Supplementary Online Content

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

eTable 1. Association between coffee intake and all-cause mortality in the UK Biobank stratified by weighted genetic caffeine metabolism score (wCMS$_G$) [d]

	Coffee Consumption (cups/day)						P-Trend [e]	P-Heterogeneity [f]
	None	<1	1	2-3	4-5	≥6		
Overall (n=403,816)								
No. of deaths	2,654	786	2,141	3,256	1,546	867		
HR (95% CI) [a]	1.00	0.94 (0.87-1.02)	0.91 (0.86-0.97)	0.87 (0.83-0.92)	0.86 (0.80-0.92)	0.84 (0.77-0.91)	<0.0001	
wCMS$_{G2}$ [b]								0.75
0 to 1 (n=139,311)								
No. of deaths	982	291	751	1,031	511	257		
HR (95% CI) [a]	1.00	0.94 (0.82-1.07)	0.90 (0.81-0.99)	0.83 (0.76-0.91)	0.93 (0.83-1.05)	0.91 (0.79-1.05)	0.11	
>1 to 2 (n=178,336)								
No. of deaths	1,151	329	939	1,468	669	371		
HR (95% CI) [a]	1.00	0.90 (0.80-1.02)	0.91 (0.83-0.99)	0.88 (0.81-0.96)	0.83 (0.75-0.92)	0.79 (0.69-0.89)	<0.0001	
>2 to 3 (n=63,086)								
No. of deaths	378	115	345	567	269	170		
HR (95% CI) [a]	1.00	0.99 (0.80-1.23)	1.02 (0.88-1.19)	0.93 (0.81-1.07)	0.82 (0.70-0.97)	0.82 (0.68-1.00)	0.004	
>3 (n=23,083)								
No. of deaths	143	51	106	190	97	69		
HR (95% CI) [a]	1.00	1.21 (0.87-1.67)	0.81 (0.63-1.05)	0.90 (0.71-1.13)	0.81 (0.61-1.06)	0.86 (0.63-1.18)	0.17	
wCMS$_{G4}$ [c]								0.17
0 to 2 (n=46,732)								
No. of deaths	313	101	236	317	145	64		
HR (95% CI) [a]	1.00	1.00 (0.79-1.25)	0.87 (0.73-1.03)	0.82 (0.70-0.97)	0.83 (0.67-1.02)	0.70 (0.53-0.94)	0.007	
>2 to 4 (n=222,328)								
No. of deaths	1,501	429	1,220	1,745	830	462		
HR (95% CI) [a]	1.00	0.91 (0.82-1.02)	0.94 (0.87-1.01)	0.85 (0.79-0.91)	0.88 (0.80-0.96)	0.89 (0.80-1.00)	0.003	

>4 to 6 (n=101,845)							
No. of deaths	652	187	526	872	428	239	
HR (95% CI) [a]	1.00	0.91 (0.77-1.097)	0.88 (0.79-0.99)	0.86 (0.77-0.95)	0.80 (0.70-0.92)	0.72 (0.61-0.84)	<0.0001
>6 (n=32,911)							
No. of deaths	188	69	159	322	143	102	
HR (95% CI) [a]	1.00	1.19 (0.90-1.57)	0.91 (0.74-1.13)	1.10 (0.91-1.33)	0.92 (0.73-1.16)	0.98 (0.75-1.28)	0.66

[a] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day)); general health status (excellent, good, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m^2); physical activity (0, 1-2, 3-4, or ≥5 days of >10 minutes of moderate or vigorous intensity activity); tea intake (none, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/day)

[b] wCMS$_{G2}$ defined using 2 SNPs, *AHR CYP1A2*

[c] wCMS$_{G4}$ defined using 4 SNPs, *AHR CYP1A2 POR CYP2A6*

[d] Genetic caffeine metabolism scores were weighted by summing the number of alleles multiplied by their beta coefficients (See Methods). The latter were estimated by z/(sqrt(p(1-p))) where z is the SNP z-score for the paraxanthine to caffeine ratio and p is the SNP minor allele frequency. Weighted scores were then calibrated such that wCMSG2 and wCMSG4 scores ranged from 0 to 4 and from 0 to 8, respectively, with higher scores predicting faster caffeine metabolism

[e] P-trend corresponds to the X^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/day

[f] P-Heterogeneity corresponds to the X^2 test statistic for the likelihood ratio test comparing the models with and without the interaction term between the coffee (cups/day) and the CMS variable of interest (continuous score)

eTable 2. Association between coffee intake and all-cause mortality in the UK Biobank stratified by *CYP1A2* genotype (rs762551)

			Coffee Consumption (cups/day)					
rs762551	None	<1	1	2-3	4-5	≥6	P-Trend [b]	P-Heterogeneity [c]
C/C (n=31,953)								0.84
No. of deaths	244	68	156	241	105	53		
HR (95% CI) [a]	1.00	0.96 (0.73-1.27)	0.78 (0.64-0.96)	0.78 (0.65-0.95)	0.77 (0.60-0.98)	0.69 (0.51-0.95)	0.009	
A/C (n=162,268)								
No. of deaths	1045	304	874	1280	642	325		
HR (95% CI) [a]	1.00	0.93 (0.82-1.06)	0.96 (0.88-1.05)	0.89 (0.81-0.97)	0.94 (0.85-1.05)	0.82 (0.72-0.94)	0.01	
A/A (n=20,9595)								
No. of deaths	1365	414	1111	1735	799	489		
HR (95% CI) [a]	1.00	0.95 (0.85-1.07)	0.90 (0.83-0.98)	0.87 (0.81-0.94)	0.81 (0.74-0.89)	0.87 (0.77-0.97)	<.0001	

[a] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day)); general health status (excellent, good, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m^2); physical activity (0, 1-2, 3-4, or ≥5 days of >10 minutes of moderate or vigorous intensity activity); tea intake (none, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/day)
[b] P-trend corresponds to the X2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/day
[c] P-Heterogeneity corresponds to the X^2 test statistic for the likelihood ratio test comparing the models with and without the interaction term between coffee (continuous) and the stratifying variable *CYP1A2* genotype (ordinal)

eTable 3. Association between coffee intake and all-cause mortality in the UK Biobank stratified by unweighted genetic caffeine metabolism score (CMS$_G$)

	Coffee Consumption (cups/day)						P-Trend [d]	P-Heterogeneity [e]
	None	<1	1	2-3	4-5	≥6		
Overall (n=40,3816)								
No. of deaths	2,654	786	2,141	3,256	1,546	867		
HR (95% CI) [a]	1.00	0.94 (0.87-1.02)	0.91 (0.86-0.97)	0.87 (0.83-0.92)	0.86 (0.80-0.92)	0.84 (0.77-0.91)	<.0001	
CMS$_{G2}$ [b]								0.81
0 or 1 (n=158,995)								
No. of deaths	1,117	331	872	1,183	574	307		
HR (95% CI) [a]	1.00	0.93 (0.83-1.06)	0.90 (0.83-0.99)	0.82 (0.75-0.90)	0.90 (0.81-1.00)	0.92 (0.80-1.05)	0.03	
2 (n=162,134)								
No. of deaths	1,040	291	840	1,344	624	337		
HR (95% CI) [a]	1.00	0.90 (0.79-1.02)	0.91 (0.83-1.00)	0.90 (0.83-0.98)	0.86 (0.77-0.96)	0.79 (0.69-0.90)	0.0006	
3 or 4 (n=82,687)								
No. of deaths	497	164	429	729	348	223		
HR (95% CI) [a]	1.00	1.08 (0.90-1.29)	0.95 (0.83-1.08)	0.91 (0.81-1.03)	0.80 (0.69-0.93)	0.80 (0.67-0.95)	0.0004	
CMS$_{G4}$ [c]								0.16
0 to 2 (n=96,734)								
No. of deaths	676	204	533	682	321	159		
HR (95% CI) [a]	1.00	0.94 (0.80-1.10)	0.92 (0.82-1.03)	0.81 (0.72-0.90)	0.87 (0.76-1.01)	0.84 (0.70-1.01)	0.007	
3 (n=113,368)								
No. of deaths	761	217	626	898	429	235		
HR (95% CI) [a]	1.00	0.92 (0.79-1.07)	0.96 (0.86-1.07)	0.86 (0.78-0.95)	0.87 (0.77-0.99)	0.85 (0.73-1.00)	0.007	
4 (n=107,630)								
No. of deaths	703	192	562	885	420	222		
HR (95% CI) [a]	1.00	0.88 (0.75-1.03)	0.89 (0.79-0.99)	0.86 (0.77-0.95)	0.83 (0.72-0.94)	0.74 (0.63-0.87)	0.0003	

≥5 (n=86,084)

No. of deaths	514	173	420	791	376	251	
HR (95% CI) [a]	1.00	1.07 (0.90-1.27)	0.89 (0.78-1.02)	0.97 (0.86-1.09)	0.88 (0.76-1.01)	0.91 (0.77-1.07)	0.14

[a] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day)); general health status (excellent, good, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m^2); physical activity (0, 1-2, 3-4, or ≥5 days of >10 minutes of moderate or vigorous intensity activity); tea intake (none, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/day)

[b] CMS$_{G2}$ defined using 2 SNPs, *AHR CYP1A2*

[c] CMS$_{G4}$ defined using 4 SNPs, *AHR CYP1A2 POR CYP2A6*

[d] P-trend corresponds to the X^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/day

[e] P-Heterogeneity corresponds to the X^2 test statistic for the likelihood ratio test comparing the models with and without the interaction term between the coffee (cups/day) and the CMS variable of interest (continuous score)

eTable 4. Association between coffee intake and all cause and cause-specific mortality in the UK Biobank by length of follow-up time

	Coffee Consumption (cups/day)						
Length of Follow-Up	None	<1	1	2-3	4-5	≥6	P-Trend [b]
Years 0 to <3 of follow-up (n=498,134)							
No. of deaths	1,055	300	834	1,242	564	317	
HR (95% CI) [a]	1.00	0.93 (0.82-1.06)	0.93 (0.85-1.02)	0.87 (0.80-0.95)	0.80 (0.72-0.89)	0.75 (0.66-0.86)	<.0001
Years 3 to <5 of follow-up (n=493,816)							
No. of deaths	1,010	278	813	1,235	615	304	
HR (95% CI) [a]	1.00	0.87 (0.76-1.00)	0.92 (0.83-1.01)	0.90 (0.82-0.98)	0.95 (0.85-1.06)	0.83 (0.72-0.95)	0.07
Years ≥5 of follow-up (n=489,561)							
No. of deaths	1,330	416	1047	1,621	778	466	
HR (95% CI) [a]	1.00	1.01 (0.91-1.13)	0.91 (0.84-0.99)	0.89 (0.82-0.96)	0.89 (0.81-0.98)	0.94 (0.84-1.06)	0.04

[a] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity (current and former smokers); time since quitting (former smokers), and cigar and pipe use (current and former smokers)); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker (<1 drink/week), occasional drinker (>1 drink/week but <1 drink/day), moderate daily drinker (1 to 3 drinks/day), or heavy daily drinker (>3 drinks/day)); general health status (excellent, good, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35 kg/m^2); physical activity (0, 1-2, 3-4, or ≥5 days of >10 minutes of moderate or vigorous intensity activity); tea intake (none, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/day)
[b] P-trend corresponds to the X^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/day