], Scott B. Teasdale[7], Alexandra Wade[8], Melissa Lane[1], Hajara Aslam[1], Jessica A. Davis[1], Adrienne O'Neil[1,9], Nitin Shivappa[10,11], James R. Hebert[10,11], Lauren C. Blekkenhorst[12,13], Michael Berk[1], Toby Segasby, Felice Jacka[1,14,15,16]

Affiliations:

1. Deakin University, IMPACT, the Institute for Mental and Physical Health and Clinical Translation, Food & Mood Centre, School of Medicine, Barwon Health, Geelong, Australia
2. University of Palermo, Department of Internal Medicine, Geriatrics Section, Palermo, Italy
3. Centre of Applied Health Economics, Griffith University, Brisbane, Australia
4. Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia
5. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, CB1 1PT, UK
6. Department of Dietetics, Nutrition and Sport, La Trobe University, Melbourne, Australia
7. School of Psychiatry, UNSW Sydney, NSW, Australia
8. Alliance for Research in Exercise, Nutrition and Activity, Allied Health and Human Performance, University of South Australia, SA 5000 Australia
9. Melbourne School of Population & Global Health, University of Melbourne, VIC 3010 Australia

10. Department of Epidemiology and Biostatistics and Cancer Prevention and Control Program, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208 USA
11. Department of Nutrition, Connecting Health Innovations LLC, Columbia, SC 29201 USA
12. School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA 6027 Australia
13. Medical School, The University of Western Australia, Perth, WA 6000 Australia
14. Black Dog Institute, NSW; Australia
15. James Cook University, QLD; Australia
16. Centre for Adolescent Health, Murdoch Children's Research Institute, VIC; Australia

^Corresponding Author:

Dr Wolfgang Marx

IMPACT – the Institute for Mental and Physical Health and Clinical Translation

Deakin University

PO Box 281

Geelong, Victoria, Australia

3220

wolf.marx@deakin.edu.au

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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

Abstract

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

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

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Introduction

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

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

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

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

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

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

Methods

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

Literature search and selection criteria

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

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

Data extraction

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

Data analysis

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

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

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

Quality assessment of the meta-analyzed studies and evidence grading

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

- Convincing (Class I); where the number of cases is >1000, statistically significant using a *P* value of $<1 \times 10^{-6}$, $I^2<50\%$, 95% prediction interval excludes the null, the largest included individual study has a statistically significant effect ($p\leq0.05$), no small-study effects, and no excess significance bias
- Highly suggestive (Class II); where the number of cases is >1000, statistically significant using a *P* value of $<1 \times 10^{-6}$, the largest included individual study has a statistically significant effect ($p\leq0.05$), and Class I criteria not met
- Suggestive (Class III); where the number of cases is >1000, *P* value of $<1 \times 10^{-3}$, and Class I–II criteria not met
- Weak (Class IV); statistically significant using a *P* value of ≤0.05 and Class I–III criteria not met
- No evidence (Class V); no statistical significance using a *P* value of >0.05

Results

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

Study characteristics

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

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

Study results

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

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

Credibility assessment

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

Quality assessment

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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Conflict of interest disclosure

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

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1. Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Doré J, Franceschi C, Lehtinen MJ, Recker T, Salvioli S. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing research reviews 2017;40:95-119.
2. Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. Current opinion in immunology 2014;29:23-8.
3. Bonaccio M, Di Castelnuovo A, Pounis G, De Curtis A, Costanzo S, Persichillo M, Cerletti C, Donati MB, De Gaetano G, Iacoviello L. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. Haematologica 2016;101(11):1434.
4. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS. Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. PloS one 2015;10(3):e0116206.
5. Calle M, Fernandez M. Inflammation and type 2 diabetes. Diabetes & metabolism 2012;38(3):183-91.
6. Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, Bianchi R, Crisci M, D'Acierno L, Giordano R. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Current atherosclerosis reports 2014;16(9):435.
7. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019;51(1):27-41.
8. Amor S, Peferoen LA, Vogel DY, Breur M, van der Valk P, Baker D, van Noort JM. Inflammation in neurodegenerative diseases–an update. Immunology 2014;142(2):151-66.
9. Kaptoge S, Seshasai SRK, Gao P, Freitag DF, Butterworth AS, Borglykke A, Di Angelantonio E, Gudnason V, Rumley A, Lowe GD. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. European heart journal 2014;35(9):578-89.
10. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Medicine 2013;11:200-. doi: 10.1186/1741-7015-11-200.
11. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. Schizophrenia bulletin 2018;44(5):973-82.
12. Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. Neuroinflammation in bipolar depression. Frontiers in psychiatry 2020;11:71.
13. Pasco JA, Nicholson GC, Williams LJ, Jacka FN, Henry MJ, Kotowicz MA, Schneider HG, Leonard BE, Berk M. Association of high-sensitivity C-reactive protein with de novo major depression. The British Journal of Psychiatry 2010;197(5):372-7.
14. Harikrishnan S, Jeemon P, Mini G, Thankappan K, Sylaja P. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. 2018.
15. Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, Mullany EC, Abate KH, Abbafati C, Abebe Z. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2019;393(10184):1958-72.
16. Meier T, Gräfe K, Senn F, Sur P, Stangl GI, Dawczynski C, März W, Kleber ME, Lorkowski S. Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: a systematic analysis of the Global Burden of Disease Study. European journal of epidemiology 2019;34(1):37-55.
17. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV. The microbiota-gut-brain axis. Physiological reviews 2019;99(4):1877-2013.

18. Tosti V, Bertozzi B, Fontana L. Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. The Journals of Gerontology: Series A 2018;73(3):318-26.
19. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, Hu FB. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. The American journal of clinical nutrition 2004;80(4):1029-35.
20. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol 2004;44(1):152-8.
21. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutrition, Metabolism and Cardiovascular Diseases 2014;24(9):929-39.
22. Reinders I, Virtanen J, Brouwer I, Tuomainen T. Association of serum n-3 polyunsaturated fatty acids with C-reactive protein in men. European journal of clinical nutrition 2012;66(6):736-41.
23. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek III EJ, Li W, Pagoto SL, Hafner AR, Ockene IS. Association between dietary fiber and serum C-reactive protein. The American journal of clinical nutrition 2006;83(4):760-6.
24. Harms LM, Scalbert A, Zamora-Ros R, Rinaldi S, Jenab M, Murphy N, Achaintre D, Tjønneland A, Olsen A, Overvad K. Plasma polyphenols associated with lower high-sensitivity C-reactive protein concentrations: a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. British Journal of Nutrition 2020;123(2):198-208.
25. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public health nutrition 2014;17(8):1689-96.
26. Phillips CM, Chen L-W, Heude B, Bernard JY, Harvey NC, Duijts L, Mensink-Bout SM, Polanska K, Mancano G, Suderman M. Dietary inflammatory index and non-communicable disease risk: A narrative review. Nutrients 2019;11(8):1873.
27. Hébert JR, Shivappa N, Wirth MD, Hussey JR, Hurley TG. Perspective: the Dietary Inflammatory Index (DII)—lessons learned, improvements made, and future directions. Advances in Nutrition 2019;10(2):185-95.
28. Hua R, Liang G, Yang F. Meta-analysis of the association between dietary inflammatory index (DII) and upper aerodigestive tract cancer risk. Medicine 2020;99(17):e19879.
29. Jayedi A, Emadi A, Shab-Bidar S. Dietary inflammatory index and site-specific cancer risk: a systematic review and dose-response meta-analysis. Advances in Nutrition 2018;9(4):388-403.
30. Li D, Hao X, Li J, Wu Z, Chen S, Lin J, Li X, Dong Y, Na Z, Zhang Y. Dose-response relation between dietary inflammatory index and human cancer risk: evidence from 44 epidemiologic studies involving 1,082,092 participants. The American journal of clinical nutrition 2018;107(3):371-88.
31. Liang Y, Jiao H, Qu L, Liu H. Positive association between dietary inflammatory index and gastric cancer risk: A systematic review and meta-analysis. Nutrition and Cancer 2019:1-7.
32. Liu Z-y, Gao X-p, Zhu S, Liu Y-h, Wang L-j, Jing C-x, Zeng F-f. Dietary inflammatory index and risk of gynecological cancers: a systematic review and meta-analysis of observational studies. Journal of gynecologic oncology 2018;30(3).
33. Lu D-L, Ren Z-J, Zhang Q, Ren P-W, Yang B, Liu L-R, Dong Q. Meta-analysis of the association between the inflammatory potential of diet and urologic cancer risk. PloS one 2018;13(10):e0204845.
34. Shivappa N, Godos J, Hébert JR, Wirth MD, Piuri G, Speciani AF, Grosso G. Dietary inflammatory index and cardiovascular risk and mortality—A meta-analysis. Nutrients 2018;10(2):200.

35. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: A systematic review and meta-analysis. Clinical Nutrition 2019;38(5):2045-52.
36. Zahedi H, Djalalinia S, Asayesh H, Mansourian M, Abdar ZE, Gorabi AM, Ansari H, Noroozi M, Qorbani M. A higher dietary inflammatory index score is associated with a higher risk of incidence and mortality of cancer: A comprehensive systematic review and meta-analysis. International journal of preventive medicine 2020;11.
37. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
38. Smith L, Luchini C, Demurtas J, Soysal P, Stubbs B, Hamer M, Nottegar A, Lawlor RT, Lopez-Sanchez GF, Firth J. Telomere length and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational studies. Ageing research reviews 2019;51:1-10.
39. Veronese N, Demurtas J, Thompson T, Solmi M, Pesolillo G, Celotto S, Barnini T, Stubbs B, Maggi S, Pilotto A. Effect of low-dose aspirin on health outcomes: An umbrella review of systematic reviews and meta-analyses. British journal of clinical pharmacology 2020.
40. Grabovac I, Veronese N, Stefanac S, Haider S, Jackson SE, Koyanagi A, Meilinger M, Stubbs B, Firth J, Soysal P. Human Immunodeficiency Virus Infection and Diverse Physical Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies. Clinical Infectious Diseases 2020;70(9):1809-15.
41. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E, Maggi S, Fontana L, Stubbs B, Tzoulaki I. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. The American journal of clinical nutrition 2018;107(3):436-44.
42. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2009;172(1):137-59.
43. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315(7109):629-34.
44. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. The Lancet Neurology 2015;14(3):263-73.
45. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. Clinical trials 2007;4(3):245-53.
46. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj 2017;358:j4008.
47. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism & related disorders 2016;23:1-9.
48. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. Cmaj 2009;181(8):488-93.
49. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. International journal of evidence-based healthcare 2015;13(3):132-40.
50. Farhangi MA, Nikniaz L, Nikniaz Z, Dehghan P. Dietary inflammatory index potentially increases blood pressure and markers of glucose homeostasis among adults: findings from an updated systematic review and meta-analysis. Public Health Nutrition 2020;23(8):1362-80.
51. Farhangi MA, Vajdi M. The association between dietary inflammatory index and risk of central obesity in adults: An updated systematic review and meta-analysis. International Journal for Vitamin and Nutrition Research 2020.

52. Fowler ME, Akinyemiju TF. Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. International journal of cancer 2017;141(11):2215-27.
53. Garcia-Arellano A, Martínez-González MA, Ramallal R, Salas-Salvadó J, Hébert JR, Corella D, Shivappa N, Forga L, Schröder H, Muñoz-Bravo C. Dietary inflammatory index and all-cause mortality in large cohorts: The SUN and PREDIMED studies. Clinical Nutrition 2019;38(3):1221-31.
54. Namazi N, Larijani B, Azadbakht L. Dietary inflammatory index and its association with the risk of cardiovascular diseases, metabolic syndrome, and mortality: A systematic review and meta-analysis. Hormone and Metabolic Research 2018;50(05):345-58.
55. Zhu Y, Li Q, Xu X. Dietary inflammatory index and the risk of prostate cancer: a dose-response meta-analysis. European journal of clinical nutrition 2019:1-8.
56. Radd-Vagenas S, Kouris-Blazos A, Singh MF, Flood VM. Evolution of Mediterranean diets and cuisine: concepts and definitions. Asia Pacific journal of clinical nutrition 2016.
57. De Mello V, Schwab U, Kolehmainen M, Koenig W, Siloaho M, Poutanen K, Mykkänen H, Uusitupa M. A diet high in fatty fish, bilberries and wholegrain products improves markers of endothelial function and inflammation in individuals with impaired glucose metabolism in a randomised controlled trial: the Sysdimet study. Diabetologia 2011;54(11):2755.
58. Souza PR, Marques RM, Gomez EA, Colas RA, De Matteis R, Zak A, Patel M, Collier DJ, Dalli J. Enriched marine oil supplements increase peripheral blood specialized pro-resolving mediators concentrations and reprogram host immune responses: a randomized double-blind placebo-controlled study. Circulation Research 2020;126(1):75-90.
59. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients 2010;2(3):355-74.
60. Blander JM, Longman RS, Iliev ID, Sonnenberg GF, Artis D. Regulation of inflammation by microbiota interactions with the host. Nature immunology 2017;18(8):851-60.
61. Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut microbiota in host health and disease. Cell host & microbe 2018;23(6):705-15.
62. Fritsche KL. The science of fatty acids and inflammation. Advances in Nutrition 2015;6(3):293S-301S.
63. Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, Tsukumo DM, Anhe G, Amaral ME, Takahashi HK. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. Journal of Neuroscience 2009;29(2):359-70.
64. Hebert JR, Clemow L, Pbert L, Ockene IS, Ockene JK. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. International journal of epidemiology 1995;24(2):389-98.
65. da Costa Silva BY, de Carvalho Sampaio HA, Shivappa N, Hebert JR, da Silva Albuquerque L, Carioca AAF, D'Almeida JAC, Maia CSC, de Melo MLP. Dietary Inflammatory Index and clinical course of multiple sclerosis. European journal of clinical nutrition 2019;73(7):979-88.
66. Shivappa N, Hebert JR, Behrooz M, Rashidkhani B. Dietary inflammatory index and risk of multiple sclerosis in a case-control study from Iran. Neuroepidemiology 2016;47(1):26-31.
67. Mayr HL, Thomas CJ, Tierney AC, Kucianski T, George ES, Ruiz-Canela M, Hebert JR, Shivappa N, Itsiopoulos C. Randomization to 6-month Mediterranean diet compared with a low-fat diet leads to improvement in Dietary Inflammatory Index scores in patients with coronary heart disease: the AUSMED Heart Trial. Nutrition research 2018;55:94-107.
68. Wirth MD, Hébert JR, Shivappa N, Hand GA, Hurley TG, Drenowatz C, McMahon D, Shook RP, Blair SN. Anti-inflammatory Dietary Inflammatory Index scores are associated with healthier scores on other dietary indices. Nutrition research 2016;36(3):214-9.

Figure 1. PRISMA flow chart of study selection

Figure 2. Credibility Assessment for each included outcome

Table 1. Summary of included health outcomes and their associations with the Dietary Inflammatory Index within the general population														
Out-come	Study design included in MA	Level of comparison	Studies, *n*	Participants, *n*	Cases, *n*	Type of effect size metric	Effect size (95% CI)	95% CI prediction intervals	*P*	I^2	Largest study effect size (95% CI)	Publication bias	Small-study effect or excess significance bias	Evidence Class
Mortality														
All-cause mortality(53)	Prospective	High versus low	12	220,206	44,809	RR	1.235 (1.157, 1.318)	1.01, 1.51	$2.27x10^{-10}$	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 $x10^{-1}$, 1.82	4.27x1 0^{-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 $x10^{-1}$, 2.70	3.01x1 0^{-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)	1.00x1 0^{-2}, 4.34 $x10^{2}$	4.45x1 0^{-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	5.08x1 0^{-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 $x10^{-1}$, 1.74	$9.53x10^{-1}$	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	$5.60x10^{-4}$	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	$3.08x10^{-2}$	89.0%	3.7 (0.04, 5.36)	No	No Small study effect*	IV

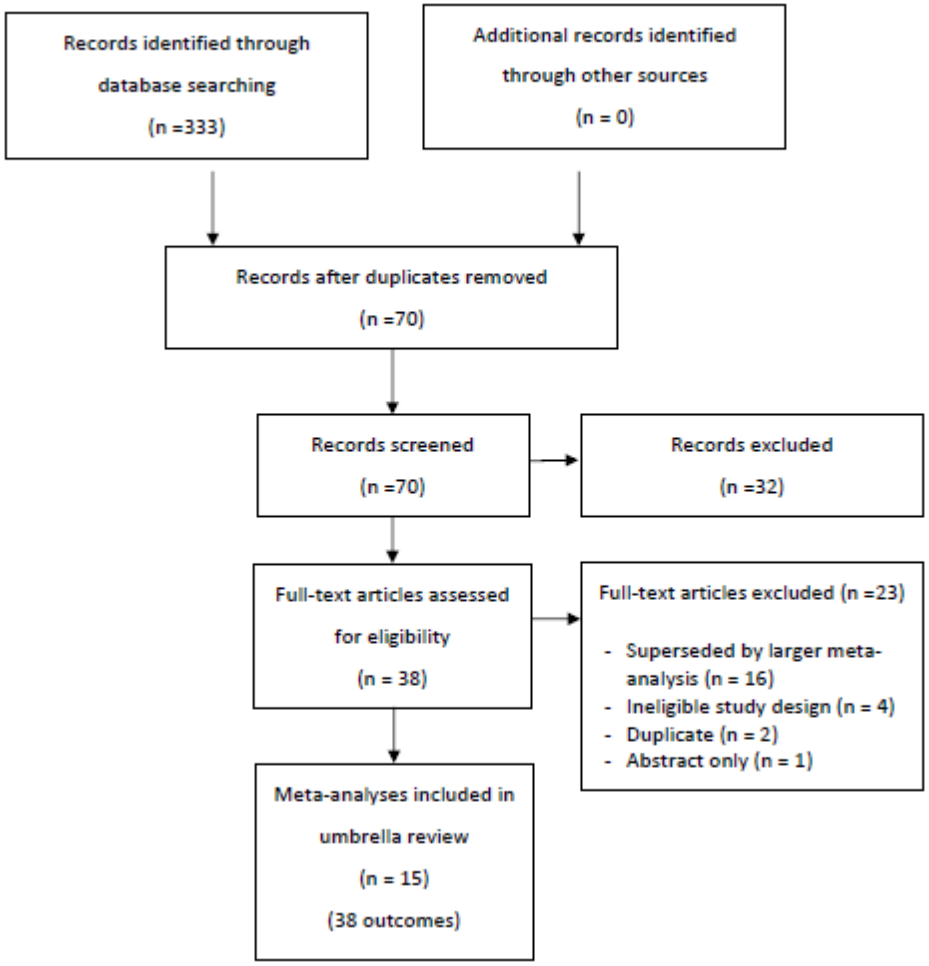
Insulin(50)	Cross-sectional	Continuous	6	38,359	-	WMD	0.829 (0.169, 1.488)	-1.27, 2.93	$1.38x10^{-2}$	86.5%	2.47 (1.64, 3.3)	No	No Small study effect*	IV
HOMA-IR(50)	Cross-sectional	Continuous	7	41,645	-	WMD	0.191 (0.021, 0.362)	$-3.90 x10^{-01}$, $7.70 x10^{-01}$	$2.80x10^{-2}$	93.2%	0.88 (0.67, 1.09)	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

Legend

1. * Either tests for small study effect, excess significance, or both, could not be conducted due to small sample size of included studies.
2. 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 $P < 0.05$.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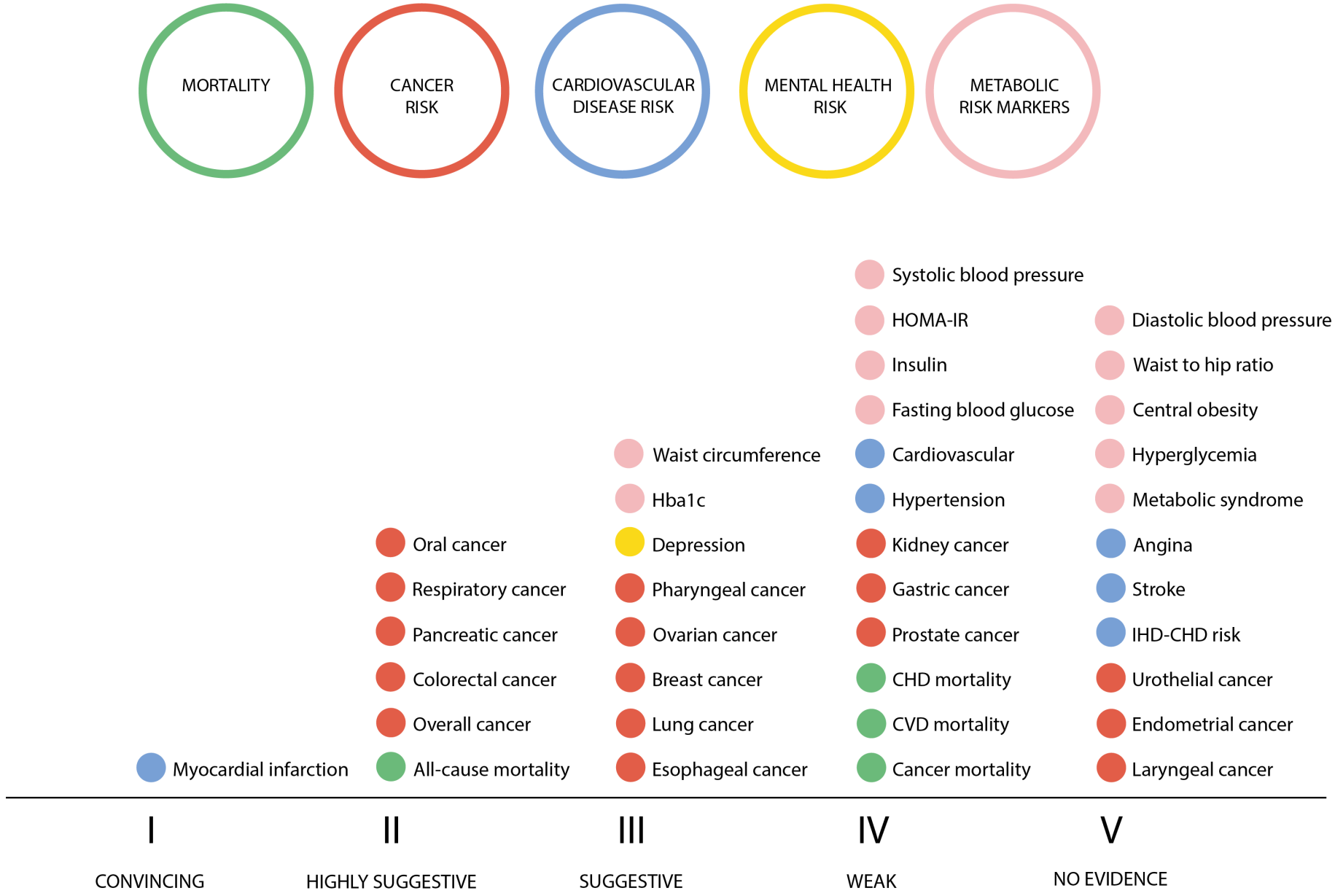
Additional records identified through other sources (n = 0)
Records after duplicates removed (n =70)
Records screened (n =70)
Records excluded (n =32)
Full-text articles assessed for eligibility (n = 38)
Full-text articles excluded (n =23)
- Superseded by larger meta-analysis (n = 16)
- Ineligible study design (n = 4)
- Duplicate (n = 2)
- Abstract only (n = 1)
Meta-analyses included in umbrella review (n = 15) (38 outcomes)


MORTALITY
CANCER RISK
CARDIOVASCULAR DISEASE RISK
MENTAL HEALTH RISK
METABOLIC RISK MARKERS
Systolic blood pressure
HOMA-IR
Diastolic blood pressure
Insulin
Waist to hip ratio
Fasting blood glucose
Central obesity
Waist circumference
Cardiovascular
Hyperglycemia
Hba1c
Hypertension
Metabolic syndrome
Oral cancer
Depression
Kidney cancer
Angina
Respiratory cancer
Pharyngeal cancer
Gastric cancer
Stroke
Pancreatic cancer
Ovarian cancer
Prostate cancer
IHD-CHD risk
Colorectal cancer
Breast cancer
CHD mortality
Urothelial cancer
Overall cancer
Lung cancer
CVD mortality
Endometrial cancer
Myocardial infarction
All-cause mortality
Esophageal cancer
Cancer mortality
Laryngeal cancer
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CONVINCING
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