Inter-individual Variation in Cancer and Cardiometabolic Health Outcomes in Response to Coffee Consumption: a Critical Review

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Abbreviations

ADORA, adenosine receptor; ADR, adrenergic receptor; AHR, aryl hydrocarbon receptor; COMT, catechol-O-methyltransferase; CYP, cytochrome P450; GGT, gamma-glutamyltransferase; NAT, N-acetyltransferase

Keywords

Coffee – Caffeine – Inter-individual variation – Biological responsiveness – Nutrigenomics

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Abstract

Scope: Coffee has been associated with a lower risk of cancer, cardiovascular disease and type 2 diabetes at the population level. However, individual susceptibility to the effects of coffee consumption will cause heterogeneity in health responses between individuals. In this critical review we systematically evaluated determinants of inter-individual variability in cancer and cardiometabolic health outcomes in response to coffee and caffeine consumption.

Methods and results: Embase and MEDLINE were searched for observational studies and clinical trials that examined variation in the response to coffee consumption. A total of 74 studies met the inclusion criteria, which reported variation in cancer (n=24) and cardiometabolic health (n=50) outcomes. Our qualitative analysis showed that sex, BMI, smoking, alcohol intake, menopausal status and genetic polymorphisms are probable or possible determinants of inter-individual variability in cancer and cardiometabolic health outcomes in response to coffee and caffeine consumption, albeit that the majority of studies had insufficient statistical power to detect significant interaction between these factors and coffee consumption.

Conclusion: We identified several genetic and non-genetic determinants of inter-individual variability in the responses to coffee and caffeine consumption, indicating that some of the health benefits of coffee may only occur in a subgroup of subjects.

1. Introduction

Globally, coffee is one of the most consumed beverages.[1] European countries account for one third of the global coffee consumption, however, in the past 5 years the highest increase in coffee consumption has been seen in Africa and Asia & Oceania.[2] Considering the widespread use of coffee, even small health effects can have considerable impact on a population level.

Initial epidemiological studies showed that coffee consumption was associated with an increased risk of disorders such as myocardial infarction, cardiac arrhythmia, peptic ulcers and certain cancers.[3-5] However, more recent epidemiological and experimental studies that have taken dose-response effects and coffee preparation methods into account, have shown that coffee consumption is associated with a lower risk of obesity, type 2 diabetes, cardiovascular diseases, chronic liver disease and several cancers, including endometrial, prostate and skin cancer.[6, 7] Although caffeine intake has been linked to acute increases in blood pressure,[7, 8] habitual moderate coffee intake is not related to hypertension.[8, 9] Long-term coffee consumption may even decrease the incidence of hypertension,[8, 10] as habitual coffee consumers can develop a tolerance to the vasoconstricting effects of caffeine.[7, 9] Lastly, coffee consumption has also been associated with a 10-20% decreased

risk of all-cause mortality.[11, 12] Yet, most of the available evidence comes from observational rather than intervention studies.

As data from observational studies are averaged for an entire study population, the health effects that might occur in subgroups of subjects, characterized by genotype or phenotype, can be overlooked.[13] This is an important observation as the individual susceptibility to coffee consumption may cause heterogeneity in health benefits between persons. Indeed, genetic and non-genetic factors can modify the bioavailability and efficacy of coffee constituents to affect health outcomes. Although coffee is known for its caffeine content, it contains a wide variety of bioactive compounds, such as methylxanthines (caffeine being one of them), phenolic compounds (e.g. chlorogenic acids), diterpenes, melanoidins, trigonelline, vitamins and minerals.[14] Inter-individual variation in the absorption and metabolism of these compounds can affect the biological response.[13, 15]

The aim of this critical and hypothesis-generating review is to identify and evaluate determinants of inter-individual variability in cancer and cardiometabolic health outcomes in relation to coffee and caffeine consumption in published observational and human intervention studies.

2. Methods

This study was conducted following the PRISMA checklist where reasonably possible.[16] To identify the factors that are associated with heterogeneity in the health response to coffee consumption and its bioactives, a systematic search of Embase (from 1996) and MEDLINE (from 1946) databases was performed up to November 2019, using Ovid. The fields title, abstract, keywords and subject headings (MeSH and Emtree) were searched, using the following search query: (((coffee OR caffeine or xanthine$ OR chlorogenic OR caffeoyl* OR caffeic OR cinnamate$) AND ((coronary adj2 disease) OR cardiovascular disease$ OR hypertension OR dyslipidemia$ OR endothelial dysfunction OR metabolic syndrome OR diabetes OR body weight OR obesity OR liver disease$ OR neoplasm$ OR cancer OR tumo?r) AND ((effect adj3 modif*) OR interindividual OR inter-individual OR between subject OR between-subject OR personali?ed OR nutrigen* OR interaction OR individual varia* OR genetic varia*)). No restrictions on the determinant of variability were applied.

A total of 842 articles were identified after removal of duplicates (Figure 1). Two investigators independently screened titles and abstracts and disagreements were resolved by consensus. We excluded papers that were not written in English, review articles and meta-analyses, animal studies, *in vitro* studies and studies assessing drug-interactions. Furthermore, studies were also excluded when they were not related to coffee (e.g. tea), or examined health outcomes other than cancer and cardiometabolic diseases. After further evaluation, a total of 74 papers describing 8 intervention

studies and 66 observational studies were eligible for inclusion in the qualitative analysis. Of these, 24 studies were related to cancer (Table 1),[17-40] and 50 studies to cardiometabolic diseases (Table 2).[41-90]

Extracted data included determinants of variability, study design and duration, study population, country of study population, the exposure, assessment of exposure, outcome of interest, findings and p-values of interaction terms between coffee/caffeine consumption and the determinant of variability.

The likelihood of existing variability in response was considered as follows:

- '*probable*': when for any one health/disease outcome and determinant of variability, at least one study reports a $p_{interaction} \leq 0.05$, and all studies report significant differential responses between determinant subgroups;
- '*possible*': when for any one health/disease outcome and determent of variability, at least one study reports a $p_{interaction} \leq 0.05$, and/or at least one study reports a significant differential response between determinant subgroups;
- '*unlikely*': when for any one health/disease outcome and determinant of variability, no single study reports a $p_{interaction} \leq 0.05$, and no single study reports significant differential responses between determinant subgroups.
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3. Results

3.1 Probable determinants for the variability in cancer outcomes in response to coffee consumption

Both sex and smoking were probable determinants for colon cancer risk in response to coffee consumption (Table 1, Figure 2). In men and in male smokers, consumption of caffeinated coffee lowered the risk of colon cancer,[29,30] whereas in women and in female smokers, a positive association between coffee intake and colon cancer was found in one study,[29] but not in another study.[31]

Smoking was a probable determinant for bladder cancer risk in response to coffee consumption in two studies, albeit that both studies found opposing results - one study reported that coffee consumption increased the risk of bladder cancer in male non-smokers, but not in smokers,[17] whereas a second study reported that coffee consumption increased this risk in smokers.[18] BMI was a probable determinant for endometrial and prostate cancer in response to coffee consumption.

Coffee consumption lowered the risk for both cancers in overweight but not in normal weight subjects.[31,32,36]

Lastly, history of breast disease was a probable determinant for breast cancer risk in response to caffeine intake. Caffeine intake increased breast cancer risk in those with a history in breast disease, but there was no association between caffeine intake and breast cancer risk in those without a disease history (Table 1).[24]

3.2 Probable determinants for the variability in cardiometabolic outcomes in response to coffee consumption

Sex, alcohol consumption, diet, BMI, heart rate variability and genetic polymorphisms were probable determinants for risk of hypertension in response to coffee and caffeine consumption (Table 2, Figure 2). In women generally, in women with a low adherence to the Mediterranean diet, or in carriers of the CYP1A2 A-allele (rs762551), an increased coffee consumption was associated with a lowered risk of hypertension,[42, 44] whereas in those with a high alcohol intake, a genetic risk of high blood pressure, or carriers of the CYP1A2 C-allele (rs762551), coffee consumption was associated with an increased incidence of hypertension.[42, 43, 87] In normal weight men, increased coffee consumption was associated with a decrease in systolic blood pressure whereas in overweight men, increased coffee consumption was associated with an increase in systolic blood pressure.[45] Furthermore, in those with a high heart rate variability, caffeine ingestion was associated with an increase in acute blood pressure.[47]

Sex was also a probable determinant of variability for cholesterol levels in response to coffee consumption. In women only, high coffee intake was associated with increased levels of HDL-cholesterol.[83] Cholesterol levels itself were also a probable determinant of cardiovascular health. In subjects with hypercholesterolemia, daily consumption of a green/roasted coffee blend for 8 weeks increased the levels of total-, LDL- and VLDL-cholesterol and triglycerides.[80] Such an effect was not seen in subjects with normal cholesterol levels.

Sex, BMI, GGT levels and a genetic risk of insulin resistance were probable determinants for risk of type 2 diabetes and insulin resistance in response to coffee consumption (Table 2). In females, in overweight men and women, and in those with high GGT levels or a high genetic risk, an increased coffee consumption was associated with a decreased risk in type 2 diabetes,[65, 66, 69] or a lower risk of insulin resistance.[60, 61, 63, 82] In females with diabetes, high coffee consumption reduced the risk of all-cause mortality, which was not shown in diabetic men.[88]

Age, physical activity, BMI, smoking and genetic risk were probable determinants for risk of weight gain or BMI in response to coffee consumption (Table 2). In men under 50, or in women who smoke, have low physical activity or are overweight, increased caffeine intake is associated with reduced weight gain.[58] In those with a high genetic risk of obesity, increased coffee consumption was linked to a lower BMI, whereas in those with a low genetic risk of obesity, increased coffee consumption was linked to a higher BMI.[59]

Both age and smoking were probable determinants of serum GGT levels in response to coffee consumption (Table 2). In those aged 46-60 years, and in smokers, daily or increased coffee consumption was associated with lower serum GGT levels.[75, 77] In those with a normal weight, increased coffee consumption was associated with decreased serum ALT levels.[76]

Both family history and genetic polymorphisms are probable determinants for risk myocardial infarction (MI) and heart failure in response to coffee consumption (Table 2). In those with a family history, or those carrying the CYP1A2 rs762551 C-allele, increased coffee consumption was associated with increased MI risk,[48, 49] whereas in those without a family history, increased coffee consumption was associated with a decreased risk in MI.[49] However, in male carriers of the CYP1A2 rs762551 C-allele, increased consumption of coffee and caffeine was probable with a decreased risk of heart failure.[51]

Both serum GGT levels and insulin resistance were probable determinants of inflammation and liver fibrosis, respectively. In men with high serum GGT levels, increased coffee consumption was associated with decreased concentrations of CRP.[72] In those with low insulin resistance, increased coffee consumption was associated with a decreased risk of advanced fibrosis.[78] Alcohol consumption was a probable determinant of variability in response to coffee, with regard to liver disease mortality. In those with a high alcohol intake, the risk of liver disease mortality was higher with a low coffee consumption.[90]

4. Discussion

This critical review identified main determinants of inter-individual variability in response to coffee and caffeine consumption, including sex, BMI, smoking, alcohol, menopausal status, CYP1A2 activity, and GGT levels. However, most studies had insufficient statistical power to detect an interaction between coffee consumption and these risk modifying factors, which may explain why such factors modified the association between coffee consumption and cancer and cardiometabolic health outcomes in some studies, but not in others. This is the first time that the available evidence of

heterogeneity in health outcomes due to coffee consumption has been systematically summarized, with the purpose to generate new research goals.

The role of these determinants can often be linked to mechanisms involved in the disease development process. For example, circulating estrogens are an important risk factor of both endometrial and breast cancer.[91-93] Caffeine lowers estrogen levels via up-regulation of the sex hormone-binding globulin, which may explain the inverse relationship between coffee consumption and these cancers.[25, 91, 93] Furthermore, hyperinsulinemia is associated with increased estrogen levels and endometrial cancer risk.[32, 33] As coffee has been demonstrated to reduce insulin levels, this may explain why overweight and obese women had the greatest reduction in endometrial cancer risk as a result of coffee intake.[33] Coffee also contains phytoestrogens which have been suggested to reduce the risk of endometrial cancer,[32] postmenopausal breast cancer,[20] and possibly the risk of estrogen receptor negative breast cancers, as these phytoestrogens may interact with the estrogen receptor.[20, 29, 94]

The variation in response can also be attributed to alterations in the efficacy of coffee bioactives. CYP1A2 is the key enzyme catalyzing the metabolism of caffeine (Supporting Information, Figure S1) and is responsible for more than 90% of caffeine clearance.[95]. Caffeine is demethylated by the hepatic enzyme CYP1A2 into paraxanthine, theobromine and theophylline.[95-97] These metabolites are then broken down by further demethylation and oxidation reactions to dimethyl and monomethyl uric acids. Genetic polymorphisms in the CYP1A2 gene region can affect the enzyme activity, for example an C to A substitution at position -163 (rs762551) results in an increased enzyme activity.[98, 99] Carriers of the C-allele will have a slower caffeine metabolism rate, compared to homozygotes of the A-allele. The inverse association between coffee consumption and breast cancer risk in C-allele carriers can be attributed to a prolonged exposure of caffeine, as caffeine might inhibit cell proliferation and can induce apoptosis.[22, 25] However, the prolonged exposure to caffeine may have detrimental effects on cardiovascular health, as was shown for the risk of myocardial infarction and hypertension.[42, 48]

The health benefits of coffee consumption may be more pronounced in high-risk subgroups. For example, increased GGT levels are a biomarker of oxidative stress and have been associated with alcohol-induced hepatic steatosis.[72, 100]. The health benefits of coffee consumption for this group may be due to the antioxidant capacity of some of the bioactive compounds in coffee such as caffeine, chlorogenic acids, melanoidins and trigonelline,[101] which may protect against the detrimental effects of oxidative stress and inflammation. A number of studies showed that coffee consumption lowered the risk of type 2 diabetes and the inflammatory marker C-reactive protein in subjects with high GGT levels.[65, 66, 72] Since overweight individuals are also more prone to inflammation and oxidative stress, this subgroup may also benefit more from the beneficial effects of coffee than normal-weight persons.[61]

Although a systematic search strategy was performed, certain papers that satisfied the scope of this study, might have been overlooked. Most studies evaluated as part of this critical review were not designed to detect variation in response between subgroups using stratified analysis, and the majority of studies lacked statistical power to detect robust interactions between coffee consumption and determinants that modulate health responses. In addition, the majority of studies had an observational study design, which makes them more prone to exposure misclassification and confounding. Therefore, we need further prospective studies with sufficient statistical power to further elucidate inter-individual variability in health outcomes in response to coffee consumption. Another limitation of most studies is an accurate assessment of coffee intake, or exposure to its bioactive compounds. Most studies employed food-frequency questionnaires to assess coffee consumption. Recall bias and the inability to capture differences in coffee cup sizes or preparation methods may have affected the accuracy to determine the level of coffee and caffeine consumption.[15, 102] Moreover, because of inter-individual variation in the absorption and metabolism of coffee bioactives, the internal exposure to coffee metabolites may not always accurately reflect coffee intake.[13] Other studies have proposed that future research complement dietary assessment methodology with the use of genetic and metabolic biomarkers that reflect exposure to, rather than intake of, coffee bioactives.[13, 102, 103]

Mendelian randomization studies use genetic variants associated with an exposure to indirectly estimate health effects in observational studies. As genetic variance is inherited randomly, this method lowers the risk of reverse causation and confounding.[104] An overview of fifteen Mendelian randomization studies of coffee and caffeine consumption has recently been published.[105] Alternatively, metabolomics approaches that measure levels of coffee metabolites in biofluids have provided valuable insights in exposure to coffee constituents in relation to individual health outcomes.[103] Examining differences in metabolic profiles between various subgroups will contribute to our knowledge of inter-individual variability in response to coffee consumption.

We found three studies that examined heterogeneity in health responses to the chlorogenic acid fraction of coffee.[79-81] A recent review on the inter-individual variability of chlorogenic acids in cardiometabolic biomarkers evaluated seven studies addressing this topic, however, they also included studies with a dietary source other than coffee, e.g. artichokes.[106] Chlorogenic acids exert favorable effects on human health, as they show anti-inflammatory, antioxidant, anti-carcinogenic, anti-diabetic and anti-atherogenic properties.[107] Because of the large inter-individual variation in the bioavailability of chlorogenic acids, this is an area of increasing interest.[108-110] Approximately 70% of the ingested chlorogenic acids are metabolized and absorbed in the colon by microbial esterases.[111-113] The large-size chlorogenic acids, which are poorly absorbed, are converted to small-size microbial metabolites (Supporting Information, Figure S2), which increases the bioavailability.[114] *In vitro* studies have monitored the microbial degradation of chlorogenic acids and the formation of colonic metabolites, by incubating human fecal samples with either chlorogenic acids or coffee.[115-117] These studies show a wide heterogeneity in the time to and quantity of the microbial catabolites of chlorogenic acids. This could be explained by determinants such as gender, age, disease, physical activity and genetic polymorphisms, but also by the composition of the gut

microbiota and the enzymatic capacity of these microbes.[118] The microbiota composition could therefore be an emerging factor of inter-individual variability in the health response to coffee consumption.

5. Conclusion

We found evidence for inter-individual variation in response to coffee consumption, indicating that some people could have more health benefits from drinking coffee than others. However, thus far, most studies have insufficient statistical power to detect variation between subgroups, and findings have often not been replicated in more than one study. Possible variability in response, caused by factors such as sex, age, BMI, alcohol, menopausal status and genetic polymorphisms should be further examined in well-designed intervention studies that prospectively recruit based on such factors, or in larger cohorts with sufficient statistical power to perform subgroup analysis. This will allow the development of more precise and personalized dietary advice regarding coffee consumption for individuals or groups of people that share similar health, genotype and phenotype, or lifestyle characteristics.

Author Contributions

E.V. and B.d.R. designed the study. E.V. created the search strategy under the supervision of B.d.R. E.V. and B.d.R. conducted the literature search, evaluated articles, and interpreted the data. E.V. drafted the manuscript and B.d.R and J.M.G. reviewed and revised the article.

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Conflict of Interest

None declared.

Supporting Information

Figure S1 and S2.

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Figure Captions

Figure 1. Flow chart of selection process, with inclusions and exclusions

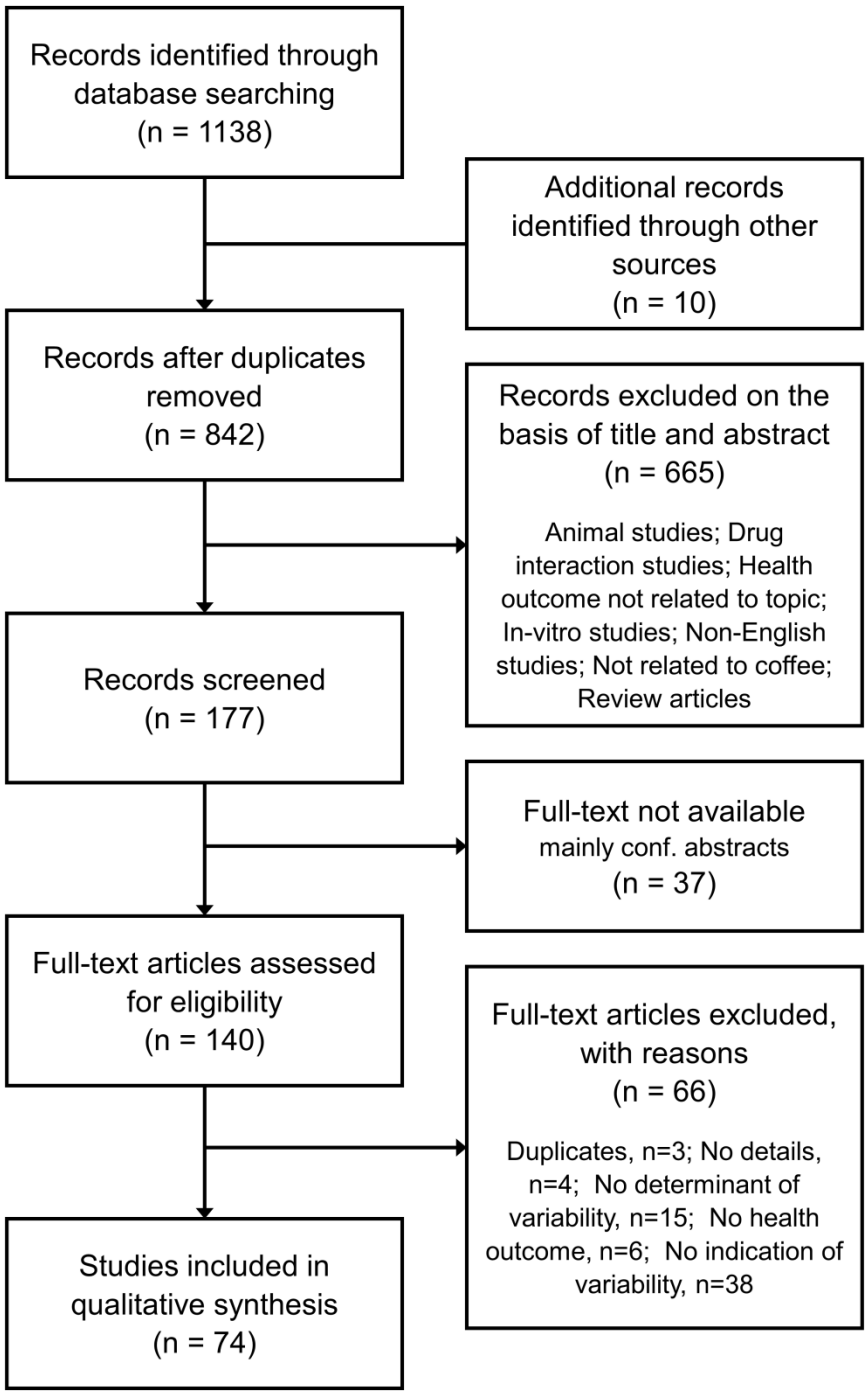

Figure 2. Percentage and number of studies in which each of the determinants is probably, possibly or unlikely to be a determinant of variability in cancer or cardiometabolic outcomes in response to coffee consumption.

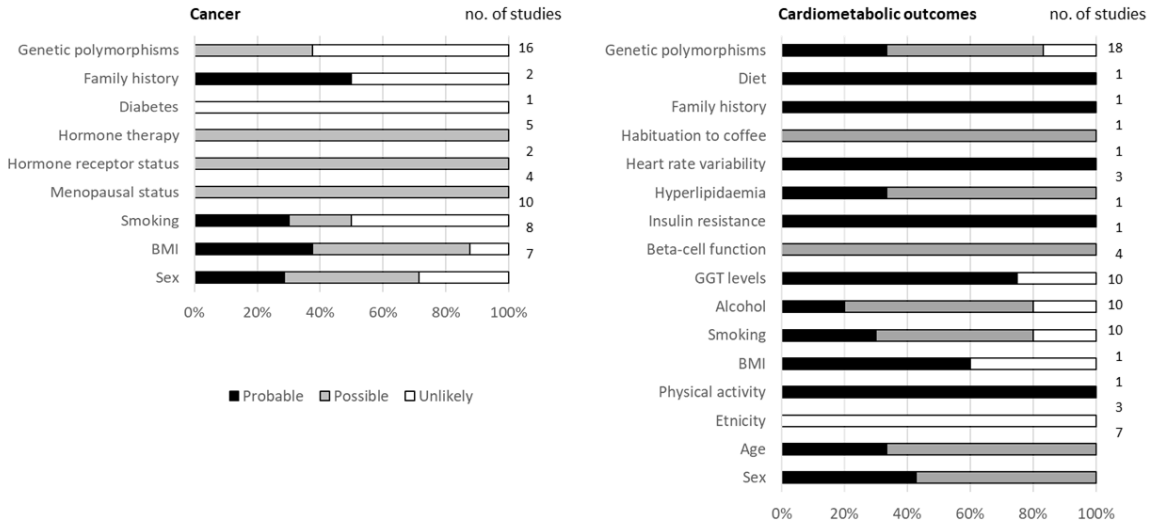

Figure S1. Pathway of caffeine metabolism [95, 96, 119]

CYP, cytochrome P450; NAT2, N-acetyltransferase 2; NE, non-enzymatically; XHD, xanthine dehydrogenase

Figure S2. Pathway of chlorogenic acids metabolism [108, 111, 115]

COMT, catechol-O-methyl transferase; DC, decarboxylase; DH, dehydrogenase; EST, esterase; RA, reductase

Tables

Table 1. Overview of studies demonstrating inter-individual variability in various types of cancer, in response to coffee or caffeine consumption, based on the following determinants of variability: sex, body mass index, smoking, menopausal status, hormone receptor status, hormone therapy, diabetes, family history and genetic polymorphisms.

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Sex								
Bladder cancer	CC	567 ca 798 co	Coffee 0 to ≥4 cups/d	Interview	Male: ↑ coffee, ↑ bladder cancer risk Female: no association in females	NR	Possible	Ciccone[17] 1988 Italy
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	No variation in response	0.655		Villanueva[18] 2009 Spain
Colon cancer	CC	1993 ca 2410 co 30-79 y	Caffeinated coffee 0 to >6 cups/d	FFQ	Male: ↑ caffeinated coffee, ↓ colon cancer risk Female: ↑ caffeinated coffee, ↑ colon cancer risk	NR	Probable	Slattery[30] 1999 USA
Colon cancer	PC 11.6 y	477 071 men and women 25-70 y	Coffee None to high	FFQ	Male: ↑ coffee, ↓ colon cancer risk Female: no association	0.03		Dik[31] 2014 Europe
Colorectal cancer	PC 11.6 y	477 071 men and women 25-70 y	Coffee None to high	FFQ	No variation in response	0.16	Unlikely	Dik[31] 2014 Europe
Pancreatic	CC	201 ca 402 co	Coffee 0 or ≥5	Interview	Male: no	NS	Possible	Gold[36] 1985

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
cancer		Mean 66.1 y	cups/d		association Female: ↑ coffee, ↑ pancreatic cancer risk			USA
Skin cancer	CC	377 ca 390 co <40 y	Coffee 0 to ≥2 cups/d	Interview	No variation in response	NR	Unlikely	Ferrucci[38] 2014 USA
BMI								
Breast cancer	PC 10 y	38 432 women >45 y	Caffeine <68.0 to ≥486.3 mg/d	FFQ	No variation in response	0.23		Ishitani[25] 2008 USA
Breast cancer	PC 11 y	198 404 women 50-71 y	Coffee 0 to ≥4 cups/d	FFQ	No variation in response	>0.10		Gierach[26] 2012 USA
Breast cancer	PC 12 y	14 593 women 35-51 y	Coffee ≤2 to ≥7 cups/d	FFQ	Normal weight: ↑ coffee, ↓ breast cancer risk Overweight: ↑ coffee, ↑ breast cancer risk	0.02	Possible	Vatten[27] 1990 Norway
Breast cancer	PC 13 y	1014 breast cancer cases 24-99 y	Coffee ≤1 to ≥5 cups/d	Questionnaire	Normal weight: ↑ coffee, ↓ IGF1R levels; no assoc. with tumour size Overweight: no association with IGFR1; ↑ coffee, ↓ tumour size	NR		Björner[39] 2018 Sweden
Colorectal cancer	PC 11.6 y	477 071 men and women 25-70 y	Coffee None to high	FFQ	No variation in response	0.35	Unlikely	Dik[31] 2014 Europe

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Endometrial cancer	PC 9.7 y	226 732 women 50-71 y	Coffee 0 to >3 cups/d	FFQ	Normal weight: no association Overweight: ↑ coffee, ↓ endometrial cancer risk	0.24	Probable	Friberg[32] 2009 Sweden
Endometrial cancer	PC 17.6 y	60 634 women 40-76 y	Coffee 0 to ≥4 cups/d	FFQ	Normal weight: no association Overweight: ↑ coffee, ↓ endometrial cancer risk	<0.001		Gunter[33] 2012 USA
Prostate cancer	PC 12 y	44 613 men 45-79 y	Coffee 0 to ≥6 cups/d	FFQ	Normal weight: less strong association Overweight: ↑ coffee, ↓ prostate cancer risk	0.03	Probable	Discacciati[37] 2013 Sweden
Smoking								
Bladder cancer	CC	567 ca 798 co	Coffee 0 to ≥4 cups/d	Interview	Smokers: no association Non-smokers: ↑ coffee, ↑ bladder cancer risk in men only	NR	Probable	Ciccone[17] 1988 Italy
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	Smokers: ever coffee, ↑ bladder cancer risk Non-smokers: no association	0.043		Villanueva[18] 2009 Spain
Breast cancer	CC	3062 ca 3427 co 25-74 y	Coffee 0 to ≥5 cups/d	FFQ	No variation in response	NR	Unlikely	Lowcock[20] 2013 Canada
Breast cancer	PC 11 y	198 404 women	Coffee 0 to ≥4 cups/d	FFQ	No variation in response	>0.10		Gierach[26] 2012 USA

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
		50-71 y						
Colon cancer	CC	1993 ca 2410 co 30-79 y	Caffeinated coffee 0 to >6 cups/d	FFQ	Smokers: ↑ caffeinated coffee, ↓ colon cancer risk in male, ↑ colon cancer risk in female Non-smokers: no association	0.02_{men} 0.03_{women}	Probable	Slattery[30] 1999 USA
Colorectal cancer	PC 11.6 y	477 071 men and women 25-70 y	Coffee None to high	FFQ	No variation in response	0.22	Unlikely	Dik[31] 2014 Europe
Endometrial cancer	PC 9.7 y	226 732 women 50-71 y	Coffee 0 to >3 cups/d	FFQ	No variation in response	0.92	Unlikely	Friberg[32] 2009 Sweden
Pancreatic cancer	CC	422 ca 312 co 63 ± 9.9 y	Caffeinated beverages <1 to ≥3 servings/d	Questionnaire	Smokers: ↑ caffeinated beverages, ↑ pancreatic cancer risk Non-smokers: no association	0.04	Possible	Anderson[35] 2009 Canada
Pancreatic cancer	CC	201 ca 402 co Mean 66.1 y	Coffee 0 or ≥5 cups/d	Interview	No variation in response	NS		Gold[36] 1985 USA
Skin cancer	CC	377 ca 390 co <40 y	Coffee 0 to ≥2 cups/d	Interview	No variation in response	NR	Unlikely	Ferrucci[38] 2014 USA
Menopausal status								
Breast cancer	CC	3062 ca 3427 co 25-74 y	Coffee 0 to ≥5 cups/d	FFQ	Premenopausal: no association Postmenopausal: ↑ caffeinated coffee, ↓ breast cancer	0.53	Possible	Lowcock[20] 2013 Canada

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					risk			
Breast cancer	PC 11 y	335 060 women 25-70 y	Coffee None to high	FFQ	Premenopausal: no assocation Postmenopausal: ↑ caffeinated coffee, ↓ breast cancer risk	NR		Bhoo-Pathy[24] 2015 Europe
Breast cancer	PC 10 y	38 432 women >45 y	Caffeine <68.0 to ≥486.3 mg/d	FFQ	No variation in response	0.53		Ishitani[25] 2008 USA
Breast cancer	PC >25 y	4130 women 25-55 y	Coffee <1 to ≥4 cups/d Caffeine <74 to ≥552 mg/d	FFQ	Premenopausal: ↑ decaf coffee, ↑ breast density in premenopausal women Postmenopausal: ↑ total and decaf coffee, ↓ breast density	<0.001		Yaghjyan, Colditz[28] 2018 USA
Hormone receptor status								
Breast cancer	CC	3062 ca 3427 co 25-74 y	Coffee 0 to ≥5 cups/d	FFQ	Receptor negative: ↑ caffeinated coffee, ↓ ER- breast cancer risk Receptor positive: no association with ER+ breast cancer	NR	Possible	Lowcock[20] 2013 Canada
Breast cancer	PC 11 y	335 060 women 25-70 y	Coffee None to high	FFQ	Receptor negative: ↑ caffeinated coffee, ↓ ER- PR- breast	0.711		Bhoo-Pathy[24] 2015 Europe

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					cancer risk Receptor positive: no association with ER+PR+ breast cancer			
Hormone therapy								
Breast cancer	PC 6 y	2636 ca 123 546 co 40-69 y	Coffee <7 cups/w to ≥4 cups/d	FFQ	Current hormone user: no association Past hormone user: ↑ coffee, ↑ breast cancer risk	0.24		Yaghjyan, Rich[23] 2018 UK
Breast cancer	PC 10 y	38 432 women >45 y	Caffeine <68.0 to ≥486.3 mg/d	FFQ	No variation in response	0.08		Ishitani[25] 2008 USA
Breast cancer	PC 11 y	198 404 women 50-71 y	Coffee 0 to ≥4 cups/d	FFQ	No variation in response	>0.10	Possible	Gierach[26] 2012 USA
Breast cancer	PC >25 y	4130 women 25-55 y	Coffee <1 to ≥4 cups/d Caffeine <74 to ≥552 mg/d	FFQ	Current hormone user: ↑ regular coffee and caffeine intake, ↓ breast density percentage Never and past hormone user: No association	NS		Yaghjyan, Colditz[28] 2018 USA
Endometrial ca	PC 9.7 y	226 732 women 50-71 y	Coffee 0 to >3 cups/d	FFQ	Ever hormone user: no association Never hormone user: ↑ coffee, ↓ endometrial cancer risk	0.03	Possible	Friberg[32] 2009 Sweden

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Endometrial ca	PC 17.6 y	60 634 women 40-76 y	Coffee 0 to ≥4 cups/d	FFQ	No variation in response	0.38		Gunter[33] 2012 USA
Diabetes								
Colorectal cancer	PC 11.6 y	477 071 men and women 25-70 y	Coffee None to high	FFQ	No variation in response	0.38	Unlikely	Dik[31] 2014 Europe
Family history								
Breast cancer	PC 11 y	198 404 women 50-71 y	Coffee 0 to ≥4 cups/d	FFQ	No variation in response based on a family history of breast cancer	>0.10	Unlikely	Gierach[26] 2012 USA
Breast cancer	PC 10 y	38 432 women >45 y	Caffeine <68.0 to ≥486.3 mg/d	FFQ	History of breast disease; ↑ caffeine intake, ↑ breast cancer risk No history of breast disease: no association	0.05	Probable	Ishitani[25] 2008 USA
Genetic polymorphisms								
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	No variation in response based on NAT2 polymorphism	NS	Unlikely	Villanueva[18] 2009 Spain
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	No variation in response based on CYP1A2 rs762551 polymorphism:	NS	Unlikely	Villanueva[18] 2009 Spain
Bladder cancer	CC	185 male ca 80 male co	Coffee 0 to ≥5 cups/d	FFQ	No variation in response based on CYP1A2 rs35694136	$0.09_{rs35694136}$		Pavanello[19] 2010 Italy

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
		63 y			polymorphism No variation in response based on CYP1A2 rs762551 polymorphism	$0.06_{rs762551}$		
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	No variation in response based on CYP1A1 polymorphism	NS	Unlikely	Villanueva[18] 2009 Spain
Bladder cancer	CC	1136 ca; 1138 co 20-80 y	Coffee 0 to ≥4 cups/d	Interview & FFQ	No variation in response based on CYP2E1 polymorphism	NS	Unlikely	Villanueva[18] 2009 Spain
Breast cancer	CC	3062 ca 3427 co 25-74 y	Coffee 0 to ≥5 cups/d	FFQ	No variation in response based on CYP1A2 rs762551 polymorphism	0.85		Lowcock[20] 2013 Canada
Breast cancer	CC	125 ca 43 co	Coffee 0 or ≥1 servings/wk	Face-to-face questionnaire	CYP1A2 rs2069514: ↓ breast cancer risk among the A-allele compared to the G-allele, ↑ breast cancer risk in coffee drinkers with the A-allele No variation in response based on other CYP1A2 polymorphisms	$0.045_{rs2069514}$ $0.111_{rs3569413}$ $0.32_{rs762551}$	Possible	Ayari[21] 2013 Tunesia
Breast cancer	CC	170 ca 241 co All BRCA1 carriers	Coffee intake prior to age 35 Ever vs never	Questionnaire	CYP1A2 rs762551 C-allele: history of coffee intake, ↓ breast	0.04		Kotsopoulos[22] 2007 Canada

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					cancer risk No variation in response based on CYP1A2 rs762551 A/A polymorphism			
Breast cancer	PC 10 y	269 at-risk women Median 29 y	Coffee 0 to ≥6 cups/d	Questionnaire	CYP1A2 rs762551 C-allele: ↑ coffee, ↓ breast volume No variation in response based on CYP1A2 rs762551 A/A polymorphism	0.02		Jernstrom[29] 2008 Sweden
Colorectal cancer	CC	1252 ca 2175 co 25-70 y	Coffee None to high	FFQ	No variation in response based on NAT2 polymorphism	0.63	Unlikely	Dik[31] 2014 Europe
Colorectal cancer	CC	1252 ca 2175 co 25-70 y	Coffee None to high	FFQ	No variation in response based on CYP1A2 rs762551 polymorphism	0.22	Unlikely	Dik[31] 2014 Europe
Ovarian cancer	CC	1354 ca 1851 co 25-55 y	Coffee < or ≥2.5 cups/d Caffeine < or ≥409.5 mg/d	FFQ	No variation in response based on CYP1A2 rs762551 polymorphism	>0.17	Unlikely	Kotsopoulos[34] 2009 USA
Ovarian cancer	CC	1354 ca 1851 co 25-55 y	Coffee < or ≥2.5 cups/d Caffeine < or ≥409.5 mg/d	FFQ	No variation in response based on CYP1A1 polymorphism	>0.17	Unlikely	Kotsopoulos[34] 2009 USA
Ovarian cancer	CC	1354 ca 1851 co 25-55 y	Coffee < or ≥2.5 cups/d Caffeine < or ≥409.5 mg/d	FFQ	No variation in response based on CYP2A6 polymorphism	>0.17	Unlikely	Kotsopoulos[34] 2009 USA

Determinant *Type of cancer*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Ovarian cancer	CC	1354 ca 1851 co 25-55 y	Coffee < or ≥2.5 cups/d Caffeine < or ≥409.5 mg/d	FFQ	CYP19011, CYP19018 and CYP19034: ↑ caffeine/coffee, ↑ ovarian cancer risk in one allele; no variation in response based on a further 18 CYP19 alleles	3 out of 21 SNPs: $<0.05_{caffeine}$ $<0.15_{coffee}$	Possible	Kotsopoulos[34] 2009 USA
Prostate cancer	PC 3 y	411 prostate cancer cases Mean 64 y	Coffee 0 to ≥4 cups/d	FFQ	CYP1A2 rs762551 C-allele: ↑ coffee, ↓ progression-free survival CYP1A2 rs762551 A/A: ↓ coffee, ↑ progression-free survival	NR	Possible	Gregg[40] 2018 USA

[a] Including follow-up time for prospective cohort studies; [b] Sample size and participant's age.

Abbreviations: BMI, body mass index; CC, case-control; CYP, cytochrome P450; ER, estrogen receptor; FFQ, food-frequency questionnaire; IGF1R, insulin-like growth factor receptor 1; NAT, N-acetyltransferase; NS, not significant; NR, not reported; PC, prospective cohort; PR, progesterone receptor; SNP, single nucleotide polymorphism; ca, cases; co, controls

Table 2. Overview of studies demonstrating inter-individual variability in cardiometabolic health outcomes, in response to coffee or caffeine consumption, based on the following determinants of variability: sex, age, ethnicity, physical activity, body mass index, smoking, alcohol, bilirubin levels, GGT levels, insulin resistance, hyperlipidemia, heart rate, family history, diet, genetic polymorphisms and genetic risk.

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Sex								
All-cause mortality in diabetes	PC 11 y	3948 diabetic men and women	Caffeine 0 to ≥200 mg/d	Interview based 24 hour recall	Male: no association Female: ↑ coffee, ↓ risk of all-cause mortality	0.015	Probable	Neves[88] 2018 USA
Coronary calcification	PC 7 y	1570 men and women ≥ 55 y	Coffee ≤3 to >4 cups/d	FFQ & interview	Male: ↑ coffee, ↑ risk of coronary calcification Female: ↑ coffee, ↓ risk of coronary calcification	NR	Possible	van Woudenbergh[57] 2008 The Netherlands
HDL cholesterol	CS	9075 men and women 30-70 y	Coffee < or ≥3 times/w	Questionnaire	Male: no association Female: ↑ coffee, ↑ HCL cholesterol levels	0.045	Probable	Hsu[83] 2019 Taiwan
Hypertension	PC 9.1 y	13 374 men and women 28-47 y	Coffee 0 to ≥2 cups/d	FFQ	Male: no association Female: ↑ caffeinated coffee, ↓ risk of hypertension	0.024	Probable	Navarro[44] 2018 Spain
Inflammation	CS	10 325 men and women 49-76 y	Coffee Never to ≥7 cups/d	Questionnaire	Male: ↑ coffee, ↓ CRP concentration Female: no association	NR	Possible	Maki[71] 2010 Japan
Live enzymes	CS	12 020 men and women	Coffee 0 to ≥4 cups/d	FFQ	Male: ↑ coffee, ↓ ALT levels	NR	Possible	Ikeda[76] 2010 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
		49-76 y			Female: no association			
Type 2 diabetes	PC 14 y	75 140 men and women 45-75 y	Coffee Almost never to ≥3 cups/d	FFQ	Male: no association Female: ↑ total and caffeinated coffee, ↓ risk of type 2 diabetes	<0.0001	Probable	Doo[69] 2014 Hawaii
Age								
Hypertension	PC 9.1 y	13 374 men and women 28-47 y	Coffee 0 to ≥2 cups/d	FFQ	No variation in response	NR		Navarro[44] 2018 Spain
Hypertension	PC 0 to 41 y	2442 men and women 18-97 y	Coffee 0 to >6 cups/d	Questionnaire	<70 y: no association >70 y: ↑ coffee (non-linear), ↑ change in systolic blood pressure in men only No variation in response by age in women	0.02_{men} NR_{women}	Possible	Giggey[45] 2011 USA
Liver enzymes	CS	1353 men 35-59 y	Coffee 0 to ≥3 cups/d	Interview	± 35-46 y: no association ± 46-60 y: daily coffee, ↓ serum GGT levels	0.003	Probable	Nakanishi[75] 2000 Japan
Weight gain	PC 12 y	58 157 men and women	Change in caffeine intake Every 2-4 y since baseline	FFQ	<50 y: ↑ caffeine, ↓ weight gain in men only ≥ 50 y: no association No variation in response by age in women	$<0.001_{men}$ 0.68_{women}	Probable	Lopez-Garcia[58] 2006 USA

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Ethnicity								
Type 2 diabetes	PC 14 y	75 140 men and women 45-75 y	Coffee Almost never to ≥3 cups/d	FFQ	No variation in response	0.20_{men} 0.88_{women}	Unlikely	Doo[69] 2014 Hawaii
Physical activity								
Weight gain	PC 12 y	58 157 men and women	Change in caffeine intake Every 2-4 y since baseline	FFQ	Low physical activity: ↑ caffeine, ↓ weight gain in women only High physical activity: no association	$<0.001_{women}$ 0.74_{men}	Probable	Lopez-Garcia[58] 2006 USA
BMI								
Blood pressure	PC 0 to 41 y	2442 men and women 18-97 y	Coffee 0 to >6 cups/d	Questionnaire	Normal weight: ↑ coffee, ↓ systolic blood pressure in men only Overweight: ↑ coffee, ↑ systolic blood pressure in men only No variation in response by BMI in women	0.04_{men} NR_{women}	Probable	Giggey[45] 2011 USA
Inflammation	CS	10 325 men and women 49-76 y	Coffee Never to ≥7 cups/d	Questionnaire	No variation in response	NS	Unlikely	Maki[71] 2010 Japan
Insulin resistance	CS	1542 men 46-58 y	Coffee <1 to ≥4 cups/d	Questionnaire	Normal weight: no association Overweight: ↑ coffee, ↓ risk of insulin resistance	0.53	Probable	Otake[60] 2014 Japan
Insulin resistance	CS	1440 men and women 18-69 y	Coffee <1 to ≥4 cups/d	Questionnaire	Normal weight: no association Overweight: ↑ coffee, ↓ insulin resistance	0.08		Pham[61] 2014 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Insulin resistance (acute)	CO	33 men and women 27.3 ± 7.2 y	Acute effects of a meal with 200 mL water or instant coffee, containing either 3 or 6 mg caffeine/kg body weight.	FFQ	Normal weight: no effect Overweight: coffee intake, ↓ post-prandial rise of insulin	NR		Gavrieli[63] 2013 Greece
Liver enzymes	CS	12 687 men and women 40-69 y	Coffee 0 to ≥5 cups/d	Questionnaire	No variation in response on GGT levels	>0.1	Unlikely	Tanaka[74] 1998 Japan
Liver enzymes	CS	1353 men 35-59 y	Coffee 0 to ≥3 cups/d	Interview	No variation in response on GGT levels	0.674		Nakanishi[75] 2000 Japan
Liver enzymes	PC 8 y	6095 men 48-59 y	Coffee <1 to ≥5 cups/d	Questionnaire	No variation in response on GGT levels	0.43		Honjo[77] 1999 Japan
Liver enzymes	CS	12 020 men and women 49-76 y	Coffee 0 to ≥4 cups/d	FFQ	Normal weight: ↑ coffee, ↓ ALT levels Overweight: no association	<0.03	Probable	Ikeda[76] 2010 Japan
Weight gain	PC 12 y	58 157 men and women	Change in caffeine intake Every 2-4 y since baseline	FFQ	Normal weight: no association Overweight: ↑ caffeine, ↓ weight gain in women only No variation in response by BMI in men	$<0.001_{women}$ 0.64_{men}	Probable	Lopez-Garcia[58] 2006 USA
Smoking								
Coronary artery	PC 20 y	127 212 men and women	Coffee Never to ≥6 cups/d	Questionnaire	Smokers: ↑ coffee, ↑ risk of coronary artery	NR	Possible	Klatsky[54] 2008 USA

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
disease					disease Non-smokers: no association			
Coronary calcification	CS	4426 men and women 35-74 y	Coffee Never to >3 cups/d	FFQ	Smokers: no association Non-smokers: ↑ coffee, ↓ risk of coronary calcification	0.028		Miranda[86] 2018 Brazil
Coronary calcification	PC 7 y	1570 men and women ≥ 55 y	Coffee ≤3 to >4 cups/d	FFQ & interview	Smokers: no association in men only Non-smokers: ↑ coffee, ↑ risk of coronary calcification in men only ↑ coffee, ↓ risk of coronary calcification in women, both smokers and non-smokers	NR	Possible	van Woudenbergh[57] 2008 The Netherlands
Hypertension	CS	16 719 men and women	Caffeinated beverages 0 to >6 cups/d	Questionnaire	Smokers: no association Non-smokers: ↑ caffeine intake, ↓ risk of hypertension	0.19	Possible	Guessous[41] 2012 Europe
Hypertension	PC 9.1 y	13 374 men and women 28-47 y	Coffee 0 to ≥2 cups/d	FFQ	No variation in response	NR		Navarro[44] 2018 Spain
Inflammation	CS	10 325 men and women 49-76 y	Coffee Never to ≥7 cups/d	Questionnaire	No variation in response	NS	Unlikely	Maki[71] 2010 Japan
Liver enzymes	CS	1353 men 35-59 y	Coffee 0 to ≥3 cups/d	Interview	Smokers: daily coffee, ↓ serum GGT levels	0.022	Probable	Nakanishi[75] 2000 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					Non-smokers: no association			
Liver enzymes	PC 8 y	6095 men 48-59 y	Coffee <1 to ≥5 cups/d	Questionnaire	Smokers: ↑ coffee, ↓ serum GGT levels Non-smokers: no association	0.03		Honjo[77] 1999 Japan
Myocardial infarction	CC	2014 ca 2014 co Median 59 y	Caffeinated coffee <1 to ≥4 cups/d	FFQ	No variation in response	NR	Unlikely	Cornelis[48] 2006 Europe
Weight gain	PC 12 y	58 157 men and women	Change in caffeine intake Every 2-4 y since baseline	FFQ	Smokers: ↑ caffeine, ↓ weight gain in female only Non-smokers: no association No variation in response by smoking status in men	$<0.001_{women}$ 0.33_{men}	Probable	Lopez-Garcia[58] 2006 USA
Alcohol								
Alcoholic liver disease mortality	PC 19 y	219 279 men and women 30-67 y	Coffee 0 to ≥9 cups/d	Questionnaire	High alcohol intake: ↓ coffee, ↑ risk of mortality No or low alcohol intake: no association	0.01	Probable	Tverdal[90] 2018 Norway
Hypertension	PC 6.4 y	1107 men and women, stage 1 hypertension 18-45 y	Caffeinated coffee 0 to >3 cups/d	Questionnaire	Coffee drinkers: ↑ incidence of hypertension with high alcohol intake No coffee drinkers: ↓ incidence of hypertension with high alcohol intake	0.005	Probable	Palatini[43] 2007 Italy
Inflammation	CS	10 325 men and women 49-76 y	Coffee Never to ≥7 cups/d	Questionnaire	High alcohol intake: ↑ coffee, ↓ CRP	0.48	Possible	Maki[71] 2010 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					concentration No or low alcohol intake: no association			
Liver enzymes	CS	12 687 men and women 40-69 y	Coffee 0 to ≥5 cups/d	Questionnaire	Alcohol consumers: ↑ coffee, ↓ serum GGT levels in men only No alcohol consumers: no association	<0.0001		Tanaka[74] 1998 Japan
Liver enzymes	CS	1353 men 35-59 y	Coffee 0 to ≥3 cups/d	Interview	No variation in response on GGT levels	0.618		Nakanishi[75] 2000 Japan
Liver enzymes	CS	12 020 men and women 49-76 y	Coffee 0 to ≥4 cups/d	FFQ	High alcohol intake: ↑ coffee, ↓ ALT, AST and GGT levels No or low alcohol intake: less strong associations	ALT: 0.54_{men} 0.02_{women} AST: 0.04_{men} 0.05_{women} GGT: 0.02_{men} 0.03_{women}	Possible	Ikeda[76] 2010 Japan
Liver enzymes	PC 8 y	6095 men 48-59 y	Coffee <1 to ≥5 cups/d	Questionnaire	High alcohol intake: ↑ coffee, ↓ GGT levels No or low alcohol intake: no association	0.09		Honjo[77] 1999 Japan
Weight gain	PC 12 y	58 157 men and women	Change in caffeine intake Every 2-4 y since baseline	FFQ	No variation in response	0.82_{men} 0.19_{women}	Unlikely	Lopez-Garcia[58] 2006 USA
Bilirubin levels								

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Glycemia	CS	10 734 men and women 49-76 y	Coffee <1 to ≥4 cups/d	FFQ	Low bilirubin levels: ↑ coffee, ↓ HbA1c concentrations in women only High bilirubin levels: no association	0.37_{women} 0.43_{men}	Possible	Wang[62] 2012 Japan
Inflammation	CS	10 397 men and women 49-76 y	Coffee 0 to ≥4 cups/d	FFQ	No variation in response	0.87_{men} 0.39_{women}	Unlikely	Pham[72] 2011 Japan
GGT levels								
Glycemia	CS	10 734 men and women 49-76 y	Coffee <1 to ≥4 cups/d	FFQ	No variation in response	0.64_{men} 0.86_{women}	Unlikely	Wang[62] 2012 Japan
Inflammation	CS	10 397 men and women 49-76 y	Coffee 0 to ≥4 cups/d	FFQ	High GGT levels: ↑ coffee, ↓ CRP concentration in men only Low GGT levels: no association	0.03_{men} 0.56_{women}	Probable	Pham[72] 2011 Japan
Type 2 diabetes	CS	5320 men 40-60 y	Coffee <1 to ≥5 cups/d	Questionnaire	High GGT levels: ↑ coffee, ↓ risk of type 2 diabetes Low GGT levels: no association	0.38	Probable	Hiramatsu[65] 2013 Japan
Type 2 diabetes	PC 20 y	21 826 men and women 35-74 y	Coffee 0-2 to ≥7 cups/d	Questionnaire	High GGT levels: ↑ coffee, ↓ incident type 2 diabetes Low GGT levels: no association	0.02		Bidel[66] 2008 Finland
Beta-cell function								
Glycemia (acute)	CO	19 men 24-53 y	Acute effects of 355 mg coffee polyphenols, or a	NA	Low insulinogenic index: ↑ coffee polyphenols, ↑ active GLP-1evels, ↓ postprandial	NR	Possible	Jokura[79] 2015 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
			placebo, along with a test meal.		blood glucose High insulinogenic index: no effect after consumption of coffee polyphenol beverage			
Insulin resistance								
Liver fibrosis	CS	782 NAFLD patients 48 ± 12 y	Coffee 0 to ≥2 cups/d	FFQ	Low insulin resistance: ↑ coffee, ↓ risk of advanced fibrosis High insulin resistance: no association	0.001	Probable	Bambha[78] 2014 USA
Hyperlipidaemia								
Biomarkers of cardiovascular health	CO	25 normocholesterolemic subjects 27 hypercholesterolemic subjects 18-45 y	Consumption of 6 g/day of a green/roasted coffee blend or a control beverage without caffeine and polyphenols, for 8 weeks	NA	Hypercholesterolemic subjects: ↑ coffee, ↓ total-, LDL-, VLDL cholesterol and triglycerides Normocholesterolemic subjects: no effect of coffee on these biomarkers	<0.03	Probable	Martínez-López[80] 2019 Spain
Metabolic syndrome	CO	25 normocholesterolemic subjects 27 hypercholesterolemic subjects 18-45 y	Consumption of 6 g/day of a green/roasted coffee blend or a control beverage without caffeine	NA	Hypercholesterolemic subjects: ↑ coffee, ↓ triglyceride levels Normocholesterolemic subjects: no effect of coffee on triglyceride levels	NS	Possible	Sarriá[81] 2018 Spain

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
			and polyphenols, for 8 weeks					
Myocardial infarction	CC	262 female ca 519 female co 22-69 y	Coffee 0 to ≥4 cups/d	Questionnaire	History of hyperlipidaemia: ↑ coffee, ↑ myocardial infarction risk No hyperlipidaemia: no association	NS	Possible	La Vecchia[50] 1989 Italy
Heart rate variability								
Blood pressure (acute)	CO	20 men and women 27.6 ± 1.53 y	Acute effects of 250 mg caffeine vs placebo	NA	High heart rate variability: caffeine ingestion, ↑ blood pressure acutely Low heart rate variability: no effect of caffeine	0.032	Probable	McIntosh[47] 2017 New Zealand
Habituation to coffee								
Aortic stiffness (acute)	CO	24 men and women 32.7 ± 9.3 y	Acute effects of 75 ml regular coffee, 75 ml decaffeinated coffee, or 240 mg caffeine	NA	Both types of coffee intake increased augmentation index, augmented pressure and pulse wave velocity more in non-habitual compared to habitual coffee consumers	NR	Possible	Ioakeimidis[84] 2018 Greece
Family history								
Myocardial infarction	CC	290 male ca 364 male co >40 y	Coffee 0 to >4 cups/d	Questionnaire	Family history: ever coffee, ↑ myocardial	0.02	Probable	Azevedo[49] 2006 Portugal

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					infarction risk No family history: ever coffee, ↓ myocardial infarction risk			
Diet								
Hypertension	PC 9.1 y	13 374 men and women 28-47 y	Coffee 0 to ≥2 cups/d	FFQ	Low adherence to Med. Diet: ↑ caffeinated coffee, ↓ risk of hypertension in women only High adherence to Med. Diet: no association	0.045_{women} NR_{men}	Probable	Navarro[44] 2018 Spain
Genetic polymorphisms								
Atrial fibrillation incidence	PC 12 y	1475 men and women 60.0 ± 16.7 y	Caffeine Tertiles	7-day food record	CYP1A2 rs762551: no variation in response	0.220	Unlikely	Casiglia[52] 2018 Italy
Blood pressure (acute)	CO	110 men 18-40 y	Acute effects of 40 mL decaffeinated coffee with or without 3 mg caffeine/kg body weight	NA	ADORA2A rs5751876 T/T: coffee with caffeine, ↑ systolic blood pressure rs5751876 C/C: no association	NR	Possible	Renda[46] 2012 Italy
Blood pressure (acute)	CO	110 men 18-40 y	Acute effects of 40 mL decaffeinated coffee with or without 3 mg caffeine/kg body weight	NA	CYP1A2 rs762551: no variation in response	NR	Unlikely	Renda[46] 2012 Italy

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
Blood pressure	CS	533 men and women >20 y	Coffee <50 to >150 ml/d	Two 24 hour recalls	High coffee intake: ↑ genetic risk of BP, ↑ risk of high BP Low coffee intake: no association	0.026	Probable	Miranda[87] 2019 Brazil
BMI	PC 12 y	20 605 men and women 40-75 y	Coffee <1 to >3 cups/d	FFQ	High genetic risk of obesity: ↑ coffee, ↓ BMI Low genetic risk of obesity: ↑ coffee, ↑ BMI	<0.0001	Probable	Wang[59] 2017 USA
Cardiovascular disease risk	CC	8368 ca 338 709 co 37-73 y	Coffee Never to >6 cups/d	Questionnaire	CYP1A2 rs762551: no variation in response	0.53	Unlikely	Zhou[85] 2019 UK
Coronary events	PC 13 y	772 men 42-60 y	Coffee 0 to ≥814 ml/d	Interview-checked 4-day food record	COMT rs4680 A/A: ↑ coffee, ↑ incidence of acute coronary events COMT rs4680 G-allele: no association	NR	Possible	Happonen[53] 2006 Finland
Glycemia	PC 6.1 y	639 men and women, stage 1 hypertension 18-45 y	Coffee 0 to >3 cups/d	Questionnaire	CYP1A2 rs762551 C-allele: ↑ coffee, ↑ risk of impaired fasting glucose CYP1A2 rs762551 A/A: no association	NR	Possible	Palatini[70] 2015 Italy
Glycemia, fatty acids suppression (acute)	PI	27 men and women >18 y	Subject received either 4 cups of coffee per day (n=19) or stayed coffee/caffeine free (n=8), for	Salivary caffeine analysis	CYP1A2 rs762551 C-allele: coffee intake, ↓ postprandial glycaemia and ↓ non-esterified fatty acids suppression CYP1A2 rs762551	NR	Possible	Robertson[64] 2018 UK

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
			12 weeks		A/A: coffee intake, ↑ postprandial glycaemia and ↑ non-esterified fatty acids suppression			
Heart failure	PC 12 y	1475 men and women 60.0 ± 16.7 y	Caffeine Quartiles	7-day food record	CYP1A2 rs762551 C-allele: ↑ coffee and caffeine intake, ↓ heart failure risk in men only CYP1A2 rs762551 A/A: no association	<0.02	Probable	Casiglia[51] 2017 Italy
Hypertension	PC 8.2 y	553 men and women, stage 1 hypertension 33.2 ± 8.6 y	Coffee 0 to ≥4 cups/d	Questionnaire	CYP1A2 rs762551 C-allele: ↑ coffee, ↑ risk of hypertension CYP1A2 rs762551 A/A: ↑ coffee, ↓ risk of hypertension	<0.01	Probable	Palatini[42] 2009 Italy
Insulin resistance	PC 11 y	8898 men and women 40-69 y	Coffee < or 10 cups/d Caffeine < or ≥220 mg/d	FFQ	High genetic risk of IR: ↑ coffee/caffeine, ↓ risk of insulin resistance Low genetic risk of IR: no association	0.021_{coffee} $0.048_{caffeine}$	Probable	Daily[82] 2019 Korea
Latent autoimmune diabetes (LADA)	CC	484 ca 885 co >35 y	Coffee <2 to ≥6 cups/d	FFQ	High genetic risk of LADA: ↑ coffee, ↑ risk of LADA Low genetic risk of LADA: no association	NR	Possible	Rasouli[89] 2018 Sweden
LDL-cholesterole	CS	397 men 53.9 ± 7.8 y	Coffee <1 to ≥4 cups/d	Questionnaire	Mt5178 rs28357984 A-	NR	Possible	Kokaze[55] 2010 Japan

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
mia					allele: ↑ coffee, ↑ risk of LDL-hypercholesterolemia Mt5178 rs28357984 C-allele: no association			
Liver enzymes	CS	421 men 54.1 ± 7.7 y	Coffee 0 to ≥3 cups/d	Questionnaire	Mt5178 rs28357984 A-allele: no association Mt5178 rs28357984 C-allele: ↑ coffee, ↓ risk of elevated AST, ALT and GGT levels	NR	Possible	Kokaze[73] 2016 Japan
Myocardial infarction	CC	2014 ca 2014 co Median 59 y	Caffeinated coffee <1 to ≥4 cups/d	FFQ	CYP1A2 rs762551 C-allele: ↑ coffee, ↑ myocardial infarction risk CYP1A2 rs762551 A/A: no association	0.04	Probable	Cornelis[48] 2006 Europe
Number of CVD risk factors	CS	332 men 52.8 ± 7.8 y	Coffee <1 to ≥4 cups/d	Questionnaire	Mt5178 rs28357984 A-allele: no association Mt5178 rs28357984 C-allele: ↑ coffee, ↓ number of cardiovascular risk factors	NR	Possible	Ito[56] 2014 Japan
Type 2 diabetes	PC 4 y	4077 men and women 40-69 y	Coffee <1 to >3 cups/d	FFQ	rs4402960, rs7754840 and rs5215 (SNPs associated with	NR	Possible	Lee[67] 2015 Korea

Determinant *Cardiometabolic health outcome*	*Study design* [a]	*Study population* [b]	*Exposure*	*Assessment of exposure*	*Result*	*p-value of interaction*	*Likelihood of existing variability in response*	*Reference* *Year* *Country*
					T2DM): habitual coffee intake, ↓ risk of pre- and type 2 diabetes in one allele; no association in other allele carriers			
Type 2 diabetes	PC 12.5 y	8086 incident ca 11035 co	Coffee <1 to >3 cups/d	FFQ or food records	High incretin-specific genetic risk: ↑ coffee, ↓ risk of type 2 diabetes Low incretin-specific genetic risk: no association	0.005		Heraclides[68] 2016 Europe

[a] Including follow-up time for prospective cohort studies; [b] Sample size and participant's age.

Abbreviations: ADORA, adenosine receptor; ADRA, α-adrenergic receptor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CO, cross-over study; COMT, catechol-O-methyltransferase; CC, case-control; CS, cross-sectional; CYP, cytochrome P450; FFQ, food-frequency questionnaire; GGT, gamma glutamyltransferase; HbA1C, haemoglobin A1C; IR, insulin resistance; LDL, low density lipoprotein; MI, myocardial infarction; NA, not applicable; NAFLD, non-alcohol fatty liver disease; NS, not significant; NR, not reported; PC, prospective cohort; PI, parallel intervention study; SNP, single nucleotide polymorphism; UCP2, uncoupling protein 2; VLDL, very low density lipoprotein; ca, cases; co, controls

Coffee is associated with a reduced risk of cancer, cardiovascular disease and type 2 diabetes. However, individual susceptibility to the effects of coffee consumption may cause heterogeneity in health responses between individuals. In this critical review, several genetic and non-genetic determinants of inter-individual variability in cancer and cardiometabolic health outcomes in response to coffee consumption were identified and evaluated, which indicated that some health benefits of coffee may only occur in a subgroup of subjects.