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Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;359:j5024 http://dx.doi.org/10.1136/bmj.j5024

Accepted: 16 October 2017

ABSTRACT

OBJECTIVES

To evaluate the existing evidence for associations between coffee consumption and multiple health outcomes.

DESIGN

Umbrella review of the evidence across meta-analyses of observational and interventional studies of coffee consumption and any health outcome.

DATA SOURCES

PubMed, Embase, CINAHL, Cochrane Database of Systematic Reviews, and screening of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Meta-analyses of both observational and interventional studies that examined the associations between coffee consumption and any health outcome in any adult population in all countries and all settings. Studies of genetic polymorphisms for coffee metabolism were excluded.

RESULTS

The umbrella review identified 201 meta-analyses of observational research with 67 unique health outcomes and 17 meta-analyses of interventional research with nine unique outcomes. Coffee consumption was more often associated with benefit than harm for a range of health outcomes across exposures including high versus low, any versus none, and one extra cup a day. There was evidence of a non-linear association between consumption and some outcomes, with summary estimates indicating largest relative risk reduction at intakes of three to four cups a day versus none, including all cause mortality (relative risk 0.83, 95% confidence interval 0.83 to 0.88), cardiovascular mortality (0.81, 0.72 to 0.90), and cardiovascular disease (0.85, 0.80 to 0.90). High versus low consumption was associated with an 18% lower risk of incident cancer (0.82, 0.74 to 0.89). Consumption was also associated with a lower risk of several specific cancers and neurological, metabolic, and liver conditions. Harmful associations were largely nullified by adequate adjustment for smoking, except in pregnancy, where high versus low/no consumption was associated with low birth weight (odds ratio 1.31, 95% confidence interval 1.03 to 1.67), preterm birth in the first (1.22, 1.00 to 1.49) and second (1.12, 1.02 to 1.22) trimester, and pregnancy loss (1.46, 1.06 to 1.99). There was also an association between coffee drinking and risk of fracture in women but not in men.

CONCLUSION

Coffee consumption seems generally safe within usual levels of intake, with summary estimates indicating largest risk reduction for various health outcomes at three to four cups a day, and more likely to benefit health than harm. Robust randomised controlled trials are needed to understand whether the observed associations are causal. Importantly, outside of pregnancy, existing evidence suggests that coffee could be tested as an intervention without significant risk of causing harm. Women at increased risk of fracture should possibly be excluded.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Coffee is highly consumed worldwide and could have positive health benefits, especially in chronic liver disease

Beneficial or harmful associations of drinking coffee seem to vary between health outcomes of interest

Understanding associations of coffee and health is important, especially in relation to exploring harmful associations, before interventional research is conducted

WHAT THIS STUDY ADDS

Coffee drinking seems safe within usual patterns of consumption, except during pregnancy and in women at increased risk of fracture

Existing evidence is observational and of lower quality, and randomised controlled trials are needed

A future randomised controlled trial in which the intervention is increasing coffee consumption would be unlikely to result in significant harm to participants

Introduction

Coffee is one of the most commonly consumed beverages worldwide.[1] As such, even small individual health effects could be important on a population scale. There have been mixed conclusions as to whether coffee consumption is beneficial or harmful to health, and this varies between outcomes.[2] Roasted coffee is a complex mixture of over 1000 bioactive compounds,[3] some with potentially therapeutic antioxidant, anti-inflammatory, antifibrotic, or anticancer effects that provide biological plausibility for recent epidemiological associations. Key active compounds include caffeine, chlorogenic acids, and the diterpenes, cafestol and kahweol. The biochemistry of coffee has been documented extensively elsewhere.[4] Coffee undergoes a chemical metamorphosis from the unroasted green bean, and the type of bean (Arabica versus Robusta), degree of roasting, and preparation method including coffee grind setting and brew type, will all have an influence on the biochemical composition of the final cup.[5-7] An individual's genotype and gut microbiome will then determine the bioavailability and type of coffee metabolites to which that individual is exposed.[8]

Existing research has explored the associations between coffee as an exposure and a range of outcomes including all cause mortality, cancer, and diseases

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of the cardiovascular, metabolic, neurological, musculoskeletal, gastrointestinal, and liver systems, as well as outcomes associated with pregnancy. Most of this research has been observational in design, relying on evidence from cross sectional, case-control, or cohort studies, and often summarised by outcome through systematic review and meta-analysis. We have previously explored the relation between coffee consumption and liver cirrhosis[9] and hepatocellular carcinoma[10] and found significant beneficial associations for both. Observational evidence can suggest association but is unable to make causative claims, though methods based on Mendelian randomisation are less prone to confounding. Interventional research, ideally in the form of randomised controlled trials, is essential before we can fully understand coffee's potential to prevent specific health outcomes.

Before an interventional approach is taken, however, it is important to systematically assess the totality of higher level evidence of the effects of coffee consumption on all health outcomes. This approach can help contextualise the magnitude of the association across health outcomes and importantly assess the existing research for any harm that could be associated with increased consumption. To assimilate the vast amount of research available on coffee consumption and health outcomes, we performed an umbrella review of existing meta-analyses.

Methods

Umbrella review methods

Umbrella reviews systematically search, organise, and evaluate existing evidence from multiple systematic reviews and/or meta-analyses on all health outcomes associated with a particular exposure.[11] We conducted a review of coffee consumption and multiple health outcomes by systematically searching for meta-analyses in which coffee consumption was all or part of the exposure of interest or where coffee consumption had been part of a subgroup analysis. Consumption, usually measured by cups a day, lends itself to combined estimates of effect in meta-analyses and we decided to include only meta-analyses in the umbrella review. Specifically, we excluded systematic reviews without meta-analysis.

Literature search

We searched PubMed, Embase, CINAHL, and the Cochrane Database of Systematic Reviews from inception to July 2017 for meta-analyses of observational or interventional studies that investigated the association between coffee consumption and any health outcome. We used the following search strategy: (coffee OR caffeine) AND (systematic review OR meta-analysis) using truncated terms for all fields, and following the SIGN guidance recommended search terms for systematic reviews and meta-analyses.[12] Two researchers (RP and OJK) independently screened the titles and abstracts and selected articles for full text review. They then independently reviewed full text articles for eligibility. A third researcher, PR, arbitrated any differences that could not be resolved by consensus. We also performed a manual search of the references of eligible articles.

Eligibility criteria and data extraction

Articles were eligible if they were meta-analyses and had been conducted with systematic methods. We included meta-analyses of both observational (cohort, case-control, and cross sectional with binary outcomes) and interventional studies (randomised controlled trials). Meta-analyses were included when they pooled any combination of relative risks, odds ratios, relative rates, or hazard ratios from studies comparing the same exposure with the same health outcome. Articles were included if the coffee exposure was in any adult population of any ethnicity or sex in all countries and all settings. Participants could be healthy or have pre-existing illness, be pregnant, and be habitual or non-habitual coffee drinkers. Articles were also included when the exposure was total coffee or coffee separated into caffeinated and decaffeinated status. We excluded meta-analyses of total caffeine exposure and health outcomes unless we could extract caffeine exposure from coffee separately from a subgroup analysis. Coffee contains numerous biologically active ingredients that can interact to produce unique health effects that could be different to effects of caffeine from other sources. Additionally, we were interested in coffee, rather than caffeine, as a potential intervention in a future randomised controlled trial. All health outcomes for which coffee consumption had been investigated as the exposure of interest were included, except studies of genetic polymorphisms for coffee metabolism. We included any study with comparisons of coffee exposure, including high versus low, any versus none, and any linear or non-linear dose-responses. If an article presented separate meta-analyses for more than one health outcome, we included each of these separately.

RP and OJK independently extracted data from eligible articles. From each meta-analysis, they extracted the first author, journal, year of publication, outcome(s) of interest, populations, number of studies, study design(s), measure(s) of coffee consumption, method(s) of capture of consumption measurement, consumption type(s), and sources of funding. For each eligible article they also extracted study specific exposure categories as defined by authors, risk estimates and corresponding confidence intervals, number of cases and controls (case-control studies), events, participant/person years and length of follow-up (cohort studies) or numbers in intervention and control groups (randomised controlled trials), type of risk used for pooling, and type of effect model used in the meta-analysis (fixed or random). When a meta-analysis considered a dose-response relation and published a P value for non-linearity this was also extracted. Finally, we extracted any estimate of variance between studies (τ^2), estimates of the proportion of variance reflecting true differences in effect size (I^2), and any

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presented measure of publication bias. Any difference in extracted data between the two researchers was resolved by consensus.

Assessment of methodological quality of included studies and quality of evidence

We assessed methodological quality of meta-analyses using AMSTAR,[13] a measurement tool to assess systematic reviews. AMSTAR has been shown to be a reliable and valid tool for quality assessment of systematic reviews and meta-analyses of both interventional and observational research.[13 14] AMSTAR includes ratings for quality in the search, analysis, and transparency of a meta-analysis. For the rating item for methodological quality in the analysis, we downgraded any study that had used a fixed rather than a random effects model for producing a summary estimate. We considered the random effects model the most appropriate to be used in pooling estimates because the heterogeneity in study designs, populations, methods of coffee preparation, and cup sizes meant we would not expect a single true effect size common to all studies.

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) working group classification to assess the quality of evidence for each outcome included in the umbrella review.[15] The GRADE approach categorises evidence from systematic reviews and meta-analyses into "high," "moderate," "low," or "very low" quality. Study design dictates baseline quality of the evidence but other factors can decrease or increase the quality level. For example, unexplained heterogeneity or high probability of publication bias could decrease the quality of the evidence, and a large magnitude of effect or dose-response gradient could increase it.

Method of analysis

We reanalysed each meta-analysis using the DerSimonian and Laird random effects model, which takes into account variance between and within studies.[16] We did this through extraction of exposure and outcome data, as published in each meta-analysis article, when these were available in sufficient detail. We did not review the primary study articles included in each meta-analysis. As is conventional for risk ratios, we computed the summary estimates using the log scale to maintain symmetry in the analysis and took the exponential to return the result to the original metric. We produced the τ^2 statistic as an estimate of true variation in the summary estimate and the I^2 statistic as an estimate of proportion of variance reflecting true differences in effect size. We also calculated an estimate for publication bias with Egger's regression test[17] for any reanalyses that included at least 10 studies. A P value <0.1 was considered significant for Egger's test. We did not reanalyse any of the dose-response meta-analyses because of the scarcity of published estimates for number of cases and controls/participants and estimates for each dose of coffee exposure needed for a dose-response analysis. When we were interested in the apparent effect modification by sex, we conducted a test of interaction using the method published by Altman and Bland.[18]

We constructed forest plots from the extracted and/or reanalysed data to display three categories of exposure for any health outcome (high versus low (or none), any (regular) versus none, and one extra cup a day (relative to none) in which that category of exposure was available. Each article presented a meta-analysis with one or more of these exposure categories or calculated combined estimates for a range of cups a day exposures for which a non-linear dose-response had been identified. A single health outcome per category of exposure was included in a forest plot representing the most recent study available. If two or more studies were published within the same 24 month period for the same category of exposure and same outcome, we selected the one with the highest number of cohort studies. We used a final tier of highest AMSTAR score if two studies published in the same period had the same number of cohort studies. When a meta-analysis included both cohort and case-control studies and when subgroup analysis was published by study design, we selected the cohort design subanalysis for inclusion in the summary forest plots or reanalysed when possible. This was deemed to represent the higher form of evidence as it was not affected by recall and selection bias and was less likely to be biased by reverse causality that can affect case-control studies. When linear dose-response analyses presented results for two or three extra cups a day we converted this to one extra cup a day by taking the square or cube root respectively (A Crippa, personal communication, 2017). We included heterogeneity, represented by the τ^2 statistic, and publication bias, represented by Egger's test. When we could not reanalyse data from a meta-analysis we included summary data as extracted from the meta-analysis article and whichever measure of heterogeneity or publication bias, if any, was available.

Patient involvement

This study was informed by feedback from a patient and public involvement focus group and from an independent survey of patients with chronic liver disease in secondary care. This preliminary work showed enthusiasm from patients in participating in a randomised controlled trial involving coffee as an intervention and in finding out more information about the wider benefits and potential harms of increasing coffee intake. Furthermore, the results of this umbrella review were also disseminated during a recent focus group session that had been arranged to gather opinions regarding the acceptability of qualitative research to investigate patterns of coffee drinking in people with non-alcoholic fatty liver disease.

Results

Figure 1 shows the results of the systematic search and selection of eligible studies. The search yielded 201 meta-analyses of observational research in 135

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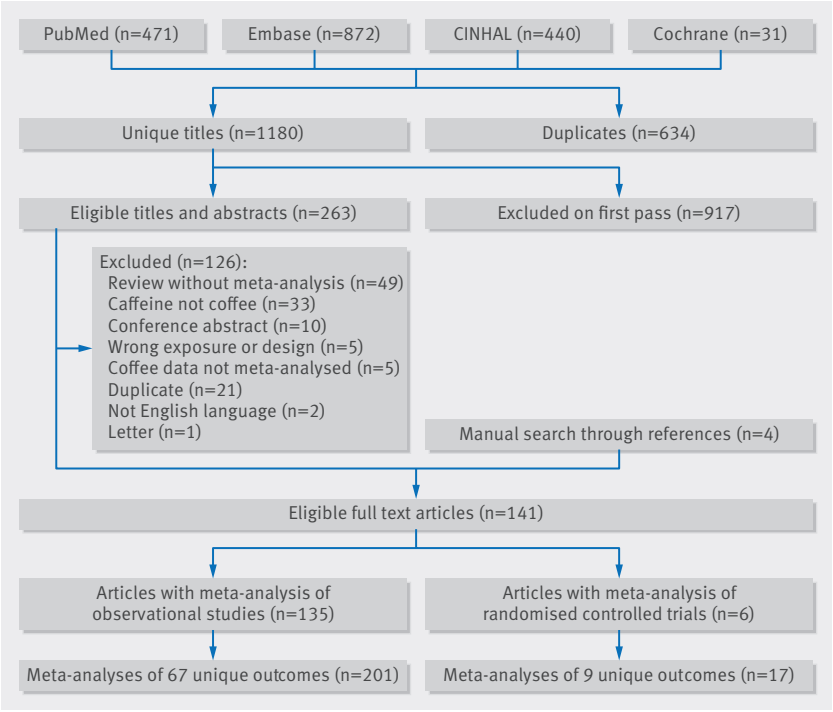
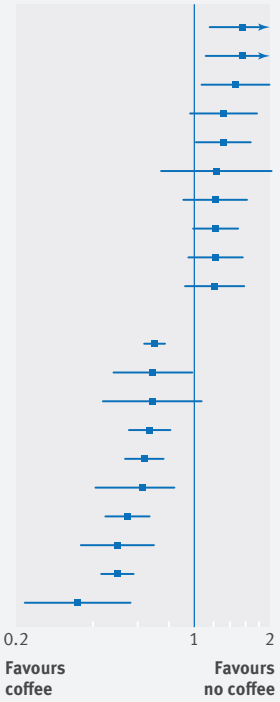


Fig 1 | Flowchart of selection of studies for inclusion in umbrella review on coffee consumption and health

articles with 67 unique outcomes and 17 meta-analyses of randomised-controlled trials in six articles with nine unique outcomes. The median number of meta-analyses per outcome for observational research was two (interquartile range 1-4, range 1-11). Twenty two outcomes had only a single meta-analysis. For meta-analyses of randomised controlled trials, outcomes were limited to systolic and diastolic blood pressure, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, and three outcomes related to pregnancy: preterm birth, small for gestational age, and birth weight. Figures 2-4 show summary data for the meta-analyses selected as the highest form of evidence for coffee consumption and each outcome for high versus low (or none) or any (regular) versus no consumption and one extra cup a day coffee consumption. These show risk estimates for each outcome from 10 most harmful associations to the 10 most beneficial associations. Full versions of the forest plots are available in appendix 1. Figure 5 shows the associations with consumption of decaffeinated coffee across the three exposure categories, and figures 6-9 show interventional exposures for coffee versus control for outcomes of blood pressure, lipids, and outcomes related to pregnancy. Risk estimates across different exposure categories for each outcome,

Outcome	No of events /total	Follow-up range (years)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful										
Acute leukaemia in childhood[87]	2453/4975	NA	1.57* (1.16 to 2.11)	6	0	6	0.06	55	ND	5
Lung cancer[46]	540/84 984	10-23	1.56* (1.12 to 2.17)	5	5	0	0.06	45	ND	3
Pregnancy loss[23]	12 311/155 831	NA	1.46* (1.06 to 1.99)	5	5	0	0.11	87	ND	5
Rheumatoid arthritis[74 75]	764/132 677	11-20	1.31 (0.97 to 1.77)	3	3	0	0.00	0	ND	4
Low birth weight[82]	2133/42 036	NA	1.31* (1.03 to 1.67)	2	2	0	0.00	0	ND	7
Lymphoma[39]	209/89 897	6-12	1.23 (0.75 to 2.02)	3	3	0	0.00	0	ND	5
Laryngeal cancer[59]	2596/NP	NP	1.22 (0.92 to 1.62)	8	1	7	0.10	74	ND	6
1st trimester preterm birth[83]	NP	NA	1.22*† (1.00 to 1.49)	NP	NP	NP	NP	NP	NP	3
3rd trimester preterm birth[83]	NP	NA	1.22*† (0.95 to 1.57)	NP	NP	NP	NP	NP	NP	3
Oral cleft malformation[85]	627/56 953	2	1.21* (0.92 to 1.59)	3	1	2	0.00	0	ND	2
10 most beneficial										
Type 2 diabetes[21]‡	45 335/1 109 272	1-24	0.70 (0.65 to 0.75)	27	27	0	0.01	50	0.05	7
Oral cancer[39]	1910/1 395 309	6-26	0.69 (0.48 to 0.99)	6	6	0	0.12	74	ND	5
Cirrhosis[63]	1785/130 305	NP	0.69* (0.44 to 1.07)	3	3	0	0.02	13	ND	7
Renal stones[66]	NP/126 382	NP	0.67 (0.56 to 0.81)	2	2	0	0.00	0	ND	6
Parkinson's disease[22]	2414/894 568	NP	0.64 (0.53 to 0.76)	7	7	0	0.01	16	ND	5
Leukaemia[38]	NP§	8-11	0.63 (0.41 to 0.84)	2	2	0	NP	0	NP	5
Post-MI mortality[30]	604/3271	3.8-9.9	0.55 (0.45 to 0.67)	2	2	0	0.00	9	ND	4
Gout[67]	NP/135 302	NP	0.50 (0.36 to 0.70)	2	2	0	0.02	35	ND	6
Liver cancer[43]	3414/2 267 143	10-44	0.50 (0.43 to 0.58)	11	11	0	0.01	20	0.62	6
Chronic liver disease[43]	1410/386 049	6-19	0.35 (0.22 to 0.56)	5	5	0	0.20	75	ND	6



NA=not appropriate; NP=not published; ND=not done
*Summary measure expressed as odds ratio in original meta-analysis article
†Fixed effects model
‡P value significant for non-linearity
§Could not be separated from other outcomes

Fig 2 | High versus low coffee consumption and associations with multiple health outcomes. Estimates are relative risks and effect models are random unless noted otherwise. For type 2 diabetes, P value was significant for non-linearity. No of events/total for leukaemia could not be split from other outcomes. All estimates were from our own reanalysis apart from preterm birth in first and third trimester and leukaemia

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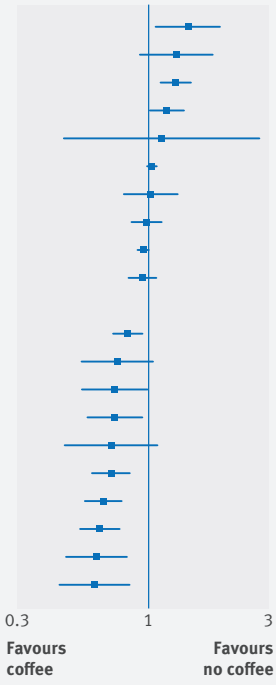
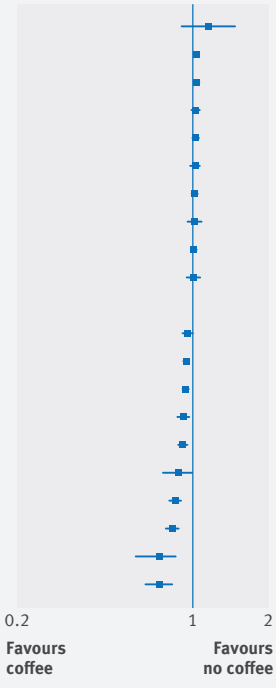
Outcome	No of events /total	Follow-up range (years)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful										
Acute leukaemia in childhood[88 89]	NP	NA	1.44*† (1.07 to 1.92)	3	0	3	NP	42	0.33	4
Lymphoma[60]	219/124 131	NP	1.29 (0.92 to 1.80)	3	3	0	0.04	18	ND	7
Lung cancer[47]	11 145/NP	NP	1.28 (1.12 to 1.47)	8	8	0	0.02	87	ND	5
Urinary tract cancer[49]	NP	NP	1.18* (1.01 to 1.38)	14	0	14	NP	NP	0.51	6
Endometriosis[81]	387/385	NP	1.13 (0.46 to 2.76)	3	1	2	0.43	70	ND	5
Hypertension[35]	36 178/1 246 388	6-33	1.03 (0.98 to 1.08)	4	4	0	0.00	73	ND	6
Gastric cancer[50]	1535/255 112	2-25	1.02 (0.79 to 1.31)	8	8	0	0.07	58	ND	7
Rectal cancer[52]	4594/NP	NA	0.98* (0.85 to 1.13)	10	0	10	NP	71	NP	4
Breast cancer[38]	NP‡	8-24	0.95 (0.90 to 1.01)	11	11	0	0.00	20	0.58	5
Venous thromboembolism[33]	4215/65 951	12-19	0.94 (0.82 to 1.07)	2	2	0	0	0	ND	3
10 most beneficial										
Colorectal cancer[52]	9568/NP	NA	0.83* (0.73 to 0.95)	13	0	13	NP	80	NP	4
Urinary incontinence[68]	7284/47 518	NP	0.75* (0.54 to 1.04)	3§	1	0	0.08	93	ND	6
Alzheimer's disease[127]	454/5497	NP	0.73 (0.54 to 0.99)	2	2	0	0.00	0	ND	3
Liver fibrosis[63]	1414/3738	NP	0.73* (0.56 to 0.94)	7	7	0	0.08	81	ND	7
Chronic kidney disease[69]	NP/14 898	NA	0.71 (0.47 to 1.08)	4§	0	0	0.11	66	ND	7
NAFLD[62]	NP/2407	NP	0.71 (0.60 to 0.85)	3§	1	1	0	0	ND	7
Liver cancer[43]	3414/2 267 143	10-44	0.66 (0.55 to 0.78)	12	12	0	0.06	80	0.24	6
Parkinson's disease[77]	1940/719 187	10-27	0.64 (0.53 to 0.77)	6	6	0	0.02	29	ND	7
Chronic liver disease[43]	1463/437 355	6-19	0.62 (0.47 to 0.82)	6	6	0	0.07	80	ND	6
Liver cirrhosis[63]	1880/130 496	NP	0.61* (0.45 to 0.84)	3	3	0	0	0	ND	7



NP=not published; NA=not appropriate; ND=not done; NAFLD=non-alcoholic fatty liver disease
*Summary measure expressed as odds ratio in original meta-analysis article
†Fixed effects model
‡Could not be separated from other outcomes
§Included cross sectional studies

Fig 3 | Any versus no coffee consumption and associations with multiple health outcomes. Estimates are relative risks and effect models are random unless noted otherwise. All estimates were from our own reanalysis apart from acute leukaemia, urinary tract cancer, and colorectal cancer

Outcome	No of events /total	Follow-up range (years)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
10 most harmful										
Low birth weight[128]	738/12 632	NA	1.16 (0.91 to 1.48)	2	1	1	NP	92	NP	7
Lung cancer[47]	19 892/623 645	NP	1.04 (1.03 to 1.05)	21	8	13	NP	75	<0.001	5
Pregnancy loss[23]*	11 951/153 259	NA	1.04† (1.03 to 1.05)	6	4	2	NP	NP	NP	5
Bladder cancer[129]	753/236 343	10-22	1.03† (0.99 to 1.06)	6	6	0	NP	44	NP	8
Fracture[71]	9597/214 059	NP	1.03 (1.00 to 1.06)	10	10	0	NP	81	NP	6
Gastric cancer[50]	2019/1 289 314	10-18	1.02 (0.98 to 1.07)	9	9	0	NP	57	0.1	7
Ovarian cancer[53]	1992/313 195	NP	1.02 (0.99 to 1.05)	6	6	0	NP	NP	NP	6
Alzheimer's disease[80]	NP/NP	5-21	1.02 (0.95 to 1.08)	2	2	0	NP	16	NP	6
Rectal cancer[20]	5812/1 751 343	4-18	1.01‡ (0.99 to 1.03)	14	14	0	NP	11	0.38	8
Glioma[61]	1361/4 777 317	8-24	1.01 (0.96 to 1.07)	3	3	0	NP	52	>0.25	6
10 most beneficial										
Gallstones[25]*	10 911/198 831	NP	0.95 (0.91 to 1.00)	3	3	0	NP	55	NP	8
Type 2 diabetes[65]	46 722/974 372	2-20	0.94 (0.93 to 0.95)	20	20	0	NP	NP	NP	8
Endometrial cancer[39]	4730/592 672	6-26	0.94§ (0.92 to 0.96)	11	11	0	NP	NP	NP	5
Depression[79]	14 506/327 608	NP	0.92 (0.87 to 0.97)	5§	2	1	NP	60	0.03	6
Renal stones[66]	NP/167 650	NP	0.91 (0.88 to 0.95)	5	3	2	NP	43	0.18	6
Parkinson's disease[76]	459/187 281	NP	0.88 (0.77 to 1.00)	4	4	0	NP	NP	NP	4
Liver cancer[43]	3414/2 267 143	10-44	0.85 (0.81 to 0.90)	12	12	0	NP	NP	0.17	6
Cirrhosis[9]	1364/427 687	14-18	0.83 (0.78 to 0.88)	5	5	0	NP	91	NP	9
Cirrhosis mortality[9]	1034/303 622	14-18	0.74 (0.59 to 0.86)	4	4	0	NP	90	NP	9
Chronic liver disease[43]	1463/437 355	10-44	0.74 (0.65 to 0.83)	6	6	0	NP	NP	0.43	6



NA=not appropriate; NP=not published
*P value significant for non-linearity
†Odds ratio
‡Fixed effect
§Included cross sectional studies

Fig 4 | Consumption of one extra cup of coffee a day and associations with multiple health outcomes. Estimates are relative risks and effect models are random unless noted otherwise. No dose response analyses were re-analysed

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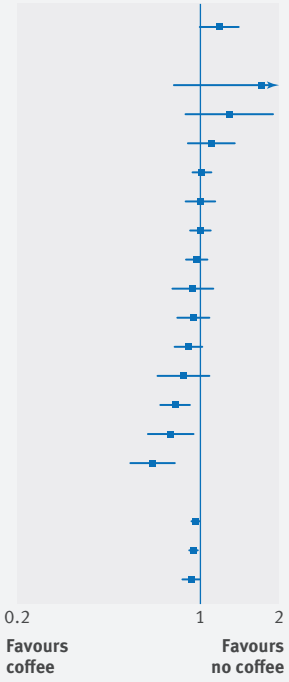
Outcome	No of events /total	Follow-up range (years)	Estimate (95% CI)	Total studies	Cohort	Case-control	τ^2	I^2 (%)	Egger's P value	AMSTAR
Any *v* none										
Urinary tract cancer[49]	NP	NA	1.18* (0.99 to 1.40)	4	0	4	NP	2	0.51	5
High *v* low										
Rheumatoid arthritis[74 75]†	638/113 822	11-20	1.71 (0.79 to 3.71)	2	2	0	NP	71	NP	5
Bladder cancer[129]	NP	10-22	1.29* (0.88 to 1.89)	5	NP	NP	NP	63	NP	8
Coronary heart disease[130]	5838/155 805	14-20	1.10 (0.90 to 1.34)	3	3	0	NP	NP	NP	4
Non-melanoma skin cancer[42]†	25 413/NP	NP	1.01 (0.94 to 1.10)	3	3	0	0	0	ND	5
Cardiovascular disease[19]	NP	NP	1.00 (0.88 to 1.14)	5	5	0	NP	NP	NP	7
Cancer mortality[28]‡	NP	NP	1.00 (0.91 to 1.09)	2	2	0	NP	NP	NP	5
Breast cancer[131]	32 790/404 188	10-22	0.97§ (0.89 to 1.06)	12	4	8	NP	30	NP	5
Parkinson's disease[22]	1210/251 300	NP	0.94¶ (0.78 to 1.12)	4	3	1	NP	NP	NP	6
Malignant melanoma[132]†	NP	NP	0.94 (0.82 to 1.08)	5	5	0	NP	0	0.116	7
All cause mortality[28]‡	NP	NP	0.90 (0.79 to 1.01)	5	5	0	NP	NP	NP	5
CVD mortality[28]‡	NP	NP	0.86 (0.69 to 1.08)	3	3	0	NP	NP	NP	5
Type II diabetes[21]†**	22 015/417 454	1-24	0.80 (0.70 to 0.91)	11	11	0	0.03	62	0.13	7
Endometrial cancer[40]	3127/363 254	9-26	0.77 (0.63 to 0.94)	4	4	0	NP	0	0.88	7
Lung cancer[48]	NP	NP	0.66 (0.54 to 0.81)	2	NP	NP	NP	0	NP	5
Extra 1 cup/day										
Endometrial cancer[40]	3127/363 254	9-26	0.96 (0.92 to 0.99)	9	9	0	NP	NP	NP	7
Type 2 diabetes[21]	22 015/417 454	1-24	0.94 (0.91 to 0.98)	14	16	0	NP	NP	NP	7
Liver cancer[10]	800/750 000	11-18	0.93 (0.86 to 1.00)	3	0	0	NP	NP	NP	8



NP=not published; NA=not appropriate
*Odds ratio
†Estimates from our own reanalysis
‡Maximum consumption in non-linear dose-response analysis
§Fixed effect
¶ Effect model not published
**P value significant for non-linearity

Fig 5 | Consumption of decaffeinated coffee and associations with multiple health outcomes. Estimates are relative risks and effect models are random unless noted otherwise

grouped by body system, are available in figures A-I in appendix 2.

The most commonly studied exposure was high versus low (or no) coffee consumption, and significance was reached for beneficial associations with 19 health outcomes and harmful associations with six. The 34 remaining outcomes were either negatively or positively associated but without reaching significance. Similarly, in comparisons of any (regular) with no consumption, significance was reached for beneficial associations with 11 outcomes and harmful associations with three. Finally, for one extra cup a day, significance was reached for beneficial associations with 11 outcomes and harmful associations with three. Eight out of 18 studies[19-27] that tested for non-linearity for the association with one extra cup a day found significant evidence for this.

All cause mortality

In the most recent meta-analysis, by Grosso and colleagues, the highest exposure category (seven cups a day) of a non-linear dose-response analysis was associated with a 10% lower risk of all cause mortality (relative risk 0.90, 95% confidence interval 0.85 to 0.96),[28] but summary estimates indicated that the largest reduction in relative risk was associated with the consumption of three cups a day (0.83, 0.83 to 0.88) compared with no consumption. Stratification by sex produced similar results. In a separate article, and despite a significant test for non-linearity (P<0.001), authors performed a linear dose-response analysis and found consumption of one extra cup a day was associated with a 4% lower risk of all cause mortality (0.96, 0.94 to 0.97).[27] The apparently beneficial association between coffee and all cause mortality was

Blood pressure	No of participants	Mean duration	Dose (cups)	Summary mean difference (95% CI)	Total studies	τ^2	I^2 (%)	Egger's P value	AMSTAR
Systolic	1466	62 days	2- ≥5	-0.66 (-2.71 to 1.39)	12	6.90	72	0.74	6
Diastolic	1466	62 days	2- ≥5	-0.45 (-1.51 to 0.61)	12	1.25	41	0.58	6

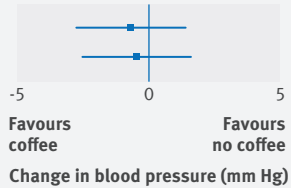


Fig 6 | Coffee consumption in randomised controlled trials[35] and change (mean difference) in blood pressure in random effects model. Estimates are from our own analysis

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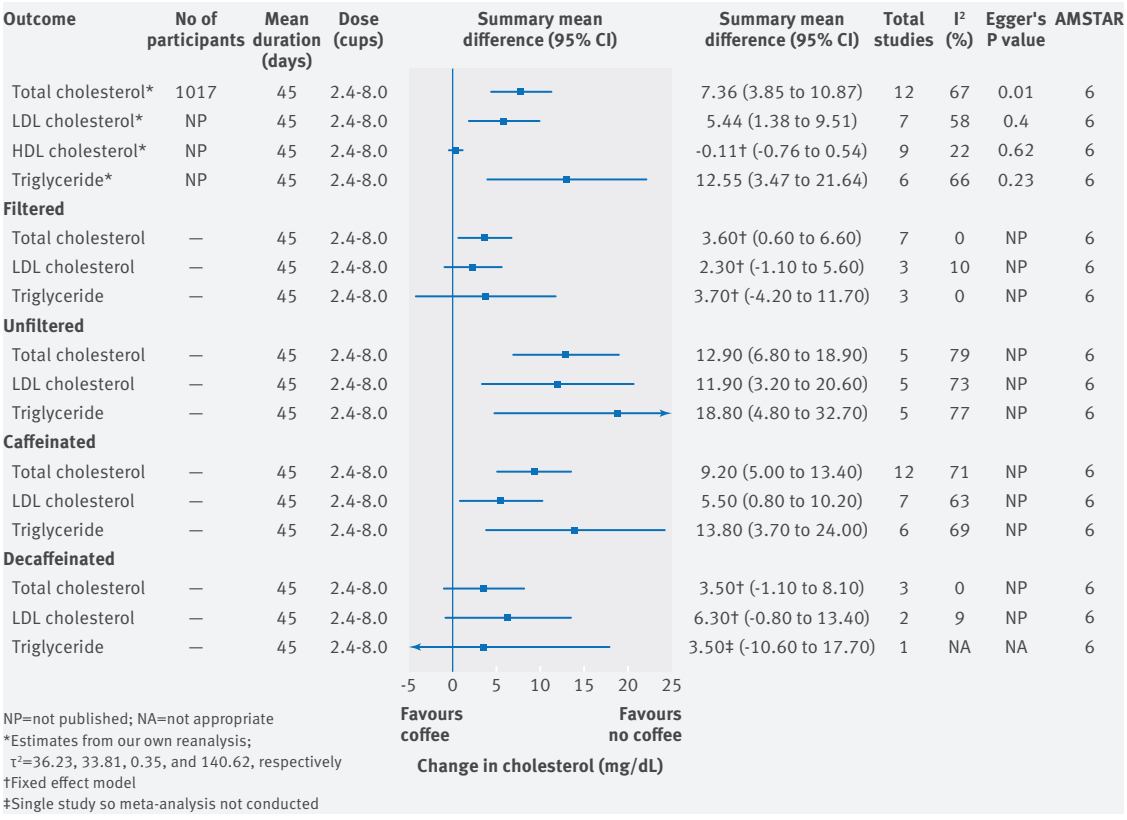

Fig 7 | Coffee consumption in randomised controlled trials[36] and change (mean difference) in cholesterol concentration. Effects are random unless noted otherwise

consistent across all earlier meta-analyses. High versus low intake of decaffeinated coffee was also associated with lower all cause mortality, with summary estimates indicating largest benefit at three cups a day (0.83, 0.85 to 0.89)[28] in a non-linear dose-response analysis.

Cardiovascular disease

Coffee consumption was consistently associated with a lower risk of mortality from all causes of cardiovascular disease, coronary heart disease, and stroke in a non-linear relation, with summary estimates indicating largest reduction in relative risk at three cups a day.[28] Compared with non-drinkers, risks were reduced by 19% (relative risk 0.81, 95% confidence interval 0.72 to 0.90) for mortality from cardiovascular disease, 16% (0.84, 0.71 to 0.99) for mortality from coronary heart disease, and 30% (0.70, 0.80 to 0.90) for mortality from stroke, at this level of intake. Increasing consumption to above three cups a day was not associated with harm, but the beneficial effect was less pronounced, and the estimates did not reach significance at the highest intakes. In stratification by sex within the same article, women seemed to benefit more than men at higher levels of consumption for outcomes of mortality from cardiovascular disease and coronary heart disease but less so from stroke.[28] In a separate meta-analysis, that did not test for non-linearity, an exposure of one extra cup a day was associated with a 2% reduced risk of cardiovascular mortality (0.98, 0.95 to 1.00).[29] There was also evidence of benefit in relation to high versus low coffee consumption after myocardial infarction and lower risk of mortality (hazard ratio 0.55, 95% confidence interval 0.45 to 0.67).[30]

Coffee consumption was non-linearly associated with a lower risk of incident cardiovascular disease (relative risk 0.85, 95% confidence interval 0.80 to 0.90), coronary heart disease (0.90, 0.84 to 0.97), and stroke (0.80, 0.75 to 0.86), with these summary estimates indicating the largest benefits at consumptions of three to five cups a day.[19] There was

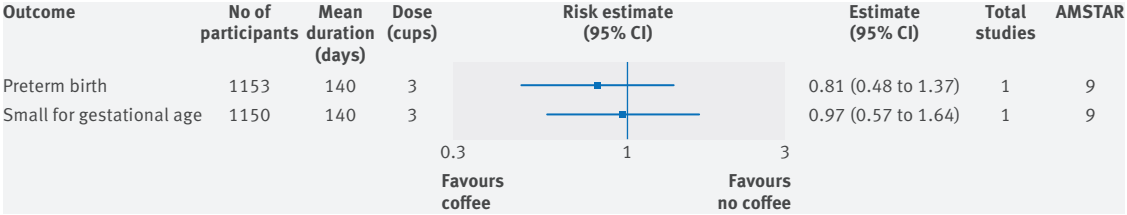

Fig 8 | Coffee consumption in randomised controlled trials[86] and effects (relative risk) on birth outcomes

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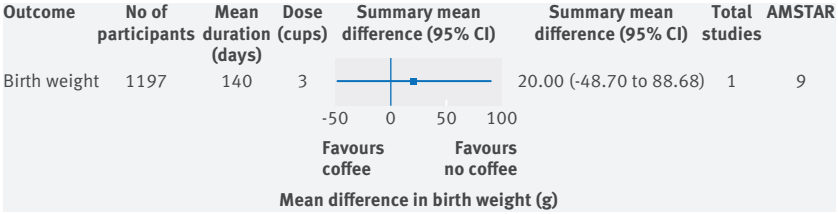

Fig 9 | Coffee consumption in randomised controlled trials[86] and change (mean difference) in birth weight

no apparent modification of this association by sex. Risk was also lower for the comparison of high versus low consumption but did not reach significance. Any versus no consumption was also associated with a beneficial effect on stroke (0.89, 0.81 to 0.97).[31] High versus low coffee and one extra cup a day were both associated with a lower risk of atrial fibrillation but neither reached significance.[32] There was no significant association between consumption and risk of venous thromboembolism.[33] There was a non-linear association between consumption and heart failure, with summary estimates indicating the largest benefit at four cups a day (0.89, 0.81 to 0.99),[24] with a slightly higher risk of heart failure at consumption of 10 or more cups a day (1.01, 0.90 to 1.14), though this did not reach significance.[24] For hypertension, there were no significant estimates of risk at any level of consumption in a non-linear dose-response analysis[34] nor in comparisons of any versus none.[35] There was no clear benefit in comparisons of high with low decaffeinated consumption and cardiovascular disease.[19]

In a meta-analysis of randomised controlled trials, coffee consumption had a marginally beneficial association with blood pressure when compared with control but failed to reach significance.[35] Consumption does, however, seem consistently associated with unfavourable changes to the lipid profile, with mean differences in total cholesterol (0.19 mmol/L, 95% confidence interval 0.10 mmol/L to 0.28 mmol/L),[36] low density lipoprotein cholesterol (0.14 mmol/L, 0.04 mmol/L to 0.25 mmol/L),[36] and triglyceride (0.14 mmol/L, 0.04 mmol/L to 0.24 mmol/L)[36] higher in the coffee intervention arms than the control arms (1 mmol/L cholesterol = 38.6 mg/dL, 1 mmol/L triglyceride = 88.5 mg/dL[37]). Consumption was associated with lower high density cholesterol (−0.002 mmol/L, −0.02 mmol/L to 0.54 mol/L), but this did not reach significance. The increases in cholesterol concentration were mitigated with filtered coffee, with a marginal rise in concentration (mean difference 0.09 mmol/L, 0.02 to 0.17)[36] and no significant changes to low density lipoprotein cholesterol or triglycerides compared with unfiltered (boiled) coffee. Similarly, decaffeinated coffee seemed to have negligible effect on the lipid profile.[36]

Cancer

A meta-analysis of 40 cohort studies showed a lower incidence of cancer for high versus low coffee consumption (relative risk 0.82, 95% confidence interval 0.74 to 0.89),[38] any versus no consumption (0.87, 0.82 to 0.92),[38] and one extra cup a day (0.97, 0.96 to 0.98).[38] In a separate article, in non-smokers there was a 2% lower risk of mortality from cancer for exposure of one extra cup a day (0.98, 0.96 to 1.00).[28] For smokers, the article provided results only from a non-linear analysis, and the risk of mortality from cancer increased at all levels of coffee exposure, reaching significance above four cups a day.

High versus low coffee consumption was associated with a lower risk of prostate cancer,[39] endometrial cancer,[40] melanoma,[41] oral cancer,[39] leukaemia,[38] non-melanoma skin cancer,[42] and liver cancer.[43] For prostate,[44] endometrial,[39] melanoma,[45] and liver cancer[43] there were also significant linear dose-response relations indicating benefit.

There were consistent harmful associations for coffee consumption with lung cancer for high versus low consumption (odds ratio 1.59, 95% confidence interval 1.26 to 2.00),[46] any versus none (relative risk 1.28, 1.12 to 1.47),[47] and one extra cup a day (1.04, 1.03 to 1.05).[47] The effect was diminished, however, in studies that adjusted for smoking, and the association was not seen in never smokers. In the most recent meta-analysis, any versus no consumption in people who had never smoked was associated with an 8% lower risk of lung cancer (0.92, 0.75 to 1.10),[47] and in studies that adjusted for smoking the risk estimate was reduced (1.03, 0.95 to 1.12)[47] compared with the overall analysis, and neither reached significance. In contrast, a meta-analysis of two studies showed that high versus low consumption of decaffeinated coffee was associated with a lower risk of lung cancer.[48]

A single meta-analysis found an association between any versus no coffee consumption and higher risk of any urinary tract cancer (odds ratio 1.18, 95% confidence interval 1.01 to 1.38).[49] In other meta-analyses of cohort studies of bladder cancer and renal cancer separately, however, associations did not reach significance.[39]

No significant association was found between coffee consumption and gastric,[39 50 51] colorectal,[20 39 52] colon,[20 52] rectal,[20 52] ovarian,[39 53] thyroid,[54 55] breast,[38 39 56] pancreatic,[57] oesophageal,[39 58] or laryngeal cancers[59] and lymphoma[39 60] or glioma.[61]

Liver and gastrointestinal outcomes

In addition to beneficial associations with liver cancer, all categories of coffee exposure were associated with lower risk for a range of liver outcomes. Any versus no coffee consumption was associated with a 29% lower risk of non-alcoholic fatty liver disease (relative risk 0.71, 0.60 to 0.85),[62] a 27% lower risk for liver fibrosis (odds ratio 0.73, 0.56 to 0.94),[63] and a 39% lower risk for liver cirrhosis (0.61, 0.45 to 0.84).[63] Coffee consumption was also associated with a lower risk of cirrhosis with high versus low consumption (0.69, 0.44 to 1.07)[63] and one extra cup a day (relative risk 0.83, 0.78 to 0.88).[9] Exposure to one extra cup a day was also significantly associated with a lower risk

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of mortality from cirrhosis (0.74, 0.59 to 0.86).[9] In a single article,[43] for meta-analyses of consumption and chronic liver disease, high versus low (0.35, 0.22 to 0.56), any versus none (0.62, 0.47 to 0.82), and one extra cup a day (0.74, 0.65 to 0.83) were all associated with benefit.

Coffee consumption was also consistently associated with significantly lower risk of gallstone disease.[25] A non-linear dose response was also apparent, though risk sequentially reduced as consumption increased from two to six cups a day.[25] High versus low consumption was associated with a marginally higher risk of gastro-oesophageal reflux disease, but this did not reach significance.[64]

Metabolic disease

Coffee consumption was consistently associated with a lower risk of type 2 diabetes for high versus low consumption (relative risk 0.70, 95% confidence interval 0.65 to 0.75)[21] and one extra cup a day (0.94, 0.93 to 0.95).[65] There was some evidence for a non-linear dose-response, but the risk was still lower for each dose of increased consumption between one and six cups.[21] Consumption of decaffeinated coffee also seemed to have similar associations of comparable magnitude.[21] For metabolic syndrome high versus low coffee consumption was associated with 9% lower risk (0.91, 0.86 to 0.95).[26] High versus low consumption was also significantly associated with a lower risk of renal stones[66] and gout.[67]

Renal outcomes

Coffee consumption of any versus none was associated with a lower risk of urinary incontinence[68] and chronic kidney disease,[69] but neither association reached significance, and the meta-analyses included cross sectional studies.

Musculoskeletal outcomes

There is inconsistency in the association between coffee consumption and musculoskeletal outcomes. There were no significant overall associations between high versus low consumption or one extra cup a day coffee and risk of fracture[70 71] or hip fracture.[72 73] In subgroup analysis by sex, however, high versus low consumption was associated with an increased risk of fracture in women (relative risk 1.14, 95% confidence interval 1.05 to 1.24) and a decreased risk in men (0.76, 0.62 to 0.94)[70] (test of interaction (ratio of relative risks (women:men) 1.50, 1.20 to 1.88; P<0.001). There was a non-significant association between high versus low consumption and risk of hip fracture in a subgroup analysis of women (relative risk 1.27, 0.94 to 1.72)[72] but not men (0.53, 0.38 to 1.00)[72] (test of interaction 2.40, 1.35 to 4.24; P<0.01). For consumption of one extra cup a day there was also an association with increased risk of fracture in women (relative risk 1.05, 1.02 to 1.07)[71] but a lower risk in men (0.91, 0.87 to 0.95)[71] (test of interaction 1.15, 1.10 to 1.21; P<0.001). These results suggest that sex might be a significant effect modifier in the association between coffee and risk of fracture. Associations were also found for total and decaffeinated coffee consumption and higher risk of rheumatoid arthritis,[74 75] but neither reached significance.

Neurological outcomes

Coffee consumption was consistently associated with a lower risk of Parkinson's disease, even after adjustment for smoking, and across all categories of exposure.[22 76 77] Decaffeinated coffee was associated with a lower risk of Parkinson's disease, which did not reach significance.[22] Consumption had a consistent association with lower risk of depression[78 79] and cognitive disorders, especially for Alzheimer's disease (relative risk 0.73, 95% confidence interval 0.55 to 0.97)[80] in meta-analyses of cohort studies.

Gynaecological outcomes

Exposures of any versus no coffee consumption were associated with a higher risk of endometriosis but did not reach significance.[81]

Antenatal exposure to coffee

There is some consistency in evidence for harmful associations of coffee consumption with different outcomes related to pregnancy. High versus low consumption was associated with a higher risk of low birth weight (odds ratio 1.31, 95% confidence interval 1.03 to 1.67),[82] pregnancy loss (1.46, 1.06 to 1.99),[23] first trimester preterm birth (1.22, 1.00 to 1.49),[83] and second trimester preterm birth (1.12, 1.02 to 1.22).[83] No significant association, however, was found for any category of coffee consumption and third trimester preterm birth,[83] neural tube defects,[84] and congenital malformations of the oral cleft[85] or cardiovascular system.[85] Only one study was included in a Cochrane meta-analysis of randomised controlled trials investigating coffee caffeine consumption on birth weight, preterm birth, and small for gestational age, and none of the outcomes reached significance.[86]

There is also consistency in associations between high versus low coffee consumption in pregnancy and a higher risk of childhood leukaemia (odds ratio 1.57, 95% confidence interval 1.16 to 2.11)[87] and any versus no consumption (1.44, 1.07 to 1.92).[88 89]

Heterogeneity of included studies

We were able to re-analyse by random effects, 83% of comparisons for high versus low and 79% for any versus none, but none for one extra cup a day. About 40% of the 83 meta-analyses that we re-analysed had significant heterogeneity, and 90% of these had an I^2 >50%. The individual studies within each meta-analysis varied by many factors, including the geography and ethnicity of the population of interest, the type of coffee consumed, the method of ascertainment of coffee consumption, the measure of coffee exposure, duration of follow-up, and outcome assessment. For the 54 that we were unable to re-analyse, 19% had significant heterogeneity, and 27% of meta-analyses did not publish heterogeneity for the

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studies included in the specific exposure comparison. Only four studies that we were unable to re-analyse used a fixed effects model.

Publication bias of included studies

We performed Egger's regression test in only 40% of the meta-analyses in our reanalysis because the remaining 60% contained insufficient numbers of studies. In those that we reanalysed, 20% had statistical evidence of publication bias. This included high versus low comparisons for type 2 diabetes (P=0.049),[21] stroke (P=0.09),[19] gastro-oesophageal reflux disease (P=0.04),[64] bladder cancer (P<0.01),[39] endometrial cancer (P=0.03),[40] and hip fracture (P=0.02),[72] and in the meta-analysis of randomised controlled trials for total cholesterol (P<0.01). For meta-analyses that we were unable to reanalyse, none reported significant publication bias or they did not conduct or publish a statistical test for publication bias for the specific exposure comparison. This could have been in part because of low number of studies included in the pooling. It is possible, however, that unmeasured publication bias exists in many of the summary estimates we have presented and not assessed.

AMSTAR and GRADE classification of included studies

The median AMSTAR score achieved across all studies was 5 out of 11 (range 2-9, interquartile range 5-7). Eleven studies were downgraded on method of meta-analysis because they used a fixed, rather than random effects, model. Appendix 3 provides a breakdown of AMSTAR scores for studies representing each outcome. In terms of quality of evidence for each outcome, about 25% were rated as being of "low" and 75% as "very low" quality with the GRADE classification. Even the meta-analyses of randomised controlled trials were graded as low quality of evidence because of risk of bias, inconsistency, or imprecision. Only outcomes identified as having a significant dose-response effect, or large magnitude of effect, without significant other biases reached a GRADE classification of "low" compared with the majority rating of "very low." Appendix 4 shows a breakdown of GRADE scores for studies representing each outcome.

Discussion

Principal findings and possible explanations

Coffee consumption is more often associated with benefit than harm for a range of health outcomes across multiple measures of exposure, including high versus low, any versus none, and one extra cup a day. Exposure to coffee has been the subject of numerous meta-analyses on a diverse range of health outcomes. We carried out this umbrella review to bring this existing evidence together and draw conclusions for the overall effects of coffee consumption on health. We identified 201 meta-analyses of observational research with 67 unique outcomes and 17 meta-analyses of randomised controlled trials with nine unique outcomes.

The conclusion of benefit associated with coffee consumption was supported by significant associations with lower risk for the generic outcomes of all cause mortality,[28] cardiovascular mortality,[28] and total cancer.[38] Consumption was associated with a lower risk of specific cancers, including prostate cancer,[39 44 90] endometrial cancer,[39 40 91] melanoma,[41 45] non-melanoma skin cancer,[42] and liver cancer.[43] Consumption also had beneficial associations with metabolic conditions including type 2 diabetes,[21 65] metabolic syndrome,[26] gallstones,[25] gout,[67] and renal stones[66] and for liver conditions including hepatic fibrosis,[63] cirrhosis,[9 63] cirrhosis mortality,[9] and chronic liver disease combined.[43] The beneficial associations between consumption and liver conditions stand out as consistently having the highest magnitude compared with other outcomes across exposure categories. Finally, there seems to be beneficial associations between coffee consumption and Parkinson's disease,[22 76 77] depression,[78 79] and Alzheimer's disease.[80]

Overall, there is no consistent evidence of harmful associations between coffee consumption and health outcomes, except for those related to pregnancy and for risk of fracture in women. After adjustment for smoking, consumption in pregnancy seems to be associated with harmful outcomes related to low birth weight,[82] preterm birth,[83] and pregnancy loss.[23] These associations were seen in subgroup analyses from articles investigating total caffeine exposure, which showed similar associations, and from a single meta-analysis for each outcome. There were also harmful associations between consumption and congenital malformations, though these did not reach significance.[85] The half life of caffeine is known to double during pregnancy,[92] and therefore the relative dose of caffeine from equivalent per cup consumption will be much higher than consumption outside pregnancy. Caffeine is also known to easily cross the placenta,[93] and activity of the caffeine metabolising enzyme, CYP1A2, is low in the fetus, resulting in prolonged fetal exposure to caffeine.[94] Though we found no significant associations between coffee exposure and neural tube defects,[84] for this outcome, all bar one of the included studies were of case-control design and therefore prone to recall bias. Maternal exposure to coffee had a harmful association with acute leukaemia of childhood,[87-89] but evidence for this also came from case-control studies.

The effect of the association between coffee consumption and risk of fracture was modified by sex. While there was no overall significant association with risk, the most recent meta-analyses found a 14% increased risk for high versus low consumption[70] and 0.6% increased risk for one extra cup a day[71] in women. Conversely, in men consumption was beneficially associated with a lower risk of fracture. Caffeine has been proposed as the component of coffee linked to the increased risk in women, with potential influence on calcium absorption[95] and bone mineral density.[96] A recent comprehensive

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systematic review of the health effects of caffeine, however, concluded, with regard to bone health, that a caffeine intake of 400 mg/day (about four cups of coffee) was not associated with adverse effects on the risk of fracture, falls, bone mineral density, or calcium metabolism.[97] There is limited evidence at higher intakes of caffeine to draw firmer conclusions. Notably, many of the studies included in the meta-analyses of coffee consumption and risk of fracture did not adjust for important confounders such as body mass index (BMI), smoking, or intakes of calcium, vitamin D, and alcohol. Some studies suggest that caffeine consumption is associated only with a lower risk of low bone mineral density in women with inadequate calcium intake,[98] and that only a small amount of milk added to coffee would be needed to offset any negative effects on calcium absorption.[95] The type of coffee consumed might therefore be an important factor. Coffee and caffeine have also been linked to oestrogen metabolism in premenopausal women[99] and increased concentrations of sex hormone binding globulin (SHBG) in observational research of postmenopausal women.[100] The increased globulin concentration was associated with lower concentrations of unbound testosterone but not unbound oestradiol.[100] Low concentrations of oestradiol and high concentrations of sex hormone binding globulin are known to be associated with risk of fracture.[101 102] An effect of coffee consumption on sex hormone binding globulin, however, has not been supported in small scale randomised controlled trials.[103] Coffee has been shown to be beneficially associated with oestrogen receptor negative, but not positive, breast cancer.[56] There is consistent evidence, however, to suggest that coffee consumption is associated with a lower risk of endometrial cancer[40] and no clear evidence for associations with ovarian cancer.[39 53] The effect of coffee consumption on endogenous sex hormones could therefore be beneficial for some hormone dependent cancers but increase the risk of fracture in women with inadequate dietary calcium[98] or with multiple risk factors for osteoporosis.[104]

When meta-analyses have suggested associations between coffee consumption and higher risk of other diseases, such as lung cancer, this can largely be explained by inadequate adjustment for smoking. Smoking is known to be positively associated with coffee consumption[105] and with many health outcomes and could act as both a confounder and effect modifier. Galarraga and Boffetta examined the possible confounding by smoking in two ways in their recent meta-analysis[47] of coffee consumption and risk of lung cancer. Firstly, they performed the meta-analysis in those who had never smoked and detected no harmful association. Next, they performed the meta-analysis in only those studies that adjusted for smoking, and the magnitude of the apparent harmful association was reduced and was no longer significant. It is likely that residual confounding by smoking, despite some adjustment, can explain this apparent harmful association. A similar pattern was seen in stratification by smoking for coffee consumption and mortality from cancer in the recent meta-analysis by Grosso and colleagues.[28] The authors highlighted the positive association between coffee consumption and smoking and concluded that residual confounding by smoking was the likely explanation.

For randomised controlled trials, coffee has been given as an intervention for only short durations and limited to a small number of outcomes, including blood pressure, lipid profiles, and one trial in pregnancy. There does seem to be consistent evidence for small increases in concentrations of total cholesterol, low density lipoprotein cholesterol, and triglyceride in meta-analyses of randomised controlled trials, and this is believed to be caused by the action of diterpenes.[106] The method of preparation is an important factor as instant and filtered coffee contain negligible amounts of diterpenes compared with espresso, with even higher amounts in boiled and cafetière coffee.[106] In the meta-analysis we included in our review, the effect of filtered coffee consumption on lipids was negligible or failed to reach significance compared with unfiltered coffee. Studies also suggest, however, that the dose of diterpenes needed to cause hypercholesterolaemia is likely to be much higher than the dose needed for beneficial anticarcinogenic effects.[107] For unfiltered coffee, the clinical relevance of such small increases in total cholesterol, low density lipoprotein cholesterol, and triglyceride due to coffee are difficult to extrapolate, especially as coffee consumption does not seem to be associated with adverse cardiovascular outcomes, including mortality after myocardial infarction.[30] Changes in the lipid profile associated with coffee also reversed with abstinence.[106]

When dose-response analyses have been conducted and when these have suggested non-linearity—for example in all cause mortality, cardiovascular disease mortality, cardiovascular disease, and heart failure—summary estimates indicate that the largest relative risk reduction is associated with intakes of three to four cups a day. Importantly, increase in consumption beyond this intake does not seem to be associated with increased risk of harm, rather the magnitude of the benefit is reduced. In type 2 diabetes, despite significant non-linearity, relative risk reduced sequentially from one through to six cups a day. Estimates from higher intakes are likely to include a smaller number of participants, and this could be reflected in the imprecision observed for some outcomes at these levels of consumption.

Coffee contains a complex mixture of bioactive compounds with plausible biological mechanisms for benefiting health. It has been shown to contribute a large proportion of daily intake of dietary antioxidant, greater than tea, fruit, and vegetables.[108] Chlorogenic acid is the most abundant antioxidant in coffee; though it is degraded by roasting, alternative antioxidant organic compounds are formed.[109] Caffeine also has significant antioxidant effects. The diterpenes, cafestol and kahweol, induce enzymes involved in carcinogen

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detoxification and stimulation of intracellular antioxidant defence,[107] contributing towards an anticarcinogenic effect. These antioxidant and anti-inflammatory effects are also likely to be responsible for the mechanism behind the beneficial associations between coffee consumption and liver fibrosis, cirrhosis, and liver cancer[110] that our umbrella review found had the greatest magnitude of effect compared with other outcomes. Additionally, caffeine could have direct antifibrotic effects by preventing hepatic stellate cell adhesion and activation.[111]

Decaffeinated coffee is compositionally similar to caffeinated coffee apart from having little or no caffeine.[112] In our umbrella review we identified 16 unique outcomes for associations with decaffeinated coffee. Decaffeinated coffee was beneficially associated with all cause and cardiovascular mortality in a non-linear dose-response, with summary estimates indicating the largest relative risk reduction at intakes of two to four cups a day and of similar magnitude to caffeinated coffee. Marginal benefit in the association between decaffeinated coffee and cancer mortality did not reach significance. The associations between high versus low consumption of decaffeinated coffee and lower risk of type 2 diabetes[21] and endometrial cancer[40] were of a similar magnitude to total or caffeinated coffee, and there was a small beneficial association between decaffeinated coffee and lung cancer.[48] The other outcomes investigated for decaffeinated coffee showed no significant associations, though it should be noted that meta-analyses of consumption would have much lower power to detect an effect. Importantly, there were no convincing harmful associations between decaffeinated coffee and any health outcome. People who drink decaffeinated coffee might be different from those who drink caffeinated coffee, and most coffee assessment tools do not adequately account for people who might have switched from caffeinated to decaffeinated coffee.[113]

Strengths and weaknesses and in relation to other studies

The umbrella review has systematically summarised the current evidence for coffee consumption and all health outcomes for which a previous meta-analysis had been conducted. It used systematic methods that included a robust search strategy of four scientific literature databases with independent study selection and extraction by two investigators. When possible, we repeated each meta-analysis with a standardised approach that included the use of random effects analysis and produced measures of heterogeneity and publication bias to allow better comparison across outcomes. We also used standard approaches to assess quality of methods (AMSTAR) and quality of the evidence (GRADE).

AMSTAR has good evidence of validity and reliability.[13] The AMSTAR score assisted us in identifying the highest quality of evidence for each outcome. It also allows judgment regarding quality of the meta-analysis presented for each outcome. A high AMSTAR score for a meta-analysis, however, does not equate to high quality of the original studies, and the assessment and use of quality scoring of the original studies accounts for only two of 11 possible AMSTAR points. Additionally, appropriate method of analysis, accounting for one score of quality, can be subjective. We downgraded any meta-analysis that used a fixed effects model irrespective of heterogeneity for reasons discussed previously. The AMSTAR system, however, allows only a 1 point loss for a poor analysis technique and would not capture multiple issues within an individual meta-analysis.

One recurring issue for many of the included meta-analyses was the assumption that summary relative risk could be pooled from a combination of odds ratio, relative rates, and hazard ratios so that they could combine studies with differing measures. Statistically, the odds ratio is similar to the relative risk when the outcome is uncommon[114] but will always be more extreme.[114] Similarly, for rare events, relative rates and hazard ratios are similar to the relative risk when censoring is uncommon or evenly distributed between exposed and unexposed groups.[114] Many meta-analyses stated their assumption but included insufficient information to allow us to judge the suitability of the pooling. Notably, only one meta-analysis produced a summary statistic with hazard ratios.[53] We did not downgrade the AMSTAR score when this assumption had been made, and we did not downgrade meta-analyses for failing to consider uncertainty in variance estimates as this was universally unstated.[115] Furthermore, the computation of dose-response meta-analyses should use methods that account for lack of independence in comparisons (same unexposed group), such as those proposed by Greenland and Longnecker.[116] Reassuringly, most dose-response meta-analyses we included in our summary tables cited this method.

Most of the studies we included were meta-analyses of observational studies. One strength of the umbrella review was the inclusion only of cohort studies, or subgroup analyses of cohort studies when available, in preference to summary estimates from a combination of study designs. In meta-analyses that we were unable to re-analyse and when subgroup analysis did not allow the disentanglement of study design, the presented results were from the combined estimates of all included studies. Observational research, however, is low quality in the hierarchy of evidence and with GRADE classification most outcomes are recognised as having very low or low quality of evidence where a dose-response relation exists. Large effect sizes of >2 or <0.5 can permit observational evidence to be upgraded in GRADE, and only the association between high versus low coffee consumption and both liver cancer[43] and chronic liver disease[43] reached this magnitude. In fact, associations between coffee consumption and liver outcomes consistently had larger effect sizes than other outcomes across exposure categories. Our reanalysis did not change our GRADE classification for any outcome.

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A possible limitation of our review was that we did not reanalyse any of the dose-response meta-analyses as the data needed to compute these were not generally available in the articles. We did not review the primary studies included in each of the meta-analyses that would have facilitated this. We decided that reanalysing the dose-response data was unlikely to result in changes to the GRADE classification. In our reanalysis of the comparison of high versus low and any versus no coffee, we used data available in the published meta-analyses and therefore assumed the exposure and estimate data for component studies had been published accurately.

We were able to produce estimates for publication bias using Egger's test for meta-analyses containing 10 or more studies.[17] Egger's test is not recommended with fewer studies. We were unable to conduct alternative tests, such as Peters' test,[117] which is more appropriate for binary outcomes, because this needed cases and non-cases for each level of exposure and this detail was largely unavailable in the meta-analyses. We did not calculate excess significance tests, which attempt to detect reporting bias by comparing the number of studies that have formally significant results with the number expected, based on the sum of the statistical powers from individual studies, and using an effect size equal to the largest study in the meta-analysis.[118] Excess significance tests, however, have not been fully evaluated and are not therefore currently recommended as an alternative to traditional tests of publication bias.[119] Further bias in methods could have occurred if the same meta-analysis authors conducted multiple meta-analyses for different health outcomes. There was also an overlap of health outcomes with data from the same original cohort studies. While the associations for different health outcomes were statistically independent, any methodological issues in design or conduct of the original cohorts could represent repeated bias filtering through the totality of evidence.

The beneficial association between coffee consumption and all cause mortality highlighted in our umbrella review is in agreement with two recently published cohort studies. The first was a large cohort study of 521 330 participants followed for a mean period of 16 years in 10 European countries, during which time there were 41 693 deaths.[120] The highest quarter of coffee consumption, when compared with no coffee consumption, was associated with a 12% lower risk of all cause mortality in men (hazard ratio 0.88, 95% confidence interval 0.82 to 0.95) and a 7% lower risk in women (0.93, 0.82 to 0.95). Coffee was also beneficially associated with a range of cause specific mortality, including mortality from digestive tract disease in men and women and from circulatory and cerebrovascular disease in women. The study was able to adjust for a large number of potential confounding factors, including education, lifestyle (smoking, alcohol, physical activity), dietary factors, and BMI. Importantly, the study found no harmful associations between coffee consumption and mortality, apart from the highest quarter versus no coffee consumption and increased risk of mortality from ovarian cancer (1.31, 1.07 to 1.61). No prevailing hypothesis was cited. In our umbrella review, high versus low coffee consumption was associated with an 8% increased risk and one extra cup a day with a 2% increased risk of incident ovarian cancer, but neither reached significance.

In the second study, a North American cohort of 185 855 participants was followed for a mean duration of 16 years, during which 58 397 participants died.[121] After adjustment for smoking and other factors, consumption of four or more cups of coffee a day was associated with an 18% lower risk of mortality (hazard ratio 0.82, 95% confidence interval 0.78 to 0.87). The findings were consistent across subgroups stratified by ethnicity that included African Americans, Japanese Americans, Latino, and white populations. Associations were also similar in men and women. Mortality from heart disease, cancer, chronic lower respiratory disease, stroke, diabetes, and kidney disease was also beneficially associated with coffee consumption. Importantly, no harmful associations were identified. Subtypes of cancer mortality, however, were not published.

Many of the associations between coffee consumption and health outcomes, which are largely from cohort studies, could be affected by residual confounding. Smoking, age, BMI, and alcohol consumption are all associated with coffee consumption and a considerable number of health outcomes. These relations might differ in magnitude and even direction between populations. Residual confounding by smoking could reduce a beneficial association or increase a harmful association when smoking is also associated with an outcome. Coffee could also be a surrogate marker for factors that are associated with beneficial health such as higher income, education, or lower deprivation, which could be confounding the observed beneficial associations. The design of randomised controlled trials can reduce the risk of confounding because the known and unknown confounders are distributed randomly between intervention and control groups. Mendelian randomisation studies can also help to reduce the effects of confounding from random distribution of confounders between genotypes of known function related to the outcome of interest. The association between coffee consumption and lower risk of type 2 diabetes[122] and all cause and cardiovascular mortality[123] was found to have no genetic evidence for a causal relation in Mendelian randomisation studies, suggesting residual confounding could result in the observed associations in other studies. The authors point out, however, that the Mendelian randomisation approach relies on the assumption of linearity between all categories of coffee intake and might not capture non-linear differences. The same genetic variability in coffee and caffeine metabolism could influence the magnitude, frequency, and duration of exposure to caffeine and other coffee bioactive

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compounds. Palatini and colleagues found that the risk of hypertension associated with coffee varied depending on the CYP1A2 genotype.[124] Those with alleles for slow caffeine metabolism were at increased risk of hypertension compared with those with alleles for fast caffeine metabolism.

Bias from reverse causality can also occur in observational studies. In case-control studies, symptoms from disease might have led people to reduce their intake of coffee. When possible, we included meta-analyses of cohort studies or cohort subgroup analyses in our review as they are less prone to this type of bias. Even prospective cohort studies, however, can be affected by reverse causality bias, in which participants who were apparently healthy at recruitment might have reduced their coffee intake because of early symptoms of a disease.

Most meta-analyses produced summary effects from individual studies that measured coffee exposure by number of cups a day. Some individual studies, however, used number of times a day, servings a day, millilitres a day, cups a week, times a week, cups a month, and drinkers versus non-drinkers to measure coffee consumption. There is no universally recognised standard coffee cup size, and the bioactive components of coffee in a single cup will vary depending on the type of bean (such as Arabica or Robusta), degree of roasting, and method of preparation, including the quantity of bean, grind setting, and brew type used. Therefore, studies that are comparing coffee consumption by cup measures could be comparing ranges of exposures. The range of number of cups a day classified as both high and low consumption from different individual studies varied substantially for inclusion in each meta-analysis. High versus low consumption was the most commonly used measure of exposure. Consistent results across meta-analyses and categories of exposure, however, suggest that measurement of cups a day produces a reasonable differential in exposure. Additionally, any misclassification in exposure is likely to be non-differential and would more likely dilute any risk estimate rather than strengthen it, pushing it towards the null.

The inclusion criteria for the umbrella review meant that some systematic reviews were omitted when they did not do any pooled analysis. Meta-analyses in relation to coffee consumption, however, have been done on most health outcomes for which there is also a systematic review, except for respiratory outcomes[125] and sleep disturbance.[126] There could also be important well conducted studies that have assessed coffee consumption in relation to outcomes for which no investigators have attempted to perform any combined review, whether pooling the estimate or not. Additionally, the umbrella review has investigated defined health outcomes rather than physiological outcomes. This means there could be physiological effects of coffee such as increased heart rate, stimulation of the central nervous system, and feelings of anxiety that have not been captured in this review and must be considered should individuals be taking drugs that have similar physiological effects or in those trying to avert anxiety.

Despite our broad inclusion criteria, we identified only one meta-analysis that focused on a population of people with established disease. This was a meta-analysis of two small cohort studies investigating risk of mortality in people who had experienced a myocardial infarction.[30] In contrast, most meta-analyses estimated the association between coffee consumption and outcomes in general population cohorts rather than those selected by pre-existing disease. Our summation of the existing body of evidence should therefore be viewed in this context and suggests that the association of coffee consumption in modifying the natural history of established disease remains unclear.

We extracted details of conflicts of interest and funding declarations from articles selected in the umbrella review. Only one article declared support from an organisation linked to the coffee industry, and a second article stated that their authors contributed to the same organisation. Neither of these articles was selected to represent the respective outcome in the summary figures, and all references for studies not included in the summary tables are available on request. We did not review the primary studies included in each meta-analysis and cannot comment on whether any of these studies were funded by organisations linked to the coffee industry.

Conclusions and recommendations

Coffee consumption has been investigated for associations with a diverse range of health outcomes. This umbrella review has systematically assimilated this vast amount of existing evidence where it has been published in a meta-analysis. Most of this evidence comes from observational research that provides only low or very low quality evidence. Beneficial associations between coffee consumption and liver outcomes (fibrosis, cirrhosis, chronic liver disease, and liver cancer) have relatively large and consistent effect sizes compared with other outcomes. Consumption is also beneficially associated with a range of other health outcomes and importantly does not seem to have definitive harmful associations with any outcomes outside of pregnancy. The association between consumption and risk of fracture in women remains uncertain but warrants further investigation. Residual confounding could explain some of the observed associations, and Mendelian randomisation studies could be applied to a range of outcomes, including risk of fracture, to help examine this issue. Randomised controlled trials that change long term behaviour, and with valid proxies of outcomes important to patients, could offer more definitive conclusions and could be especially useful in relation to coffee consumption and chronic liver disease. Reassuringly, our analysis indicates that future randomised controlled trials in which the intervention is increasing coffee consumption, within usual levels of intake, possibly optimised at three to four cups a day, would be unlikely to result in significant harm to participants. Pregnancy,

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doi: 10.1136/bmj.j5024 | BMJ 2017;359:j5024 | the bmj

or risk of pregnancy, and women with higher a risk of fracture, however, would be justified exclusion criteria for participation in a coffee treatment study.

Contributors: RP conceptualised the umbrella review, conducted the search, study selection, data extraction, and drafted and revised the paper. OJK conceptualised the umbrella review, conducted the study selection and data extraction, and revised the draft paper. JP conceptualised the umbrella review and revised the draft paper. JAF revised the draft paper. PCH revised the draft paper. PR conceptualised the umbrella review, arbitrated the study selection, and revised the draft paper. All authors reviewed and approved the final version of the manuscript. RP is guarantor.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors; the authors remain independent of any funding influence.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; JAF reports research grants from GlaxoSmithKline and from Intercept Pharmaceuticals, and personal fees from Novartis and from Merck, outside the submitted work; PCH reports personal fees from MSD, personal fees from Gilead, personal fees from Abbvie, personal fees from Jannsen, personal fees from BMS, personal fees from Pfizer, grants and personal fees from Roche, personal fees from Novartis, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: References for studies included in the umbrella review but not selected to represent the outcome in the summary figures are available on request.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Appendix 1: Full versions of forest plots
Appendix 2: Coffee consumption and outcome groups
Appendix 3: AMSTAR scores for individual studies
Appendix 4: GRADE classification of quality of evidence

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