Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Coffee, Caffeine and Health

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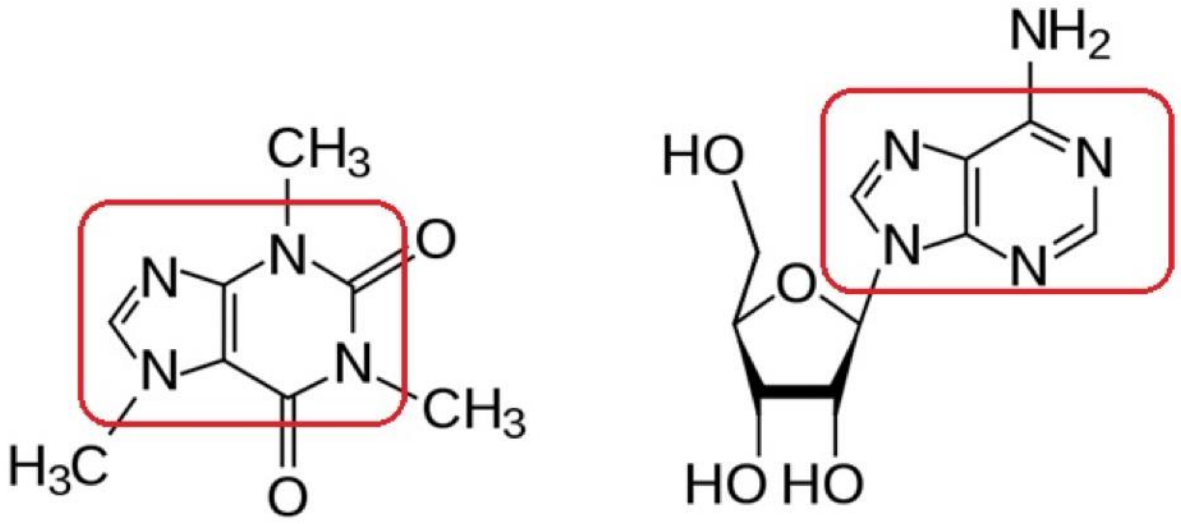

Figure S1. The molecular structure of caffeine and adenosine. The molecular structure of caffeine and adenosine are partly similar allowing caffeine to bind to and block adenosine receptors. As a result, caffeine antagonizes the effects of adenosine. Adenosine modulates the release and action of neurotransmitters such as acetylcholine, adenosine, dopamine, serotonin, norepinephrine, and gamma-aminobutyric acid (GABA).[1] Adenosine accumulates when adenosine triphosphate is used to generate energy during waking hours and its central action results in drowsiness. Adenosine also has peripheral effects and its receptors are present in many tissues including the vascular endothelium, heart, liver, lung, muscle and adipose tissue. Caffeine blockage of adenosine receptors results in greater excitatory neurotransmitter action. Adenosine receptor antagonism (mainly through the A_1 and A_{2A} receptors) is believed to be the main mechanism of action of caffeine at normal levels of caffeine. However, at high or toxic levels caffeine may also act through other mechanisms including elevation of intracellular cyclic adenosine monophosphate (cAMP) concentrations through phosphodiesterase inhibition and the release of intracellular Ca^{2+} through ryanodine-sensitive calcium channels.[1,2]

Table S1. Coffee and caffeine intake and relative risk (RR) of selected health outcomes in meta-analyses of prospective epidemiological studies.*

	Coffee intake				
	N studies (N dose-response)	N cases	RR (95% CI) 3 vs. 0 cups/d†	Evidence for non-linear association	Heterogeneity, coffee type, and publication bias‡
All-cause mortality[3]	36 (28)	323,120	0.85 (0.82-0.89)	Yes (P value < 0.01‡), U-shaped, lowest risk at 3.5-5 cups/d	High heterogeneity (I^2=77%). Similar association for caffeinated [n= 8 cohorts, RR 0.90 (95% CI 0.82-0.99) for high vs. low intake] and decaffeinated [n=11, RR 0.89 (0.85-0.93)] coffee.
Cancer mortality[3]	26 (17)	229,884	0.97 (0.93-1.00)	Yes (P value < 0.01), lowest risk at 2-2.5 cups/d	Moderate heterogeneity (I^2=58%)
Atrial fibrillation[4]	6 (6)	10,406	0.99 (0.91-1.05)	No	Moderate heterogeneity (I^2=66%)
Cardiovascular diseases[5]	36 (29)	36,352	0.89 (0.85-0.93)	Yes (P value <0.01), U-shaped, lowest risk at 3-5 cups/d	Low heterogeneity (P value =0.09). Significant for caffeinated coffee [n=11, RR 0.83 (0.79-0.88) for moderate (median 3.5 cups/d) vs. low intake], but not decaffeinated coffee [n=5, RR 0.98 (0.87-1.10)].
Type 2 diabetes[6]	30 (30)	53,018	0.83 (0.80-0.86)	No	Moderate heterogeneity (I^2=67%). Similar association for caffeinated [n=10, RR=0.80 (0.73-0.88) for 3 vs. 0 cups/d] and decaffeinated [n=10, RR=0.83 (0.73-0.94)] coffee.
Gallstones[7]	5 (3)	11,282	0.85 (0.76-0.94)	Yes (P value=0.01), low risk levels off at >3 cups/d	Moderate heterogeneity (I^2=36%)
Liver cirrhosis[8]	5 (5)	1,364	0.45 (0.26-0.66)	No	High heterogeneity (I^2=91%)
Hepatocellular carcinoma[9]	18 (18)	2,905	0.60 (0.52-0.68)	No	Moderate heterogeneity (I^2=41%). Significant association for caffeinated [n=2, RR=0.62 (0.50-0.78) for 3 vs. 0 cups/d], but not decaffeinated [n=3, RR=0.80 (0.64-1.00)] coffee. Evidence for publication bias (Egger P value <0.01).
Endometrium cancer[10]	10 (9)	10,548	0.85 (0.78-0.92)	No	Moderate heterogeneity (I^2=59%). Similar for caffeinated [n=4, RR=0.65 (0.50-0.85) for high vs. low intake] and decaffeinated [n=4, RR=0.76 (0.62-0.93)] coffee.
Parkinson's Disease[11]	7 (7)	2,414	0.69 (0.61-0.77)	Yes (P value <0.01), low risk levels off at >3 cups/d	Low (I^2=16%). Significant for caffeine intake [n=4, RR=0.78 (0.68-0.90) for 300 vs. 0 mg/d), but not for decaffeinated coffee [n=4, RR=0.94 (0.78-1.12) for high vs. low intake].

	Caffeine intake				
	N studies (N dose-response)	N cases	RR (95% CI) 300 vs. 0 mg/d†	Evidence for non-linear association	Heterogeneity and publication bias
Pregnancy loss[12]	14 (13)	3,429	1.23 (1.09-1.40)	No	High (I^2=81%). Evidence for publication bias (Egger P value <0.01).
Low birth Weight[13]	9 (7)	6,303	1.44 (1.19-1.77)	No	High (I^2=82%).

CI denotes confidence interval

*Selected meta-analyses were based on a reasonably large number of prospective studies and reported on health outcomes relevant for hypotheses on the health effects of coffee and caffeine.

†'Coffee' refers to total coffee consumption. Calculated for a 3 cup per day (for coffee) or 300 mg per day (for caffeine) increment if the association was linear and using cubic spline analyses if the association was non-linear. For the mortality meta-analysis, relative risks are for 3.5 versus 0 cups/day, because results for intake of 3.0 cups/day were not reported.

‡Results for caffeinated and decaffeinated coffee are only provided if available from the meta-analysis. There was no statistical evidence for publication bias unless this is mentioned.

Table S2. Coffee consumption and all-cause mortality in large prospective cohort studies*

Cohort	Country	N	Baseline age (y)	Baseline exclusion	Follow-up (y)	N deaths	Total coffee intake	RR (95% CI) Men	RR (95% CI) Women	Adjustments	Additional analyses
NIH-AARP Diet and Health Study[14]	US	402,260	50-71	Cancer, CAD, stroke	14	52,515	0 cups/d	1.00 (ref)	1.00	Age, ethnicity, education, marital status, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, health status, diabetes.	Similar association for caffeinated and decaffeinated coffee. Inverse associations remained in those with good self-rated health at baseline or after excluding the first 4-9 y of follow-up.
							<1 cup/d	0.99 (0.95-1.04)	1.01 (0.96-1.07)		
							1 cup/d	0.94 (0.90-0.99)	0.95 (0.90-1.01)		
							2-3 cups/d	0.90 (0.86-0.93)	0.87 (0.83-0.92)		
							4-5 cups/d	0.88 (0.84-0.93)	0.84 (0.79-0.90)		
							≥6 cups/d	0.90 (0.85-0.96)	0.85 (0.78-0.93)		
Nurses' Health Studies (NHS, NHSII), Health Professionals Follow-up Study (HPFS)[15]	US	208,501	38-63 (NHS) 27-44 (NHSII) 40-75 (HPFS)	Cancer, CAD, stroke	28 (NHS) 21 (NHSII) 26 (HPFS)	31,956	0 cups/d	1.00 (ref)		Age, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, baseline disease status, PMH use, menopausal status.	Similar association for caffeinated and decaffeinated coffee.
							≤1.0 cup/d	0.95 (0.91-0.99)			
							1.1-3.0 cups/d	0.91 (0.88-0.95)			
							3.1-5.0 cups/d	0.93 (0.89-0.97)			
							>5.0 cups/d	1.02 (0.96-1.07)			
Multiethnic Cohort[16]	US	185,855	45-75	No	16	58,397	0 cups/d	1.00 (ref)		Age, sex, ethnicity, education, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, baseline disease status.	Similar association for caffeinated and decaffeinated coffee and for European, Asian, and African Americans. Inverse association remained in those without chronic diseases at baseline or after excluding the first 5 y of follow-up.
							1-3 cups/mo	1.00 (0.95-1.05)			
							1-6 cups/wk	0.97 (0.93-1.01)			
							1 cup/d	0.88 (0.85-0.91)			
							2-3 cups/d	0.82 (0.79-0.86)			
							≥4 cups/d	0.82 (0.78-0.87)			
European Prospective Investigation into Cancer and Nutrition[17]	10 European countries	521,330	≥35	Cancer, CAD, stroke, diabetes	16	41,693	0 ml/d	1.00 (ref)	1.00 (ref)	Age, center, education, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, menopausal status, OC and PMH use.	Similar association for caffeinated and decaffeinated coffee. Inverse association remained in those with good self-rated health at baseline and after excluding the first 5-8 y of follow-up.
							Q1 (low)	0.94 (0.87-1.00)	0.94 (0.89-0.99)		
							Q2	0.88 (0.82-0.95)	0.90 (0.85-0.95)		
							Q3	0.84 (0.78-0.90)	0.90 (0.85-0.95)		
							Q4 (high)	0.88 (0.82-0.95)	0.93 (0.87-0.98)		

UK Biobank[18]	UK	387,494	38-73	No	10	14,225	0 cup/d	1.00 (ref)		Age, sex, ethnicity, education, BMI, smoking status and intensity, physical activity, alcohol use, tea intake, health status.	Similar association for caffeinated and decaffeinated coffee and for slow and rapid caffeine metabolizers according to genotypes. Inverse association remained in those without chronic diseases or with good self-rated health at baseline and after excluding first 3 y of follow-up.
							<1 cup/d	0.94 (0.88-1.01)			
							1 cup/d	0.92 (0.87-0.97)			
							2-3 cups/d	0.88 (0.84-0.93)			
							4-5 cups/d	0.88 (0.83-0.93)			
							6-7 cups/d	0.84 (0.77-0.92)			
							≥ 8 cups/d	0.86 (0.77-0.95)			
Japan Collaborative Cohort Study for Evaluation of Cancer Risk[19]	Japan	97,753	40-79	No	16	19,532	<1 cup/d	1.00 (ref)	1.00 (ref)	Age, education, marital status, BMI, smoking status, walking, sleep duration, stress, alcohol use, tea, green leafy vegetables, baseline disease status.	No data on decaffeinated coffee. Inverse association remained in those without chronic diseases at baseline and after excluding the first 2-8 y of follow-up.
							1 cup/d	0.95 (0.89-1.01)	0.82 (0.76-0.89)		
							2-3 cup/d	0.86 (0.81-0.93)	0.83 (0.75-0.91)		
							≥ 4 cups/d	0.80 (0.68-0.95)	0.89 (0.66-1.20)		
Japan Public Health Center-based Prospective Study[20]	Japan	90,914	40-69	Cancer, CAD, stroke	19	12,874	Almost never	1.00 (ref)		Age, sex, center, job status, BMI, smoking status and intensity, physical activity, alcohol use, tea, dietary factors, baseline disease status.	No data on decaffeinated coffee. Inverse associations remained after excluding first 5 y of follow-up.
							<1 cup/d	0.93 (0.88-0.98)			
							1-2 cups/d	0.89 (0.84-0.94)			
							3-4 cups/d	0.81 (0.74-0.89)			
							≥5 cups/d	0.87 (0.75-1.00)			
Three-Prefecture Cohort[21]	Japan	82,809	40-79	No	15	13,680	Never	1.00 (ref)	1.00 (ref)	Age, center, urbanicity, job type, insurance type, BMI, smoking status and intensity, alcohol use, tea, dietary factors, baseline disease status.	No data on decaffeinated coffee.
							<1 cup/d	0.85 (0.80-0.92)	0.91 (0.84-0.98)		
							1-2 cups/d	0.76 (0.71-0.82)	0.82 (0.75-0.90)		
							3-4 cups/d	0.74 (0.67-0.81)	0.73 (0.63-0.86)		
							≥5 cups/d	0.73 (0.64-0.83)	0.83 (0.68-1.02)		

CAD denotes coronary artery disease; BMI denotes Body Mass Index; PMH denotes postmenopausal hormone; OC denotes oral contraceptives. Cups/d, cups/wk, and cups/mo refer to cups per day, week, and month respectively.

*All published cohort analyses of coffee consumption and mortality with >12,000 deaths.

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