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Coffee, Caffeine, and Health Outcomes: An Umbrella Review

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Keywords

coffee, caffeine, cardiovascular disease, cancer, diabetes, neurodegenerative disease

Abstract

To evaluate the associations between coffee and caffeine consumption and various health outcomes, we performed an umbrella review of the evidence from meta-analyses of observational studies and randomized controlled trials (RCTs). Of the 59 unique outcomes examined in the selected 112 meta-analyses of observational studies, coffee was associated with a probable decreased risk of breast, colorectal, colon, endometrial, and prostate cancers; cardiovascular disease and mortality; Parkinson's disease; and type-2 diabetes. Of the 14 unique outcomes examined in the 20 selected meta-analyses of observational studies, caffeine was associated with a probable decreased risk of Parkinson's disease and type-2 diabetes and an increased risk of pregnancy loss. Of the 12 unique acute outcomes examined in the selected 9 meta-analyses of RCTs, coffee was associated with a rise in serum lipids, but this result was affected by significant heterogeneity, and caffeine was associated with a rise in blood pressure. Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet.

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INTRODUCTION

Coffee, among the most commonly consumed beverages worldwide, has been demonstrated to exert a number of effects on human health (41). The association between coffee consumption and a variety of conditions and diseases has been examined extensively, often with contrasting results. The main safety concerns arise in regard to its caffeine content; caffeine is the most widely consumed physiological stimulant worldwide, with side effects that may affect cardiovascular outcomes (156). The caffeine content has been considered mainly responsible for cardiovascular effects due to its ability to raise blood pressure as a result of increases in total peripheral resistance. However, the short duration of randomized controlled trials (RCTs) has emphasized mostly the acute effects of coffee consumption, and observational studies have often lacked adequate controls for confounding factors (i.e., smoking status) that may contribute to the negative outcomes associated with coffee consumption. Nonetheless, improvements in analytic techniques have uncovered numerous potentially beneficial compounds in coffee, including antioxidant polyphenols, which are highly concentrated in coffee (82). These findings have attracted a growing scientific audience aimed at finding potential beneficial effects of coffee. During the past 20 years, a number of studies on a broad range of outcomes in addition to cardiovascular-related conditions, such as cancer and overall mortality, suggested that coffee may exert beneficial effects on human health. These

results are of great interest from a public health standpoint due to the high frequency of coffee drinking.

There is a need to address the broad scope of benefits and issues related to coffee consumption and health, and to describe the evidence comprehensively but concisely to decision-makers. Thus, we evaluated the content of and findings from meta-analyses of observational studies and RCTs that examined associations between coffee consumption or caffeine intake and any clinical condition. We summarized the pooled results of observational studies and RCTs, and evaluated the consistency of findings and evidence of potential bias throughout the studies.

Umbrella review: review that aims to systematically examine existing research syntheses of different outcomes for the same intervention or phenomena of interest

METHODS

Study Selection

For this umbrella review, we search MEDLINE and Embase for quantitative reviews of coffee consumption or administration and any health outcome from inception to August 2016. The search terms were "coffee," "caffeine," and "meta-analysis"; only studies conducted on humans and articles in English were considered eligible for review. The search was independently performed by two authors (G.G. and J.G.) and any discrepancies were resolved by discussion. The following types of studies were included: (*a*) meta-analyses of observational studies considering coffee consumption or caffeine intake as the exposure variable of interest and any health outcome and (*b*) meta-analyses of RCTs assessing the effects of coffee or caffeine administration from any source and for any clinical outcome. The following types of studies were excluded: (*a*) studies in which coffee consumption was part of the outcome, (*b*) studies on genetic polymorphisms related to coffee consumption, (*c*) studies that evaluated the prevalence of coffee consumption, (*d*) RCTs that combined coffee administration with other treatments.

Data Extraction

From each eligible meta-analysis, the following information was abstracted: name of the first author and year of publication, outcome, design of included studies (including case-control, cross-sectional and prospective), type of coffee (any or decaffeinated), number of studies included, total population, number of cases, measure of exposure [including highest versus lowest (reference) category of exposure, second and third highest versus lowest (reference) category of exposure, incremental cups/day (linear), dose-response per cup or fixed dose], effect sizes (risk ratio, odds ratio, hazard ratio, or standardized weighted difference). Outcomes were categorized as cancer, cardiovascular, and other.

Data Evaluation

Whenever more than one meta-analysis was conducted using the same outcome, and the same study design and type of population, concordance was evaluated for the main outcome of interest, including concordance in the direction and magnitude of the association by comparing risk estimates and confidence intervals. For further analyses, the most recent or most exhaustive study was considered. When more than one study design was evaluated, results were considered and reported in the following order of importance: (*a*) meta-analyses of prospective studies, (*b*) comprehensive prospective and case-control studies, and (*c*) case-control studies. The pooled analyses of the highest versus the lowest (reference) category of exposure and dose-response analyses were evaluated. Direction, magnitude, and heterogeneity (I^2) were considered when grading the

Table 1 Criteria used to define the level of evidence for relationships among coffee, caffeine, and health

Level of evidence[a]	Definition
Convincing	Level 1a (high): concordance between meta-analyses of RCTs and meta-analyses of observational studies (any)
	Level 1b (low): meta-analyses of RCTs with results contrary to those from meta-analyses of observational studies (any)
Probable	Level 2a (high): meta-analyses of prospective studies with no heterogeneity, no potential confounding factors identified, and agreement of results over time and among meta-analyses, including studies with different designs
	Level 2b (medium): meta-analyses of prospective studies with no heterogeneity and no potential confounding factors identified
	Level 2c (low): meta-analyses of prospective and case-control studies with no heterogeneity and no potential confounding factors identified
Possible	Level 3a (high): meta-analyses of prospective studies lacking information on heterogeneity and potential confounding factors
	Level 3b (medium): meta-analyses of prospective and case-control studies lacking information on heterogeneity and potential confounding factors
	Level 3c (low): meta-analyses of case-control studies or meta-analyses of any other study design with significant heterogeneity ($I^2 > 50\%$) and potential confounding factors
Limited/ contrasting	Level 4: Limited studies included in meta-analyses ($n \leq 3$) or evident contrasting results from meta-analyses with the same level of evidence

Table modified from the joint World Health Organization–United Nations Food and Agriculture Organization expert consultation (131). Abbreviations: RCT, randomized controlled trial.

[a]All of the associations should be biologically plausible; potential confounding factors should be taken into account.

level of evidence. When meta-analyses reported subgroup analyses or stratified analyses, potential confounding factors were investigated. Finally, the relationship between coffee consumption or caffeine intake and outcomes of interest was categorized as (*a*) convincing, (*b*) probable, (*c*) possible, or (*d*) limited/contrasting evidence. The criteria used for evidence categorization were modified from the joint World Health Organization–United Nations Food and Agriculture Organization Expert Consultation (**Table 1**) (131). Given the nature of the exposure, we also considered that (*a*) smoking is a well-known confounding factor when considering coffee drinking, and thus evidence (especially on outcomes that may be affected by smoking) should be based on adjusted results and, when possible, stratified for smoking status; (*b*) the time frame of RCTs should be considered, as acute effects may differ from those associated with chronic consumption of coffee.

RESULTS

The search strategy yielded 244 articles, 56 of which were excluded on the basis of title evaluation and 24 of which were excluded for the following reasons: 14 were narrative or systematic reviews, 6 were meta-analyses on the effects of a number of exposures that were not limited to coffee, 2 were meta-analyses of selected cohorts, 1 was a meta-analysis of a nonrandomized and non-controlled trial, 1 was a meta-analysis of the effects of a coffee derivate (**Figure 1**). In total, 127 articles were considered in this umbrella review (1, 3–8, 10, 12–18, 20–22, 25–35, 37–40, 43, 45, 47–58, 60–81, 83, 84, 86, 88, 89, 92, 94, 96–98, 101–104, 106, 108, 109, 111–121, 123, 124, 126–151, 153–155), including 112 meta-analyses of observational studies on coffee (1, 3–8, 10, 13–16, 20, 22, 26–35, 37, 39, 40, 43, 45, 48–57, 60–79, 81, 83, 84, 86, 89, 92, 94, 96, 98, 101–104, 108, 111–121, 123,

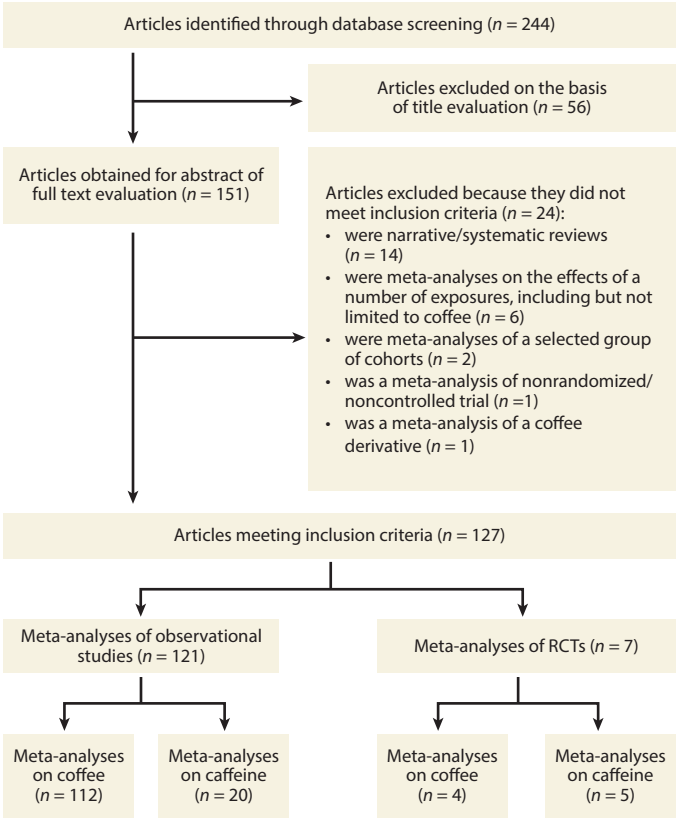

Figure 1

Flowchart of studies selected for inclusion in the umbrella review of coffee, caffeine, and health outcomes.

124, 126–129, 131–151, 153, 154) and 20 on caffeine (13, 14, 17, 18, 21, 22, 25, 28, 38, 39, 52, 53, 58, 66, 80, 103, 106, 109, 127, 153), 4 meta-analyses of RCTs on coffee (12, 51, 97, 117), and 5 on caffeine (47, 88, 97, 130, 155). A total of 59 outcomes related to coffee exposure and 14 related to caffeine were examined in observational studies, and 6 outcomes related to coffee and 9 related to caffeine were examined in RCTs (**Figure 1**).

Meta-Analyses of Observational Studies of Coffee or Caffeine Intake and Health Outcomes

The characteristics and summaries of risk estimates for 40 nonoverlapping meta-analyses of 59 unique outcomes related to coffee consumption (4, 8, 10, 13, 22, 27, 29, 32, 34, 35, 39, 40, 43, 49, 52, 53, 60, 63, 64, 66, 68, 71–73, 79, 81, 83, 84, 102, 104, 111, 114, 117, 120, 134, 138, 140, 148, 150, 153) are shown in **Figure 2**; those of 11 nonoverlapping meta-analyses for 11 unique outcomes related to decaffeinated coffee consumption (13, 29, 34, 49, 52, 53, 64, 134, 140, 142, 153) and 9 nonoverlapping meta-analyses for 14 unique outcomes related to caffeine intake (13, 21, 22, 39, 53, 58, 66, 80, 106) are shown in **Figure 3**. A total of 38 (64.4%) of the nonoverlapping meta-analyses reported statistically significant associations between coffee or caffeine intake and health outcomes.

Outcome	Number of studies	Number of subjects	Number of cases		RR (95% CI)	I^2 (%)	Reference
Coffee							
Cancer							
Hepatocellular carcinoma	11 P	2,266,671	2,942		0.50 (0.43–0.58)	13	9
Colorectal adenoma	1 P, 2 CC	NA	NA		0.57 (0.44–0.72)	NA	35
Oral cancer	4 P	2,331,316	1,758		0.66 (0.45–0.98)	79	71
Pancreatic cancer	20 P	1,341,876	2,872		0.75 (0.63–0.86)	38	100
Skin cancer (melanoma)	9 P	925,484	3,327		0.76 (0.64–0.91)	NA	134
Endometrial cancer	13 P	1,534,039	10,100		0.80 (0.74–0.86)	31	147
Skin cancer (nonmelanoma)	3 P, 1 CC	NA	33,352		0.82 (0.75–0.89)	48	14
Esophageal cancer	4 P	NA	NA		0.88 (0.65–1.19)	31	144
Proximal colon cancer	4 P	NA	NA		0.90 (0.78–1.04)	65	34
Prostate cancer	13 P	539,577	34,105		0.90 (0.85–0.95)	17	75
Colon cancer	16 P	NA	NA		0.91 (0.84–0.98)	30	34
Distal colon cancer	4 P	NA	NA		0.92 (0.79–1.07)	0	34
Adult glioma	4 P	1,322,407	1,486		0.98 (0.79–1.23)	6	83
Colorectal cancer	19 P	2,046,575	22,629		0.98 (0.90–1.06)	41	34
Breast cancer	17 P	NA	30,931		0.98 (0.95–1.02)	0	52
Renal cancer	4 P	310,625	366		0.99 (0.52–1.89)	45	43
Bladder cancer	5 P	236,343	753		0.99 (0.70–1.39)	63	128
Cancer mortality	10 P	NA	NA		1.03 (0.97–1.09)	Yes	84
Rectal cancer	15 P	NA	NA		1.07 (0.97, 1.18)	13	34
Lung cancer	8 P, 13 CC	623,645	19,892		1.09 (1.00–1.19)	84	32
Ovarian cancer	6 P	644,044	3,236		1.13 (0.89–1.43)	50	5
Gastric cancer	13 P	1,324,559	3,484		1.16 (1.03–1.32)	27	27
CALL	6 CC	4,869	2,483		1.43 (1.22–1.68)	0	116
CAL	6 CC	3,989	2,417		1.57 (1.16–2.11)	55	116
CAML	4 CC	4,041	387		1.81 (0.93–3.53)	54	116
Cardiovascular outcomes							
Death after acute MI	2 P	3,271	604		0.54 (0.45–0.65)	13	11
CVD mortality	17 P	NA	NA		0.89 (0.77–1.02)	75	84
Coronary heart disease	30 P	NA	NA		0.93 (0.84–1.02)	52	29
Stroke	22 P	NA	NA		0.95 (0.84–1.07)	54	29
CVD	35 P	NA	NA		0.95 (0.87–1.03)	No	29
Atrial fibrillation	6 P	248,910	10,406		0.96 (0.84–1.08)	60	60
Venous thromboembolism	1 P, 2 CC	67,754	NA		0.97 (0.88–1.08)	NA	73
Hypertension	4 P	1,467,361	36,178		1.03 (0.98–1.08)	73	113
Other							
Chronic liver disease	5 P	386,049	1,410		0.35 (0.22–0.56)	16	9
Gout	2 P	135,302	1,653		0.50 (0.36–0.70)	36	98
Parkinson's disease	4 P	187,740	459		0.70 (0.56–0.88)	NA	40
Type-2 diabetes	26 P	1,096,647	50,595		0.71 (0.67–0.76)	54	53
Alzheimer's disease	4 P	15,761	396		0.73 (0.55–0.97)	0	79
Cognitive impairment	3 P	6,649	NA		0.78 (0.48–1.26)	49	79
Gallstone disease	5 P	226,627	11,282		0.83 (0.76–0.89)	35	142
Neural tube defects	1 RP, 6 CC	NA	2,077		0.86 (0.51–1.45)	86	72
All-cause mortality	20 P	973,904	129,538		0.86 (0.80–0.92)	69	49
Gastric ulcer	3 P, 2 CC	9,517	633		0.88 (0.49–1.60)	79	110
Depression	3 P	316,894	4,656		0.88 (0.79–0.99)	43	39
Urolithiasis	3 P	NA	NA		0.90 (0.82–0.98)	51	132
Metabolic syndrome	3 P	106,855	31,770		0.91 (0.87–0.96)	0	107
Cognitive disorders	10 P	29,155	NA		0.97 (0.84–1.11)	25	79
Peptic ulcer	5 P, 3 CC	NA	1,824		0.99 (0.75–1.32)	77	110
Fractures	9 P	NA	NA		0.99 (0.86–1.14)	69	63
Cognitive decline	4 P	9,254	NA		1.02 (0.88–1.18)	0	79
Gastroesophageal reflux	15 CC	89,608	12,816		1.06 (0.94–1.19)	66	57
Dementia	5 P	12,607	NA		1.08 (0.81–1.44)	28	79
Pregnancy loss	13 P	NA	NA		1.10 (1.01–1.19)	50	66
Endometriosis	2 P, 1 CC	772	387		1.13 (0.46–2.76)	70	23
Hip fracture	9 P	205,930	5,408		1.13 (0.86–1.48)	79	68
Duodenal ulcer	3 P, 5 CC	NA	966		1.17 (0.79–1.73)	59	110
Spina bifida	4 CC	NA	1,496		1.30 (0.67–2.52)	87	72
Rheumatoid arthritis	2 P	114,460	638		1.31 (0.96–1.77)	0	64
Vascular dementia	1 P	3,734	80		1.96 (0.76–5.04)	NA	79

Figure 2

Findings from 40 nonoverlapping meta-analyses of observational studies on coffee, with effect size for highest versus lowest (reference) category of exposure. Abbreviations: CAL, childhood acute leukemia; CALL, childhood acute lymphoblastic leukemia; CAML, childhood acute myeloid leukemia; CC, case control; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; NA, not applicable; P, prospective; RP, retrospective; RR, relative risk.

For coffee consumption, meta-analyses of endometrial (153), liver (8), prostate (75), pancreatic (104), and colon (34) cancers and gallstone disease (148) reported statistically significant reduced risks for the highest versus the lowest category of coffee consumption; the meta-analyses of atrial fibrillation (21), Parkinson's disease (80), or type-2 diabetes (53) reported reduced risks for the highest versus the lowest category of caffeine intake; the meta-analyses of childhood leukemia (20) and pregnancy loss (66) reported increased risks for the highest versus the lowest category of coffee consumption; finally, meta-analyses of low birth weight (20, 106) and pregnancy loss (66) reported increased risks for the highest versus the lowest category of caffeine intake during pregnancy; no analyses had evidence of significant heterogeneity (**Figure 2**). In addition, meta-analyses of colorectal adenoma (35), oral cancer (71), skin cancers (melanoma and nonmelanoma) (13, 140), all-cause mortality (49), death after myocardial infarction (10), Parkinson's disease (40), Alzheimer's disease (79), type-2 diabetes (53), metabolic syndrome, urolithiasis (138), and depression (39) reported significantly reduced risks for the highest versus the lowest category

Outcome	Number of studies	Number of subjects	Number of cases	RR (95% CI)	I^2 (%)	Reference
Decaffeinated coffee						
Endometrial cancer	4 P	NA	NA	0.77 (0.63–0.94)	0	147
Type-2 diabetes	10 P	491,485	29,165	0.79 (0.69–0.91)	65	53
All-cause mortality	5 P	NA	NA	0.86 (0.80–0.92)	NA	49
Colorectal cancer	3 P	NA	NA	0.89 (0.80–0.99)	2	34
Skin cancer (melanoma)	5 P, 1 CC	718,231	3,269	0.92 (0.82–1.05)	NA	134
Breast cancer	4 P, 8 CC	NA	31,790	0.97 (0.89–1.06)	29	52
Coronary heart disease	5 P	NA	NA	1.00 (0.88–1.14)	NA	29
Skin cancer (nonmelanoma)	3 P	NA	32,975	1.01 (0.85–1.21)	0	14
Rheumatoid arthritis	2 P	NA	NA	1.05 (0.78–1.42)	0	64
Urinary tract cancer	4 P+CC	NA	NA	1.18 (0.99–1.40)	NA	136
Bladder cancer	5 P+CC	NA	NA	1.29 (0.88–1.89)	62	128
Caffeine						
Parkinson's disease	9 P	NA	NA	0.67 (0.57–0.80)	46	80
Type-2 diabetes	6 P	321,960	9,302	0.70 (0.65–0.75)	49	53
Dementia	3 P, 2 CC	NA	NA	0.72 (0.34–1.51)	76	58
Alzheimer's disease	2 P, 3 CC	NA	NA	0.78 (0.50–1.22)	71	58
Cognitive impairment	5 CS	NA	NA	0.79 (0.61–1.04)	21	58
Cognitive disorders	19 P+CC	31,479	NA	0.82 (0.67–1.01)	63	58
Depression	3 P	58,756	2,656	0.84 (0.75–0.93)	0	39
Skin cancer (nonmelanoma)	2 P, 2 CC	NA	25,993	0.86 (0.80–0.91)	48	14
Atrial fibrillation	6 P	228,465	4,261	0.88 (0.78–0.99)	41	22
Cognitive decline	4 P	NA	NA	0.99 (0.70–1.39)	62	58
Breast cancer	9 P+CC	NA	15,775	0.99 (0.94–1.04)	0	52
Pregnancy loss	13 P	NA	NA	1.21 (1.08–1.37)	21	66
Endometriosis	1 P, 4 CC	3,441	1,020	1.26 (0.95–1.66)	68	23
Low birth weight	8 P	74,885	3,887	1.43 (1.14–1.79)	49	102

Figure 3

Findings from 20 nonoverlapping meta-analyses of observational studies on decaffeinated coffee and caffeine, with effect size for highest versus lowest (reference) category of exposure. Abbreviations: CC, case control; CI, confidence interval; NA, not applicable; P, prospective; RR, relative risk.

of coffee consumption, and the meta-analyses of all-cause mortality (49) and type-2 diabetes (53) reported reduced risks for the highest versus the lowest category of decaffeinated coffee consumption, but there were a limited number of studies (≤3) or significant heterogeneity (I^2 > 50%). However, none of these studies clearly reported an exposure dose; thus the results can be interpreted only generically for high coffee intake compared with low intake or no consumption.

Supplemental Material

The variation in effects by the dose of coffee or caffeine was evaluated in 25 nonoverlapping meta-analyses testing for linear association with 39 outcomes (8, 18, 21, 25, 28, 32, 34, 38, 39, 49, 55, 68, 69, 76–79, 83, 84, 104, 127, 134, 151, 153) (see **Supplemental Figure 1**) and 16 using a nonlinear dose-response meta-analysis of 24 outcomes (26, 29, 34, 39, 52, 53, 61, 67, 92, 103, 111, 120, 126, 129, 148, 154) (**Figure 4**). Meta-analyses of liver (8), breast (69), endometrial (153), skin (melanoma) (78), colon (34), and prostate (151) cancers; all-cause mortality (49) and mortality from cardiovascular disease (CVD) (84); Parkinson's disease (25); depression; type-2 diabetes (28); cirrhosis (55); and chronic liver disease (8) reported significantly decreased risks for the incremental intake of coffee from 1 to 4 cups/day (depending on the study reference); and significantly decreased risks were also reported for endometrial cancer (153), Parkinson's disease (25), depression (39), atrial fibrillation (21), and type-2 diabetes (28) for incremental intake of 100 to 300 ml/day of caffeine (depending on the study reference) (**Supplemental Figure 1**). In contrast, increasing intakes of coffee or caffeine were associated with pregnancy loss, stillbirth, low birth weight and small-for-gestational-age infants (38), lung cancer (32), and fracture risk (77) (**Supplemental Figure 1**). Meta-analyses calculating the nonlinear dose-response relationship between coffee or caffeine and several outcomes showed significantly decreased risks of stroke (61), heart failure (92), cardiovascular and all-cause mortality (26) for up to 4 cups/day; there was also a linear dose-response relationship showing decreased risks of colorectal and colon cancers (34), breast cancer (52), skin cancer (melanoma) (126), Parkinson's disease (both coffee and caffeine exposure) (103), type-2 diabetes (53), metabolic syndrome (111), and gallstone disease (148) (**Figure 4**). An increased intake of coffee was associated with increased risks of lung cancer (129) and childhood acute lymphoblastic and myeloid leukemia (120); an inverted U-shaped increased risk for moderate coffee consumption was found for bladder cancer (154) and childhood acute leukemia (120). Similarly, nonoverlapping meta-analyses of caffeine intake showed a linear dose-response for decreased risks of type-2 diabetes (53), Parkinson's disease (103), and depression (39) (**Figure 4**).

Subgroup analyses were evaluated to test potential sources of heterogeneity for all nonoverlapping meta-analyses. These analyses mostly evaluated sex, geographical area, and adjustments for smoking status; a limited number also reported stratifying analyses for specific subgroups, including smokers and nonsmokers (**Supplemental Figure 2**). Some differences were found by sex: in men coffee was associated with an increased risk of bladder and lung cancer and with a decreased risk of fractures, but these associations were not found for women. In contrast, meta-analyses showed significantly reduced risks for women for gallstone disease, skin cancer (melanoma), and lung cancer. The association between coffee and health outcomes varied geographically and did not show a discernible pattern. Subgroup analyses adjusted by smoking status were conducted in only a limited number of meta-analyses and showed reduced risks of prostate cancer and all-cause mortality and an increased risk of an infant having low birth weight, but results were not significant in studies that did not adjust for smoking status; in contrast, significantly increased risks were found in the meta-analyses of oral (71), laryngeal, and lung (32) cancers only when considering studies that did not adjust for smoking status. Even fewer meta-analyses provided subgroup analyses that stratified smokers and nonsmokers; these showed increased risks of adult glioma (83) and childhood acute leukemia (120) among nonsmokers, but no association was found with lung cancer risk (32).

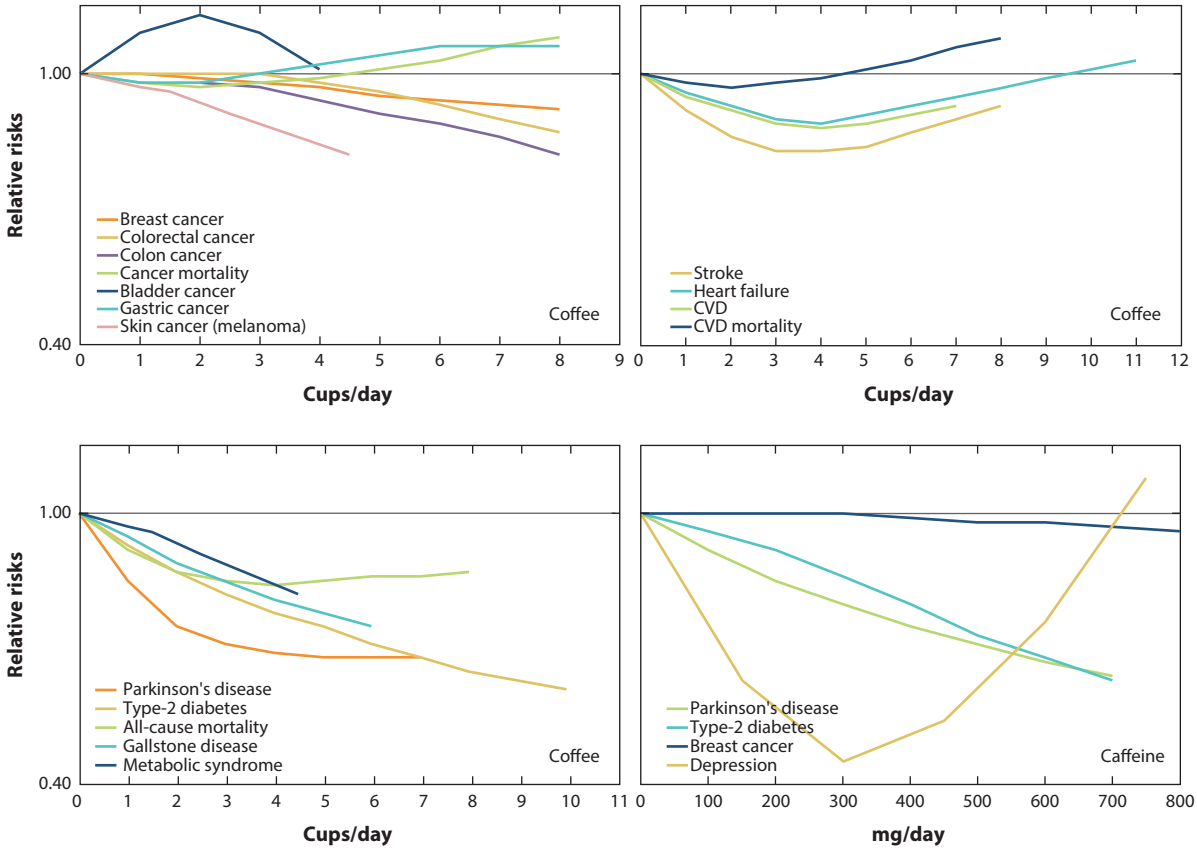

Figure 4

Findings from dose-response meta-analyses of observational studies on coffee or caffeine using relative risk as the metric.

Supplemental Material

The general characteristics of meta-analyses of outcomes for which more than one meta-analysis was published are presented in **Supplemental Table 1**. Agreement over time in terms of the direction, magnitude, and statistical significance of the associations was found in meta-analyses of atrial fibrillation (14, 60), all-cause mortality (49, 84), childhood acute leukemia (20, 89, 120), endometrial cancer (7, 48, 141, 153), liver cancer (5, 6, 8, 108, 141), lung cancer (32, 118, 137), prostate cancer (15, 43, 75, 81, 101, 151), skin cancer (melanoma) (78, 126, 140), type-2 diabetes (28, 45, 53), metabolic syndrome (86, 111), Parkinson's disease (caffeine exposure) (25, 80), depression (39, 127), and low birth weight (caffeine exposure) (17, 106). In contrast, meta-analyses conducted for colorectal, colon and rectal cancers (33–35, 50, 65, 141); breast cancer (52, 69, 119, 141); and pancreatic cancer (31, 96, 104, 123, 141) showed differences in the statistical significance of the effects, but not in the direction. Moreover, increments in statistical significance or changes in the direction of the association were found in meta-analyses of oral or laryngeal cancer (16, 98, 124), atrial fibrillation (caffeine exposure) (14, 21), gastric cancer (3, 27, 67, 76, 112, 135, 136, 143), bladder cancer (43, 134, 141, 154), and Alzheimer's disease and cognitive disorders (caffeine exposure) (58, 79, 109) (**Supplemental Table 1**).

Meta-Analyses of Randomized Controlled Trials of Coffee Consumption or Caffeine Intake and Health Outcomes

Seven nonoverlapping meta-analyses [including 2 RCTs of coffee (12, 117) and 5 of caffeine (47, 88, 97, 130, 155)] explored cardiovascular (blood pressure and ventricular arrhythmia), metabolic (blood lipids), respiratory (asthma), and pregnancy-related outcomes (**Table 2**). The number of studies included ranged from 1 to 12, and the number of individuals ranged from 78 to 1,488. All RCTs included in the meta-analyses investigated acute outcomes, as the length of the trials ranged from 180 minutes to 12 weeks. No meta-analysis was conducted to test the effects of the long-term consumption of coffee or caffeine.

Among the nonoverlapping meta-analyses of RCTs of coffee, significant increases were found in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides despite the significant heterogeneity among included studies (12); however, no effects were found on blood pressure (117) and ventricular fibrillation (only one RCT was included) (155). Among the 6 nonoverlapping meta-analyses of RCTs of caffeine, 2 studies (88, 97) demonstrated significant incremental increases in blood pressure in both healthy and hypertensive individuals after the administration of caffeine from coffee, and one meta-analysis (that included only one RCT) (47) reported a significant increase in serum insulin levels in newborns of mothers who were given caffeinated coffee compared with those who were given decaffeinated, but there were no significant changes in birth weight and in the risks of preterm birth and infants being small for gestational age. In contrast, another meta-analysis showed a significant increase in forced expiratory volume in 1 second in newborns following caffeine administration (130).

Supplemental Material

Three meta-analyses of RCTs of coffee explored the same outcomes over time (**Supplemental Table 2**). The findings of the meta-analyses of the effects on systolic blood pressure changed over time, varying from statistically significant to nonsignificant. Similarly, meta-analyses of effects on diastolic blood pressure showed differences in statistical significance, despite two of the three most recent meta-analyses reporting the same results.

Summary of Evidence from Observational Studies and Randomized Controlled Trials

Only blood pressure and pregnancy-related outcomes have been examined in meta-analyses of observational studies and RCTs. Meta-analyses of observational studies of blood pressure showed no substantial effects of coffee drinking on the risk of hypertension, whereas RCTs of caffeine showed significant increases in both systolic and diastolic blood pressure, suggesting that caffeine itself, rather than coffee, exerts effects that raise blood pressure, but coffee probably does not have a significant effect. The findings of meta-analyses of pregnancy-related outcomes diverged in the relationship between caffeine intake during pregnancy and birth weight, as well as for the risks of preterm birth and an infant being small for gestational age; however, the evidence was considered to be probable for an increased risk of pregnancy loss related to caffeine intake and it was considered possible for an increased risk of low birth weight, both of which persisted in the studies conducted in the United States. Among other meta-analyses of RCTs, the evidence was considered to be probable for the acute effects of coffee on serum lipids, despite a lack of evidence for long-term consumption.

A summary of evidence from the meta-analyses of observational studies of coffee or caffeine consumption and various outcomes is shown in **Table 3**. The details of the process for evaluating the evidence are presented in **Supplemental Figure 3**. The evidence for coffee was assessed as probable for the association of decreased risks for breast, colorectal and colon, endometrial, and prostate cancers; for CVD-related outcomes considered as a whole (including coronary heart

Table 2 Characteristics of nonoverlapping meta-analyses of randomized controlled trials reporting unique outcomes for coffee consumption or caffeine intake

Outcome	Intervention	Type of placebo	Number of studies	Total number of participants	Duration (range)	Exposure (range)	Analysis	Effect size (95% CI)	I^2 (%)	Reference
Coffee										
Total cholesterol	Regular, decaffeinated, filtered, instant	None or tea	12	1,017	2–11 weeks	2.4–8 cups/day	WMD	8.05 (4.48–11.62)	67	125
LDL cholesterol	Regular, decaffeinated, filtered, instant	None or tea	8	686	2–11 weeks	2.4–8 cups/day	WMD	5.44 (1.38–9.51)	58	125
HDL cholesterol	Regular, decaffeinated, filtered, instant	None or tea	9	830	2–11 weeks	2.4–8 cups/day	WMD	−0.12 (−0.62–0.38)	21	125
Triglycerides	Regular, decaffeinated, filtered, instant	None or tea	7	697	2–11 weeks	2.4–8 cups/day	WMD	12.55 (3.47–21.64)	66	125
SBP	Filtered, boiled, instant, decaffeinated	NA	10	1,488	6–14 weeks	2–6 cups/day	WMD	−0.55 (−2.46–1.36)	72	35
DBP	Filtered, boiled, instant, decaffeinated	NA	10	1,488	6–14 weeks	2–6 cups/day	WMD	−0.45 (−1.52–0.61)	41	35
Caffeine										
SBP	Filtered, boiled, instant	No coffee, decaffeinated coffee	5	1,010	1–12 weeks	295–750 mg	WMD (mm Hg)	4.16 (2.13–6.20)	NA	124
DBP	Filtered, boiled, instant	No coffee, decaffeinated coffee	5	1,010	1–12 weeks	295–750 mg	WMD (mm Hg)	0.41 (0.98–3.84)	NA	124

(*Continued*)

Table 2 (*Continued*)

Outcome	Intervention	Type of placebo	Number of studies	Total number of participants	Duration (range)	Exposure (range)	Analysis	Effect size (95% CI)	I^2 (%)	Reference
Asthma	Various sources	Decaffeinated coffee	6	78	1–2 weeks	5–450 mg	SMD (change in FEV_1)	0.72 (0.25–1.20)	0	126
SBP (in hypertensive individuals)	NA	NA	5	207	180 min	200–300 mg	WMD (mm Hg)	8.14 (5.68–10.61)	0	127
DBP (in hypertensive individuals)	NA	NA	6	207	180 min	200–300 mg	WMD (mm Hg)	5.75 (4.09–7.41)	0	127
Birth weight	Instant caffeinated coffee	Instant decaffeinated coffee	1	1,207	Up to 4 weeks after delivery	62 mg/day (mean)	WMD (g)	20.00 (−48.68–88.68)	NA	128
Preterm birth	Instant caffeinated coffee	Instant decaffeinated coffee	1	1,207	Up to 4 weeks after delivery	62 mg/day (mean)	RR	0.81 (0.48–1.37)	NA	128
Small for gestational age	Instant caffeinated coffee	Instant decaffeinated coffee	1	1,207	Up to 4 weeks after delivery	62 mg/day (mean)	RR	0.97 (0.57–1.64)	NA	128
Serum insulin level	Instant caffeinated coffee	Instant decaffeinated coffee	1	1,207	Up to 4 weeks after delivery	62 mg/day (mean)	WMD (pmol/L)	38.8 (13.57–64.03)	NA	128
Ventricular arrhythmia	Instant coffee	Decaffeinated coffee	1	52	5 days	175–450 mg/day	RR	0.98 (0.93–1.03)	NA	129

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 second; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; RR, relative risk; SBP, systolic blood pressure; SMD, standardized mean difference; WMD, weighted mean difference.

Table 3 Evidence from observational studies of association between coffee or caffeine intake and health outcomes

Level of evidence	Outcome		
	Coffee	Decaffeinated coffee	Caffeine
Probable	Decreased risks of breast cancer, colorectal cancer, colon cancer, endometrial cancer, prostate cancer, cardiovascular disease, cardiovascular disease mortality, Parkinson's disease, and type-2 diabetes	–	Decreased risks of Parkinson's disease and type-2 diabetes
			Increased risk of pregnancy loss
Possible	Decreased risks of liver cancer, oral and laryngeal cancer, melanoma, coronary heart disease, all-cause mortality, chronic liver disease and cirrhosis, Alzheimer's disease, and gallstone disease	Decreased risks of all-cause mortality and endometrial cancer	Decreased risk of cognitive disorders
	Increased risks of childhood acute leukemia (myeloid and lymphoblastic), gastric cancer, and pregnancy loss	–	Increased risk of infant having low birth weight
No associations	Adult glioma, bladder cancer, cancer mortality, esophageal cancer, ovarian cancer, pancreatic cancer, renal cancer, atrial fibrillation, hypertension, stroke, hip fractures, peptic ulcer, rectal cancer, and cognitive disorders (including cognitive decline, impairment, and dementia)	Breast cancer, coronary heart disease, and melanoma	Breast cancer and cognitive disorders
Limited	Decreased risks of colorectal adenoma, nonmelanoma skin cancer, death after myocardial infarction, venous thromboembolism, depression, gout, metabolic syndrome, and urolithiasis	Decreased risk of colorectal cancer	Decreased risk of depression
	No association with gastroesophageal reflux, duodenal and gastric ulcers, endometriosis, neural tube defects and spina bifida in offspring, and rheumatoid arthritis	No association with bladder cancer, urinary tract cancer, rheumatoid arthritis, and nonmelanoma skin cancer	No association with Alzheimer's disease, cognitive impairment, endometriosis, and nonmelanoma skin cancer
Contrasting	Risk of lung cancer and fractures in men	Risk of atrial fibrillation	–

disease, stroke, heart failure, and mortality), Parkinson's disease, and type-2 diabetes; and with no probable effect on the risk of pancreatic and rectal cancers. Notably, the evidence for decreased risks of liver cancer, chronic liver disease, stroke, and Alzheimer's disease was graded as highly possible. The evidence for associations between coffee consumption and increased risks of childhood acute leukemia and gastric cancer was considered to be possible. Contrasting results on lung cancer were due to the different associations found for men and women, the reliance on studies that did not adjust for smoking status, and for findings considered to be not significant when studies were conducted only among nonsmokers. Caffeine was associated with probable decreased risks for Parkinson's disease and type-2 diabetes. Several other associations were retrieved but often affected by heterogeneity or potential confounding factors.

DISCUSSION

In this study, the findings of 127 meta-analyses of coffee and caffeine exposure were reviewed; the meta-analyses examined 62 outcomes, including cancer, and cardiovascular and other outcomes.

Most of the evidence came from meta-analyses of observational studies; only a few meta-analyses included RCTs. Comparisons of pooled analyses of observational studies and RCTs were possible only for blood pressure and hypertension, and low birth weight; the findings for these analyses were inconclusive. Based on these results, there is probable evidence of the beneficial effects of coffee consumption for a number of chronic diseases, including some cancers (endometrial, prostate, colorectal, and liver), CVD and metabolic-related outcomes (such as type-2 diabetes and metabolic syndrome), and neurological conditions (such as Parkinson's disease, Alzheimer's disease, and depression). The risk estimate relations in most of the meta-analyses were calculated as high versus low consumption; thus, they did not allow a clear reference exposure to be defined. Among the studies providing dose-response analyses, some relations were linear but others showed the lowest risk at about 4–5 cups/day. Adverse effects were limited mainly to pregnancy-related outcomes following caffeine intake rather than other components in coffee, as controls were administered decaffeinated coffee.

Antioxidant Properties of Coffee

Most of the potential beneficial effects of coffee rely on the assumption that coffee may have antioxidant and anti-inflammatory actions that, over the long term, may induce protection against subclinical inflammation and chronic diseases triggered by inflammation (85). Experimental models and studies on humans have demonstrated, albeit with some contrasting results, the attenuation of inflammatory markers—such as interleukin 6, tumor necrosis factor-α, interferon-γ, and transforming growth factor-β—after administration of coffee (85). The main components of coffee described as exerting such effects are phenolic compounds, caffeine, diterpenes, trigonelline, and melanoidins.

The phenolic component of coffee is mostly characterized by chlorogenic acids, a family of esters of hydroxycinnamic acids (mostly caffeic acid and ferulic acid) with D-(−)-quinic acid. These compounds represent the highest phenolic component of green coffee seeds, together with tannins, lignans, and anthocyanins, and they significantly determine coffee's quality, aroma, and flavor. Chlorogenic acids have been demonstrated to induce antioxidant effects, decreasing the production of inflammatory mediators through several mechanisms, including (*a*) inhibiting protein tyrosine phosphatase 1B, (*b*) inhibiting expression of proinflammatory cytokine genes, and (*c*) modulating inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation via the redox-related tyrosine protein kinase/extracellular signal-regulated kinase and NF-kB–inducing kinase/IκB kinase pathways via the reduction of oxidative stress (36).

Caffeine has been by far the most studied coffee component due to its effects on adenosine receptors in the brain, as well as in the cardiovascular, respiratory, renal, and gastrointestinal systems, and in adipose tissue. However, caffeine has been reported to have the ability to inhibit induced NF-κB activation through mechanisms similar to those described for chlorogenic acids (156).

Cafestol and kahweol are two diterpenes that naturally occur in coffee beans. It is unclear whether coffee diterpenes may exert direct antioxidant properties, but it has been shown that (*a*) they may increase the expression of NAD(P)H:quinone oxidoreductase 1, an enzyme implicated in the synthesis of endogenous antioxidants through the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) pathway; and (*b*) they increase the production of glutathione and γ-glutamylcysteine synthase, the limiting enzyme for glutathione synthesis, which is an important endogenous antioxidant and cofactor of detoxifying metabolism (42).

Trigonelline is a plant alkaloid derivate of vitamin B6 contained in coffee beans, and it is one of the main components that contributes to bitterness in coffee. Animal studies have shown that

trigonelline decreases malonaldehyde and nitric oxide concentrations and increases the activity of superoxide dismutase, catalase, glutathione, and inducible nitric oxide synthase in the pancreas, suggesting that trigonelline may also exert antioxidant effects by upregulating antioxidant enzyme activities and decreasing lipid peroxidation (152).

Melanoidins are high molecular weight, nitrogenous, brown-colored polymers that may exert antioxidant and anti-inflammatory activity based on their radical scavenging or their metal chelating capacities, or both, despite depending on the degree of coffee roasting (it seems that coffee antioxidant activity may decrease as coffee is roasted longer) (91).

Coffee and Microbiota

The anti-inflammatory effects of coffee may be also mediated by alteration of the gut microbiota. There is evidence from cellular, animal, and human studies that administration of coffee induces changes in the structure and function of the gut microbiota, modifying the ratio among major phyla (*Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, and *Firmicutes*) in favor of an anti-obese profile (i.e., decreased *Firmicutes*-to-*Bacteroidetes* ratio) (100). Increases in bifidobacteria have been associated with anti-inflammatory effects, which, in turn, may mitigate local inflammation, decrease procarcinogenic processes, and lower misfolding rates of α-synuclein in the enteric nervous system, thus reducing the risk of Parkinson's disease by minimizing propagation of the protein to the central nervous system (93). In addition to the direct effects of gut microbiota on metabolism (lower energy expenditure, higher energy harvest, fat deposition, and weight gain), microbiota alterations may have an important role in the biotransformation of polyphenols, which, in turn, may exert collateral benefits associated with coffee consumption, such as a rise in polyphenol metabolites, which have antioxidant properties (90).

Coffee and Cancer

A number of plausible mechanisms may explain the observed associations between coffee and cancer risk. Phytochemical compounds contained in coffee (diterpenes, melanoidins, and polyphenols) may exert beneficial effects, including inhibiting oxidative stress and oxidative damage irrespective of the site involved. These actions may have a role, particularly in the early process of the transformation of a normal cell into a malignant tumor. Coffee has been demonstrated to play a part in defense mechanisms, including regulating DNA repair, phase II enzymatic activity, and apoptosis, as well as having antiproliferative, antiangiogenic, and antimetastatic effects; the expression of antioxidant defense and detoxification genes depends on transcription factors that can be regulated by coffee, such as the complex of Nrf2 and Kelch-like ECH-associated protein 1, activator protein 1, or the aryl hydrocarbon receptor (2).

In addition to having general effects at the cellular level, coffee consumption may exert specific benefits at individual cancer sites. A high intake of caffeine has been positively associated with increases in sex hormone binding globulin and inversely associated with bioavailable testosterone, which may influence the risks of endometrial and breast cancers (46). For colorectal cancer, the effects of coffee consumption are related to the excretion of bile acids and neutral sterols into the colon, alteration of microbiota composition, and increases in bowel mobility in the rectal region (125). Coffee consumption also increases the detoxification capacity and antimutagenic properties of the colorectal mucosa by increasing glutathione concentration (44). A key part is played by coffee diterpenes, which have been found to reduce mutagenesis by strongly metabolizing carcinogenic compounds, inducing glutathione *S*-transferases, and inhibiting *N*-acetyltransferases, all mechanisms that are beneficial in preventing cancer (44).

Coffee and Liver Health

Coffee is also associated in a dose-dependent manner with improved serum concentrations of γ-glutamyltransferase, aspartate aminotransferase, and alanine aminotransferase; with the severity of steatohepatitis in patients with nonalcoholic fatty liver disease and with decreased liver fibrosis, both of which are chronic alterations preceding hepatocellular carcinoma. The main mechanisms proposed for the hepatoprotection of coffee involve caffeine, phenolic compounds, and melanoidins. Caffeine may counteract the hepatic fibrinogenesis pathway by downregulating the production of connective tissue growth factor induced by transforming growth factor-β1, by upregulating the PPARγ receptor, and by inhibiting the synthesis of focal adhesion kinase and actin (107). Phenolic compounds, melanoidins, and caffeine are responsible for antioxidant effects at the hepatic level that prevent free radical tissue damage by reducing reactive oxygen species, which, in turn, play a central part in the inflammation processes characterizing nonalcoholic fatty liver disease, steatohepatitis and, ultimately, liver fibrosis (19).

Coffee and Metabolic Health

Coffee consumption and caffeine intake have been also associated with decreased risks for a number of metabolic outcomes. Consistent evidence has demonstrated the beneficial effects of coffee compounds on insulin and glucose metabolism. Consumption of chlorogenic acids has been demonstrated to reduce fasting plasma glucose concentrations, increase sensitivity to insulin, and slow the appearance of glucose in circulation after glucose load (87). The mechanisms underlying these actions include (*a*) competitive inhibition of the glucose-6-phosphate translocase, an enzyme involved in regulating the homeostasis of blood glucose levels; (*b*) activation of adenosine monophosphate-activated protein kinase, a sensor and regulator of cellular energy balance, which may induce inhibition of fatty acid synthesis and hepatic glucose production; (*c*) reduction of sodium-dependent glucose transport in brush-border membrane vesicles of the small intestine; and (*d*) inhibition of α-amylase and α-glucosidase activity, two key enzymes responsible for digesting dietary carbohydrates, resulting in a reduction of intestinal absorption of glucose (11).

Coffee and Cardiovascular Health

The association between coffee consumption and cardiovascular outcomes may be the result of the aforementioned beneficial effects of coffee on cardiometabolic health. Most of the effects are thought to be related to the antioxidant effects of coffee, specifically (*a*) the reduction of LDL oxidation susceptibility, which is a key step in the development and progression of atherosclerosis; and (*b*) the ability of methyltetrahydrofolate, the main circulating metabolite of folate, and caffeine to increase nitric oxide production and scavenge superoxide radicals (105).

Coffee and Lithiasis

Coffee has also been demonstrated to decrease the risk of gallstone disease and, possibly, urolithiasis. In experimental studies, coffee has been shown to stimulate cholecystokinin release, enhance gallbladder contractility, improve gallbladder mucosal function, and decrease cholesterol crystallization in bile; these effects have been hypothesized to depend on its caffeine content (110). Insulin resistance has also been associated with gallstone risk. Moreover, caffeine also increases urinary calcium and oxalate excretion (23). Finally, the anti-inflammatory effects of coffee are postulated to have a protective role in the pathogenesis of lithiasis.

Coffee and Mental Health

The potentially beneficial effects of coffee on Parkinson's disease and, more generally, mental health may reflect the neuroprotective action of (*a*) caffeine acting as an adenosine receptor antagonist, which results in the release of mainly excitatory transmitters, including dopamine; (*b*) trigonelline, *N*-methylpyridinium, chlorogenic acid, catechol, pyrogallol, and 5-hydroxytryptamides, all of which have been demonstrated to increase calcium signaling and dopamine release; and (*c*) the local antioxidant effects of chlorogenic acids, which have been associated with neurogenesis (the process by which neurons are generated) (95).

Potential Detrimental Effects of Coffee and Caffeine Consumption

The only potentially adverse outcomes related to coffee consumption have been found to be increased risks of lung and gastric cancers, and increases in serum lipids. The increased risks of lung and gastric cancers are highly sensitive to the potentially modifying effect of smoking habits, which is a more important risk factor than coffee drinking. In fact, for both lung and gastric cancers a subgroup analysis revealed that the association was significant only in studies that did not adjust for smoking status, and no increased risk of lung cancer was observed in a subgroup analysis of studies conducted on nonsmokers. In studies of coffee's potential to increase serum lipids, it has been documented that unfiltered coffee may contain a significant quantity of diterpenes that may affect the LDL receptor, which is responsible for the endocytic processes of Apo B- and Apo E-containing lipoproteins, and, consequently, lead to extracellular accumulation of cholesterol (36). However, there is no evidence that long-term coffee consumption is associated with an increased risk of dyslipidemia or other outcomes related to a rise in serum lipids.

Caffeine has been associated with acute rises in blood pressure. There is no definitive consensus on a mechanism that would explain the weaker effects demonstrated in long-term, habitual coffee drinkers. It is biologically plausible that chronic administration of coffee could induce tolerance and, thus, a lack of significant effects at the level of blood vessels. Moreover, the antioxidant compounds contained in coffee may somehow counteract the effects of caffeine in raising blood pressure.

The adverse associations with caffeine were mostly pregnancy-related outcomes (including low birth weight, pregnancy loss, and childhood leukemia). Caffeine passes through placental barriers, and cytochrome P450 1A2 (CYP1A2) activity is reduced during pregnancy, thus potentially exposing the fetus to caffeine for a long period of time, which may affect fetal growth (9). Moreover, caffeine may act as an inhibitor for DNA topoisomerase II and DNA repair systems, which, in turn, may induce chromosomal aberrations and translocations, such as abnormalities related to leukemia (122). Some evidence suggests that caffeine may influence DNA methylation by altering responsible genes, resulting in a notable increase in total methylation as well as increased methylation frequency (122). However, the studies included in the meta-analyses did not stratify by smoking status, which is itself a known risk factor for the aforementioned outcomes. Moreover, early caffeine therapy in newborns (administered intravenously) has been demonstrated to exert certain benefits toward malformation of the respiratory tract, significantly decreasing the risk of bronchopulmonary dysplasia (59).

LIMITATIONS OF THE STUDY

This umbrella review should be considered in light of two major limitations. The first is the lack of consistent data among studies of a clear and unequivocal exposure dose to which the associations refer. Indeed, most of the evidence gathered relies on effect sizes referring to "the highest

compared with the lowest" category of exposure. Although we may arbitrarily hypothesize what high, moderate, and low coffee consumption refer to (perhaps, respectively, >6 cups/day, 3–5 cups/day, and <3 cups/day), this is not sufficient to draft adequate dietary guidelines with scientific accuracy. However, several meta-analyses presented dose-response analyses for numerous outcomes, strengthening the evidence of a potential effect and resolving, at least in part, the aforementioned limitation. The second major issue is the ubiquitous lack of information on potentially important concerns relative to genetic polymorphisms. Although outside of the scope of this umbrella review, it is worth mentioning that polymorphisms of the *CYP1A2* gene have been demonstrated to affect caffeine metabolism, which, in turn, may result in potentially different risk estimates, depending on its activity (especially for cardiovascular outcomes) (24, 99). Thus, the possibility that the association of coffee consumption with health benefits may not be reproducible in individuals with specific genetic profiles should be taken into account and investigated in future studies. Other limitations concern the lack of consistent information on methods of coffee preparation [filtered or boiled, or drying method (for soluble coffee)], roasting characteristics, as well as coffee add-ins (sugar, dairy products).

IMPLICATIONS FOR PUBLIC HEALTH EXPERTS AND FUTURE RESEARCH

Essentially all of the data on chronic conditions, for which long-term consumption of coffee may be required for any effect to occur, are based on observational studies. RCTs considered what are presumed to be intermediate biomarkers (e.g., lipids) or physiologic effects (e.g., blood pressure), but direct estimates of the long-term effects of coffee have not been explored. Although observational data cannot definitively prove causality, as a whole they include a number of strengths: Overall coffee consumption is reasonably well measured; the findings for many of the conditions were based on large numbers of people and diverse populations; they covered long-term intake over multiple time periods and, in some cases, considered regular and decaffeinated coffee; the low heterogeneity observed in some studies also reinforces the strength of the findings. However, drinking coffee is generally not considered a health-conscious behavior and, in fact, in many populations those who consume large amounts of coffee tend to smoke more and are more likely to consume alcohol excessively. Thus, uncontrolled or residual confounding cannot be excluded definitively. In fact, as studies have become better able to control for confounding factors, particularly for tobacco use, inverse associations have emerged or been strengthened. Despite examining the characteristics of individuals in numerous studies who consumed large quantities of coffee, we could not identify an obvious candidate confounding factor that could plausibly explain the potential beneficial effect of coffee consumption on human health, but in some cases (i.e., lung and gastric cancers) the role of tobacco use as an effect modifier appeared quite evident.

To date, the broad research from observational studies on the beneficial effects of coffee on cancer, CVD, and metabolic and neurological disorders is promising. The main limitation in drawing strong conclusions from causal associations is the lack of data from long-term RCTs. Nonetheless, given that coffee consumption is a widespread behavior in numerous populations, these results are largely reassuring when compared with the adverse effects (except in the context of pregnancy) and, if anything, are suggestive of potential benefits. Consumption of 4–5 cups/day seems to have benefits for many of the outcomes examined, although higher intakes could require caution, especially during pregnancy and for people with CVD-related conditions, but these may be due to residual confounding from smoking. Given the lack of RCTs, the extensive studies using observational data, the robustness of the findings—which have generally been strengthened by better study design and controls for confounding—it is unlikely that the level of evidence will

change appreciably in the foreseeable future. In any case, our findings indicate that coffee can be part of a healthful diet.

SUMMARY POINTS

1. There is probable evidence that coffee consumption has beneficial effects for a number of chronic diseases, including cancers, and cardiovascular, metabolic, and neurological conditions.
2. The dose-response effect in most meta-analyses was linear, with the lowest risk reached with the consumption of about 4–5 cups/day.
3. Adverse effects were mainly limited to pregnancy-related outcomes associated with caffeine intake rather than other components in coffee.
4. Evidence retrieved for other potential adverse effects, such as lung and gastric cancers, seems to have been affected by the confounding effect of smoking.

FUTURE ISSUES

1. Future studies should include stratification by smoking status to most definitively exclude confounding and to better characterize the dose-response relationship.
2. Taking into account genetic variation in caffeine metabolism could strengthen associations and conclusions.
3. Interventions with end points based on physiologic parameters, hormones, and metabolomics may offer mechanistic insights and, thereby, strengthen conclusions.
4. Separating the consumption of regular coffee from decaffeinated coffee is critical to determine whether benefits are due to caffeine or other components, such as chlorogenic acid.

CONTRIBUTIONS

G.G. conceived the idea for the study. G.G. and J.G. performed the systematic review and extracted the data; G.G., F.G., and E.L.G. wrote the manuscript. All authors reviewed the manuscript. All authors contributed equally to the article.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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