RESEARCH ARTICLE

Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses

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Abstract

Background
Type 2 diabetes mellitus (T2DM) is a global epidemic associated with increased health expenditure, and low quality of life. Many non-genetic risk factors have been suggested, but their overall epidemiological credibility has not been assessed.

Methods
We searched PubMed to capture all meta-analyses and Mendelian randomization studies for risk factors of T2DM. For each association, we estimated the summary effect size, its 95% confidence and prediction interval, and the I² metric. We examined the presence of small-study effects and excess significance bias. We assessed the epidemiological credibility through a set of predefined criteria.

Results
We captured 86 eligible papers (142 associations) covering a wide range of biomarkers, medical conditions, and dietary, lifestyle, environmental and psychosocial factors. Adiposity, low hip circumference, serum biomarkers (increased level of alanine aminotransferase, gamma-glutamyl transferase, uric acid and C-reactive protein, and decreased level of adiponectin and vitamin D), an unhealthy dietary pattern (increased consumption of processed meat and sugar-sweetened beverages, decreased intake of whole grains, coffee and heme iron, and low adherence to a healthy dietary pattern), low level of education and conscientiousness, decreased physical activity, high sedentary time and duration of television watching, low alcohol drinking, smoking, air pollution, and some medical conditions (high systolic blood pressure, late menarche age, gestational diabetes, metabolic syndrome, preterm birth) presented robust evidence for increased risk of T2DM.
Conclusions
A healthy lifestyle pattern could lead to decreased risk for T2DM. Future randomized clinical trials should focus on identifying efficient strategies to modify harmful daily habits and predisposing dietary patterns.

Background
Type 2 diabetes mellitus (T2DM) ranks highly on the international health agenda as a global pandemic and as a threat to human health and global economies. The number of people with T2DM worldwide has more than doubled during the past 20 years [1]. According to the International Diabetes Federation, 415 million people are living with T2DM in 2015, and by 2040 the number will be almost 642 million [2]. These estimates correspond to a global prevalence of 8.8% (95% confidence interval, 7.2–11.4%) in 2015, and a projected global prevalence of 10.4% (95% confidence interval, 8.5–13.5%) in 2040 [2]. Epidemiological data predict an inexorable and unsustainable increase in global health expenditure attributable to T2DM, so disease prevention should be given high priority.

T2DM results from an interaction between genetic and environmental factors [3]. Genes and the environment together are important determinants of insulin resistance and β-cell dysfunction [4]. Because changes in the gene pool cannot account for the rapid increase in prevalence of T2DM in recent decades, environmental changes are essential to the understanding of the epidemic.

Systematic reviews and meta-analyses of observational studies have indicated numerous risk factors for T2DM. However, the epidemiological credibility of these associations has not been appraised across the field. In the present work, we performed an umbrella review of the evidence across existing systematic reviews and meta-analyses of observational studies that examine any non-genetic risk factor for T2DM. We primarily aim to provide an overview of the range and validity of the reported associations of diverse environmental risk factors and biomarkers with T2DM. Furthermore, we assessed whether there is evidence for diverse biases and which of the previously studied associations have robust evidence.

Materials and methods
Search strategy and eligibility criteria
We conducted an umbrella review, i.e. a comprehensive and systematic collection and evaluation of systematic reviews and meta-analyses performed on a specific research topic using previously described and applied methodology [5–12].

We systematically searched PubMed from inception until February 10, 2016 to identify systematic reviews and meta-analyses of observational studies examining associations of non-genetic risk factors with T2DM. We used the following search strategy: diabetes AND (“systematic review” OR meta-analysis). Two independent investigators (VB, LB) retrieved and abstracted the full text of potentially eligible articles. We excluded meta-analyses that investigated the association between genetic polymorphisms and risk for T2DM; that included less than 3 component studies; that included studies with overlapping populations; that included studies using different units of comparison of the same exposure without transforming the effect estimates appropriately. We further excluded meta-analyses performing comparison between drug agents and subsequent risk for developing T2DM in population at high risk. When an association was covered by more than one meta-analyses, we kept the meta-analysis.
including the largest number of component studies and adequately presenting the study-specific effect estimates and sample sizes of component studies. We did not apply any language restrictions in our search strategy.

Finally, in order to assess the causality of the associations between the reported risk factors and T2DM, we conducted an additional systematic search on PubMed to capture mendelian randomization (MR) studies for T2DM. This search algorithm used the keywords: “mendelian randomization” OR “mendelian randomisation”. MR studies were eligible if they studied T2DM and examined the potentially causal effect of a risk factor that was also included in our umbrella review. We excluded studies focused on impaired glucose tolerance, impaired fasting glucose or insulin resistance as outcomes.

Data extraction
Two independent investigators (VB, LB) extracted the data, and in case of discrepancies consensus was reached. From each eligible article, we abstracted information on the first author, journal and year of publication, the examined risk factors and the number of studies considered. We also extracted the study-specific risk estimates (i.e. risk ratio, odds ratio, hazard ratio, standardized mean difference) along with their 95% confidence interval (CI) and the number of cases and controls in each study. If a meta-analysis included multiple effect estimates from the same observational study using the same control group, we included only the effect estimate that corresponded to the largest sample size.

From each eligible MR study, we extracted the first author and year of publication, the definition of outcome, the risk factor considered, the level of comparison for exposure, the genetic instrument used, the applied statistical approach, the sample size, the causal odds ratio and its 95% CI, the P-value for the association, and whether the authors claimed that a causal relationship exists. If an MR study used a genetic instrument based on a single variant and a genetic instrument based on polygenic risk score (PRS), we extracted the information from the PRS, as this approach is more powerful.

Statistical analysis
For each meta-analysis, we estimated the summary effect size and its 95% CI using both fixed-effect and random-effects models. [13,14] We also estimated the 95% prediction interval (PI), which accounts for the between-study heterogeneity and evaluates the uncertainty for the effect that would be expected in a new study addressing that same association. [15,16]

Between-study heterogeneity was quantified using the I² metric. I² ranges between 0% and 100% and quantifies the variability in effect estimates that is due to heterogeneity rather than sampling error. [17] Values exceeding 50% or 75% are considered to represent large or very large heterogeneity, respectively. This step is necessary to ensure that all results from each meta-analysis are available to assess the epidemiological credibility of the associations.

We assessed small-study effects using the Egger’s regression asymmetry test. [18,19] A P <0.10 combined with a more conservative effect in the largest study than in random-effects meta-analysis was judged to provide adequate evidence for small-study effects. We further applied the excess statistical significance test, which evaluates whether there is a relative excess of formally significant findings in the published literature due to any reason. [20] We used the effect size of the largest study (smallest standard error) in each meta-analysis to calculate the power of each study using a non-central t distribution. [21,22] Excess statistical significance was claimed at two-sided P <0.10. [21] In two meta-analyses (glycemic load as dichotomous exposure, and breastfeeding), the excess significance test was not performed, because the sample size was not reported in some of the component studies.
Assessment of epidemiological credibility

We identified associations that had the strongest evidence and no signals of large heterogeneity or bias. We considered as convincing the associations that fulfilled all the following criteria: statistical significance per random-effects model at $P < 10^{-6}$; based on $>1,000$ cases; without large between-study heterogeneity ($I^2 < 50\%$); 95% PI excluding the null value; and no evidence of small-study effects and excess significance bias. Associations with $>1,000$ cases, $P < 10^{-6}$ and largest study presenting a statistically significant effect were graded as highly suggestive. The associations supported by $>1,000$ cases and a significant effect at $P < 10^{-3}$ were considered as suggestive. The remaining nominally significant associations ($P < 0.05$) were considered as having weak evidence.

For associations with convincing and highly suggestive evidence, we performed a sensitivity analysis limited to prospective cohort studies and nested case-control studies, and we examined whether there was a change in the level of epidemiological credibility. Also, we compared the findings from the meta-analyses of observational studies with the findings from MR studies.

The statistical analysis and the power calculations were done with STATA version 12.0 and RStudio version 1.0.44.

Results

Eligible studies

Our literature search yielded 7,303 papers, of which 86 papers met our inclusion criteria (Fig 1). Fourteen papers, including 16 associations (i.e., sedentary time, breakfast skipping, psoriasis, psoriatic arthritis, breastfeeding, adverse childhood experience, height, hip circumference, serum osteocalcin, spousal diabetes, osteoarthritis, polycystic ovary syndrome, schizophrenia, major depressive disorder, and bipolar disorder), combined cross-sectional studies with either cohort studies or case-control studies in their analysis.

The 86 eligible papers examined 109 unique risk factors and 142 associations related to risk for developing T2DM. These associations covered a wide range of exposures: biomarkers ($n = 25$ associations), dietary factors ($n = 53$ associations), lifestyle factors and environmental exposures ($n = 22$ associations), medical history ($n = 16$ associations), metabolic factors and anthropometric traits ($n = 15$ associations), and psychosocial factors ($n = 11$ associations). The median number of cases per meta-analysis was 8,825 (IQR, 2,892–17,782), and the median number of datasets was 10 (IQR, 6–14). Only 7 meta-analyses included less than 1,000 T2DM cases.

Statistically significant associations, heterogeneity and biases

One hundred and sixteen of 142 associations (82%) presented a statistically significant effect at $P < 0.05$ under the random-effects model, whereas 46 associations had a statistically significant effect at $P < 10^{-6}$ (Table 1). Fig 2 displays the distribution of the P-values in each category of associations. Only 33 of 142 associations (23%) had a 95% PI that excluded the null value and 26 of these also had a $P < 10^{-6}$.

Thirty-eight associations (27%) were very heterogeneous ($I^2 > 75\%$), and 50 associations (35%) had large heterogeneity estimates ($I^2 \geq 50\%$ and $I^2 \leq 75\%$). The Egger’s test was statistically significant in 32 meta-analyses (23%), and 27 of them presented evidence for small-study effects. Thirty-nine meta-analyses (28%) had evidence for excess significance bias.
Assessment of epidemiological credibility

Eleven associations (8%) presented convincing evidence (>1,000 cases, $P < 10^{-6}$, not large between-study heterogeneity, 95% PI excluding the null value, no evidence for small-study effects and excess significance bias) for risk of T2DM. Low whole grains consumption, metabolically healthy obesity, increased sedentary time, low adherence to a healthy dietary pattern, high level of serum uric acid, low level of serum vitamin D, decreased conscientiousness, preterm birth, high consumption of sugar-sweetened beverages, high level of serum ALT, and exposure to high level of PM$_{10}$ were associated with increased risk for T2DM and supported by convincing evidence.

Thirty-four associations (24%) were supported by highly suggestive evidence. The associations that were linked with a higher risk for T2DM and presented highly suggestive evidence were the following: high BMI (obese vs. lean, overweight vs. lean, and per 1 SD increase), low educational status, gestational diabetes, increased processed meat consumption, high level of total and leisure-time physical activity, metabolically unhealthy obesity, psoriasis, low coffee consumption, high systolic blood pressure, high level of serum gamma-glutamyl transferase.
Table 1. Characteristics of 142 associations between non-genetic risk factors and type 2 diabetes mellitus.

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|-------------------|-------------------|---------------------------------------------|----------|------------------------|-----|-------------------------|---------|
| **Markers** |             |                     |                          |                   |                   |                                             |          |                        |     |                        |         |
| Aune, 2015 [57] | Resting heart rate | Per 10 bpm increase | 6217/106,601             | 9                 | RR                | 1.20 (1.07–1.35)                            | 1.74 × 10⁻⁴ | 0.80–1.79 | 93.4 | No/Yes                  | Weak    |
| Chen, 2014 [58] | Serum leptin | Per 1 log ng/ml increase | 4084/22,367               | 17                | RR                | 1.13 (1.01–1.27)                            | 0.038    | 0.74–1.73 | 76   | Yes/Yes                 | Weak    |
| Emdin, 2015 [29] | Systolic blood pressure | Per 20 mmHg increase | 204,803/4,212,999         | 40                | RR                | 1.75 (1.56–1.97)                            | 6.15 × 10⁻²¹ | 0.97–3.16 | 85.7 | No/No                  | Highly suggestive |
| Fraser, 2009 [59] | Serum ALT | Per 1 log unit increase | 2009/32,292               | 14                | HR                | 1.85 (1.57–2.18)                            | 2.85 × 10⁻¹³ | 1.31–2.61 | 19.2 | No/No                  | Convincing |
| Fraser, 2009 [59] | Serum ALT | Highest vs. lowest category | 1087/22,729               | 10                | HR                | 2.07 (1.54–2.79)                            | 1.52 × 10⁻⁶ | 1.07–4.02 | 27.3 | No/No                  | Suggestive |
| Fraser, 2009 [59] | Serum γGT | Highest vs. lowest category | 1352/20,955               | 10                | HR                | 3.07 (2.22–4.23)                            | 1.02 × 10⁻¹¹ | 1.60–5.86 | 19.9 | Yes/No                  | Highly suggestive |
| Fraser, 2009 [59] | Serum γGT | Per 1 log unit increase | 2742/60,173               | 18                | HR                | 1.92 (1.66–2.21)                            | 1.58 × 10⁻¹⁹ | 1.20–3.07 | 54.8 | No/No                  | Highly suggestive |
| Jia, 2013 [60] | Serum uric acid | Highest vs. lowest category | 5115/43,693               | 11                | RR                | 1.60 (1.44–1.78)                            | 4.60 × 10⁻¹⁸ | 1.39–1.85 | 3.4  | No/No                  | Convincing |
| Kodama, 2009 [61] | Serum uric acid | Per 1 mg/dl increase | 3305/39,529               | 14                | RR                | 1.17 (1.09–1.25)                            | 1.15 × 10⁻⁵ | 0.92–1.48 | 74.8 | Yes/Yes                 | Suggestive |
| Kunutsor, 2013 [25] | Serum ferritin | Highest vs. lowest category | 3391/22,948               | 9                 | RR                | 1.73 (1.35–2.22)                            | 1.23 × 10⁻⁵ | 0.84–3.56 | 58.2 | No/No                  | Suggestive |
| Kunutsor, 2013 | Serum AST | Highest vs. lowest category | 5985/79,958               | 11                | RR                | 1.26 (1.11–1.42)                            | 1.98 × 10⁻⁴ | 0.89–1.78 | 56.4 | Yes/Yes                 | Suggestive |
| Kunutsor, 2013 | Serum AST | Per 1 SD increase | 1828/20,290               | 7                 | RR                | 1.13 (1.02–1.25)                            | 0.021    | 0.85–1.49 | 52.5 | No/Yes                  | Weak    |
| Kunutsor, 2015 [62] | Serum osteocalcin | Highest vs. lowest category | 1673/6963                | 9                 | RR                | 0.43 (0.29–0.65)                            | 5.56 × 10⁻⁵ | 0.12–1.52 | 87.8 | Yes/Yes                 | Suggestive |
| Lee, 2009 [63] | Serum CRP | Highest vs. lowest category | 3920/24,914               | 16                | RR                | 1.79 (1.51–2.13)                            | 3.30 × 10⁻¹¹ | 1.03–3.11 | 53.4 | No/No                  | Highly suggestive |
| Li, 2009 [64] | Serum adiponectin | Per 1 log µg/ml increase | 2623/11,986               | 14                | RR                | 0.72 (0.67–0.78)                            | 4.51 × 10⁻¹⁶ | 0.59–0.89 | 42.4 | No/Yes                  | Highly suggestive |
| Sabanayagam, 2015 [65] | Central retinal arteriolar equivalent | Per 20 µm decrease | 2581/16,190              | 5                 | HR                | 0.95 (0.86–1.06)                            | 0.369    | 0.68–1.33 | 61.6 | No/No                  | Not significant |
| Sabanayagam, 2015 [65] | Central retinal venular retinal equivalent | Per 20 µm decrease | 2581/16,190              | 5                 | HR                | 1.08 (1.02–1.15)                            | 7.80 × 10⁻³ | 0.93–1.26 | 30.7 | Yes/No                  | Weak    |
| Sing, 2015 [66] | Serum calcium | Highest vs. lowest category | 1476/32,641               | 3                 | HR                | 1.40 (1.11–1.75)                            | 4.19 × 10⁻³ | 0.19–10.08 | 24.6 | Yes/Yes                 | Weak    |
| Song, 2013 [44] | Serum vitamin D | Highest vs. lowest category | 5142/71,115               | 21                | RR                | 0.62 (0.54–0.70)                            | 1.44 × 10⁻¹³ | 0.46–0.83 | 19.4 | No/No                  | Convincing |
| Wang, 2013 [67] | Serum CRP | Per 1 log pm/ml increase | 5750/35,097               | 22                | RR                | 1.26 (1.16–1.37)                            | 5.79 × 10⁻⁸ | 0.92–1.71 | 63.9 | No/Yes                  | Highly suggestive |
| Wang, 2013 [67] | Serum IL-6 | Per 1 log pm/ml increase | 4480/15,229               | 11                | RR                | 1.31 (1.17–1.46)                            | 3.40 × 10⁻⁶ | 0.97–1.75 | 42.5 | No/Yes                  | Suggestive |
| Wang, 2015 [68] | Resting heart rate | Highest vs. lowest category | 10,049/169,329            | 9                 | HR                | 1.57 (1.29–1.92)                            | 6.11 × 10⁻⁶ | 0.83–2.98 | 84.3 | No/No                  | Suggestive |
| Wu, 2012 [69] | Serum EPA and DHA | Per 3% of total fatty acids increase | 1581/8801               | 5                 | RR                | 0.94 (0.75–1.17)                            | 0.566    | 0.50–1.76 | 40.1 | No/No                  | Not significant |

(Continued)
### Table 1. (Continued)

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|-------------------|-------------------|---------------------------------------------|----------|----------------------------|-----|-------------------------------------------|---------|
| Wu, 2012 [69] | Serum ALA | Per 0.1% of total fatty acids increase | 13,308/216,908 | 6 | RR | 0.87 (0.81–0.93) | 9.49 × 10⁻⁵ | 0.75–1.01 | 21.1 | No/No | Suggestive |
| Alhazmi, 2012 [72] | Total protein intake | Highest vs. lowest category | 6290/201,223 | 3 | HR | 1.02 (0.90–1.17) | 0.733 | 0.35–2.99 | 19 | No/No | Not significant |
| Aune, 2009 [23] | Processed meat consumption | Highest vs. lowest category | 9999/370,607 | 9 | RR | 1.41 (1.25–1.59) | 3.03 × 10⁻⁸ | 1.01–1.98 | 52.5 | No/No | Highly suggestive |
| Aune, 2009 [23] | Processed meat intake | Per 50 g/day increase | 9,456/362,749 | 8 | RR | 1.57 (1.28–1.93) | 1.85 × 10⁻⁵ | 0.84–2.94 | 74.1 | No/No | Suggestive |
| Aune, 2009 [23] | Total meat consumption | Highest vs. lowest category | 6525/438,798 | 5 | RR | 1.17 (0.92–1.48) | 0.193 | 0.49–2.81 | 86.9 | No/No | Not significant |
| Aune, 2009 [23] | Total meat intake | Per 120 g/day increase | 5579/174,626 | 4 | RR | 1.26 (0.84–1.88) | 0.259 | 0.21–7.61 | 90.8 | No/No | Not significant |
| Aune, 2009 [23] | Total red meat consumption | Highest vs. lowest category | 12,226/420,844 | 10 | RR | 1.21 (1.07–1.38) | 3.08 × 10⁻³ | 0.83–1.76 | 58.5 | No/No | Weak |
| Aune, 2009 [23] | Total red meat intake | Per 120 g/day increase | 10,305/387,067 | 9 | RR | 1.20 (1.04–1.38) | 0.014 | 0.76–1.87 | 68.4 | No/No | Weak |
| Aune, 2013 [73] | Dairy products | Per 400g/day increase | 21,996/319,537 | 12 | RR | 0.93 (0.87–0.99) | 0.019 | 0.81–1.07 | 31.9 | No/No | Weak |
| Aune, 2013 [73] | Dairy products | Highest vs. lowest category | 26,966/399,089 | 14 | RR | 0.89 (0.82–0.96) | 3.24 × 10⁻³ | 0.72–1.10 | 42.2 | No/No | Weak |
| Aune, 2013 [26] | Refined grains | Highest vs. lowest category | 9547/248,531 | 6 | RR | 0.94 (0.82–1.09) | 0.444 | 0.61–1.47 | 63.8 | Yes/No | Not significant |
| Aune, 2013 [26] | Refined grains | Per 3 servings/day increase | 9547/248,531 | 6 | RR | 0.96 (0.88–1.04) | 0.320 | 0.75–1.22 | 52.6 | No/No | Not significant |
| Aune, 2013 [26] | Whole grains | Highest vs. lowest category | 19,107/364,443 | 9 | RR | 0.74 (0.70–0.78) | 5.45 × 10⁻³ | 0.70–0.79 | 0 | No/No | Convincing |
| Aune, 2013 [26] | Whole grains | Per 3 servings/day increase | 19,831/366,037 | 10 | RR | 0.68 (0.57–0.81) | 1.47 × 10⁻⁵ | 0.38–1.24 | 82.5 | No/Yes | Suggestive |
| Bhupathiraju, 2014 [74] | Glycemic index | Highest vs. lowest category | 36,562/400,485 | 20 | RR | 1.12 (1.03–1.21) | 8.98 × 10⁻³ | 0.82–1.52 | 68.5 | No/No | Weak |
| Bhupathiraju, 2014 [74] | Glycemic load | Highest vs. lowest category | NA/NA | 30 | RR | 1.12 (1.06–1.17) | 3.07 × 10⁻⁵ | 0.96–1.29 | 26.4 | No/NA | Suggestive |
| Bi, 2015 [75] | Breakfast skipping | Yes vs. no | 7419/99,516 | 8 | RR | 1.15 (1.04–1.27) | 6.35 × 10⁻³ | 0.90–1.47 | 50 | No/No | Weak |
| de Souza, 2015 [76] | Total saturated fat | Highest vs. lowest category | 8739/228,715 | 8 | RR | 0.95 (0.88–1.03) | 0.206 | 0.87–1.05 | 0 | No/No | Not significant |
| de Souza, 2015 [76] | Total saturated fatty acids | Highest vs. lowest category | 9758/234,788 | 10 | RR | 1.00 (0.90–1.12) | 0.945 | 0.76–1.33 | 41.6 | No/No | Not significant |
| de Souza, 2015 [76] | Total trans fat | Highest vs. lowest category | 8690/221,445 | 6 | RR | 1.10 (0.95–1.26) | 0.216 | 0.70–1.71 | 66 | No/No | Not significant |
| de Souza, 2015 [76] | Total trans unsaturated fat | Highest vs. lowest category | 9923/227,734 | 9 | RR | 0.98 (0.82–1.18) | 0.828 | 0.54–1.77 | 78.1 | No/No | Not significant |
| de Souza, 2015 [76] | Trans palmitoleic acid | Highest vs. lowest category | 1153/11,789 | 5 | RR | 0.38 (0.46–0.74) | 1.09 × 10⁻⁵ | 0.31–1.08 | 30.8 | No/No | Suggestive |

(Continued)
| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|-------------------|------------------|--------------------------------------------|----------|------------------------|-----|------------------------|---------|
| Ding, 2014 [27] | Coffee consumption | Highest vs. lowest category | 50,273/1,046,597 | 32 | RR | 0.70 (0.65–0.75) | 1.52 × 10⁻²⁵ | 0.54–0.90 | 50.3 | No/No | Highly suggestive |
| Djourousse, 2016 [78] | Eggs consumption | Highest vs. lowest category | 8911/211,068 | 12 | RR | 1.06 (0.86–1.30) | 0.610 | 0.53–2.10 | 73.6 | No/No | Not significant |
| Dong, 2012 [79] | Dietary calcium intake | Highest vs. lowest category | 11,195/253,023 | 7 | RR | 0.85 (0.75–0.97) | 0.018 | 0.59–1.23 | 53.4 | No/No | Weak |
| Esposito, 2014 [28] | Healthy dietary pattern | Highest vs. lowest category | 15,574/350,610 | 18 | RR | 0.80 (0.76–0.84) | 4.86 × 10⁻¹⁷ | 0.73–0.88 | 8.6 | No/No | Convincing |
| Greenwood, 2013 [80] | Glycemic index | Per 5 units/day increase | 16,419/422,326 | 15 | RR | 1.08 (1.02–1.14) | 0.013 | 0.87–1.34 | 87.6 | No/Yes | Weak |
| Greenwood, 2013 [80] | Glycemic load | Per 20 units/day increase | 24,942/486,351 | 16 | RR | 1.03 (1.00–1.05) | 0.034 | 0.96–1.10 | 52.7 | No/Yes | Weak |
| Greenwood, 2013 [80] | Carbohydrates consumption | Per 50 g/day increase | 11,976/285,117 | 8 | RR | 0.97 (0.90–1.06) | 0.514 | 0.75–1.26 | 75.5 | No/Yes | Not significant |
| Guo, 2015 [81] | Nuts consumption | Highest vs. lowest category | 11,580/251,083 | 6 | RR | 0.98 (0.84–1.15) | 0.827 | 0.61–1.58 | 67.7 | No/Yes | Not significant |
| Hu, 2012 [82] | Rice consumption | Highest vs. lowest category | 13,583/338,765 | 7 | RR | 1.27 (1.04–1.54) | 0.020 | 0.67–2.38 | 72 | No/No | Weak |
| Imamura, 2015 [24] | Artificially-sweetened beverages | Per 1 serving/day increase | 29,448/263,765 | 9 | RR | 1.07 (1.03–1.10) | 1.32 × 10⁻⁴ | 0.99–1.14 | 28.8 | No/Yes | Suggestive |
| Imamura, 2015 [24] | Fruit juice consumption | Per 1 serving/day increase | 33,172/363,805 | 12 | RR | 1.07 (1.01–1.14) | 0.031 | 0.90–1.27 | 50.9 | No/No | Weak |
| Imamura, 2015 [24] | Sugar-sweetened beverages | Per 1 serving/day increase | 38,253/422,326 | 17 | RR | 1.12 (1.06–1.20) | 2.47 × 10⁻⁴ | 0.90–1.40 | 77.2 | No/Yes | Suggestive |
| InterAct consortium, 2015 [83] | Total dietary fiber intake | Per 10 g/day increase | 57,407/326,028 | 15 | RR | 0.91 (0.87–0.96) | 3.43 × 10⁻⁴ | 0.81–1.03 | 31 | No/No | Suggestive |
| Koloverou, 2014 [84] | Mediterranean diet | Highest vs. lowest category | 19,663/115,923 | 10 | RR | 0.83 (0.74–0.93) | 2.03 × 10⁻³ | 0.60–1.15 | 59 | No/No | Weak |
| Kunutsor, 2013 [25] | Dietary heme iron | Highest vs. lowest category | 7708/151,415 | 3 | RR | 1.28 (1.16–1.41) | 3.35 × 10⁻⁷ | 0.69–2.37 | 0 | No/No | Highly suggestive |
| Larsson, 2007 [85] | Magnesium intake | Per 100 mg/day increase | 10,912/275,988 | 8 | RR | 0.85 (0.79–0.92) | 1.43 × 10⁻⁵ | 0.69–1.06 | 65.8 | No/Yes | Suggestive |
| Leermakers, 2016 [86] | Lutein intake | Highest vs. lowest category | 1661/33,581 | 5 | RR | 0.97 (0.77–1.22) | 0.783 | 0.50–1.89 | 48.8 | No/No | Not significant |
| Li, 2014 [87] | Vegetables consumption | Highest vs. lowest category | 20,933/269,994 | 9 | RR | 0.90 (0.80–1.01) | 0.068 | 0.64–1.27 | 66.5 | No/No | Not significant |
| Li, 2016 [88] | Alcohol consumption | Moderate drinkers vs. never drinkers | 30,436/647,388 | 25 | RR | 0.74 (0.67–0.82) | 4.86 × 10⁻⁹ | 0.49–1.10 | 74.4 | No/No | Highly suggestive |
| Liu, 2014 [89] | Flavonoids intake | Highest vs. lowest category | 18,146/266,460 | 6 | RR | 0.92 (0.87–0.98) | 6.68 × 10⁻³ | 0.81–1.05 | 25.8 | No/No | Weak |
| Tajima, 2014 [90] | Cholesterol intake | Highest vs. lowest category | 7589/196,314 | 6 | RR | 1.24 (1.10–1.40) | 4.93 × 10⁻⁴ | 0.91–1.68 | 41.4 | No/No | Suggestive |
| Tajima, 2014 [90] | Cholesterol intake | Per 100 mg/day increase | 6268/155,131 | 5 | RR | 1.09 (1.03–1.16) | 4.34 × 10⁻³ | 0.91–1.31 | 50.4 | No/No | Weak |
| Wang, 2015 [91] | Fruit consumption | Highest vs. lowest category | 33,987/474,591 | 13 | RR | 0.92 (0.87–0.97) | 1.92 × 10⁻³ | 0.83–1.01 | 11.2 | No/No | Weak |
Table 1. (Continued)

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|-------------------|-------------------|-------------------------------------------|----------|------------------------|-----|------------------------------|---------|
| Wang, 2015 [92] | Sugar-sweetened beverages | Highest vs. lowest category | 30,005/347,941 | 9 | RR | 0.70 (0.70–0.79) | 4.71 × 10⁻²² | 0.54–1.03 | 0.98–1.34 | 0.97–1.54 | Weak |
| Wu, 2012 [69] | Dietary ALA | Per 0.5 g/day increase | 55 | 10 | RR | 0.75 (0.66–0.85) | 4.44 × 10⁻⁶ | 0.51–1.11 | 5.24–7.65 | 0.97–1.54 | Weak |
| Wu, 2012 [69] | Dietary EPA and DHA | Per 250 mg/day increase | 17,103/87,459 | 14 | RR | 0.65 (0.59–0.71) | 2.87 × 10⁻⁸ | 0.54–0.78 | 1.52–2.39 | 0.97–1.54 | Weak |
| Zhao, 2014 [96] | Vitamin D intake | Highest vs. lowest category | 9456/178,096 | 5 | RR | 0.93 (0.85–1.01) | 0.067 | 0.81–1.06 | 0.97–1.54 | Weak |

### Lifestyle and environmental factors

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|-------------------|-------------------|-------------------------------------------|----------|------------------------|-----|------------------------------|---------|
| Aune, 2015 [97] | Leisure time physical activity | Highest vs. lowest category | 151,523/1,669,717 | 55 | RR | 0.75 (0.70–0.79) | 4.71 × 10⁻²² | 0.54–1.03 | Yes/Yes | Highly suggestive |
| Aune, 2015 [97] | Leisure time physical activity | Per 5 hours/week increase | 63,049/891,089 | 10 | RR | 0.75 (0.66–0.85) | 4.44 × 10⁻⁶ | 0.51–1.11 | Yes/Yes | Highly suggestive |
| Aune, 2015 [97] | Total physical activity | Highest vs. lowest category | 17,103/87,459 | 14 | RR | 0.65 (0.59–0.71) | 2.87 × 10⁻⁸ | 0.54–0.78 | Yes/Yes | Highly suggestive |
| Biswas, 2015 [98] | Sedentary time | Highest vs. lowest category | 6712/157,247 | 5 | HR | 1.91 (1.66–2.19) | 9.30 × 10⁻¹⁰ | 1.52–2.39 | 0 | No/No | Convincing |
| Capuccio, 2010 [99] | Difficulty in initiating sleep | Yes vs. no | 787/23,405 | 6 | RR | 1.57 (1.26–1.97) | 8.54 × 10⁻⁵ | 1.14–2.17 | 0 | No/No | Weak |
| Capuccio, 2010 [99] | Difficulty in maintaining sleep | Yes vs. no | 544/17,669 | 6 | RR | 1.84 (1.39–2.43) | 2.16 × 10⁻⁵ | 1.00–3.37 | 0 | No/No | Weak |
| Capuccio, 2010 [99] | Sleep duration | Long vs. normal | 2903/85,708 | 7 | RR | 1.48 (1.12–1.96) | 5.48 × 10⁻⁵ | 0.77–2.84 | 22.3 | No/No | Weak |
| Galling, 2016 [100] | Antipsychotics | Yes vs. no | 796/530,315 | 8 | RR | 3.02 (1.70–5.35) | 1.56 × 10⁻⁴ | 0.46–19.63 | 37.9 | No/No | Weak |
| Gronvold, 2011 [101] | Television watching | Per 2 hours/day increase | 6428/169,510 | 4 | RR | 1.20 (1.14–1.27) | 5.66 × 10⁻¹¹ | 0.98–1.47 | 50.3 | No/No | Highly suggestive |
| Holliday, 2013 [102] | Sleep duration | Short vs. normal | 17,660/429,464 | 12 | OR | 1.38 (1.18–1.60) | 3.23 × 10⁻⁵ | 0.96–1.97 | 33.2 | No/No | Suggestive |
| Leong, 2014 [103] | Spousal diabetes | Yes vs. no | 5689/69,809 | 4 | OR | 1.39 (1.04–1.87) | 0.206 | 0.44–4.47 | 59.6 | Yes/No | Weak |
| Pan, 2015 [52] | Passive smoking | Ever vs. never | 7843/148,596 | 7 | RR | 1.22 (1.10–1.35) | 1.21 × 10⁻⁴ | 0.97–1.54 | 31.8 | No/Yes | Suggestive |
| Pan, 2015 [52] | Smoking | Former vs. never smokers | 161,938/2,714,859 | 47 | RR | 1.14 (1.10–1.19) | 5.97 × 10⁻¹² | 0.98–1.34 | 64 | Yes/No | Highly suggestive |
| Pan, 2015 [52] | Smoking | Current vs. never smokers | 270,705/5,580,157 | 88 | RR | 1.39 (1.33–1.44) | 6.10 × 10⁻⁶ | 1.10–1.74 | 70.2 | Yes/Yes | Highly suggestive |
| Pan, 2015 [52] | Smoking cessation | New quitters vs. never smokers | 49,457/1,046,789 | 13 | RR | 1.54 (1.36–1.75) | 2.13 × 10⁻¹¹ | 0.99–2.40 | 82.5 | Yes/Yes | Highly suggestive |
| Pan, 2015 [52] | Smoking cessation | Middle-term quitters vs. never smokers | 39,130/1,033,615 | 11 | RR | 1.18 (1.07–1.29) | 5.24 × 10⁻⁴ | 0.92–1.50 | 55.8 | No/No | Suggestive |

(Continued)
### Table 1. (Continued)

| Reference | Risk factor                  | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|------------------------------|---------------------|--------------------------|--------------------|--------------------|---------------------------------------------|----------|------------------------|-----|--------------------------|---------|
| Pan, 2015 [52] | Smoking cessation | Long-term quitters vs. never smokers | 48,357/988,055 | 11 | RR | 1.11 (1.02–1.21) | 0.014 | 0.85–1.44 | 76.3 | Yes/No | Weak |
| Wang, 2014 [104] | NO₂ | Per 10 μg/m³ increase | 5113/69,922 | 6 | RR | 1.11 (1.07–1.16) | 6.44 × 10⁻⁷ | 1.00–1.24 | 46.1 | No/Yes | Highly suggestive |
| Wang, 2014 [104] | PM₁₀ | Per 10 μg/m³ increase | 4974/92,653 | 4 | RR | 1.34 (1.22–1.47) | 4.26 × 10⁻¹⁰ | 1.10–1.65 | 0 | No/No | Convincing |
| Wang, 2014 [104] | PM₂.⁵ | Per 10 μg/m³ increase | 16,165/2,284,699 | 5 | RR | 1.39 (1.14–1.68) | 8.18 × 10⁻⁴ | 0.73–2.63 | 86.3 | No/No | Suggestive |
| Wu, 2013 [105] | Persistent organic pollutants | Highest vs. lowest category | 381/3672 | 8 | OR | 1.70 (1.23–2.35) | 1.24 × 10⁻³ | 0.93–3.13 | 16 | No/No | Weak |
| Zaccardi, 2015 [106] | Cardiorespiratory fitness | Per 1 metabolic equivalent increase | 856/84,428 | 8 | HR | 0.95 (0.92–0.98) | 2.98 × 10⁻³ | 0.86–1.05 | 88.1 | No/Yes | Weak |

### Medical history

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|--------------------|--------------------|---------------------------------------------|----------|------------------------|-----|--------------------------|---------|
| Aune, 2014 [107] | Breastfeeding* | Highest vs. lowest category | 10,842/263,119 | 6 | RR | 0.68 (0.57–0.82) | 3.75 × 10⁻⁵ | 0.38–1.22 | 74.7 | No/Yes | Suggestive |
| Aune, 2014 [107] | Breastfeeding* | Per 12 months increase | 10,306/261,523 | 4 | RR | 0.91 (0.86–0.96) | 7.24 × 10⁻⁴ | 0.72–1.16 | 81.1 | No/Yes | Suggestive |
| Bellamy, 2009 [37] | Gestational diabetes | Yes vs. no | 10,859/664,396 | 20 | RR | 7.43 (4.79–11.51) | 3.09 × 10⁻¹⁹ | 1.57–35.07 | 85.9 | No/No | Highly suggestive |
| Coto, 2013 [108] | Psoriasis | Yes vs. no | 255,203/5,393,406 | 38 | OR | 1.69 (1.50–1.89) | 1.60 × 10⁻¹⁹ | 0.88–3.24 | 98.1 | No/No | Highly suggestive |
| Coto, 2013 [108] | Psoriatic arthritis | Yes vs. no | 1420/15,494 | 3 | OR | 2.18 (1.36–3.48) | 1.20 × 10⁻³ | 0.01–395.32 | 77.2 | Yes/No | Weak |
| Ford, 2008 [38] | Metabolic syndrome | Yes vs. no | 2248/29,401 | 14 | HR | 3.35 (2.75–4.08) | 4.69 × 10⁻³³ | 1.66–6.74 | 74.6 | Yes/No | Highly suggestive |
| Horta, 2015 [109] | Breastfeeding** | Ever vs. never | NA/NA | 11 | OR | 0.65 (0.49–0.86) | 2.66 × 10⁻³ | 0.31–1.37 | 52.6 | No/NA | Weak |
| Janghorban, 2014 [110] | Age at menarche | Highest vs. lowest category | 21,095/294,333 | 12 | RR | 1.25 (1.15–1.35) | 5.77 × 10⁻⁸ | 0.99–1.58 | 66.6 | No/No | Highly suggestive |
| Li, 2014 [111] | Preterm birth | Preterm vs. normal term | 1898/29,580 | 5 | RR | 1.51 (1.33–1.72) | 4.54 × 10⁻¹⁰ | 1.22–1.87 | 0 | No/No | Convincing |
| Louati, 2015 [112] | Osteoarthritis | Yes vs. no | 130,457/909,718 | 20 | OR | 1.41 (1.21–1.65) | 1.36 × 10⁻⁵ | 0.81–2.47 | 95.2 | No/No | Suggestive |
| Moran, 2010 [113] | PCOS | Yes vs. no | 2337/66,727 | 13 | OR | 3.14 (1.86–5.31) | 1.80 × 10⁻⁵ | 0.86–11.49 | 55.5 | No/No | Suggestive |
| Stubbs, 2015 [114] | Schizophrenia | Yes vs. no | 131,675/2,147,884 | 26 | OR | 1.83 (1.53–2.18) | 2.63 × 10⁻¹¹ | 0.79–4.20 | 98.1 | Yes/Yes | Suggestive |
| Ungprasert, 2015 [115] | Giant cell arteritis | Yes vs. no | 284/1683 | 5 | OR | 0.74 (0.57–0.96) | 0.025 | 0.49–1.13 | 0 | No/No | Weak |
| Vancampfort, 2015 [116] | Major depressive disorder | Yes vs. no | 128,807/2,123,622 | 10 | OR | 1.48 (1.28–1.71) | 8.11 × 10⁻⁸ | 0.95–2.33 | 87.2 | No/No | Highly suggestive |
| Vancampfort, 2015 [117] | Bipolar disorder | Yes vs. no | 87,168/702,464 | 5 | OR | 1.98 (1.62–2.41) | 1.14 × 10⁻¹⁰ | 1.01–3.86 | 76.8 | No/No | Highly suggestive |
| Wang, 2013 [118] | Obstructive sleep apnea | Yes vs. no | 422/5940 | 6 | RR | 1.63 (1.09–2.45) | 0.018 | 0.60–4.48 | 41.2 | No/Yes | Weak |

### Metabolic and anthropometric traits

| Reference | Risk factor | Level of comparison | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-----------|-------------|---------------------|--------------------------|--------------------|--------------------|---------------------------------------------|----------|------------------------|-----|--------------------------|---------|
| Abdullah, 2010 [119] | BMI | Obese vs. lean | 16,109/574,142 | 18 | RR | 6.85 (5.39–8.78) | 4.20 × 10⁻³⁴ | 2.39–19.81 | 91.1 | No/No | Highly suggestive |

(Continued)
| Reference                | Risk factor                        | Level of comparison | Number of cases/ controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading       |
|--------------------------|------------------------------------|---------------------|---------------------------|--------------------|-------------------|---------------------------------------------|----------|-------------------------|-----|-------------------------------------------|---------------|
| Abdullah, 2010 [119]     | BMI                                | Overweight vs. lean | 15,796/419,466            | 17                 | RR                | 2.93 (2.33–3.68)                             | 2.80 × 10⁻²⁰ | 1.11–7.76                | 90.6| No/No                                     | Highly suggestive |
| Bell, 2014 [120]         | Metabolically healthy obesity      | Metabolically healthy obese vs. metabolically healthy non-obese | 1285/26,196          | 10                 | RR                | 4.40 (2.83–6.84)                             | 4.97 × 10⁻¹¹ | 1.29–14.95              | 47.8| No/No                                     | Convincing     |
| Bell, 2014 [120]         | Metabolically healthy obesity      | Metabolically unhealthy obese vs. metabolically healthy non-obese | 1266/24,668          | 8                  | RR                | 9.50 (7.48–12.08)                            | 8.79 × 10⁻⁷⁶ | 7.05–12.82               | 0   | Yes/No                                    | Highly suggestive |
| Harder, 2007 [121]       | Birth weight                       | >4,000 g vs. <4,000 g | 6005/108,400             | 9                  | OR                | 1.27 (1.01–1.59)                             | 0.044    | 0.62–2.58               | 68.2| No/No                                     | Weak           |
| Janghorbani, 2012 [122] | Height                             | Highest vs. lowest category | 2858/66,199           | 17                 | OR                | 0.85 (0.76–0.96)                             | 6.65 × 10⁻⁵ | 0.58–1.25               | 61.3| Yes/Yes                                   | Weak           |
| Kodama, 2012 [123]       | BMI                                | Per 1 SD increase   | 10,043/132,442          | 15                 | RR                | 1.59 (1.40–1.80)                             | 3.99 × 10⁻¹³ | 0.95–2.65               | 94.3| No/Yes                                    | Highly suggestive |
| Kodama, 2012 [123]       | Waist circumference                | Per 1 SD increase   | 10,043/132,442          | 15                 | RR                | 1.66 (1.47–1.88)                             | 1.14 × 10⁻¹⁵ | 1.00–2.76               | 94.5| No/Yes                                    | Highly suggestive |
| Kodama, 2012 [123]       | Waist-height ratio                 | Per 1 SD increase   | 10,043/132,442          | 15                 | RR                | 1.67 (1.46–1.90)                             | 3.68 × 10⁻¹⁴ | 0.97–2.87               | 94.2| No/Yes                                    | Highly suggestive |
| Kodama, 2012 [123]       | Waist-to-hip ratio                 | Per 1 SD increase   | 10,043/132,442          | 15                 | RR                | 1.54 (1.36–1.75)                             | 1.86 × 10⁻¹¹ | 0.93–2.56               | 93.7| No/Yes                                    | Highly suggestive |
| Kodama, 2014 [124]       | Weight gain in early adulthood     | Per 5 kg/m² increase | 15,701/327,002          | 10                 | RR                | 3.07 (2.49–3.80)                             | 1.92 × 10⁻²⁵ | 1.39–6.78              | 98.2| No/No                                    | Highly suggestive |
| Whincup, 2008 [125]      | Birth weight                       | Per 1 kg increase   | 6090/145,994            | 31                 | OR                | 0.80 (0.72–0.88)                             | 1.84 × 10⁻⁵ | 0.52–1.21              | 66.5| No/No                                    | Suggestive     |
| Agardh, 2011 [36]        | Educational status                 | Lowest vs. highest category | 20,649/234,796      | 23                 | OR                | 1.41 (1.28–1.55)                             | 1.01 × 10⁻¹² | 1.02–1.96              | 65.5| Yes/No                                    | Highly suggestive |
| Agardh, 2011 [36]        | Income level                       | Lowest vs. highest category | 1837/19,049           | 7                  | RR                | 1.40 (1.04–1.88)                             | 0.029    | 0.56–3.47               | 72   | Yes/Yes                                   | Weak           |
| Agardh, 2011 [36]        | Occupation                         | Lowest vs. highest category | 2691/42,476           | 11                 | RR                | 1.31 (1.09–1.57)                             | 3.69 × 10⁻³ | 0.77–2.21              | 52.7| No/No                                    | Weak           |
| Huang, 2015 [126]        | Adverse childhood experience       | Yes vs. no          | 3481/83,770            | 7                  | OR                | 1.28 (1.05–1.55)                             | 0.014    | 0.76–2.16              | 60.9| No/No                                    | Weak           |
| Jokela, 2014 [35]        | Agreeableness                      | Per 1 SD increase in personality score | 1845/33,058         | 5                  | OR                | 1.05 (0.98–1.13)                             | 0.193    | 0.85–1.30              | 40.6| No/No                                    | Not significant |
| Jokela, 2014 [35]        | Conscientiousness                  | Per 1 SD increase in personality score | 1845/33,058         | 5                  | OR                | 0.86 (0.82–0.91)                             | 9.94 × 10⁻⁸ | 0.79–0.94              | 0   | No/No                                    | Convincing     |
(highest vs. lowest category, and per 1 log unit increase), metabolic syndrome, increased time of television watching, low hip circumference, late age at menarche, weight gain in early adulthood, weight gain after the age of 25 years, increased dietary heme iron intake, high level of serum C-reactive protein (highest vs. lowest category, and per 1 log pm/mL), low level of serum adiponectin (per 1 log μg/ml increase), low alcohol consumption, smoking (former vs. never smokers, and current vs. never smokers), smoking cessation (new quitters vs. never smokers), major depressive disorder, bipolar disorder, high waist-height ratio, high waist circumference, high waist-to-hip ratio, and exposure to high level of NO₂ (per 10 μg/m³ increase). Twenty-nine associations had suggestive evidence (20%), and 42 associations had weak evidence (30%) for risk of T2DM.

All but 6 associations with convincing or highly suggestive evidence were exclusively based on prospective cohort studies, case-cohort studies and/or nested case-control studies. The remaining six associations (i.e., sedentary time, psoriasis, hip circumference, age at menarche, bipolar disorder, and major depressive disorder) were based on a combination of cross-sectional studies and cohort studies. In a sensitivity analysis limited to prospective cohort studies, the associations for sedentary time, hip circumference, and age at menarche remained highly suggestive (Table 2). For psoriasis, the level of evidence became suggestive due to a P-value greater than 10⁻⁶ under random-effects model (Table 2). In the meta-analysis for bipolar disorder, no prospective cohort studies were included. In the meta-analysis for major depressive disorder, only 1 retrospective cohort study was included. All the risk factors with convincing and highly suggestive evidence are summarized in Fig 3, and they are graphically presented using forest plots in Figs 4 and 5.

Table 1. (Continued)

| Reference         | Risk factor       | Level of comparison                      | Number of cases/controls | Number of datasets | Effect size metric | Random-effects summary effect size (95% CI) | P random | 95% prediction interval | I² | Small-study effects/Excess significance bias | Grading |
|-------------------|-------------------|-----------------------------------------|--------------------------|--------------------|-------------------|-------------------------------------------|----------|----------------------------|----|-------------------------------------------|---------|
| Jokela, 2014      | Extraversion      | Per 1 SD increase in personality score  | 1845/33,058              | 5                  | OR                | 1.01 (0.94–1.09)                           | 0.742    | 0.84–1.22                  | 32.5 | No/No                                     | Not significant |
| Jokela, 2014      | Neuroticism       | Per 1 SD increase in personality score  | 1845/33,058              | 5                  | OR                | 1.06 (1.00–1.13)                           | 0.062    | 0.91–1.24                  | 26.7 | No/No                                     | Not significant |
| Jokela, 2014      | Openness          | Per 1 SD increase in personality score  | 1845/33,058              | 5                  | OR                | 0.96 (0.85–1.08)                           | 0.453    | 0.62–1.46                  | 77.7 | No/No                                     | Not significant |
| Kivimaki, 2015    | Working hours     | Long vs. standard working hours         | 4963/217,157             | 23                 | RR                | 1.09 (0.91–1.30)                           | 0.366    | 0.58–2.04                  | 53.3 | No/No                                     | Not significant |
| Nyberg, 2014      | Job strain        | Highest vs. lowest category             | 3703/121,105             | 13                 | HR                | 1.15 (1.06–1.25)                           | 1.46 × 10⁻³| 1.04–1.27                  | 0    | No/No                                     | Weak    |

γGT: gamma-glutamyl transferase, ALA: α-linolenic acid, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, CI: confidence interval, CRP: C-reactive protein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HR: hazard ratio, IL-6: interleukin-6, NA: not available, NO₂: nitrogen dioxide, OR: odds ratio, PAI-1: plasminogen activator inhibitor-1, PCOS: polycystic ovary syndrome, PM₂.₅: particulate matter with a diameter of 2.5 μm or less, PM₁₀: particulate matter with a diameter between 2.5 and 10 μm, RR: risk ratio, SD: standard error

*maternal risk for T2DM
**offspring risk for T2DM

https://doi.org/10.1371/journal.pone.0194127.t001
Mendelian randomization studies

We identified 22 MR studies assessing the causal effect of a risk factor that was included in our umbrella review (Table 3). The median number of T2DM cases was 4,407 (IQR, 1,164–

Fig 2. Manhattan plot for 142 associations between risk factors and T2DM. The horizontal line corresponds to the significance threshold of $P < 10^{-6}$.

https://doi.org/10.1371/journal.pone.0194127.g002

Table 2. Sensitivity analysis of prospective cohort studies for associations with convincing or highly suggestive evidence that were based on a combination of cross-sectional and cohort studies.

| Reference | Risk factor | Level of comparison | Number of datasets | Number of cases/controls | Effect size metric | Random-effects summary effect size (95% CI) | $P_{	ext{random}}$ | 95% prediction interval | $I^2$ |
|-----------|-------------|---------------------|--------------------|--------------------------|-------------------|---------------------------------|----------------|----------------------|-------|
| Biswas, 2015 [98] | Sedentary time | Highest vs. lowest category | 4 | 6428/151,290 | HR | 1.88 (1.63–2.17) | $1.52 \times 10^{-17}$ | 1.37–2.58 | 0 |
| Coto, 2013 [108] | Psoriasis | Yes vs. no | 8 | 49,064/1,564,468 | OR | 1.53 (1.29–1.81) | $1.15 \times 10^{-6}$ | 0.83–2.80 | 96.7 |
| Janghorbani, 2012 [112] | Hip circumference | Highest vs. lowest category | 11 | 4460/137,666 | OR | 0.63 (0.53–0.75) | $3.76 \times 10^{-7}$ | 0.39–1.01 | 50.4 |
| Janghorbani, 2014 [110] | Age at menarche | Highest vs. lowest category | 9 | 20,092/289,532 | RR | 1.26 (1.15–1.38) | $5.44 \times 10^{-7}$ | 0.96–1.64 | 72.7 |

CI: confidence interval, HR: hazard ratio, OR: odds ratio, RR: risk ratio

https://doi.org/10.1371/journal.pone.0194127.t002
15,255). Two MR studies used a single SNP as instrumental variable and twenty MR studies constructed a polygenic risk score (PRS). In studies with PRS, the median number of variants

Fig 3. Schematic representation of risk factors for T2DM with convincing or highly suggestive evidence. The symbol ↑ denotes a higher exposure to a risk factor, and the symbol ↓ represents a lower exposure to a risk factor. For alcohol consumption, never drinkers presented a higher risk for T2DM than moderate drinkers.

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Fig 4. Forest plot of risk factors (measured as continuous variables) for T2DM supported by convincing or highly suggestive evidence.

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was 5 (IQR, 3–8). The eligible MR studies assessed the following 13 exposures: alcohol intake, birth weight, BMI, coffee intake, milk intake, systolic blood pressure, serum adiponectin, serum CRP, serum ferritin, serum gamma-glutamyl transferase, serum uric acid, serum vitamin D, and waist circumference. Seven risk factors were examined by more than one MR study. A causal effect was claimed for 4 risk factors graded as highly suggestive in our umbrella review: BMI, systolic blood pressure, serum gamma-glutamyl transferase, and waist circumference. A causal association was also claimed for birth weight, but a relatively small number of T2DM cases was included in this analysis. The observed effects for alcohol intake, coffee intake, serum CRP, serum ferritin, serum uric acid and serum vitamin D were not causal. Milk intake presented weak evidence in our analysis and an MR study did not show a causal effect. Serum adiponectin was graded as highly suggestive in our analysis, but the findings from MR studies were conflicting, and the largest MR study indicated absence of a causal effect.

**Discussion**

We performed a mapping of environmental factors and biomarkers examined for an association with T2DM in systematic reviews and meta-analyses. Overall, more than 100 associations...
Table 3. Characteristics of mendelian randomization studies for type 2 diabetes mellitus.

| Reference                          | Exposure                  | Level of comparison          | Genetic instrument                  | N of SNPs in instrument | N cases | Effect size metric | Causal effect size (95% CI) | P-value |
|------------------------------------|---------------------------|-----------------------------|-------------------------------------|-------------------------|---------|-------------------|-----------------------------|---------|
| Holmes, 2014 [29]                 | Alcohol intake           | Per units/week increase     | Single variant (rs1229984)          | 1                       | 14,549  | OR 1.02 (0.95–1.09) | 1.02 (0.95–1.09)            | 0.627   |
| Wang, 2016 [54]                   | Birth weight             | Per 1 SD decrease           | PRS                                 | 5                       | 3627    | OR 2.94 (1.70–5.16) | <0.001                      |         |
| Afzal, 2014 [31]                  | BMI                      | Per 10 kg/m² increase       | PRS                                 | 3                       | 5037    | HR 19.40 (6.40–59.10) | NR                          |         |
| Corbin, 2016 [32]                 | BMI                      | Per 1 kg/m² increase        | PRS                                 | 96                      | 12,171  | OR 2.94 (1.70–5.16) | <0.001                      |         |
| Fall, 2013 [33]                   | BMI                      | Per 1 kg/m² increase        | Single variant (rs939609)           | 1                       | 1991    | OR 1.35 (1.12–1.62) | 0.001                      |         |
| Holmes, 2014 [34]                 | BMI                      | Per 1 kg/m² increase        | PRS                                 | 14                      | 4407    | OR 1.27 (1.18–1.36) | 2.0 × 10⁻¹¹                   |         |
| Nordestgaard, 2015 [129]          | Coffee intake            | Per 1 cup/day               | PRS                                 | 5                       | 26,632  | OR 1.00 (0.99–1.01) | NR                          |         |
| Bergholdt, 2015 [130]             | Milk intake              | Per 1 glass/week increase   | Single variant (rs4988235)          | 1                       | 951     | OR 0.99 (0.93–1.06) | NR                          |         |
| Aikens, 2016 [131]                | SBP                      | Per 1 mmHg increase         | PRS                                 | 13                      | 37,293  | OR 1.02 (1.01–1.03) | 9.1 × 10⁻⁵                   |         |
| Marott, 2016 [132]                | SBP                      | Per 1 mmHg increase         | PRS                                 | 6                       | 2859    | OR 0.97 (0.95–1.00) | 0.030                      |         |
| Peters, 2013 [50]                 | Serum adiponectin        | Per 1 SD decrease           | PRS                                 | 3                       | 967     | OR 0.86 (0.75–0.99) | 0.013                      |         |
| Yaghootkar, 2013 [51]             | Serum adiponectin        | Per 1 SD decrease           | PRS                                 | 3                       | 2777    | OR 0.94 (0.75–1.19) | 0.610                      |         |
| Yaghootkar, 2013 [51]             | Serum adiponectin        | Per 1 SD decrease           | PRS                                 | 3                       | 15,960  | OR 0.99 (0.95–1.04) | 0.770                      |         |
| Prins, 2016 [40]                  | Serum CRP                | Per 10-s% increase          | PRS                                 | 4                       | 6698    | OR 1.11 (0.94–1.32) | 0.230                      |         |
| Prins, 2016 [40]                  | Serum CRP                | Per 10-s% increase          | PRS                                 | 18                      | 6698    | OR 1.09 (0.95–1.24) | 0.210                      |         |
| Gan, 2012 [133]                   | Serum ferritin           | Per 1 ng/mL increase        | Single variant (rs855791)           | 1                       | 272     | OR 0.80 (0.65–0.98) | 0.031                      |         |
| Gan, 2012 [133]                   | Serum ferritin           | Per 1 ng/mL increase        | Single variant (rs4820268)          | 1                       | 272     | OR 0.80 (0.66–0.98) | 0.031                      |         |
| Lee, 2016 [134]                   | Serum gamma-glutamyl     | Per 1 unit increase         | PRS                                 | 7                       | 343     | OR 1.05 (1.01–1.08) | NR                          |         |
| Kleber, 2015 [41]                 | Serum uric acid          | Per 1 mg/dL increase        | PRS                                 | 8                       | 1236    | OR 0.83 (0.57–1.23) | 0.360                      |         |
| Pfister, 2011 [42]                | Serum uric acid          | Per 1 mg/dL increase        | PRS                                 | 8                       | 7504    | OR 0.99 (0.94–1.04) | 0.620                      |         |
| Sluijs, 2015 [43]                 | Serum uric acid          | Per 1 mg/dL increase        | PRS                                 | 24                      | 41,508  | HR 0.99 (0.92–1.06) | NR                          |         |
| Afzal, 2014 [31]                  | Serum vitamin D          | Per 20 nmol/L decrease      | PRS                                 | 2                       | 5037    | HR 1.51 (0.98–2.33) | 0.240                      |         |
| Afzal, 2014 [31]                  | Serum vitamin D          | Per 20 nmol/L decrease      | PRS                                 | 2                       | 5037    | HR 1.02 (0.75–1.37) | 0.390                      |         |
| Buijsse, 2013 [45]                | Serum vitamin D          | Per 5 nmol/L increase       | PRS                                 | 4                       | 1572    | HR 0.98 (0.89–1.08) | NR                          |         |
| Jorde, 2012 [46]                  | Serum vitamin D          | Highest vs. lowest quartile | PRS                                 | 5                       | 1092    | HR 1.01 (0.86–1.20) | NR                          |         |
| Leong, 2014 [47]                  | Serum vitamin D          | Per 1 SD increase           | Single variant (rs2282679)          | 1                       | 201     | OR 0.99 (0.79–1.24) | 0.930                      |         |
| Ye, 2015 [48]                     | Serum vitamin D          | Per 1 SD increase           | PRS                                 | 4                       | 28,144  | OR 1.01 (0.75–1.36) | 0.940                      |         |
| Marott, 2016 [132]                | Waist circumference      | Per 1 unit increase         | PRS                                 | 5                       | 3762    | OR 1.05 (1.01–1.10) | 0.020                      |         |

BMI: body mass index, CI: confidence interval, CRP: C-reactive protein, HR: hazard ratio, NR: not reported, OR: odds ratio, PRS: polygenic risk score, SBP: systolic blood pressure, SD: standard deviation. SNPs: single nucleotide polymorphisms

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were considered. We identified eleven associations supported by convincing evidence and thirty-four additional associations having highly suggestive evidence for risk of T2DM. These associations mainly pertained to comorbid medical conditions, lifestyle and dietary factors, as well as serum biomarkers.

Even though more than one third of the associations examined various dietary factors, only six of them showed convincing or highly suggestive relationship with T2DM and the demonstrated effect sizes were modest. These factors were processed meat, whole grain products, healthy dietary pattern, sugar-sweetened beverages and dietary heme iron. Increased processed meat and sugar-sweetened beverages consumption are linked with other unhealthy lifestyle factors which showed highly significant association with T2DM, such as physical inactivity, increased BMI, smoking and unhealthy dietary patterns. [23,24] The association between dietary heme iron and T2DM could be explained by the fact that red meat is the main dietary source of heme iron. [25] The observed protective effect of whole grain products is independent of BMI as almost all observational studies have adjusted for its effect. Whole grain products have high concentration of fibers, which delay gastric emptying, therefore slowing glucose release in circulation. This results in reduced postprandial insulin response and could improve insulin sensitivity [26,27] The aforementioned associations are also supported by the observed protective effect of healthy dietary pattern against developing T2DM. Although the term “healthy dietary pattern” includes a variety of diets, the same principles apply: reduced red and processed meat consumption, moderate alcohol drinking, low intake of sugar-sweetened beverages and increased consumption of whole grain products. [28]

Moderate alcohol consumption has a protective effect against developing T2DM. This relationship could be explained by increased insulin sensitivity, lower fasting insulin resistance and lower glycated hemoglobin concentrations, which are induced by moderate amounts of alcohol. Moreover, moderate amount of alcohol drinking is a common feature of healthy diet pattern, who also lowered the risk for developing T2DM. Furthermore, coffee consumption lowers the risk for T2DM, which is attributed to the reduction of insulin resistance and the improvement of glucose metabolism. However, it is unclear whether this association is causal, given the findings of a recently published MR study [29].

Most of the associations yielded from our analyses were proxies of obesity and include body mass index (BMI), weight gain, and anthropometric characteristics (i.e., hip circumference, waist-height ratio, waist-hip ratio, waist circumference). The observed association between BMI and T2DM demonstrated a large effect size and was highly significant (RR = 6.88, \( P = 4.2 \times 10^{-54} \)). Increased BMI, waist-height ratio, waist-hip ratio and waist circumference express the presence of increased intra-abdominal visceral fat, which disrupts insulin metabolism through release of serum free fatty acids. [30] Not surprisingly, findings from MR studies further support a causal role of BMI in the pathogenesis of T2DM. [31–34] However, not all obese have the same risk for developing T2DM; it seems that the risk is affected by their metabolic profile. Metabolically unhealthy obese carry an about 10-fold risk for T2DM, whereas metabolically healthy obese have an about 4.5-fold risk for T2DM. Moreover, weight gain during early adulthood was more harmful than weight gain after the age of 25. On the contrary, peripheral fat accumulation has been linked to a better metabolic profile, which is depicted in the observed protective effect of larger hip circumference on T2DM.

Several lifestyle factors presented either convincing or highly suggestive evidence. Total and leisure-time physical activity lowered the relative risk for T2DM. High sedentary time and TV watching are inter-correlated, and they are surrogates of physical inactivity, which is a common feature in people with high BMI. Additionally, the convincing association of low conscientiousness with increased risk for T2DM could be explained by the correlation of this personality trait with physical inactivity and high risk for obesity. [35] Our analysis also
indicated that there is highly suggestive evidence for the association of lower educational attainment and higher risk for T2DM. Educational level constitutes a component of socioeconomic status. Lower socioeconomic status is associated with higher stress levels, leading to disruption in endocrine function through perturbations in the neuroendocrine system. [36] Also, people with low socioeconomic status are more prone to an unhealthy lifestyle pattern and they have limited access to healthcare care facilities. [36]

Several medical conditions have been traditionally linked to increased risk for T2DM. Patients with metabolic syndrome and gestational diabetes presented higher risk for T2DM. The seven-fold increase of risk for developing T2DM in women with gestational diabetes could be attributed to common underlying genetic and environmental risk factors between the two conditions. [37] Metabolic syndrome is considered a predictor of T2DM and has a stronger association with T2DM than its components. [38] Furthermore, higher systolic blood pressure was associated with increased risk for T2DM, but this association might not be causal. Some antihypertensive drugs have been associated with an increased risk, whereas the use of antihypertensive drugs inhibiting the renin-angiotensin system showed a protective effect. In turn, increased activity of renin-angiotensin system induces systemic inflammation processes that may exert a diabetogenic effect. [39]

Our analysis showed that a set of serum biomarkers is highly associated with the risk for T2DM. These biomarkers pertained to serum level of alanine aminotransferase (ALT), gamma-glutamyl transferase, C-reactive protein (CRP), uric acid, adiponectin, and vitamin D. High serum ALT and gamma-glutamyl transferase in patients with T2DM could be a manifestation of ongoing low-grade hepatic inflammation or hepatocellular damage, which is common in T2DM and metabolic syndrome. Among hepatic enzymes, ALT is the most specific indicator of hepatic pathology in non-alcoholic fatty liver disease and most closely related to liver fat accumulation. The presence of systemic inflammation is linked to β-cell dysfunction, leading to impaired glucose metabolism and the development of T2DM. [4] Both CRP and uric acid are inflammatory markers associated with systemic inflammation. Also, meat consumption is directly associated with serum uric acid level, and, as we have already shown, processed meat consumption is linked to higher risk for T2DM. However, MR studies for serum CRP [40], and serum uric acid [41–43] suggested that the associations with T2DM might not be causal.

Furthermore, our results indicated an inverse association between vitamin D level and risk for T2DM. It is unclear if this is a true association or the effect of adiposity as a potential confounder or intermediate factor. Obesity leads to storage of vitamin D in adipose tissue and to less sun exposure, on the grounds of limited mobility and accumulation of subcutaneous fat [44]. All the former result in low circulating level of vitamin D in obese individuals. Also, vitamin D may directly affect adiposity and other metabolic parameters, such as dyslipidemia, hypertension, and systemic inflammation, that mediate the pathway from vitamin D status to T2DM. Adiponectin is another serum biomarker that expresses the body composition. It affects the glucose metabolism, and higher serum level of adiponectin are associated with higher insulin sensitivity. However, MR studies examining the role of serum vitamin D indicated a non-causal association that might be explained by confounding factors [31,45–48], whereas the evidence on the causal role of serum adiponectin are contradictory [49–51].

The association between smoking and T2DM has biological foundation because smoking is associated with central obesity and increased oxidative stress and inflammation, and eventually leads to insulin resistance and hyperglycaemia. However, residual confounding can be the case since smoking is often linked to other unhealthy lifestyle factors (e.g., poor diet, physical inactivity) and comorbidities. The increased risk of T2DM associated with smoking cessation in new quitters could be mediated by weight gain or be due to reverse causation because people
who try to quit smoking are more likely to have preclinical conditions or high cumulative smoking exposure [52].

Based on our assessment, adults delivered preterm presented a larger risk for development of T2DM during adulthood than adults delivered full-term. According to the "fetal origin of disease" hypothesis, the biological mechanisms that mediate this association could be explained through intrauterine growth restriction. Preterm newborns have low birth weight and they are prone to disrupted glucose metabolism in later life [53], which in turn predisposes to an increased risk of T2DM. Although the association between birth weight and T2DM had weak epidemiological credibility [12], an MR study indicated that there is a potential causal association between birth weight and risk for T2DM [54].

Two components of ambient air pollution, PM\textsubscript{10} and NO\textsubscript{2}, were found to have robust association with risk for T2DM. It has been suggested that air pollution causes elevated systemic inflammation and oxidative stress, whereas it increases the insulin resistance leading to abnormal glucose metabolism and elevated fasting glucose. [55]

Furthermore, older age at menarche was associated with risk for T2DM. However, there are doubts whether it constitutes a genuine association. Observational studies found that this association is attenuated after adjustment for BMI in adulthood, suggesting that adult adiposity may mediate this association. The inverse association between age at menarche and BMI in adulthood could explain this finding. [56]

We presented an exposure-wide mapping of the meta-analyses on non-genetic risk factors for T2DM. Our umbrella review indicated that a very wide range of risk factors has been considered for T2DM. Compared to previously published umbrella reviews [6–10], there is tremendous amount of meta-analyses for risk factors of T2DM. Also, the majority of these associations were examined in large prospective cohort studies. The increasing incidence and large burden of T2DM could explain the observed interest in the field of non-genetic and modifiable risk factors for T2DM.

Our study has some caveats. First, the statistical test for small-study effects should be interpreted with caution in case of large between-study heterogeneity. Second, the observational studies did not often clearly report the sample sizes for the statistical analyses. Thus, the power calculations might be conservative, and the extent of excess significance bias is probably conservative. Furthermore, genetic instruments of the MR studies were not assessed, and power calculations for the MR studies could not be performed, because the percentage of variance explained often was not available. Consequently, the claims of MR studies should be interpreted with caution.

**Conclusions**

Our paper identified several robust risk factors for T2DM. Our findings indicate specific strategies for public health interventions to reduce the future incidence of T2DM. Interventions for the promotion of physical activity and a healthy lifestyle and dietary pattern combined with interventions against the increased incidence of obesity could alleviate the projections for an increase of T2DM incidence in near future. However, these findings are based on observational data and should be interpreted with caution. Even though MR studies may support or not causality, the power of those studies could not be assessed. Therefore, randomized clinical trials and additional well-designed MR studies are needed to clarify which of these observations are causal associations. Also, these findings should be replicated by large-scale environment-wide association studies in various ethnic groups, and they could be used for the development of reliable risk prediction models in combination with known genetic polymorphisms.
Supporting information

S1 File. PRISMA checklist.

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