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Original article

Ultra-processed foods and human health: An umbrella review and updated meta-analyses of observational evidence

Shuhui Dai [a, 1], Judith Wellens [b, c, 1], Nan Yang [a], Doudou Li [d], Jingjing Wang [a], Lijuan Wang [a, e], Shuai Yuan [a, f], Yazhou He [g], Peige Song [h], Ron Munger [i], Monique Potvin Kent [j], Amanda J. MacFarlane [k], Patrick Mullie [l, m], Susan Duthie [n], Julian Little [j], Evropi Theodoratou [e, o, 2], Xue Li [a, p, 2, *]

[a] Department of Big Data in Health Science School of Public Health, Center of Clinical Big Data and Analytics of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Translational Gastro-Intestinal Unit, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK
[c] KU Leuven Department of Chronic Diseases and Metabolism, Translational Research Center for Gastrointestinal Disorders (TARGID), Leuven, Belgium
[d] School of Public Health, Zhengzhou University, Zhengzhou, China
[e] Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK
[f] Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
[g] West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China
[h] School of Public Health and Women's Hospital, Zhejiang University School of Medicine, Hangzhou, China
[i] Department of Nutrition and Food Sciences and the Center for Epidemiologic Studies, Utah State University, Logan, UT, USA
[j] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[k] Nutrition Research Division, Health Canada, Ottawa, Ontario, Canada
[l] International Prevention Research Institute, Lyon, France
[m] Belgian Centre for Evidence-Based Medicine, Leuven, Belgium
[n] School of Pharmacy and Life Sciences, The Robert Gordon University, Aberdeen, UK
[o] Cancer Research UK Edinburgh Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK
[p] The Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province, Hangzhou, Zhejiang, China

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SUMMARY

Background & aims: Ultra-processed food (UPF) intake has increased sharply over the last few decades and has been consistently asserted to be implicated in the development of non-communicable diseases. We aimed to evaluate and update the existing observational evidence for associations between ultra-processed food (UPF) consumption and human health.

Methods: We searched Medline and Embase from inception to March 2023 to identify and update meta-analyses of observational studies examining the associations between UPF consumption, as defined by the NOVA classification, and a wide spectrum of health outcomes. For each health outcome, we estimated the summary effect size, 95% confidence interval (CI), between-study heterogeneity, evidence of small-study effects, and evidence of excess-significance bias. These metrics were used to evaluate evidence credibility of the identified associations.

Results: This umbrella review identified 39 meta-analyses on the associations between UPF consumption and health outcomes. We updated all meta-analyses by including 122 individual articles on 49 unique health outcomes. The majority of the included studies divided UPF consumption into quartiles, with the lowest quartile being the reference group. We identified 25 health outcomes associated with UPF consumption. For observational studies, 2 health outcomes, including renal function decline (OR: 1.25; 95% CI: 1.18, 1.33) and wheezing in children and adolescents (OR: 1.42; 95% CI: 1.34, 1.49), showed convincing

Abbreviations: BMI, Body Mass Index; CC, case–control; CD, Crohn's disease; CI, confidence interval; CKD, chronic kidney disease; CO, cohort study; CS, cross-sectional study; CVD, cardiovascular disease; IBD, inflammatory bowel disease; LSS, lumbar spinal stenosis; NAFLD, non-alcoholic fatty liver disease; PI, prediction interval; RDI, recommended daily intake; UC, ulcerative colitis; UPF, ultra processed food; UN, United Nations; WC, waist circumference; WMD, weighted mean difference.

* Corresponding author. School of Public Health and the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.
E-mail address: xueli157@zju.edu.cn (X. Li).

[1] Joint first authors.
[2] joint last authors.

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evidence (Class I); and five outcomes were reported with highly suggestive evidence (Class II), including diabetes mellitus, overweight, obesity, depression, and common mental disorders.
Conclusions: High UPF consumption is associated with an increased risk of a variety of chronic diseases and mental health disorders. At present, not a single study reported an association between UPF intake and a beneficial health outcome. These findings suggest that dietary patterns with low consumption of UPFs may render broad public health benefits.

1. Introduction

With obesity, cardiovascular disease and cancer on the rise globally, the United Nations (UN) have designated the years 2016–2025 as the Decade of Action on Nutrition [1]. They state that the ever-increasing production and consumption of ultra-processed foods (UPFs) represents a global crisis, contributing to the current non-communicable disease epidemic. In response to the need to characterize foods according to their processing level, several classification systems have been proposed [2,3]. The NOVA food classification system is the most widely used classification system and categorizes food products based on the nature, extent and purpose of food processing [1,2,4]. The category of UPFs in NOVA refers to industrial formulations manufactured from substances derived from foods or synthesized from other organic sources. They typically contain little or no whole foods and are ready-to-consume or heat up [1]. They tend to be high in fat, salt or sugar (nutrients associated with higher health risk) and/or lower amounts of dietary fibre, protein, micro-nutrients and other bioactive compounds (nutrients or other food substances associated with lower health risks) [5]. Usually, these products contain a variety of food additives to render the final products hyper-palatable, highly profitable and ready-to-consume with a prolonged shelf-life [6]. Fostered by these characteristics, lobbying by the food industry [7], and effective marketing strategies [8,9], UPF consumption has sharply increased worldwide and is now an increasingly prominent component in the diet [10,11], accounting for more than 50% of energy intake in many high-income countries such as the United States [12,13] and the UK [14].

A previous review of UPFs published by Lane et al., has showed that UPF consumption was associated with adverse health outcomes, including overweight, obesity, abdominal obesity, all-cause mortality, metabolic syndrome, and depression in adults as well as wheezing in adolescents [15]. Since then, there has been a large and rapidly growing body of observational studies linking UPFs to wider range of health outcomes, it is necessary to synthesize the current evidence to obtain an accurate and comprehensive understanding of the associations between the consumption of UPFs and health outcomes. We conducted an umbrella review of observational studies, including cohort, case–control or cross-sectional studies, with meta-analysis updates to provide an updated evaluation of the relevant health consequences. In particular, we presented the magnitude, direction, and significance of associations, assessed the potential biases, and identified the most convincing evidence for associations between UPF consumption and health outcomes to date.

2. Material and methods

2.1. Study design and literature search

The protocol for the present study was registered in PROSPERO (CRD 42022355054). We searched Medline and Embase from inception to 1st March 2023 for meta-analyses of observational (cohort, case–control, or cross-sectional) studies that investigated the associations between UPF consumption and health outcomes, using a predefined search strategy (Supplementary Table 1). Given that the associations between UPF consumption and different health outcomes have previously been assessed in many studies, we also searched for individual observational studies that investigated the association between UPF consumption and any health outcome (if possible) to update the identified meta-analyses and to produce meta-analyses of new health outcomes (if possible). Predefined search strategy for primary studies is presented in Supplementary Table 2. Two investigators (SD and JW) independently screened the titles, abstracts and selected eligible articles through full text review based on predefined inclusion and exclusion criteria. Any discrepancies were resolved by discussion.

2.2. Eligibility criteria

The inclusion criteria consisted of the following: 1) meta-analyses of observational (cohort, case–control, or cross-sectional) studies with summary risk estimates and corresponding 95% confidence intervals; 2) population-based observational studies including cohort, case–control, or cross-sectional studies; 3) studies that used the NOVA classification system to measure exposure; 4) studies that evaluated the associations between UPF consumption and health outcomes; 5) if there were several published studies of the same health outcome based on the same study population, the most recent report was used. Studies were excluded if they: 1) were conference abstracts, letters, guidelines, narrative reviews, literature reviews, genetic or animal studies; 2) focused on specific UPF subgroups; 3) were not published in English.

2.3. Data extraction

For each eligible meta-analysis, we extracted the following data: study design, type of comparison, investigated outcome, number of included studies, number of cases and participants, type of metric, and estimated summary effect and corresponding 95% confidence interval (CI). Furthermore, we searched for original articles on UPFs and combined them with studies identified from the previous meta-analyses to update the included meta-analyses. At this stage, we extracted data similar to those from the meta-analyses, along with the mean changes and corresponding standard deviations (SDs) of quantitative variables if available. Given that most studies used energy ratio (energy intake from UPF as a proportion to total energy) to express intake of UPFs, we extracted these data when original studies used multiple approaches.

2.4. Statistical analyses

For each unique health outcome, we estimated the following metrics: 1) summary effect estimates [relative risk (RR), odds ratio (OR), hazard ratio (HR), or weighted mean difference (WMD)] and corresponding 95% CI using the DerSimonian and Laird random effects model [16]; 2) heterogeneity among studies (Q statistic and I^2 metric); 3) 95% prediction interval (95% PI) to predict the range of

effect size in a new original study, after accounting for both the heterogeneity among individual studies and the uncertainty of the summary effect estimated in the random-effects model [17]; 4) Egger's regression test investigates if small studies tend to give larger effect estimates than large studies (significance threshold $P < 0.10$) [18]; and 5) excess significance test assesses if the observed number (O) of studies with significant results is greater than the expected number (E) using the χ^2 test [19]. The expected number of significant studies for each meta-analysis was calculated by summing the statistical power estimates for each component study. The statistical power of each component study was calculated with an algorithm that uses a non-central t distribution, by assuming the true effect size to be the same as that of the largest component study (with smallest variance) in the meta-analysis [20]. All statistical analyses were performed using the "metafor" and "forestplot" R packages, R software version 4.2.1.

2.5. Evaluation of evidence credibility

We applied standard credibility assessment criteria (Supplementary Table 3) to assess the confidence in the estimated association, as described in previous umbrella review [21–25]. We classified evidence from meta-analyses of observational studies with statistically significant summary results ($P < 0.05$) into 4 categories: 1) convincing evidence (Class I); 2) highly suggestive evidence (Class II); 3) suggestive evidence (Class III); and 4) weak evidence (Class IV). Even when a health outcome has Class I or II evidence for association, this still does not prove causation. Therefore, for each association initially graded as convincing (Class I) or highly suggestive (Class II), we performed sensitivity analyses by confining the meta-analyses to prospective cohort studies to reevaluate the evidence credibility. Additionally, we evaluated the strength of the evidence for each health outcome by using the GRADE system, and graded it as "high," "moderate," "low," or "very low" quality.

3. Results

3.1. Studies identified and their characteristics

Figure 1A presents the literature search and selection process for this umbrella review. We identified 129 articles across two databases. After deduplication and the application of the inclusion and exclusion criteria, 13 articles [15,26–37] were included, which contained 39 meta-analyses for 21 unique outcomes. Specifically, there was a single meta-analysis published specifically for heart disease mortality [38], cancer mortality [38], cardiovascular mortality [38], wheezing [15], asthma [15], hypertriglyceridemia [31], hyperglycemia [31], low HDL-cholesterol levels [31], Crohn's disease (CD) [37], ulcerative colitis (UC) [37], anxiety and common mental disorders (anxiety and depression, which were assessed together) [28] respectively. There were two meta-analyses on cardiovascular events (including cardiovascular disease (CVD) morbidity and mortality) [31,35], hypertension [31,34] and the metabolic syndrome [15,31], and three meta-analyses on overweight [15,26,29], obesity [15,26,29], abdominal obesity [15,29,31] and diabetes mellitus [27,30,36], and four meta-analyses on depression [15,28,31]. Five meta-analyses reported on all-cause mortality [15,31–33,35] (Supplementary Table 4). Figure 1B presents the process of literature searching and screening of original studies in conducting the updated and new meta-analyses. After literature screening, we identified 98 new articles. Thirty-two articles were used to update 19 existing meta-analyses and 60 articles were included in 28 new meta-analyses. In total, 49 unique health outcomes were included in our analyses.

3.2. UPF consumption and health outcomes reported in the updated meta-analyses

The 49 unique outcomes are broadly classified as follows: mortality, adverse maternal and neonatal reactions, cardiovascular outcomes, cancer, metabolic diseases, mental health, respiratory diseases, kidney, liver and gastrointestinal diseases, and other outcomes. Summary effect estimates and evidence credibility assessment for each outcome are listed in Fig. 2 and Supplementary Figs. 1–49. Twenty-five (51.0%) of the 49 unique health outcomes had a nominally statistically significant summary effect estimate ($P < 0.05$). Among these 25 associations, 8 outcomes (32.0%) had $P < 10^{-6}$, 12 (48.0%) had a 95% PI that excluded the null, 23 (92.0%) had more than 1000 cases or more than 20,000 participants, 8 (32.0%) did not have a large heterogeneity (I^2<50%), and 9 (36.0%) had neither small study effects nor excess significance.

After the credibility assessment, 2 outcomes initially showed convincing evidence (Class I), indicating higher confidence in the estimated association. Our updated meta-analysis revealed that UPF consumption was associated with an increased risk of renal function decline (OR: 1.25; 95% CI: 1.18, 1.33; $P = 7.42 \times 10^{-13}$) and wheezing in children and adolescents (OR: 1.42; 95% CI: 1.34, 1.49; $P = 2.72 \times 10^{-39}$). Five outcomes were reported with highly suggestive evidence (Class II), including diabetes mellitus (OR: 1.23; 95% CI: 1.13, 1.33; $P = 3.69 \times 10^{-7}$), overweight (OR: 1.18; 95% CI: 1.11, 1.26; $P = 9.15 \times 10^{-7}$), obesity (OR: 1.26; 95% CI: 1.18, 1.36; $P = 1.62 \times 10^{-10}$), depression (OR: 1.40; 95% CI: 1.26, 1.55; $P = 3.24 \times 10^{-10}$), and common mental disorders (OR: 1.41; 95% CI: 1.27, 1.58; $P = 6.79 \times 10^{-10}$). Six outcomes showed suggestive evidence (Class III: all-cause mortality, cardiovascular mortality, hypertension, cardiovascular events, anxiety, and abdominal obesity). In addition, twelve outcomes showed only weak evidence (Class IV: colorectal cancer, colon cancer, CD, inflammatory bowel disease (IBD), metabolic syndrome, hypertriglyceridemia, low HDL-cholesterol level, hyperuricemia, asthma, body mass index (BMI), waist circumference (WC), and HDL-cholesterol).

Additionally, on the basis of the GRADE guidelines, evidence for 8 outcomes was classified as of low-quality level, including renal function decline, CD, IBD, wheezing, asthma, premenopausal breast cancer, postmenopausal breast cancer and prostate cancer. The evidence for other outcomes was of very low quality (Fig. 2).

3.3. Sensitivity analyses

For the convincing (Class I) and highly suggestive outcomes (Class II), we restricted the meta-analysis to prospective cohort studies to re-evaluate the evidence credibility. In-depth assessment, the credibility of the evidence for the associations between UPF consumption with renal function decline remained unchanged, whereas the evidence for depression upgraded to Class I (convincing evidence), for diabetes mellitus and overweight was downgraded to Class III (suggestive evidence), for common mental disorders to Class IV (weak evidence); one of these associations (wheezing in children and adolescents) that did not have any cohort studies was downgraded to Class IV (weak evidence) (Supplementary Table 5).

3.4. Other health outcomes with insufficient number of studies for a meta-analysis

We identified 33 original articles that reported associations between UPF and other health outcomes (Supplementary Table 6) for which quantitative meta-analyses could not be performed owing to the limited number of studies. For these

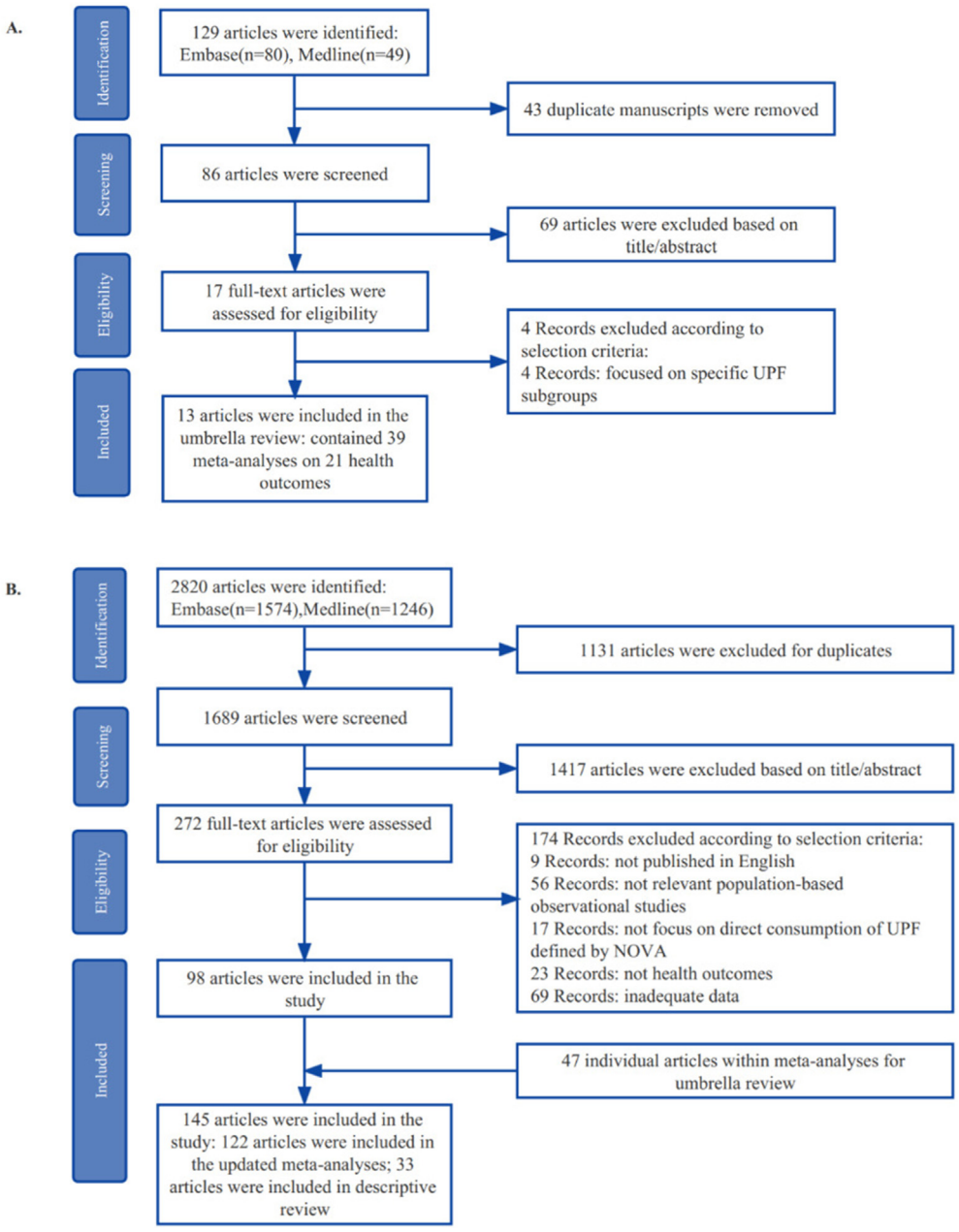

Fig. 1. Flow diagram of study selection. (A) Study selection for umbrella review; (B) study selection for the updated meta-analyses. UPF, ultra-processed food.

studies, nominally statistically significant associations with UPF consumption were reported for dementia [39], binge eating disorders [40], COVID-19 [41], sleep quality [42], grip strength [43], telomere length [44], dental caries [45], colorectal adenomas [46], colorectal cancer precursors [47], central nervous system tumors [48], central nervous system demyelination [49], multiple sclerosis severity [50], overweight/obesity in adolescents [51], irritable bowel syndrome [52], functional dyspepsia [52], lumbar spinal stenosis (LSS) [53], subclinical hyperthyroidism [54], food addiction [55], cardiovascular health [56–58], subclinical coronary atherosclerosis [59], asthenozoospermia [60], and offspring overweight or obesity [61,62]. There were no statistically significant associations between UPF intake and periodontitis [63], functional constipation [52], functional diarrhea [52], restrictive eating disorders [40], chronic lymphocytic leukemia [64], subclinical hypothyroidism [54], severe hypertension or preeclampsia [65], child attention deficit hyperactivity disorder (ADHD) [66], anemia in children or adolescents [67], and overweight/obesity/malnutrition in children [68,69]. Additionally, there were two large-scale prospective cohort studies investigating the association between UPF consumption and risk of many site-specific cancers. One reported that every 10% increment in UPF content of diet was associated with an increased incidence of ovarian cancer by 19%, and an increased mortality of ovarian cancer by 30% [70]. Another one reported the substitution of 10% of UPFs with 10% of minimally processed foods was associated with a reduced risk of head and neck cancers, colon cancer, and hepatocellular carcinoma [71].

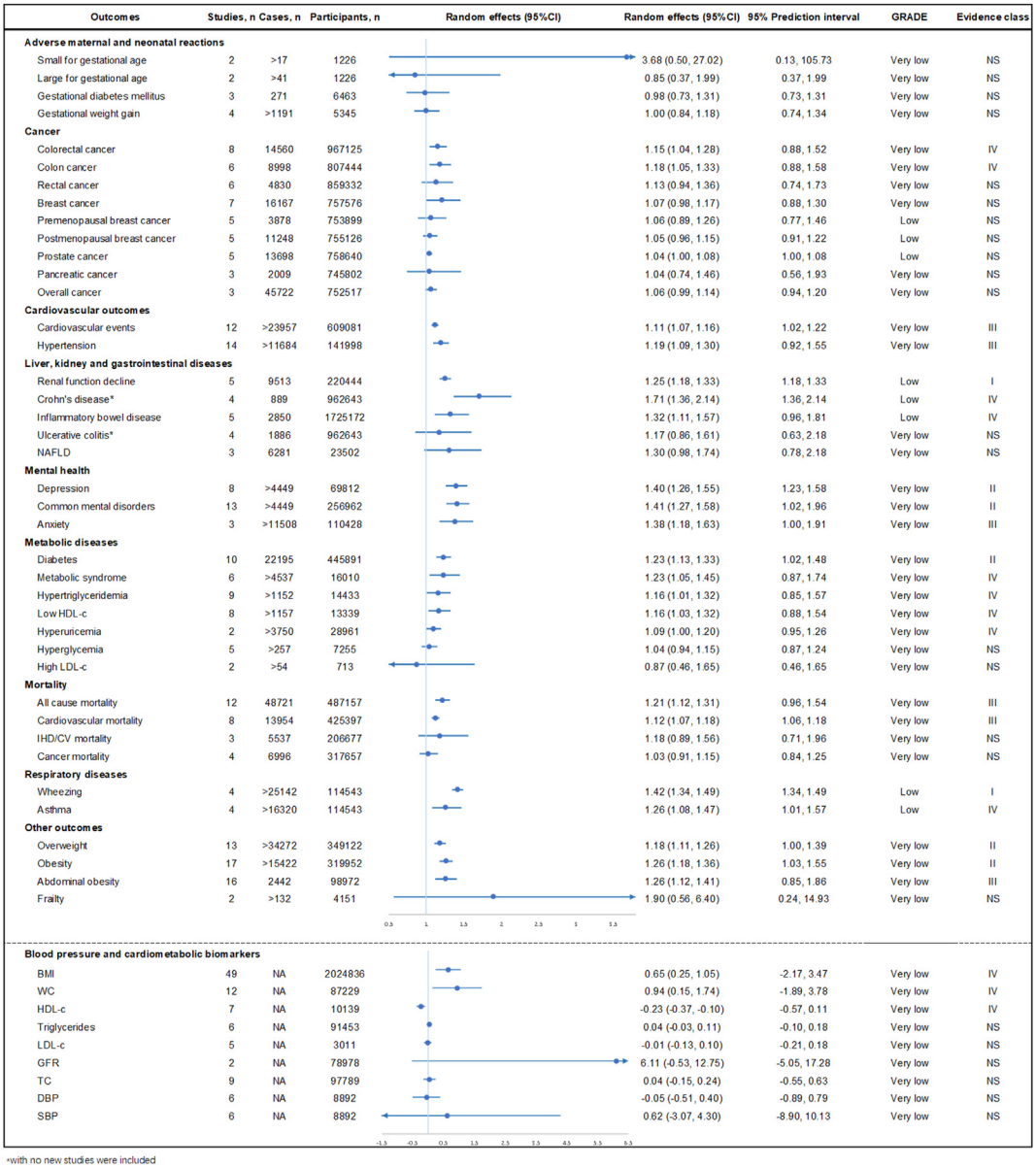

Fig. 2. High UPF consumption compared to low consumption and their associations with multiple health outcomes. An I2 value $\geq$ 50% is considered to indicate substantial heterogeneity. NAFLD, non-alcoholic fatty liver disease; HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; IHD, ischemic heart disease; CV, cerebrovascular disease; BMI, Body Mass Index; WC, waist circumference; GFR, glomerular filtration rate; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

4. Discussion

The previously published meta-analysis of 43 observational studies by Lane et al. found the UPF consumption was associated with overweight, obesity, abdominal obesity, all-cause mortality, metabolic syndrome, and depression in adults as well as wheezing in adolescents. Since then, the number of new observational reports on these topics has increased considerably. Hence, we conducted this update on the current literature to encompass all new evidence on relevant health consequences. Furthermore, we applied standard credibility assessment criteria to assess the confidence in the estimated association. Compared to Lane et al., our updated meta-analyses included a total of 79 new individual articles and unveiled associations of UPF consumption with 25 health outcomes, including 18 new health outcomes. After assessing the evidence credibility, two health outcomes presented convincing evidence, including renal function decline, and wheezing in children and adolescents. The associations between UPF consumption and diabetes mellitus, obesity/overweight, depression and common mental disorders were classified as highly suggestive. All-cause mortality, cardiovascular mortality, hypertension, cardiovascular events, anxiety, and abdominal obesity were associated with UPF consumption as well, although with low confidence. In addition, weak evidence was reported for the associations between UPF intake and colorectal cancer, colon cancer, CD, IBD, metabolic syndrome, hypertriglyceridemia, low HDL-cholesterol levels, hyperuricemia, asthma, BMI, and WC.

Many epidemiological studies have assessed the associations between UPF consumption and the development of overweight and (abdominal) obesity and reported a positive association, in line with our findings [15,26,29,31]. UPFs may contribute to weight gain since these products are usually calorically dense, i.e., a high

energetic content per gram, rich in added sugars and saturated fats, and have low density and diversity of nutrients that induce satiety [72,73]. Furthermore, these foods are often engineered to have supernormal appetitive properties such as salt content and texture that can promote poor dietary habits, such as overeating and high-energy intake [74–79]. In this regard, a recent randomized controlled trial evaluating the effect of UPFs vs. an unprocessed foods diet has demonstrated that the UPFs diet was correlated with high energy intake and weight gain even when the UPFs diet offered to participants was closely matched to the control diet in calories, sugar, fat, sodium, fibre and macronutrients [80]. These findings suggest that something other than nutrient profile in UPFs may add to its obesogenic effect. Reducing UPF consumption in the diet and increasing the content of unprocessed or minimally processed whole foods could represent an effective strategy for obesity management and prevention.

Previous studies linking UPF intake to diabetes mellitus have shown a positive association, as is the case in our analysis [36,81,82]. As mentioned, the macro nutritional dietary characteristics of UPFs were associated with overweight and obesity, which are risk factors for diabetes [83]. An experimental study supported that UPFs were, on average, more hyperglycemic than minimally and moderately processed foods due to the altered food structure [73]. A study in mice showed that carrageenan, an additive commonly used in UPFs, elevated fasting blood glucose and insulin resistance [84]. Furthermore, UPF is often packaged in synthetic substances that may be a source of endocrine hormone-disrupting chemicals, such as bisphenol A (BPA), which are associated with diabetes [85].

Regarding respiratory health, previously published studies investigating the association between UPF and wheezing in children and adolescents showed inconsistent results, while our updated meta-analyses revealed a significant association with convincing evidence [86,87]. Food additives widely used in industrial processing might mediate the associations between UPFs and respiratory disease. Certain food additives like tartrazine and carmine (E−120), might induce pro-inflammatory cytokines and hypersensitivity reactions, which can play a key role in the development of asthma and wheezing [86,88,89]. Human studies have also found an association between food additives, such as sodium benzoate, an important antiseptic agent, and augmented histamine release from basophils, which is one of the substances that triggers allergic symptoms [90,91]. However, existing epidemiological studies investigating UPFs and respiratory health were of cross-sectional design, and the reverse causation cannot be excluded. Thus, large-scale cohort studies as well as mechanistical and interventional trials seem necessary to further understand the relationship between UPF consumption and respiratory disease and its primary manifestation in younger age groups.

Our updated meta-analysis found a significant association between UPF consumption and depression. A possible mechanistic basis might lie in the macro nutritional characteristics of UPFs (rich in saturated fats and sugar, and low in dietary fiber, micronutrients, and phytochemicals) that may influence a variety of interacting pathways, including inflammation, and oxidative stress [92]. Non-nutritive ingredients used in industrial processing, such as aspartame might also add to the problem as this artificial sweetener was shown to inhibit the synthesis and release of neurotransmitters, dopamine, norepinephrine, and serotonin, which are important in the development of depression [93]. Of note, most included studies used self-reported screening questionnaires to diagnose depression, which might overestimate the prevalence of depression [94]. In addition, the majority of studies included in our meta-analyses used a cross-sectional design, where inferences regarding the direction of associations are limited. Thus, large-scale cohort studies and intervention studies using validated diagnostic interviews as diagnostic modalities for depression are needed.

Our analysis adds to the evidence that high consumption of UPFs is associated with renal function decline [95–97]. Previous studies have shown that high intake of saturated fats, added sugar and salt are associated with poor kidney outcomes, as they induce dyslipidemia, oxidative stress, and inflammation, which are known risk factors for chronic kidney disease (CKD) progression [98–101]. In addition, inorganic phosphate food additives can influence variations in serum phosphorus levels [95]. Early intervention studies in humans have revealed that large doses of phosphate, as in oral therapy (>2250 mg/day on top of dietary phosphate) over 1–7 years increase progressive renal impairment [102].

Although meta-analyses of UPFs and adverse health outcomes have been conducted previously, our study provides a systematic and complete overview of associations between UPF consumption and multiple health outcomes by incorporating information from individual observational studies. Furthermore, our study evaluated the reliability of these associations based on established credibility criteria. For the convincing and highly suggestive outcomes, sensitivity analyses further evaluated the associations by only including cohort studies, further strengthening our findings.

We acknowledge certain limitations. First, there was high heterogeneity in the current meta-analyses, possible reasons being the inclusion of different populations, different study designs and inconsistent outcome definitions. Second, all included studies were observational. Although we extracted data from relatively well-developed multivariable models from each included study, adjustments for confounding variables differed among the studies, and due to different and residual confounding, causal associations between UPF consumption and related outcomes cannot be inferred. Third, approximately half of the included studies were cross-sectional by design and the self-reported dietary intake may not be representative of long-term habitual dietary intake, and will suffer from random errors and systematic biases depending on the method of exposure assessment employed in each individual study [103]. Fourth, from the convincing (Class I) outcomes with higher confidence in the estimated associations, only abdominal obesity had a large number of studies (majority of them were cross sectional studies). Fifth, different studies contributed to our meta-analyses of related adiposity measures such as BMI, overweight, WC and abdominal obesity. The included studies differed in several factors including study design, population, and methodological quality, and these variations likely contributed to the inconsistent findings between the continuous and categorical outcomes. In addition, although the NOVA food classification system has been used in several observational studies as well as in nutritional guidelines and recommendations, this classification is an over-simplification which does not always allow for robust and functional food assignments [104]. For example, a recent large cohort study in the USA that investigated the association between UPF intake and type 2 diabetes risk indeed showed a positive relationship [36]. However, when looking into specific UPF subgroups, it became clear that certain products such as whole-grain breads, yogurt and dairy-based desserts were associated with lower T2D risk [36]. In addition, while UPFs are often described with pejorative overtones, we should acknowledge that the processing of foods has considerably improved food safety and security, which has saved lives and improved the quality of life of many [105]. Lastly, fortified products that contain for example fiber supplements or additional vitamins and minerals would convert products into a UPF according to the NOVA classification, although these are potentially beneficial additions. So clearly, while NOVA is currently accepted as a classification system to categorize the processing of foods and has helped us to explore associations between overall

UPF consumption and health outcomes, further work at improving this classification is needed to improve our understanding of UPFs. Finally, while most of the studies reported UPF intake as a proportion of total energy intake, some studies used weight proportion or number of servings, which contributed to inconsistent findings. Therefore, our findings should be considered as preliminary, and more studies related to these outcomes are needed.

Given the large body of evidence implicating UPFs in human diseases, and the ever-increasing consumption of UPFs around the world, there is a pressing need to recognize the contribution of UPFs to the global burden of disease. At present, not a single study reported an association between UPF intake and a beneficial health outcome. In addition, a large body of literature supports the health benefits of fruits, vegetables, whole grains, etc. [106,107]. Most of these earlier studies did not categorize UPF explicitly, but since UPF and whole foods are inversely correlated, all of these studies and our findings suggest that dietary patterns with low consumption of UPFs, which include higher consumption of minimally processed foods such as whole grains, fruits, vegetables, eggs, meat, milk, etc. may render broad public health benefits. However, large-scale, high-quality prospective cohort studies, intervention studies and experimental studies are needed to confirm our findings, allow for mechanistic understandings of the health associations, and provide a safe recommended daily intake (RDI) of UPFs in the future. Given the current evidence, public health policies regarding UPFs, such as food labelling and price adjustments, are increasingly relevant and should be prioritized [108]. In addition, food industry will continue to produce UPFs because they cater to consumers' needs for convenience and good taste. Hence, it is necessary to enhance consumers' awareness of healthy eating and encourage them to re-examine their choice of products from the perspective of health needs. Change within food industries depend not only on economic, regulatory factors, and shifting public attitudes, but also on the willingness of corporations to take social responsibility, and placing similar weight on social, health, and environmental goals as they do on profits, and to shift their focus towards expanding the markets for healthier and more sustainable foods [109]. Since UPFs are here to stay, from a research point of view, it will be critical to better understand which aspects of UPFs are detrimental to human health, and which alternatives could be offered to producers and consumers.

5. Conclusions

In conclusion, our umbrella review and updated meta-analyses identified 25 adverse health outcomes associated with higher UPF consumption. Of these, renal function decline, and wheezing in children and adolescents were convincingly associated with higher UPF consumption. These findings suggest that dietary patterns with low consumption of UPFs, which include higher consumption of minimally processed foods such as whole grains, fruits, vegetables, eggs, meat, milk, etc. may render broad public health benefits. Further large-scale, high-quality prospective cohort studies, intervention studies and experimental studies are needed to confirm our findings, allow for mechanistic understandings of the health associations, and provide a safe recommended daily intake (RDI) of UPFs in the future.

Authors' contribution

XL and ET: Conceptualization, Supervision, Funding acquisition, Writing – Review & Editing; SD: Investigation, Formal analysis, Writing – Original draft preparation; JW: Investigation; NY and DL: Formal analysis; JW: Writing – Original draft preparation, Funding acquisition; YH: Funding acquisition; LW, JS, SY, PS, RM, MK, AM, PM, JL and SD: provided significant advice and consultation; and all authors critically reviewed the manuscript, contributed important intellectual content, read and approved the final manuscript.

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Data availability

All data relevant to the study are included in the article or as supplementary information.

Conflicts of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.04.016.

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Supplementary Material

Shuhui Dai, Judith Wellens, Nan Yang, Doudou Li, Jingjing Wang, Ying Lu, Lijuan Wang, Jing Sun, Jianhui Zhao, Shuai Yuan, Yazhou He, Peige Song, Evropi Theodoratou, Xue Li, et al. Ultra-processed foods and human health: an umbrella review and updated meta-analyses of observational evidence

(RR: risk ratio, OR: odds ratio, HR: hazard ratio. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic(t^2) at a significance level of $P<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% is considered to indicate substantial heterogeneity.)

Supplementary table 1. Search strategy for systematic reviews and meta-analyses on ultra-processed food consumption and health outcomes

1: “ultra processed food*” OR “ultraprocessed food*” OR “ultra-processed food*” OR “nova food classif*” OR “nova food*” OR “nova food classification system”
2: “meta” OR “meta-analysis” OR “systematic overview” OR “systematic review”
3: 1 and 2

Supplementary table 2. Search strategy for original articles on ultra-processed food consumption and health outcomes

1: “ultra processed food*” OR “ultraprocessed food*” OR “ultra-processed food*” OR “nova food classif*” OR “nova food*” OR “nova food classification system”

Supplementary table 3. Credibility assessment criteria(1-3)

Category	**Criteria**
Convincing: class Ⅰ	● No. of cases >1000 or (more than 20000 participants for continuous outcomes) ● $P < 1\times10^{-6}$ ● I^2 <50% ● 95% prediction intervals excluding the null value ● No small study effects ● No excess significance bias
Highly suggestive: class II	● No. of cases >1000 or (more than 20000 participants for continuous outcomes) ● $P < 1\times10^{-6}$ ● The largest component study reporting a statistically significant result
Suggestive: class III	● No. of cases >1000 or (more than 20000 participants for continuous outcomes) ● $P < 1\times10^{-3}$
Weak: class IV	● $P < 0.05$
Not significant	● $P > 0.05$

Supplementary table 4. Description of meta-analyses of ultra-processed foods and health outcomes included in umbrella review

Study, Year	Outcome	Population	Study design	Comparison	Studies, n	Cases, n	Participants, n	Metric	Random effects (95% CI)
Mortality									
Pagliai, 2021(4)	all-cause mortality	general	CO	high vs low	5	4687	111056	RR	1.25(1.14,1.37)
Lane, 2021(5)	all-cause mortality	general	CO	high vs low	4	3828	88247	HR	1.28(1.11,1.48)
Suksatan, 2021(6)	all-cause mortality	general	CO	high vs low	6	5494	115400	HR	1.21(1.13,1.30)
Taneri, 2022(7)	all-cause mortality	general	CO	high vs low	5	5044	110721	RR	1.29(1.17,1.42)
Yuan, 2023(8)	all-cause mortality	general	CO	each additional daily serving of UPF	9	35080	295651	RR	1.02(1.01,1.03)
Suksatan, 2021(6)	cardiovascular mortality	general	CO	high vs low	4	6648	146163	HR	1.50(1.37,1.63)
Suksatan, 2021(6)	heart disease mortality	general	CO	high vs low	2	4240	114366	HR	1.66(1.50,1.85)
Suksatan, 2021(6)	cancer mortality	general	CO	high vs low	2	641	42374	HR	1.00(0.81,1.24)
Cardiovascular outcomes									
Pagliai, 2021(4)	hypertension	general	CS	high vs low	2	NA	1113	OR	1.31(0.50,3.43)
Wang，2022(9)	hypertension	general	CO/CS	high vs low	9	>5454	11594	OR	1.23(1.11,1.37)
Pagliai, 2021(4)	cardiovascular events	general	CO	high vs low	3	2501	139867	RR	1.29(1.12,1.48)
Yuan, 2023(8)	cardiovascular events	general	CO	each additional daily serving of UPF	8	11054	278023	RR	1.04(1.02,1.06)
Mental health									
Pagliai, 2021(4)	depression	general	CO	high vs low	2	2995	41637	RR	1.20(1.03,1.40)
Lane, 2021(5)	depression	general	CO	high vs low	2	2995	41637	HR	1.22(1.16,1.28)

Lane, 2022(10)	depression	general	CO	high vs low	2	2995	41637	HR	1.22(1.16,1.28)
Lane, 2022(10)	depression		CS	high vs low	3	>1208	15555	OR	1.44(1.14,1.82)
Lane, 2022(10)	anxiety	general	CS	high vs low	3	NA	101709	OR	1.48(1.37,1.59)
Lane, 2022(10)	common mental disorders	general	CS	high vs low	5	>1208	185773	OR	1.53(1.43,1.63)
Metabolic diseases									
Moradi, 2021(11)	diabetes	general	CO/CS	high vs low	5	>2429	230526	RR	1.74(1.36,2.22)
Delpino, 2021(12)	diabetes	general	CO	high vs low	2	480	41790	RR	1.48(1.16,1.89)
Chen, 2023(13)	diabetes	general	CO	each 10% increment in UPF	7	21932	415554	RR	1.12(1.10,1.13)
Lane, 2021(5)	metabolic syndrome	general	CS	high vs low	2	>459	1113	OR	1.81(1.12,2.93)
Pagliai, 2021(4)	metabolic syndrome	general	CS	high vs low	2	>459	1113	OR	1.79(1.10,2.90)
Pagliai, 2021(4)	hyperglycaemia	general	CS	high vs low	2	NA	1113	OR	1.10(0.34,3.52)
Pagliai, 2021(4)	hypertriacylglycerolaemia	general	CS	high vs low	2	NA	1113	OR	0.95(0.60,1.50)
Pagliai, 2021(4)	low HDL-cholesterol	general	CS	high vs low	2	NA	1113	OR	2.02(1.27,3.21)
Overweight/ Obesity/ Abdominal obesity									
Askari, 2020(14)	overweight	general	CO/CS	high vs low	10	NA	87219	ES	1.18(1.09,1.27)
Lane, 2021(5)	overweight	general	CS	high vs low	3	NA	55197	OR	1.36(1.23,1.51)
Moradi, 2021(15)	overweight	general	CS	high vs low	4	NA	44820	OR	1.36(1.14,1.63)
Askari, 2020(14)	obesity	general	CS	high vs low	6	NA	77519	ES	1.26(1.13,1.41)
Lane, 2021(5)	obesity	general	CS	high vs low	5	NA	61340	OR	1.51(1.34,1.70)
Moradi, 2021(15)	obesity	general	CO/CS	high vs low	6	NA	99393	OR	1.55(1.36,1.77)
Moradi, 2021(15)	abdominal obesity	general	CO/CS	high vs low	4	NA	48265	OR	1.41(1.18,1.68)
Pagliai, 2021(4)	abdominal obesity	general	CS	high vs low	4	NA	31908	OR	1.39(1.16,1.67)
Lane, 2021(5)	abdominal obesity	general	CS	high vs low	3	NA	31097	OR	1.49(1.34,1.66)

Respiratory system disease									
Lane, 2021(5)	wheezing	adolescents	CS	high vs low	2	NA	111294	OR	1.40(1.27,1.55)
Lane, 2021(5)	asthma	adolescents	CS	high vs low	2	NA	111294	OR	1.20(0.99,1.46)
Inflammatory bowel disease									
Narula, 2023(16)	Crohn's disease	general	CO	high vs low	4	916	1068426	HR	1.71(1.36,2.14)
Narula, 2023(16)	ulcerative Colitis	general	CO	high vs low	4	1934	1068426	HR	1.17(0.86,1.61)

[1] NA=not available

[2] CO= cohort study; CS= cross-sectional study.

[3] RR= relative risk; OR= odds ratio; HR=hazard ratio.

Supplementary table 5. Recheck the credibility of convincing or highly suggestive evidence

Outcomes	Population	Study design	Comparison	Studies, n	Cases, n	Participants, n	Metric	Random effects (95% CI)	P value	95% prediction interval	Egger's P	I^2 (%)	P value for excess significance test	GRADE	Evidence class
Renal function decline	General	CO	high vs low	5	9513	220444	OR	1.25(1.18,1.33)	7.42E-13	1.18 to 1.1.33	0.152	0.00	0.28	Low	I
Depression	General	CO/ CS	high vs low	8	>4449	69812	OR	1.40(1.26,1.55)	3.24E-10	1.23 to 1.58	0.034	4.54	0.04	Very low	II
	General	CO		3	3241	44209	HR	1.35(1.21,1.50)	8.58E-08	1.21 to 1.50	0.227	0.00	0.86	Low	I
Diabetes	General	CO/ CS	high vs low	10	>22195	445891	OR	1.23(1.13,1.33)	3.69E-07	1.02 to 1.48	0.000	58.71	0.05	Very low	II
	General	CO		9	22195	432283		1.22(1.13,1.33)	1.65E-06	1.01 to 1.48	0.000	61.20	0.97	Very low	III
Overweight	General	CO/ CS	high vs low	13	>34272	349122	OR	1.18(1.11,1.26)	9.15E-07	1.00 to 1.39	0.010	76.35	0.27	Very low	II
	General	CO		5	>34272	271721		1.14(1.06,1.22)	2.19E-04	1.00 to 1.30	0.164	82.56	0.23	Very low	III
Obesity	General	CO/ CS	high vs low	17	>15422	319952	OR	1.26(1.18, 1.36)	1.62E-10	1.03 to 1.55	0.000	89.02	0.01	Very low	II
	General	CO		5	>15422	202801		1.09(0.99,1.21)	0.084	0.91 to 1.32	0.410	76.36	0.21	Very low	NS

Common mental disorders	General	CO/ CS	high vs low	13	>4449	256962	OR	1.41(1.27,1.58)	6.79E-10	1.02 to 1.96	0.092	82.93	0.20	Very low	II
	General	CO		4	>3241	50504	HR	1.27(1.05,1.53)	0.013	0.90 to 1.79	0.365	63.98	0.79	Very low	IV

[1] CO= cohort study; CS= cross-sectional study.

[2] OR= odds ratio; HR=hazard ratio.

Supplementary table 6. Information of other outcomes included in the review based on single studies.

Author	Year	Study design	Comparison	Outcome	Cases, n	Participants, n	Metrix	Random effects (95% CI)	P value
Schnabel(17)	2018	CO	high vs low	irritable bowel syndrome	3516	33343	OR	1.25(1.12,1.39)	<0.001
				functional constipation	1785	33343	OR	0.98(0.85,1.12)	0.66
				functional diarrhea	396	33343	OR	0.92(0.69,1.24)	0.70
				functional dyspepsia	1303	33343	OR	1.25(1.05,1.47)	0.004
Filgueiras(18)	2019	CS	high vs low	food addiction	33	139	OR	1.15(1.01,1.31)	0.035
Figueiredo(19)	2022	CS	Per 10% increment of UPF	restrictive disorders	444	43993	OR	1.09(0.98,1.21)	0.12
				bulimic disorders	1575	43993	OR	1.08(1.01,1.14)	0.02
				binge eating disorders	3124	43993	OR	1.21(1.16,1.26)	<0.001
Bidinotto(20)	2021	CS	high vs low	dental caries	/	5720	RR	1.10(1.04,1.16)	<0.05
Bidinotto(21)	2022	CS	high vs low	periodontitis	1948	4809	OR	0.96(0.91,1.01)	/
Zhang(22)	2021	CS	high vs low	cardiovascular health metrics	/	11246	OR	2.57(1.79,3.70)	P<0.001
Zhang(23)	2022	CS	high vs low	cardiovascular health metrics	/	5565	OR	2.59(1.49,4.55)	<0.001
Montero-Salazar(24)	2020	CS	high vs low	subclinical coronary atherosclerosis	/	1876	OR	2.00(1.26,3.16)	0.005
Yang(25)	2020	CS	high vs low	excess heart age	/	12640	OR	1.66(1.29,2.13)	<0.001
De Melo(26)	2021	CO	high vs low	offspring overweight or obesity in the first year	/	196 mother-child pairs	HR	3.02(1.28,7.13)	0.012

				of life					
Wang(27)	2022	CO	high vs low	offspring overweight or obesity during childhood and adolescence	2471	19958 mother-child pairs	RR	1.26(1.08,1.47)	<0.001
Asgari(28)	2022	CS	high vs low	obesity in children	/	788	OR	0.97(0.31,3.01)	0.98
Asgari(28)	2022	CS	high vs low	wasting in children	/	788	OR	0.94(0.30,2.87)	0.87
Asgari(28)	2022	CS	high vs low	overweight/obesity in children	/	788	OR	0.86(0.59,1.25)	0.45
Asgari(28)	2022	CS	high vs low	underweight/wasting in children	/	788	OR	0.69(0.40,1.17)	0.17
González(29)	2023	CO	high vs low	obesity in children	/	6468	RR	1.02(0.93,1.12)	0.68
Neri(30)	2022	CS	high vs low	overweight/obesity in adolescents	/	3545	OR	1.45(1.03,2.06)	0.04
Neri(30)	2022	CS	high vs low	abdominal overweight/obesity in adolescents	/	3484	OR	1.52(1.06,2.18)	0.026
Neri(30)	2022	CS	high vs low	visceral overweight/obesity in adolescents	/	3469	OR	1.63(1.19,1.24)	0.005
Alonso-Pedrero(31)	2020	CS	high vs low	short telomere length	177	886	OR	1.82(1.05,3.22)	0.03
Borge(32)	2021	CO	one SD increase in maternal UPFI scores	ADHD diagnosis	2546	77768 mother-child pairs	RR	1.07(0.99,1.18)	/
Li(33)	2022	CO	high vs low	dementia	518	72083	HR	1.51(1.16,1.96)	<0.001

Lv(34)	2022	CC	high vs low	asthenozoospermia odds	549	1130	OR	1.53(1.12,2.10)	<0.05
Menezes-Junior(35)	2022	CS	high vs low	poor sleep quality	925	1762	OR	2.44(1.32,4.50)	0.013
Oviedo-Solis(36)	2022	CS	high s low	anemia in children	/	11008	OR	0.97(0.88,1.06)	/
Oviedo-Solis(36)	2022	CS	high s low	anemia in adolescents	/	8599	OR	0.99(0/89,1.10)	/
Ruggiero(37)	2022	CC	1% increase in the proportion of UPF in the diet	lumbar spinal stenosis	156	468	OR	1.09(1.04,1.14)	/
Zhang(38)	2022	CO	high vs low	subclinical hypothyroidism	176	7155	HR	0.87(0.60,1.27)	0.47
				subclinical hyperthyroidism	151	7227	HR	1.69(1.12,2.56)	0.01
Zhang (39)	2022	CO	high vs low	low grip strength	/	5409	HR	1.36(1.06,1.74)	0.01
Zhou(40)	2022	CO	high vs low	COVID-19	6358	41012	OR	1.22(1.12,1.34)	P<0.001
Solans(41)	2021	CC	Per 10% increment of UPF	chronic lymphocytic leukemia	230	1864	OR	1.09(0.94,1.25)	0.67
Fliss-Isakov(42)	2020	CC	high vs low	colorectal adenomas	294	652	OR	1.75(1.14,2.68)	0.009
Hang(43)	2023	CO	high vs low	conventional adenomas of colorectal cancer	11644	142052	OR	1.18(1.11,1.26)	/
Hang(43)	2023	CO	high vs low	serrated lesions of colorectal cancer	10478	142052	OR	1.20(1.13,1.28)	/
Chang(44)	2023	CO	Per 10% increment in UPF	head and neck cancer	342	197426	HR	0.89(0.80,1.00)	/
Chang(44)	2023	CO	Per 10% increment in	gastrointestinal cancer	2937	197426	HR	1.03(1.00,1.07)	<0.05

			UPF						
Chang(44)	2023	CO	Per 10% increment in UPF	oesophagus cancer	283	197426	HR	1.08(0.97,1.21)	/
Chang(44)	2023	CO	Per 10% increment in UPF	stomach cancer	189	197426	HR	1.08(0.95,1.22)	/
Chang(44)	2023	CO	Per 10% increment in UPF	small intestine cancer	77	197426	HR	1.20(0.98,1.48)	/
Chang(44)	2023	CO	Per 10% increment in UPF	anal cancer	60	197426	HR	0.98(0.77,1.25)	/
Chang(44)	2023	CO	Per 10% increment in UPF	hepatobiliary tract cancer	243	197426	HR	1.03(0.92,1.16)	/
Chang(44)	2023	CO	Per 10% increment in UPF	liver cancer	157	197426	HR	1.03(0.89,1.20)	/
Chang(44)	2023	CO	Per 10% increment in UPF	lung cancer	935	197426	HR	1.05(0.99,1.11)	/
Chang(44)	2023	CO	Per 10% increment in UPF	melanoma skin cancer	974	197426	HR	1.00(0.94,1.06)	/
Chang(44)	2023	CO	Per 10% increment in UPF	kidney cancer	451	197426	HR	1.05(0.97,1.14)	/
Chang(44)	2023	CO	Per 10% increment in UPF	bladder cancer	320	197426	HR	1.01(0.91,1.13)	/
Chang(44)	2023	CO	Per 10% increment in UPF	brain cancer	277	197426,	HR	1.09(0.98,1.21)	/
Chang(44)	2023	CO	Per 10% increment in UPF	thyroid cancer	126	19742	HR	1.11(0.95,1.29)	/
Chang(44)	2023	CO	Per 10% increment in	lymphatic and	1429	197426	HR	1.01(0.96,1.06)	/

			UPF	haematopoietic tissue cancer					
Chang(44)	2023	CO	Per 10% increment in UPF	non-Hodgkin lymphoma	1091	197426	HR	0.99(0.94,1.05)	/
Chang(44)	2023	CO	Per 10% increment in UPF	multiple myeloma	286	197426	HR	0.98(0.88,1.10)	/
Chang(44)	2023	CO	Per 10% increment in UPF	leukaemia	400	197426	HR	1.01(0.92,1.11)	/
Chang(44)	2023	CO	Per 10% increment in UPF	uterus cancer	439	197426	HR	1.02(0.94,1.11)	/
Chang(44)	2023	CO	Per 10% increment in UPF	ovary cancer	291	197426	HR	1.19(1.08,1.30)	<0.001
Chang(44)	2023	CO	Per 10% increment in UPF	head and neck cancer mortality	54	197426	HR	0.95(0.71,1.27)	/
Chang(44)	2023	CO	Per 10% increment in UPF	gastrointestinal cnacer mortality	1408	197426	HR	1.04(0.99,1.09)	/
Chang(44)	2023	CO	Per 10% increment in UPF	oesophagus	194	197426	HR	1.08(0.95,1.24)	/
Chang(44)	2023	CO	Per 10% increment in UPF	stomach cancer mortality	121	197426	HR	1.16(0.99,1.35)	/
Chang(44)	2023	CO	Per 10% increment in UPF	hepatobiliary tract cancer mortality	182	197426	HR	1.04(0.91,1.19)	/
Chang(44)	2023	CO	Per 10% increment in UPF	liver cancer mortality	150	197426	HR	1.03(0.88,1.20)	/
Chang(44)	2023	CO	Per 10% increment in UPF	pancreas cancer mortality	371	197426	HR	1.00(0.90,1.10)	/

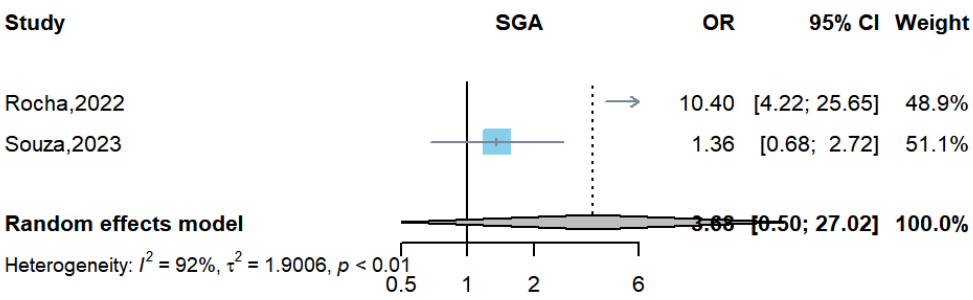
Chang(44)	2023	CO	Per 10% increment in UPF	lung cancer mortality	633	197426	HR	1.06(0.99,1.14)	/
Chang(44)	2023	CO	Per 10% increment in UPF	melanoma skin cancer mortality	63	197426	HR	1.15(0.89,1.49)	/
Chang(44)	2023	CO	Per 10% increment in UPF	kidney cancer mortality	117	197426	HR	1.04(0.89,1.22)	/
Chang(44)	2023	CO	Per 10% increment in UPF	bladder cancer mortality	112	197426	HR	1.05(0.87,1.25)	/
Chang(44)	2023	CO	Per 10% increment in UPF	brain and central nervous system cancer mortality	251	197426	HR	1.05(0.93,1.18)	/
Chang(44)	2023	CO	Per 10% increment in UPF	lymphatic and haematopoietic tissue cancer mortality	376	197426	HR	1.05(0.95,1.15)	/
Chang(44)	2023	CO	Per 10% increment in UPF	non-Hodgkin lymphoma mortality	141	197426	HR	1.02(0.87,1.20)	/
Chang(44)	2023	CO	Per 10% increment in UPF	multiple myeloma mortality	91	197426	HR	1.08(0.89,1.31)	/
Chang(44)	2023	CO	Per 10% increment in UPF	leukaemia mortality	137	197426	HR	1.02(0.87,1.19)	/
Chang(44)	2023	CO	Per 10% increment in UPF	uterus cancer mortality	61	197426	HR	1.01(0.76,1.33)	/
Chang(44)	2023	CO	Per 10% increment in UPF	ovary cancer mortality	143	197426	HR	1.30(1.13,1.50)	<0.001
Kliemann(45)	2023	CO	Replace 10% of UPF with 10% of minimally	overall cancer	47573	450111	HR	0.99(0.97,1.00)	<0.05

			processed food						
Kliemann(45)	2023	CO	Replace 10% of UPF with 10% of minimally processed food	head and neck cancer	821	450111	HR	0.80(0.74,0.88)	<0.05
Kliemann(45)	2023	CO	Replace 10% of UPF with 10% of minimally processed food	hepatocellular carcinoma	/	450111	HR	0.73(0.62,0.86)	<0.05
Esposito(46)	2023	CC	1% increment in UPF	central nervous system tumours	44	132	OR	1.06(1.01,1.11)	/
Mannino(47)	2023	CC	high vs low	central nervous system demyelination	257	734	OR	1.08(1.00,1.15)	0.039
Yisahak(48)	2022	CO	high vs low	severe hypertension or preeclampsia	63	1948	OR	1.25(0.5,3.47)	/
Guglielmetti(49)	2023	CS	high vs low	moderate-to-high multiple sclerosis	/	106	OR	2.97(1.13,7.77)	/

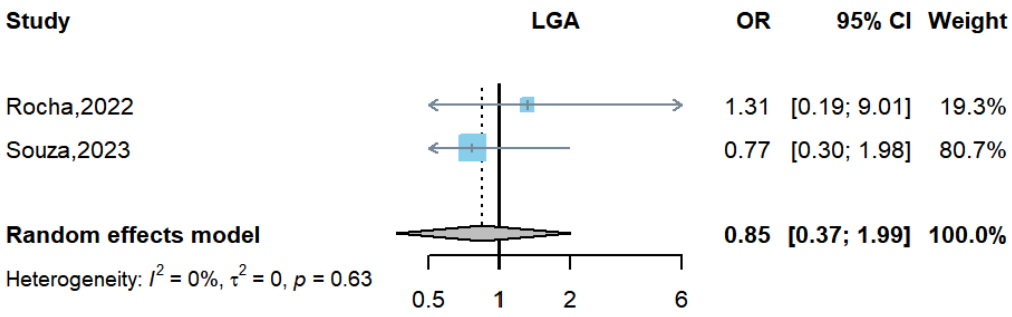
[1] ADHD: attention deficit hyperactivity disorder; COVID-19: Corona Virus Disease 2019.

[2] CC: case-control study; CO= cohort study; CS= cross-sectional study.

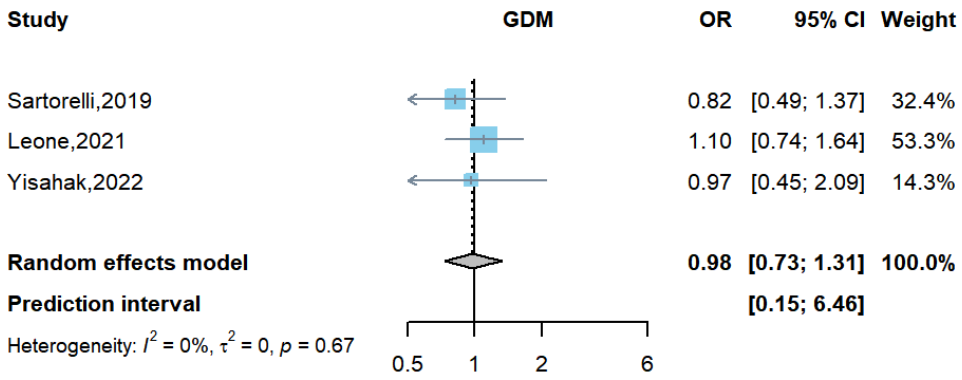
[3] RR= relative risk; OR= odds ratio; HR=hazard ratio.



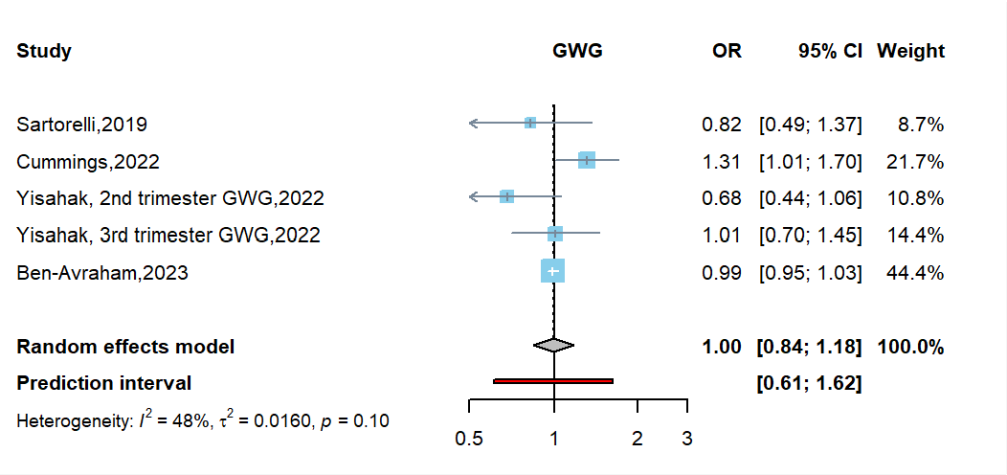
Supplemental Figure 1. Adverse maternal and neonatal reactions—Small for gestational age



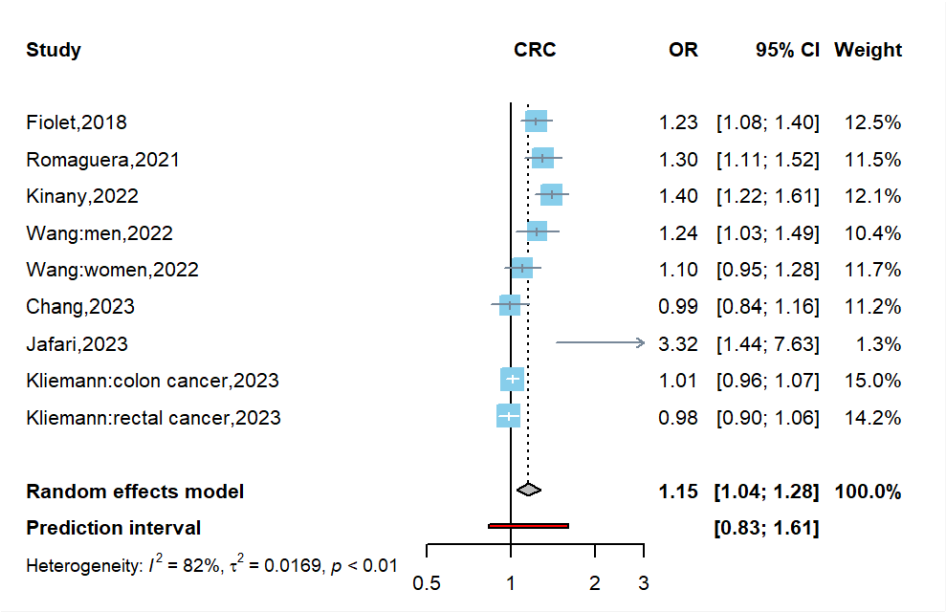
Supplemental Figure 2. Adverse maternal and neonatal reactions—Large for gestational age



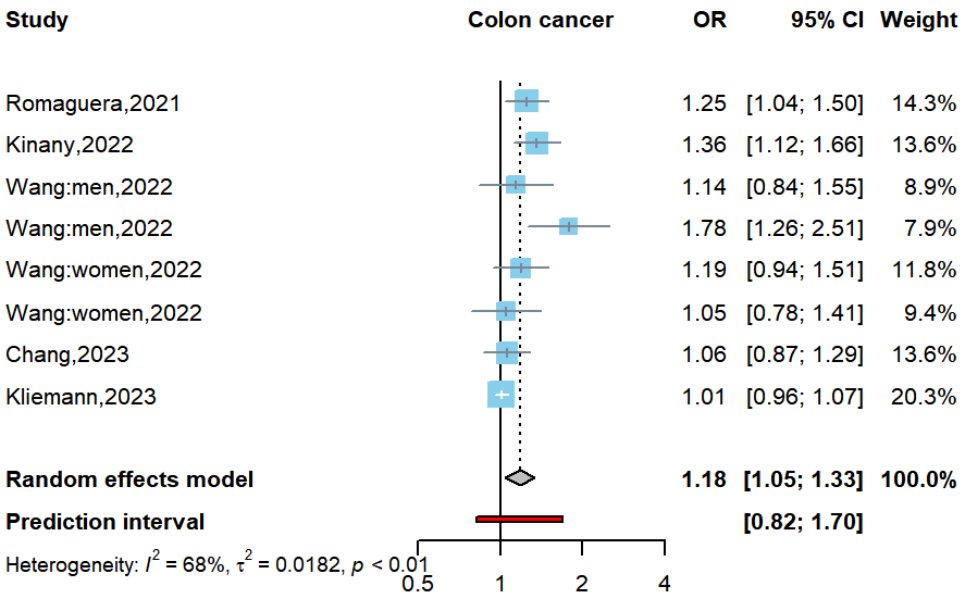
Supplemental Figure 3. Adverse maternal and neonatal reactions—Gestational diabetes mellitus



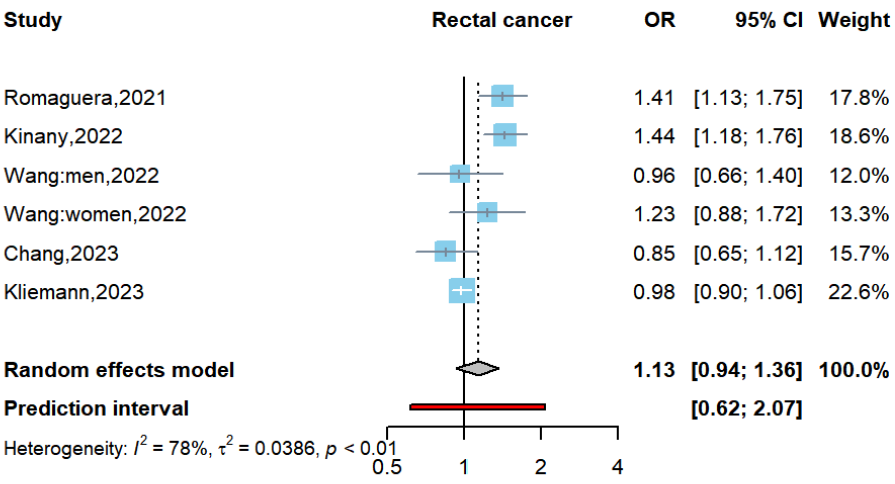
Supplemental Figure 4. Adverse maternal and neonatal reactions—Gestational weight gain



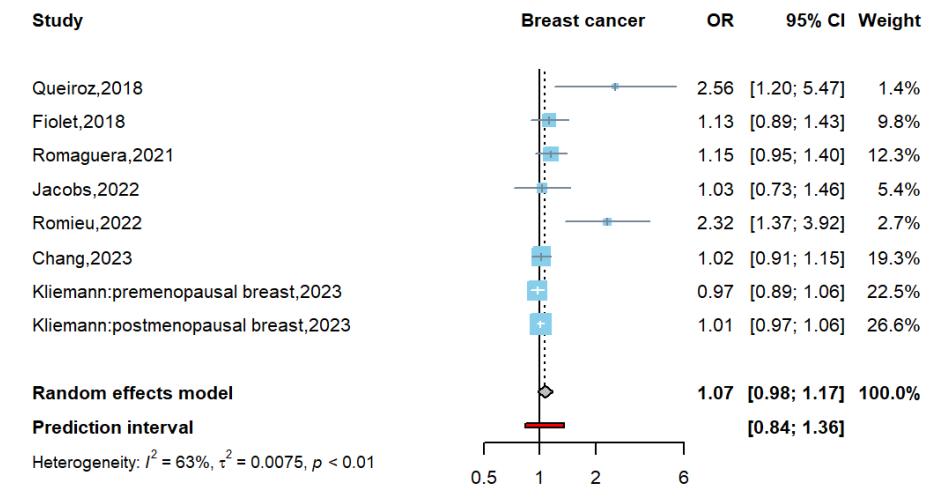
Supplemental Figure 5. Cancer—Colorectal cancer



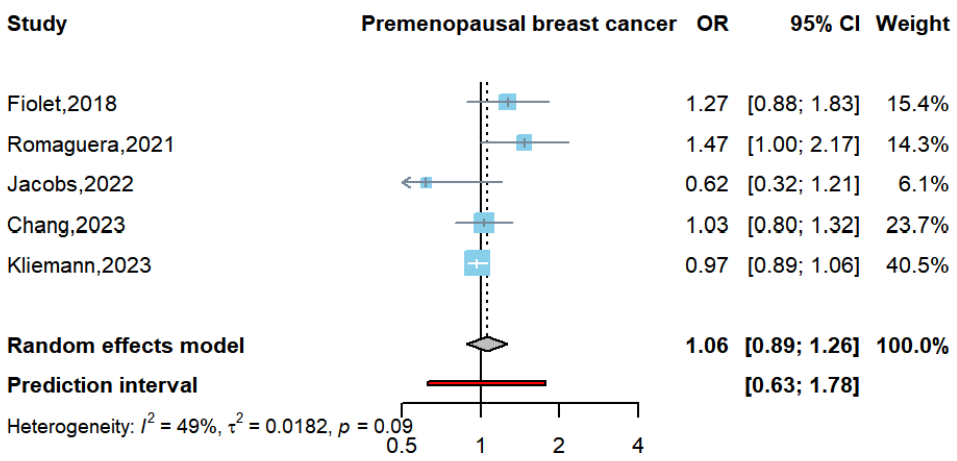
Supplemental Figure 6. Cancer—Colon cancer



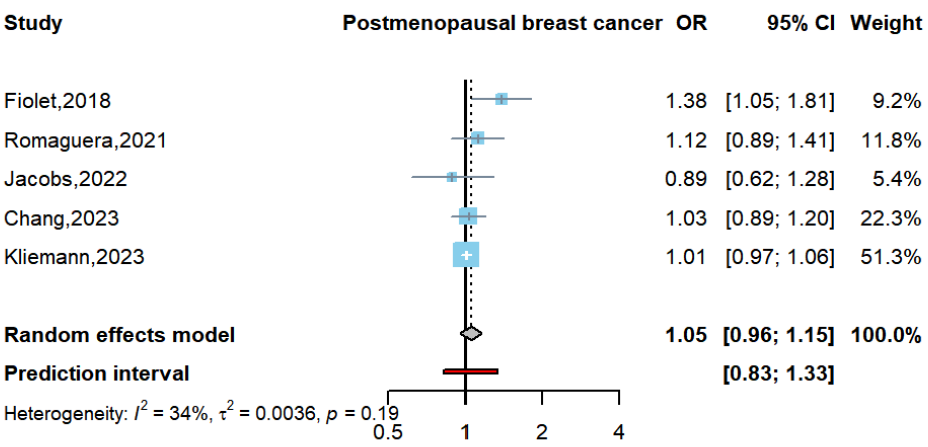
Supplemental Figure 7. Cancer—Rectal cancer



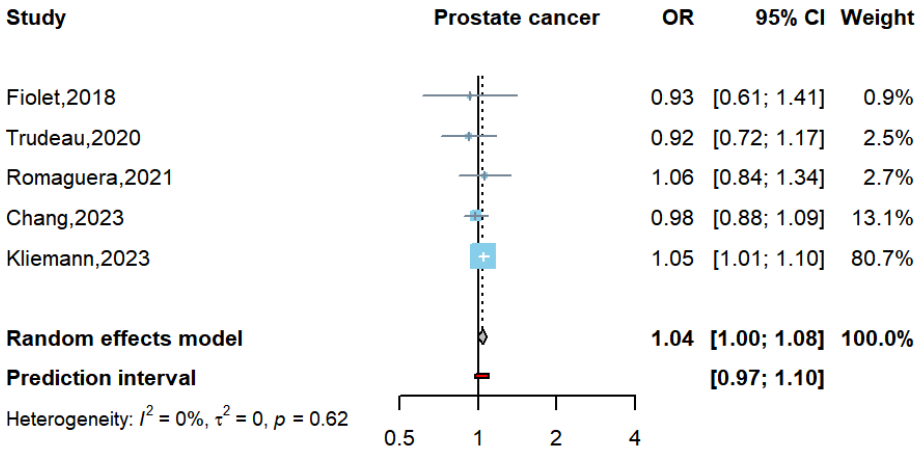
Supplemental Figure 8. Cancer—Breast cancer



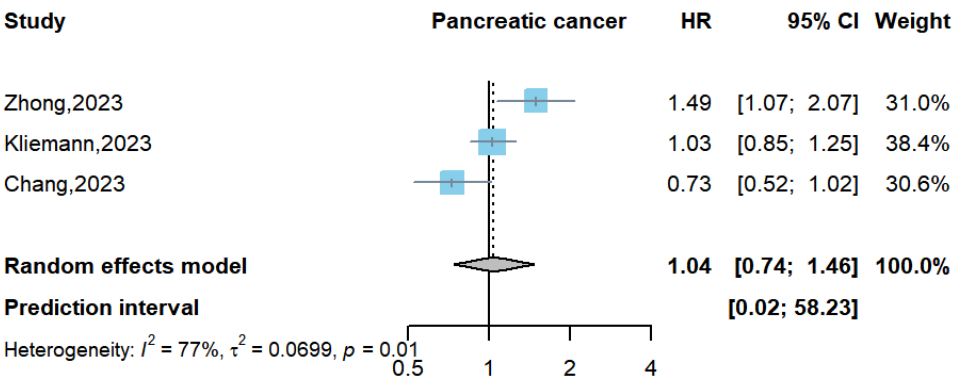
Supplemental Figure 9. Cancer—Premenopausal breast cancer



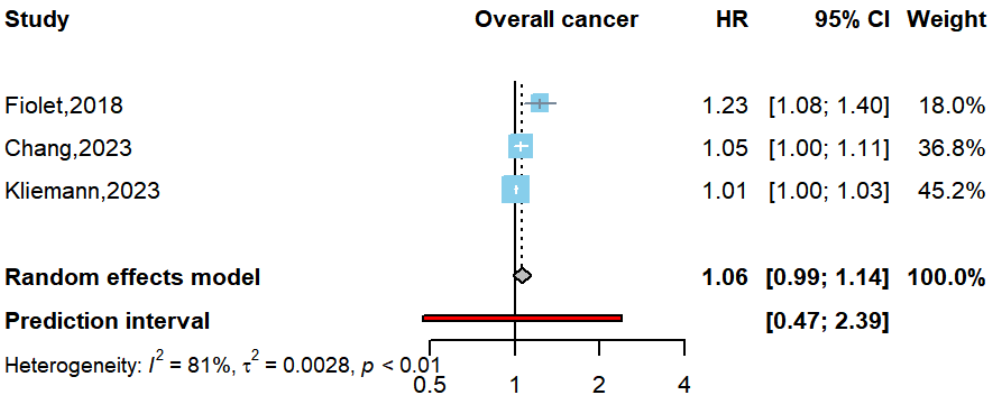
Supplemental Figure 10. Cancer—Postmenopausal breast cancer



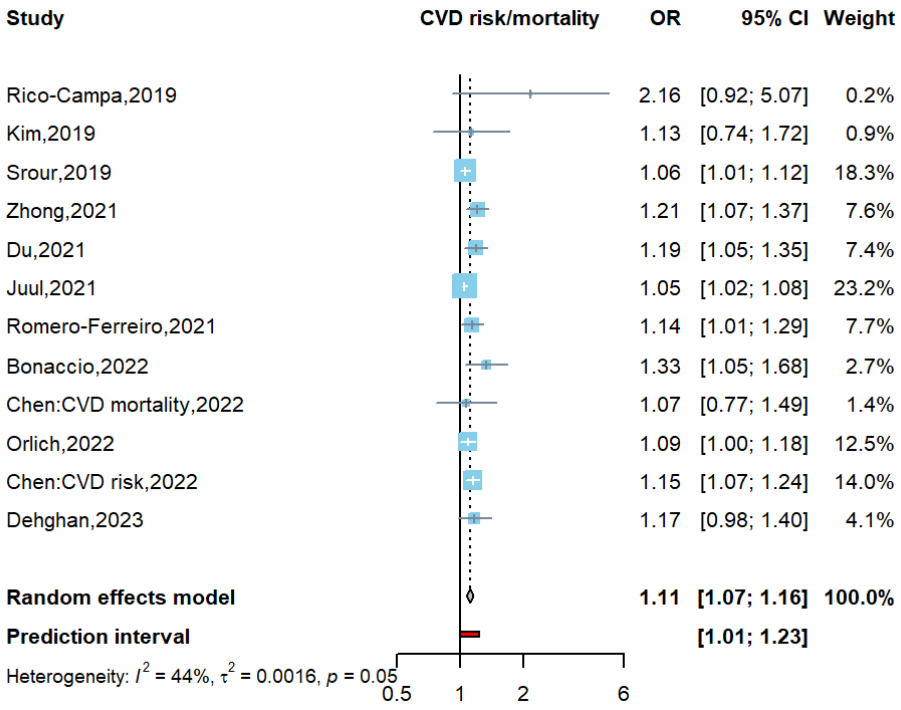
Supplemental Figure 11. Cancer—Prostate cancer



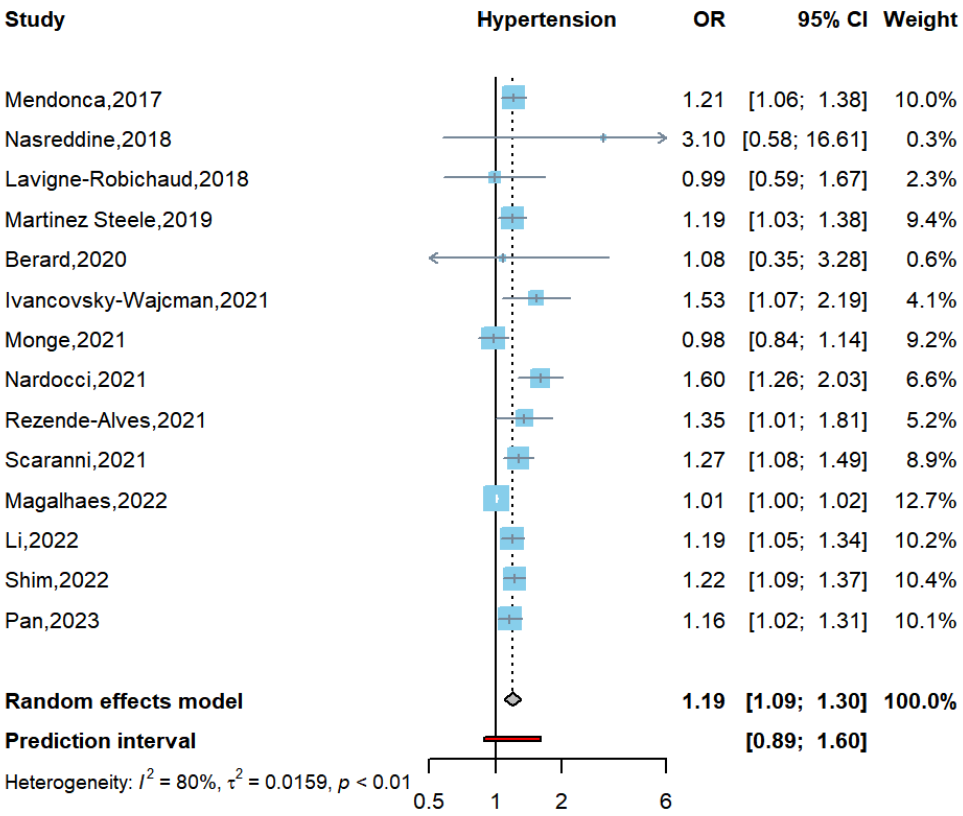
Supplemental Figure 12. Cancer—Pancreatic cancer



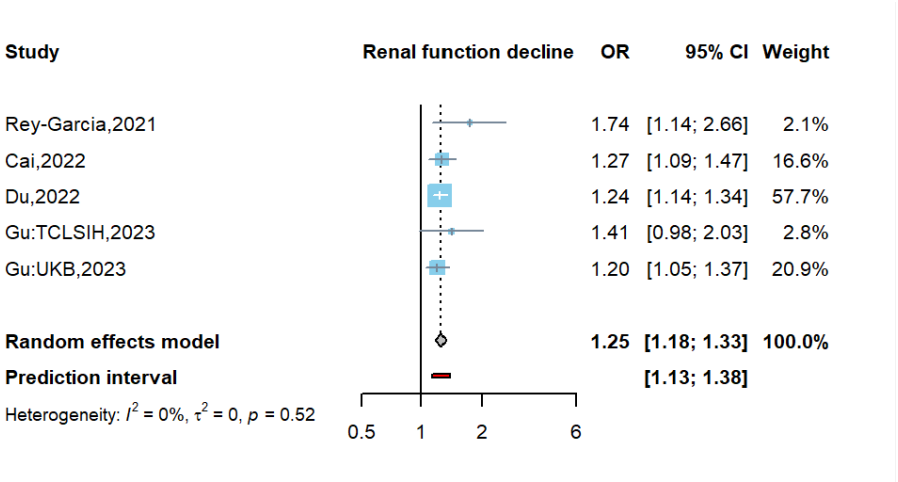
Supplemental Figure 13. Cancer—Overall cancer



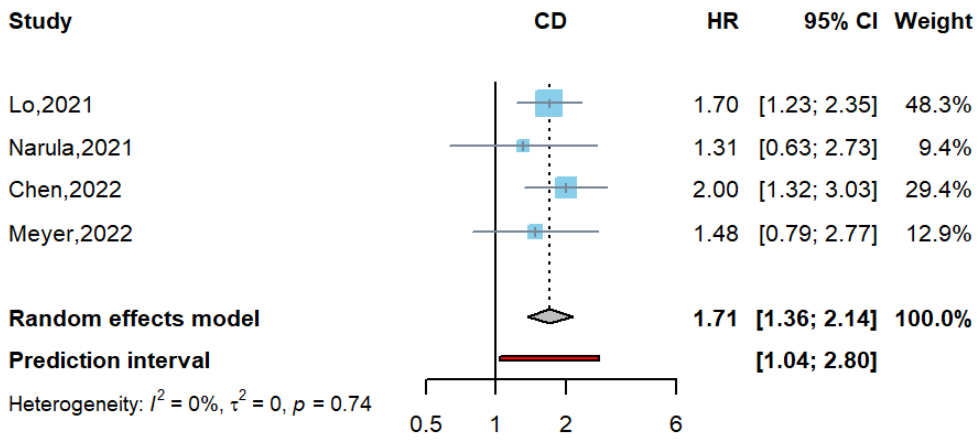
Supplemental Figure 14. Cardiovascular outcomes—Cardiovascular events



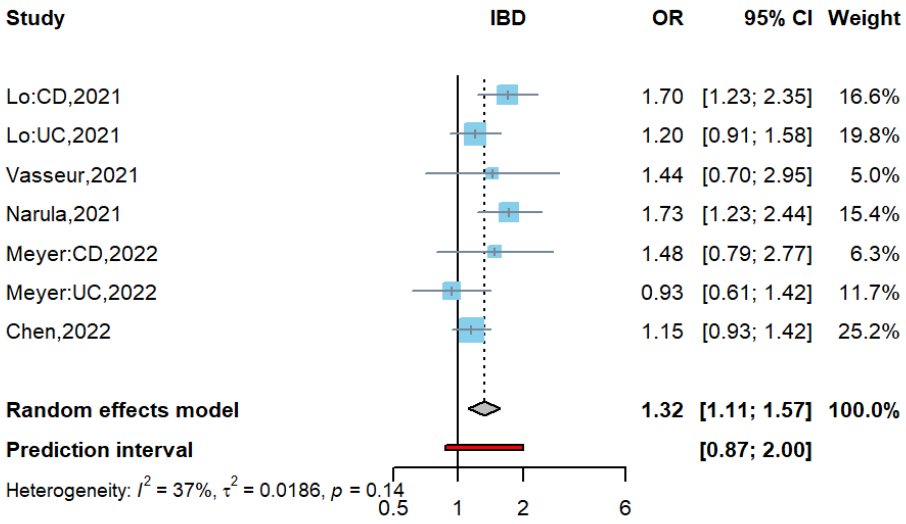
Supplemental Figure 15. Cardiovascular outcomes—Hypertension



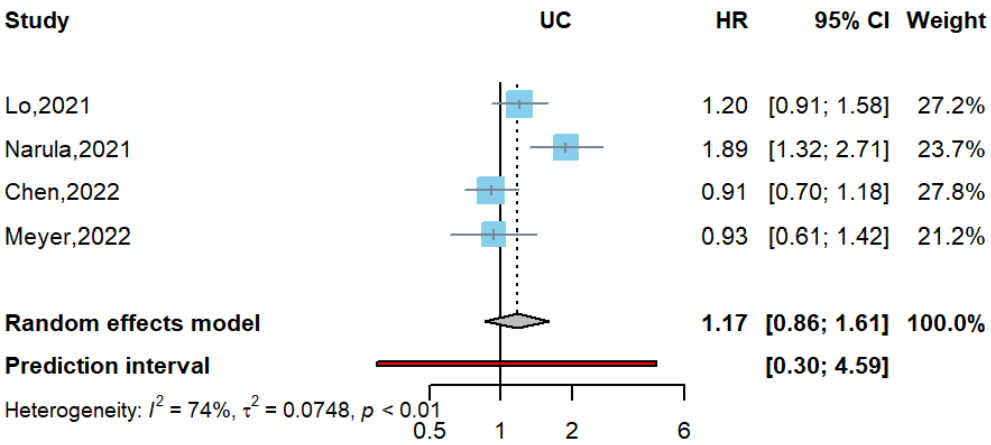
Supplemental Figure 16. Liver, kidney and gastrointestinal diseases—Renal function decline



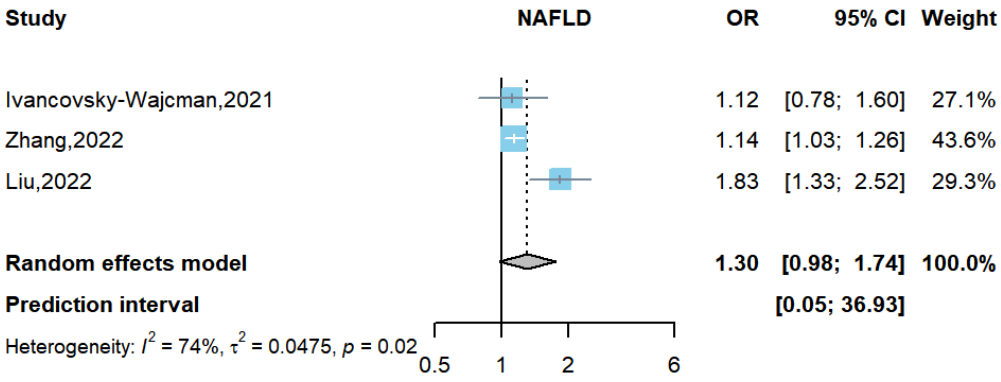
Supplemental Figure 17. Liver, kidney and gastrointestinal diseases—Crohn's disease



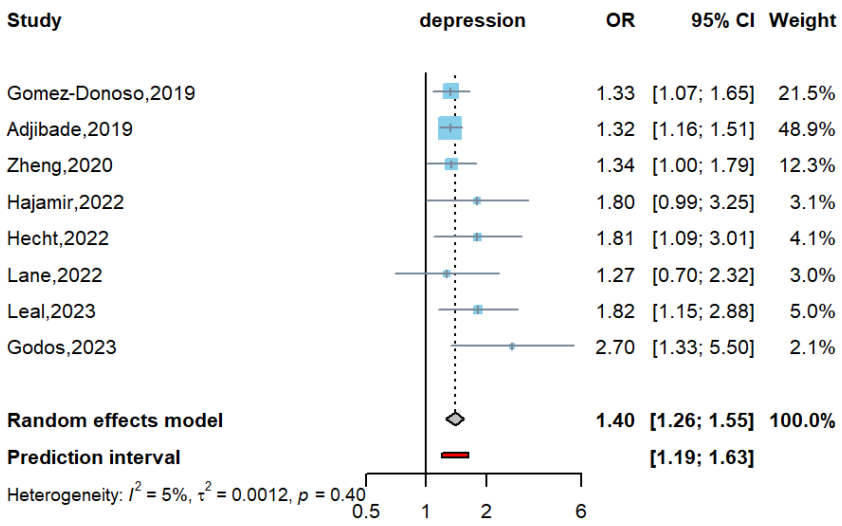
Supplemental Figure 18. Liver, kidney and gastrointestinal diseases—Inflammatory bowel disease



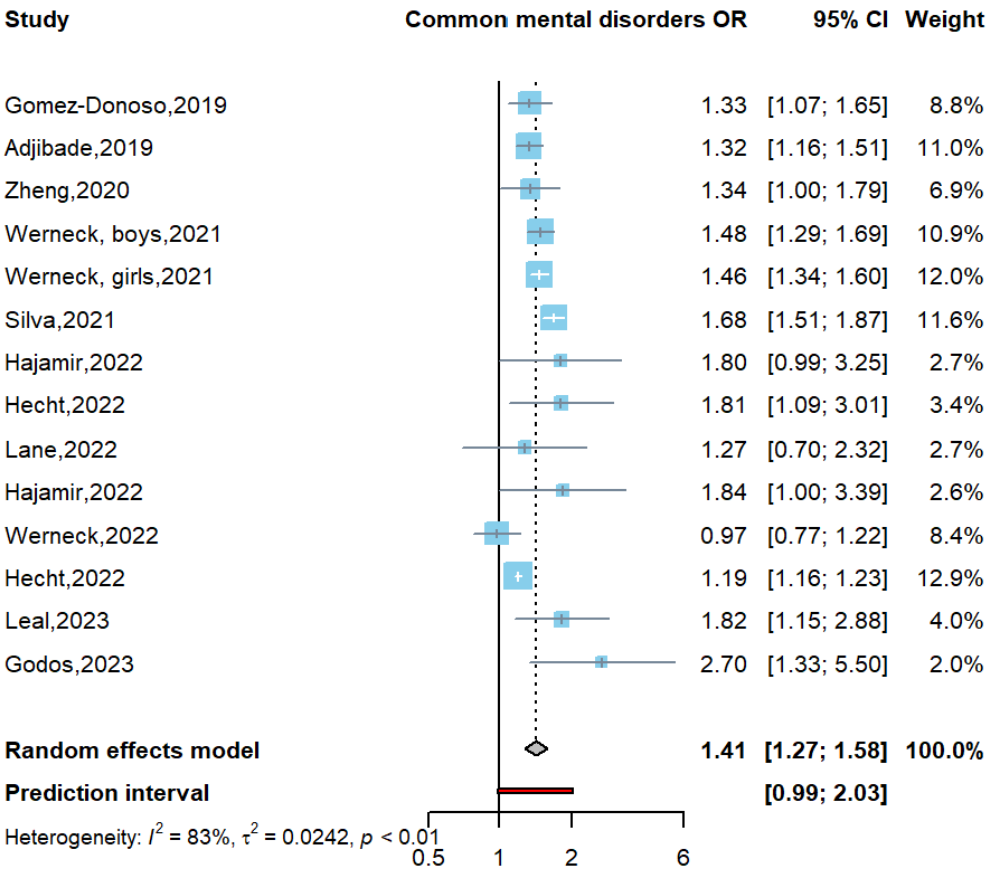
Supplemental Figure 19. Liver, kidney and gastrointestinal diseases—Ulcerative colitis



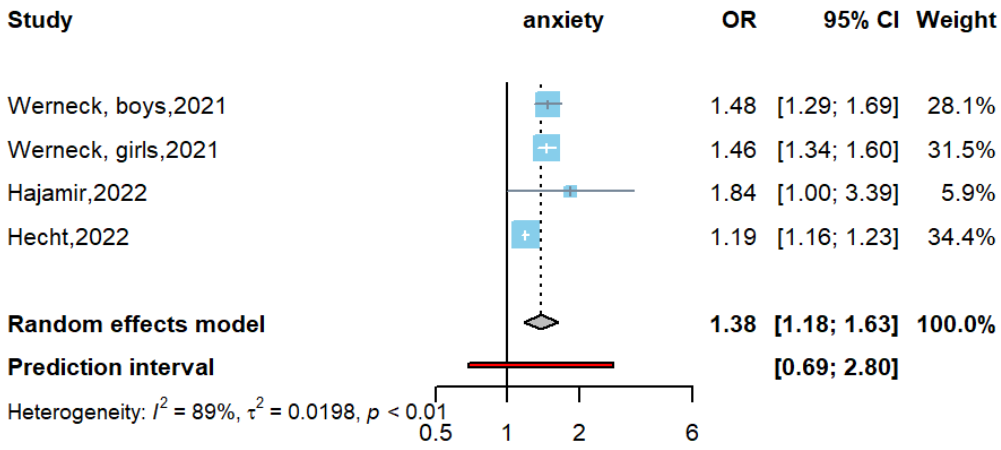
Supplemental Figure 20. Liver, kidney and gastrointestinal diseases—Non-alcoholic fatty liver disease



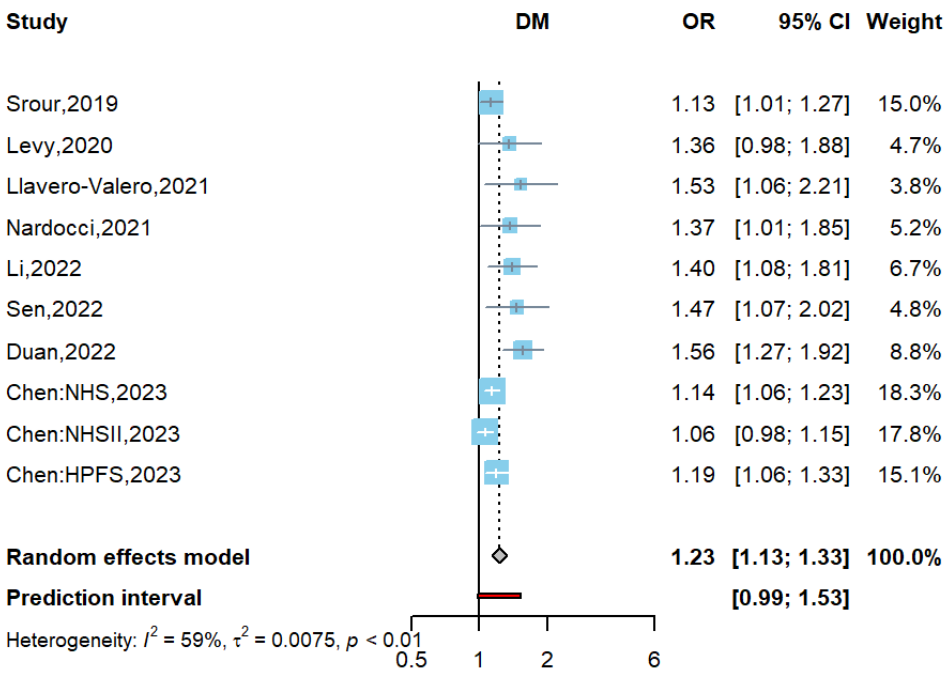
Supplemental Figure 21. Mental health—Depression



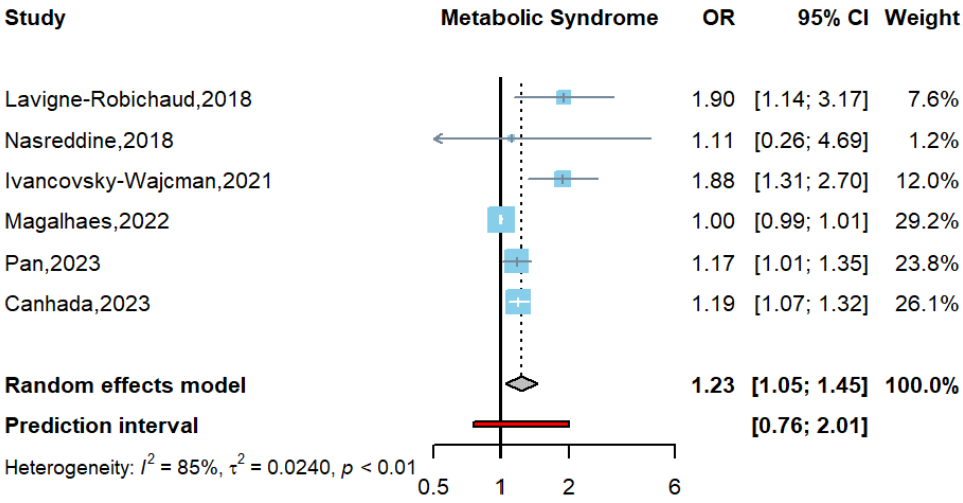
Supplemental Figure 22. Mental health—Common mental disorders



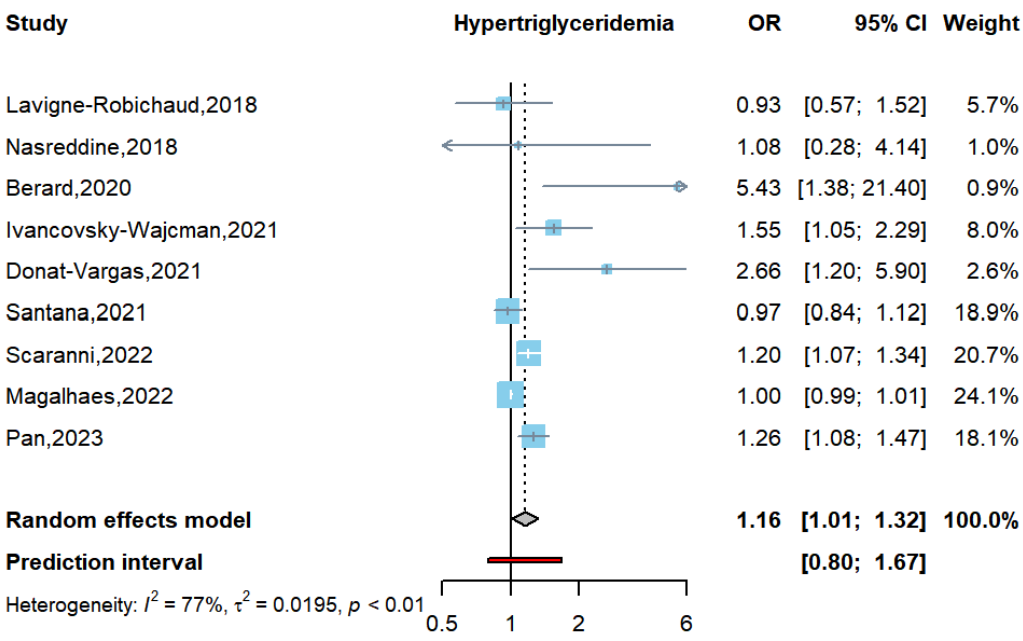
Supplemental Figure 23. Mental health—Anxiety



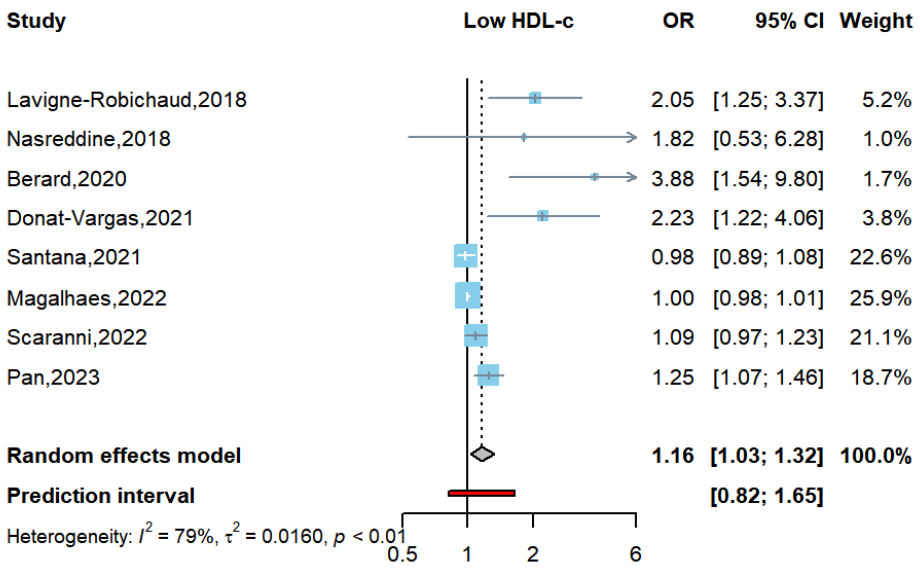
Supplemental Figure 24. Metabolic disease—Diabetes



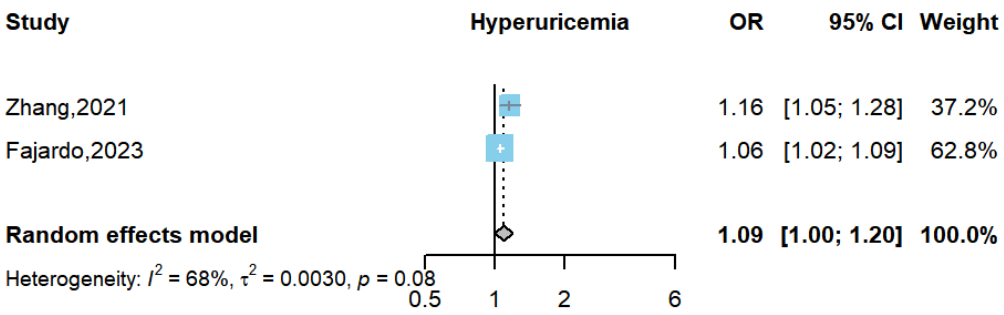
Supplemental Figure 25. Metabolic disease—Metabolic syndrome



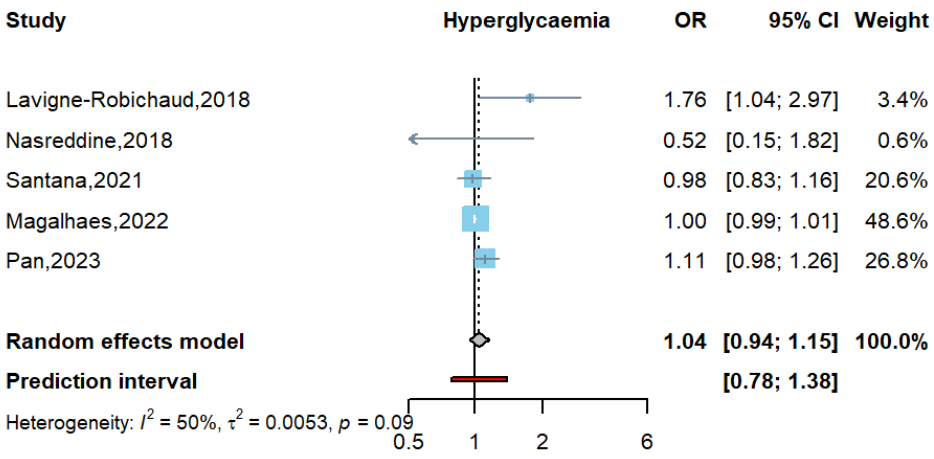
Supplemental Figure 26. Metabolic disease—Hypertriglyceridemia



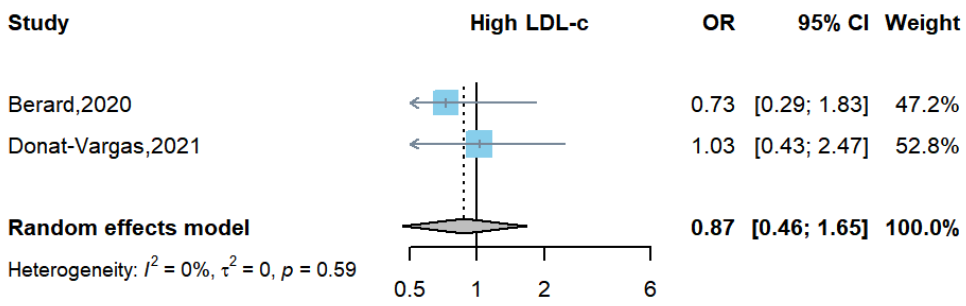
Supplemental Figure 27. Metabolic disease—Low HDL cholesterol



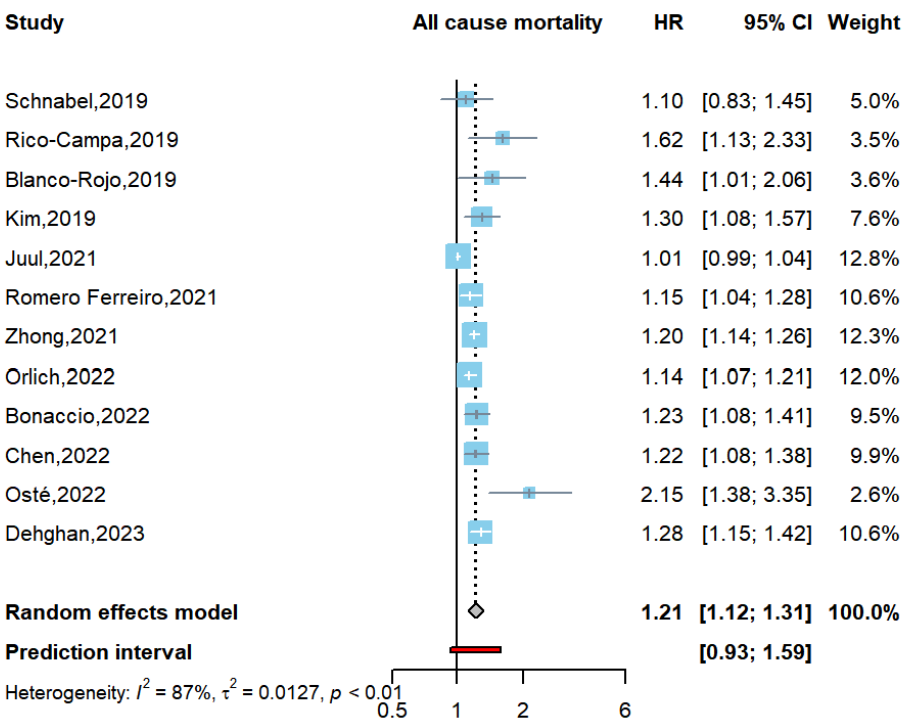
Supplemental Figure 28. Metabolic disease—Hyperuricemia



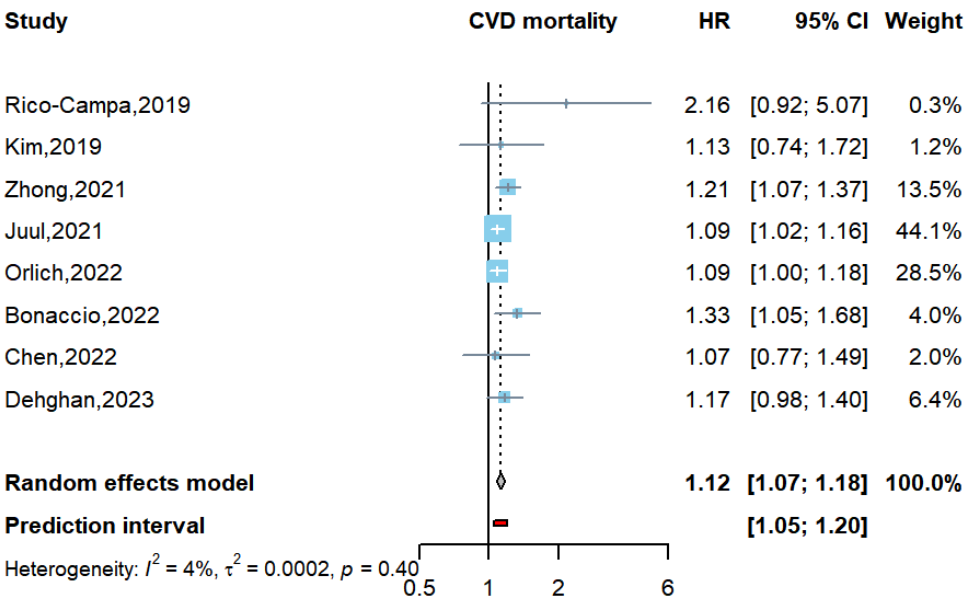
Supplemental Figure 29. Metabolic disease—Hyperglycemia



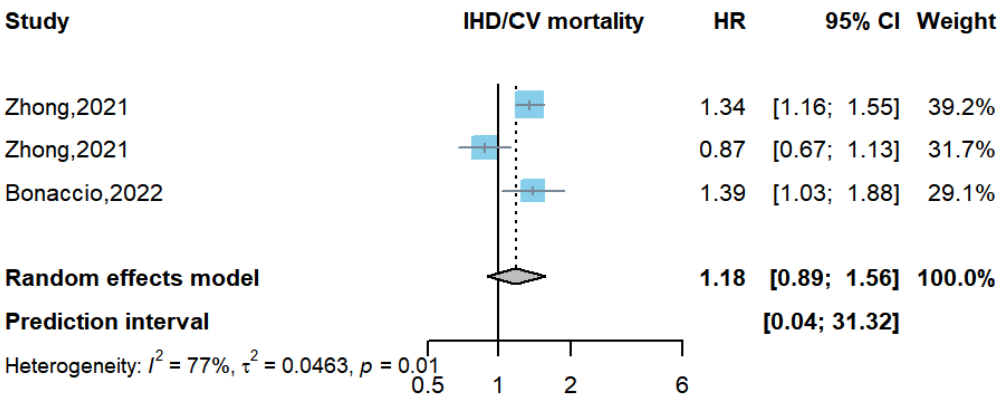
Supplemental Figure 30. Metabolic disease—High LDL cholesterol



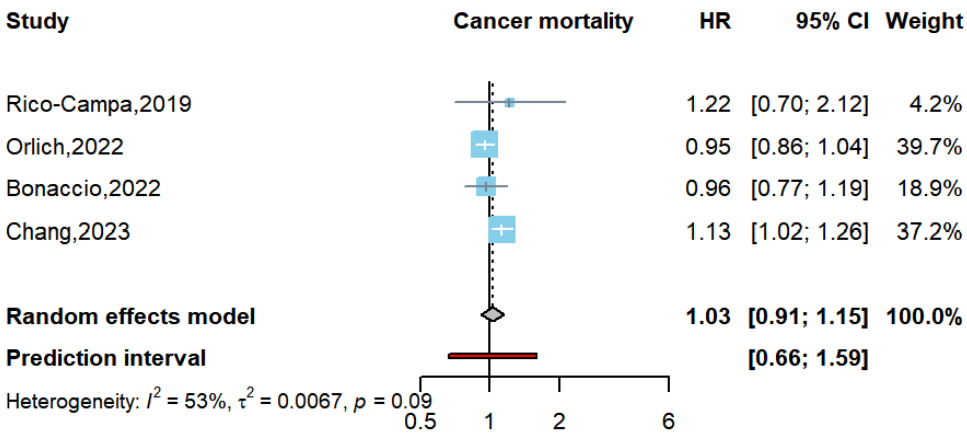
Supplemental Figure 31. Mortality—All cause mortality



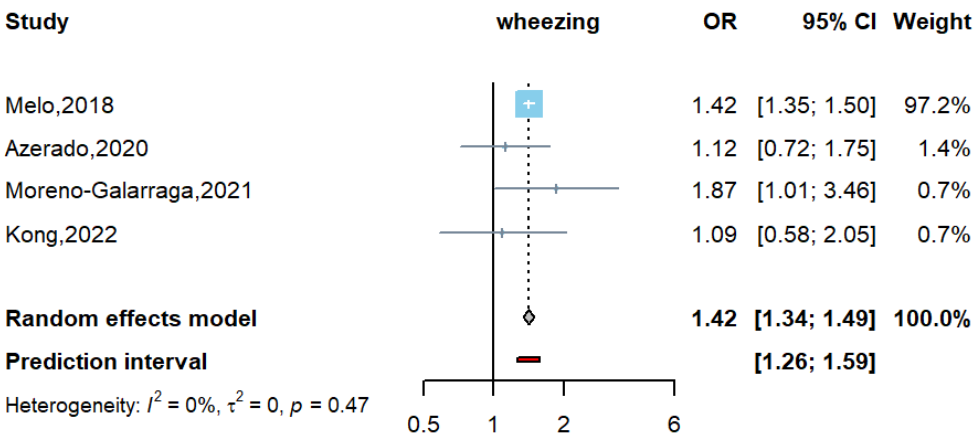
Supplemental Figure 32. Mortality—Cardiovascular mortality



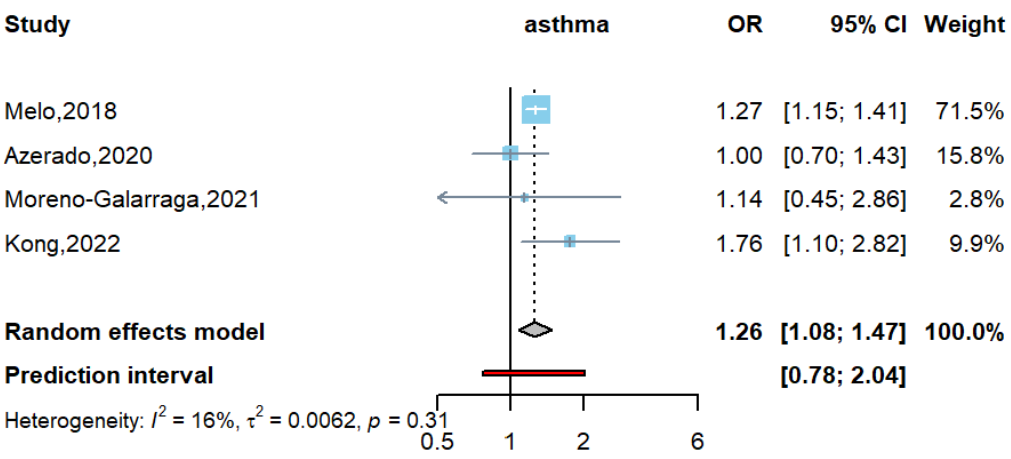
Supplemental Figure 33. Mortality—Ischemic heart disease/cerebrovascular disease mortality



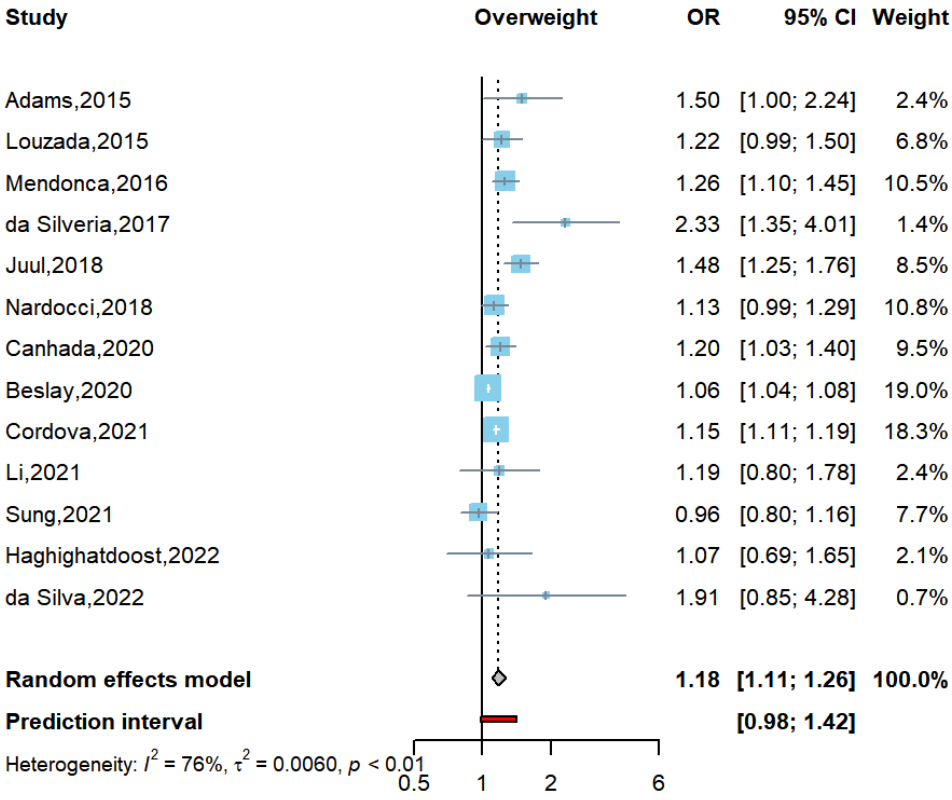
Supplemental Figure 34. Mortality—Cancer mortality



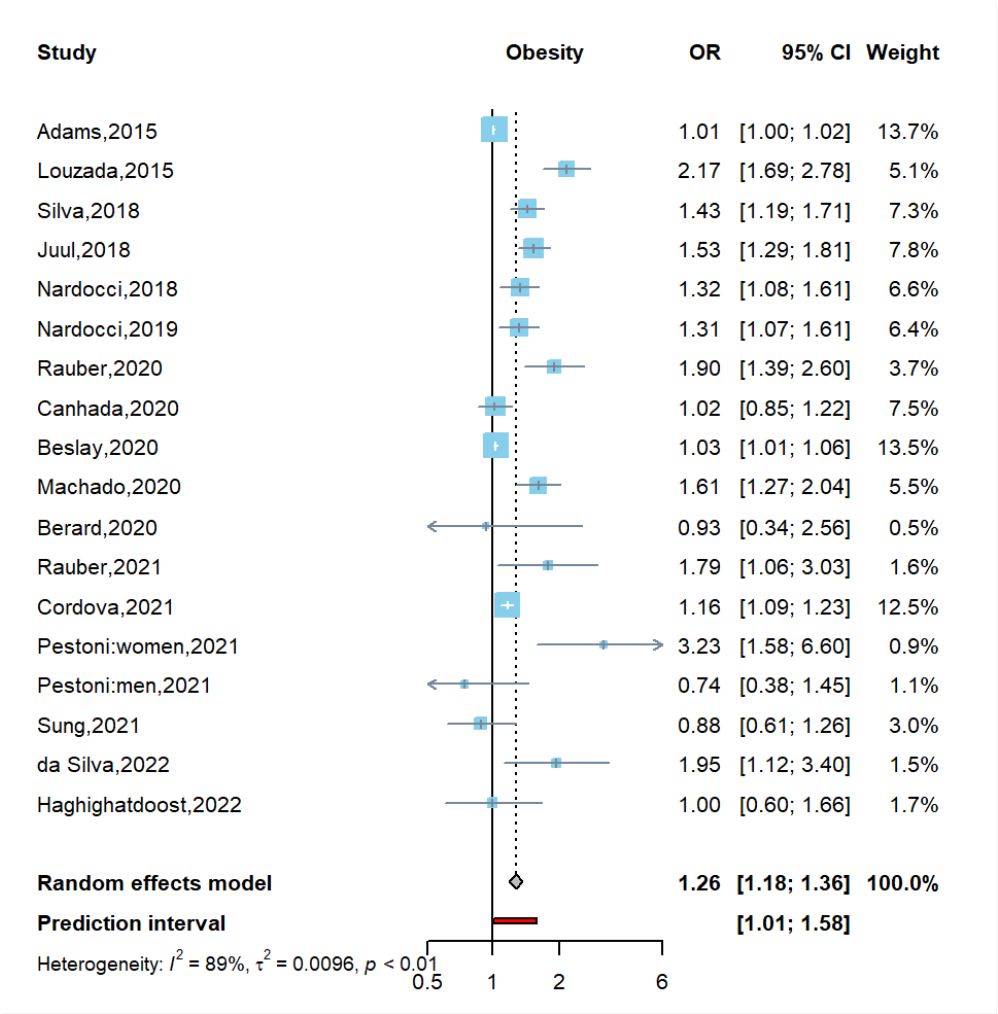
Supplemental Figure 35. Respiratory diseases—Wheezing



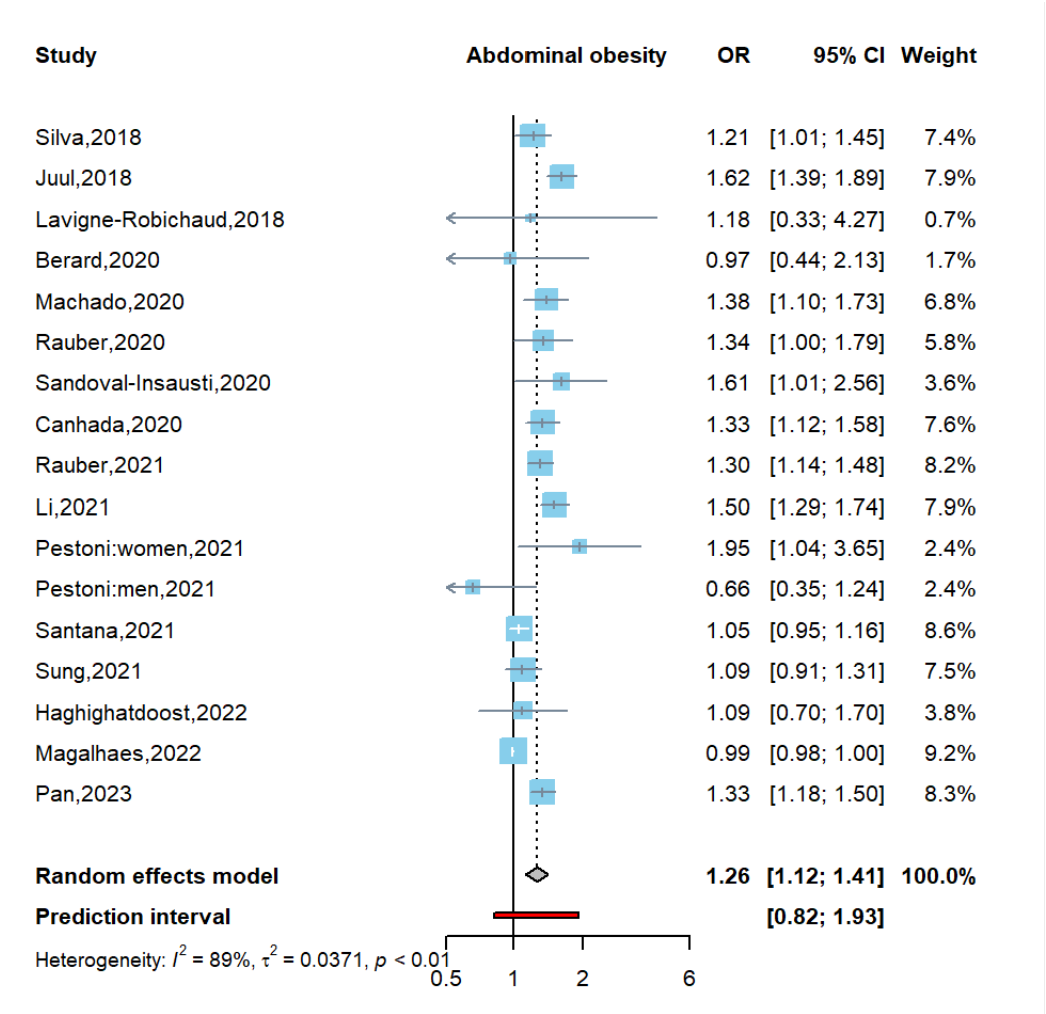
Supplemental Figure 36. Respiratory diseases—Asthma



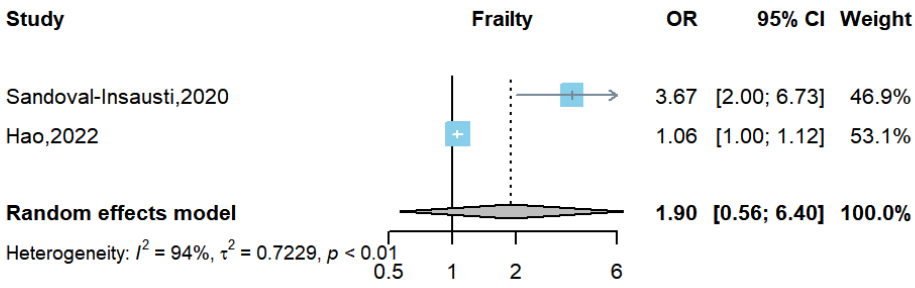
Supplemental Figure 37. Other outcomes—Overweight



Supplemental Figure 38. Other outcomes—Obesity



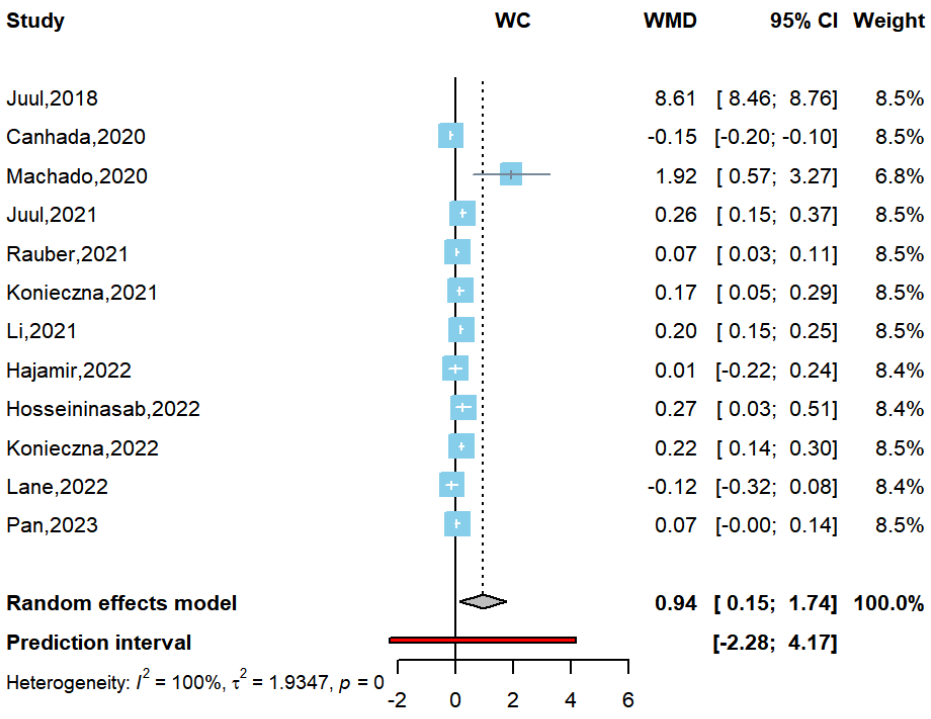
Supplemental Figure 39. Other outcomes—Abdominal obesity



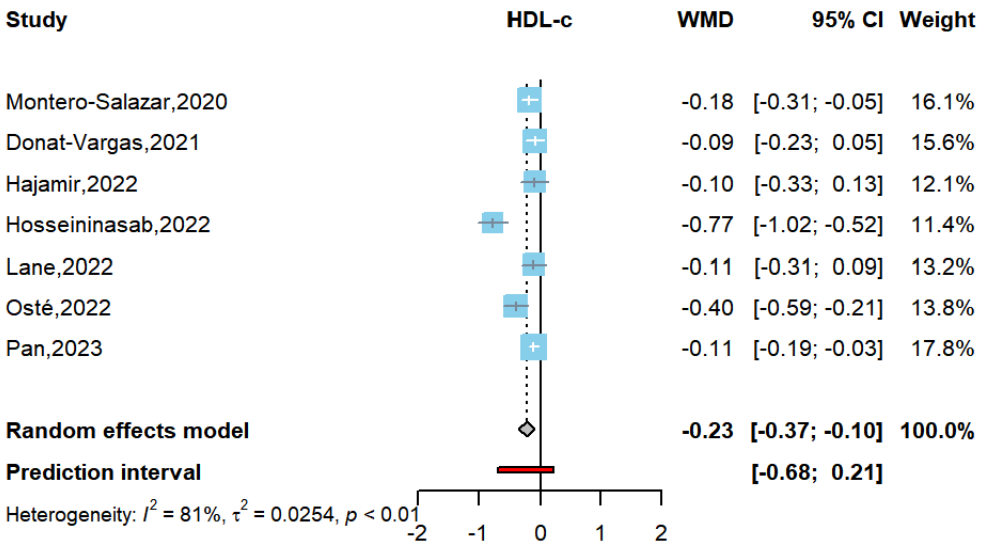
Supplemental Figure 40. Other outcomes—Frailty


Study
BMI
WMD
95% CI
Weight
Louzada,2015 0.95 [0.43; 1.47] 2.0%
Mendonca,2016 0.10 [0.00; 0.20] 2.1%
Mendonca,2017 -0.10 [-0.23; 0.03] 2.1%
Juul,2018 1.80 [1.79; 1.81] 2.1%
Fiolet,2018 0.00 [-0.08; 0.08] 2.1%
Rico-Campa,2019 0.50 [0.36; 0.64] 2.1%
Srour,2019 0.20 [0.12; 0.28] 2.1%
Gomez-Donoso,2019 0.60 [0.44; 0.76] 2.1%
Levy,2020 1.10 [0.94; 1.26] 2.1%
Machado,2020 0.97 [0.43; 1.51] 2.0%
Canhada,2020 0.00 [-0.24; 0.24] 2.1%
Alonso-Pedrero,2020 0.40 [-0.19; 0.99] 2.0%
Beslay,2020 0.10 [0.02; 0.18] 2.1%
Llavero-Valero,2021 0.50 [0.38; 0.62] 2.1%
Ivancovsky-Wajcman,2021 0.50 [-0.26; 1.26] 1.9%
Monge,2021 0.70 [0.52; 0.88] 2.1%
Juul,2021 1.50 [0.96; 2.04] 2.0%
Rauber,2021 0.09 [0.05; 0.13] 2.1%
Konieczna,2021 0.60 [0.13; 1.07] 2.0%
Li,2021 0.30 [0.12; 0.48] 2.1%
Rey-Garcia,2021 0.50 [-0.04; 1.04] 2.0%
Solans,2021 0.10 [-0.42; 0.62] 2.0%
Whyte,2021 0.50 [-1.49; 2.49] 1.4%
Orlich,2022 3.67 [3.54; 3.80] 2.1%
Duan,2022 1.10 [1.01; 1.19] 2.1%
Shim,2022 0.20 [0.03; 0.37] 2.1%
Meyer,2022 0.00 [-0.04; 0.04] 2.1%
Asgari,2022 -0.07 [-0.38; 0.24] 2.1%
Bonaccio,2022 -0.60 [-0.77; -0.43] 2.1%
Cai,2022 0.00 [-0.08; 0.08] 2.1%
Kinany,2022 -0.10 [-0.52; 0.32] 2.0%
Hajamir,2022 -0.47 [-1.51; 0.57] 1.8%
Hosseininasab,2022 -0.68 [-0.79; -0.57] 2.1%
Kityo,2022 -0.40 [-0.40; -0.40] 2.1%
Konieczna,2022 0.80 [0.52; 1.08] 2.1%
Li,2022 1.50 [1.41; 1.59] 2.1%
Li,2022 0.90 [0.70; 1.10] 2.1%
Li,2022 0.40 [0.22; 0.58] 2.1%
Osté,2022 0.70 [-0.20; 1.60] 1.9%
Wang:men,2022 0.70 [0.60; 0.80] 2.1%
Wang:women,2022 1.10 [0.98; 1.22] 2.1%
Wang,2022 0.90 [0.72; 1.08] 2.1%
Zhou,2022 1.69 [1.56; 1.82] 2.1%
Yisahak,2022 2.25 [1.55; 2.95] 2.0%
Dehghan,2023 3.40 [3.32; 3.48] 2.1%
Goncalves,2023 0.10 [-0.14; 0.34] 2.1%
Leal,2023 1.20 [0.73; 1.67] 2.0%
Weinstein,2023 -0.70 [-1.16; -0.24] 2.0%
Zhong,2023 2.20 [2.12; 2.28] 2.1%
Random effects model 0.65 [0.25; 1.05] 100.0%
Prediction interval [-2.25; 3.55]
Heterogeneity: I^2 = 100%, τ^2 = 2.0343, p = 0
-2
-1
0
1
2

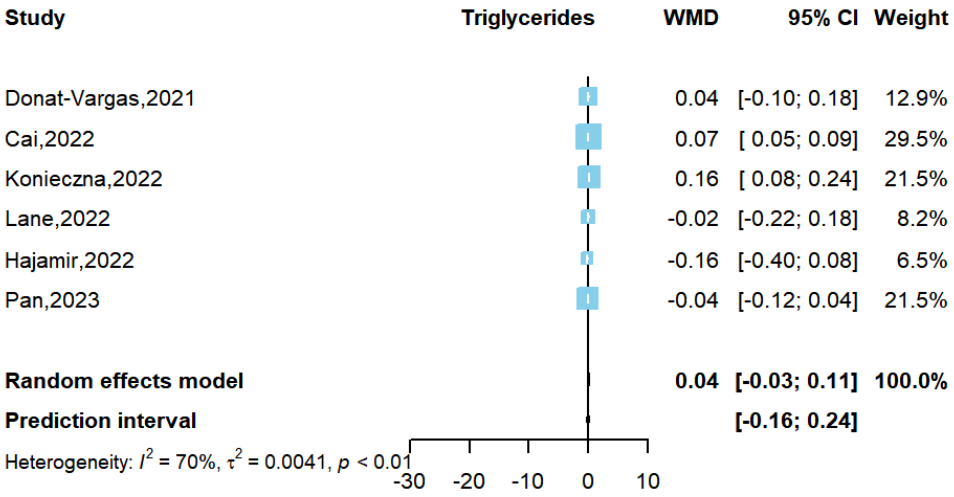
Supplemental Figure 41. Blood pressure and cardiometabolic biomarkers—Body Mass Index



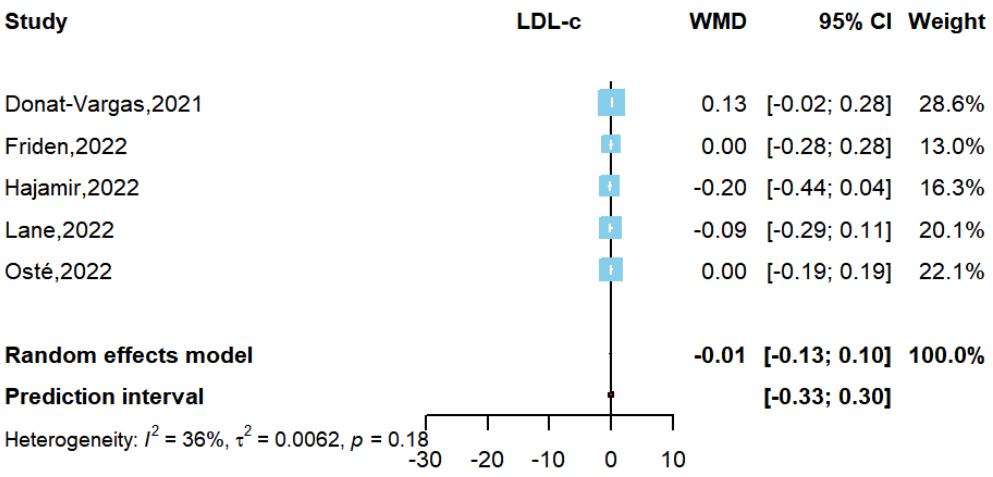
Supplemental Figure 42. Blood pressure and cardiometabolic biomarkers—Waist circumference



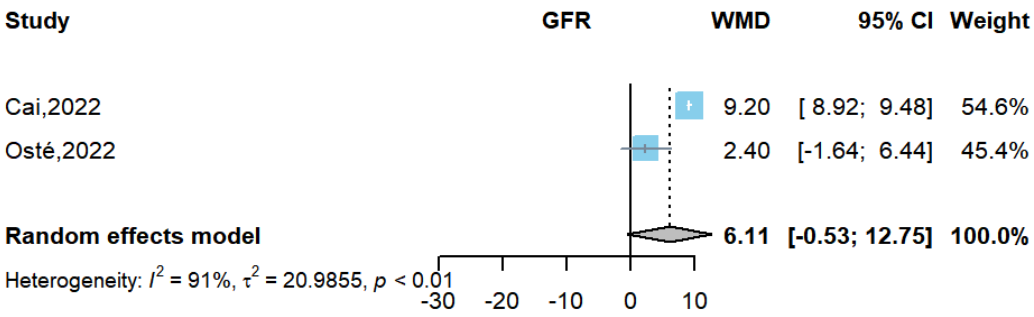
Supplemental Figure 43. Blood pressure and cardiometabolic biomarkers—HDL cholesterol



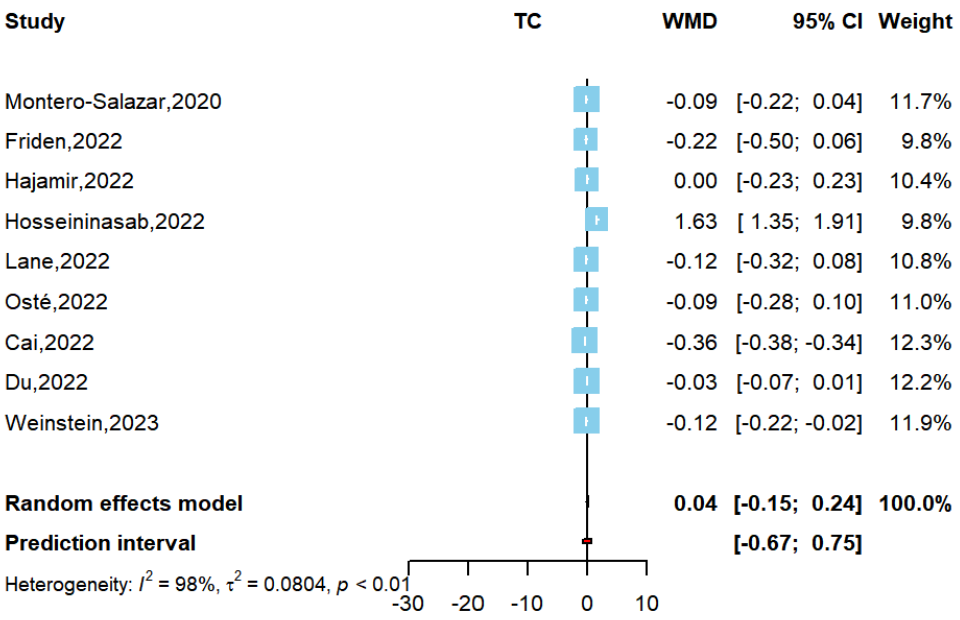
Supplemental Figure 44. Blood pressure and cardiometabolic biomarkers—Triglycerides



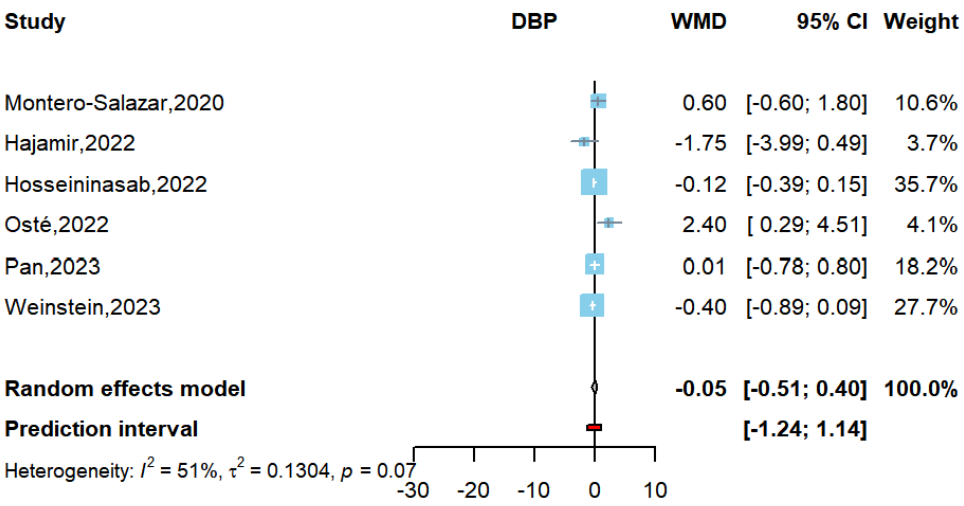
Supplemental Figure 45. Blood pressure and cardiometabolic biomarkers—LDL cholesterol



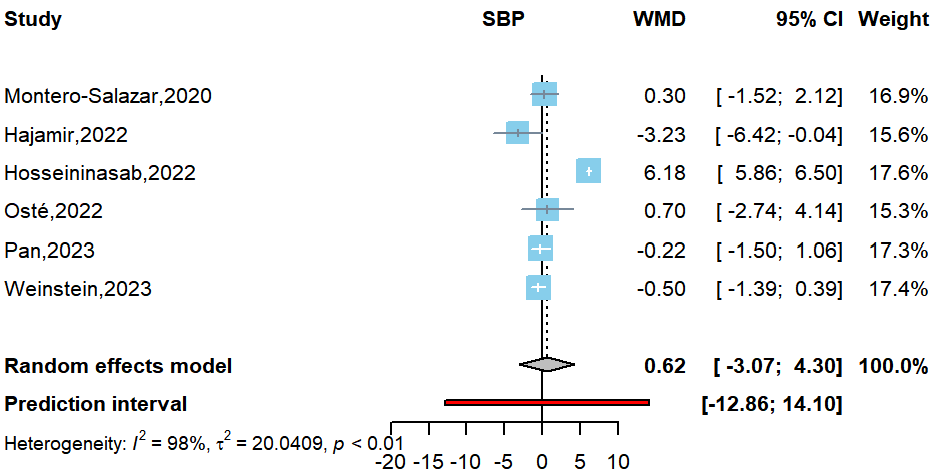
Supplemental Figure 46. Blood pressure and cardiometabolic biomarkers—Glomerular filtration rate



Supplemental Figure 47. Blood pressure and cardiometabolic biomarkers—Total cholesterol



Supplemental Figure 48. Blood pressure and cardiometabolic biomarkers—Diastolic blood pressure



Supplemental Figure 49. Blood pressure and cardiometabolic biomarkers—Systolic blood pressure

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