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ORIGINAL RESEARCH

Associations of Observational and Genetically Determined Caffeine Intake With Coronary Artery Disease and Diabetes Mellitus

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BACKGROUND: Caffeine is the most widely consumed psychostimulant and is associated with lower risk of coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM). However, whether these associations are causal remains unknown. This study aimed to identify genetic variants associated with caffeine intake, and to investigate evidence for causal links with CAD or T2DM. In addition, we aimed to replicate previous observational findings.

METHODS AND RESULTS: Observational associations were tested within UK Biobank using Cox regression analyses. Moderate observational caffeine intakes from coffee or tea were associated with lower risks of CAD or T2DM, with the lowest risks at intakes of 121 to 180 mg/day from coffee for CAD (hazard ratio [HR], 0.77 [95% CI, 0.73–0.82; $P<1\times10^{-16}$]), and 301 to 360 mg/day for T2DM (HR, 0.76 [95% CI, 0.67–0.86]; $P=1.57\times10^{-5}$). Next, genome-wide association studies were performed on self-reported caffeine intake from coffee, tea, or both in 407 072 UK Biobank participants. These analyses identified 51 novel genetic variants associated with caffeine intake at $P<1.67\times10^{-8}$. These loci were enriched for central nervous system genes. However, in contrast to the observational analyses, 2-sample Mendelian randomization analyses using the identified loci in independent disease-specific cohorts yielded no evidence for causal links between genetically determined caffeine intake and the development of CAD or T2DM.

CONCLUSIONS: Mendelian randomization analyses indicate genetically determined higher caffeine intake might not protect against CAD or T2DM, despite protective associations in observational analyses.

Key Words: caffeine intake ■ coronary artery disease ■ genetics ■ Mendelian randomization ■ type 2 diabetes mellitus

Caffeine is the most commonly consumed psychostimulant in the world and is readily available in coffee, tea, and other food products.[1] Previous observational studies and meta-analyses have generally reported beneficial associations between moderate intake of coffee, the main dietary source of caffeine,[1] and risk of cardiovascular disease[2] and type 2 diabetes mellitus (T2DM),[3] as well as cardiovascular and all-cause mortality.[4,5] Contrasting results have been reported as well for cardiovascular disease outcomes, including coronary artery disease (CAD),[2,6–9] and therefore coffee and tea are not generally included in dietary guidelines.[10] Given its widespread consumption, altering caffeine intake might be an interesting way to influence population-wide risk of developing CAD and T2DM.

Because of the observational design of previous studies, which include many cross-sectional and case-control studies, it is difficult to provide insight into causal relationships. Genome-wide association studies (GWASs) have identified several single-nucleotide polymorphisms (SNPs) associated with caffeine or coffee

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CLINICAL PERSPECTIVE

What Is New?

- Leveraging data from >400 000 individuals, we identified 51 novel genetic loci associated with caffeine intake.
- We confirmed phenotypic associations between caffeine intake and the development of coronary artery disease or type 2 diabetes mellitus, but by exploiting instrumental variable analyses we found no evidence for causality of this association.

What Are the Clinical Implications?

- Our data do not support recommending caffeine intake to protect against the development of coronary artery disease of type 2 diabetes mellitus.

Nonstandard Abbreviations and Acronyms

CARDIoGRAMplusC4D	Coronary Artery Disease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics
DIAGRAM	Diabetes Genetics Replication And Meta-analysis
eQTL	expression quantitative trait locus
MR	Mendelian randomization
T2DM	type 2 diabetes mellitus

intake through genes such as *AHR* and *CYP1A2*, which affect the metabolism of caffeine.[11–17] Unlike traditional observational studies, Mendelian randomization (MR) analyses have the advantageous applicability of uncovering causal links using genetic variants, which are randomly allocated at conception, as instrumental variables for modifiable risk factors to test potential causal links with disease outcomes. So far, MR analyses between genetically determined higher caffeine intake and risk of CAD[7,18] or T2DM[19] failed to provide support for a causal link. However, these studies used only few SNPs and investigated coffee as the sole source of caffeine.

Here, we investigated the observational associations between habitual caffeine intake from coffee, tea, or both with new-onset CAD and T2DM in a large prospective observational cohort. To further our knowledge of the genetic architecture underlying caffeine intake, we carried out GWASs for caffeine intake from coffee, tea, or both in over 400 000 participants from the UK Biobank to identify novel variants for caffeine intake. Using this set of SNPs, we aimed to investigate the causal relationship between caffeine intake with CAD and T2DM in large independent cohorts.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. GWAS summary statistics generated during the present study will be made available in the following repository: https://doi.org/10.17632/d8nwkm7p9p.1.

Study Population

The UK Biobank study is a population-based prospective cohort whose design and population have been described previously.[20] From 2006 to 2010, >500 000 individuals between the ages of 40 and 69 years were recruited in the United Kingdom. All participants gave informed consent,[21] and the UK Biobank study was approved by the North West Multi-centre Research Ethics committee.[22] Details regarding the UK Biobank study population are provided in Data S1.

Ascertainment of Coffee and Tea Intake

During the first visit to the assessment center, daily coffee and tea intake were assessed by asking participants, "*How many cups of coffee do you drink each day? (Include decaffeinated coffee)*" and "*How many cups of tea do you drink each day? (Include black and green tea)*." In addition, coffee drinkers were asked what type of coffee they usually drink. Caffeine intake was calculated as the number of cups of coffee or tea multiplied by the caffeine content per cup.[23] Combined caffeine intake from both coffee and tea was calculated as the sum of the daily caffeine intake from coffee and tea from individuals who provided data on both. Full details on the ascertainment of coffee, tea, and daily caffeine intake are provided in Data S1.

CAD and T2DM Prevalence and Incidence in the UK Biobank

Prevalence at baseline and incidence of new-onset CAD and T2DM cases within UK Biobank were, per prior analysis,[24] based on self-reported data, *International Classification of Diseases, Ninth Revision*

(*ICD-9*) and *Tenth Revision* (*ICD-10*)[25] coded primary and secondary diagnoses, operation codes,[26] and death attributable to either condition from inclusion in the UK Biobank until end of follow-up (March 31, 2017, for participants from England; February 29, 2016, for Wales; and October 31, 2016, for Scotland) as described in Data S1. Incident cases that were based on self-reported diagnoses during follow-up visits were included only if there were no events recorded according to the *ICD-9* or *ICD-10* or operation codes data and only if the participant did not report this in the previous visit. If the participant was the same age as the reported age of diagnosis, the median date between the visit and the participant's birthday was taken as date of event. If the age of diagnosis was before the participant's current age, we took the median date of the year of the reported age of diagnosis counted from the participant's birthday. If age of diagnosis was not available, we took the median date between the visit of the first self-reported diagnosis and the previous visit. Individuals with a history of CAD or T2DM at inclusion were excluded from the respective observational analyses.

Covariates

At the first visit, weight (in kilograms) and height (in centimeters) were measured and used to calculate the body mass index (in kilograms per square meter). Age was calculated as the difference between date of birth and date of inclusion in the UK Biobank. Sex, ethnicity, weekly alcohol intake (UK units) and active smoking at inclusion were self-reported. Weekly alcohol intake was right-skewed and therefore log2 transformed for participants who provided this data. For participants without these accurate data on the number of units, we estimated the weekly alcohol intake using a more crude questionnaire of alcohol intake frequency where participants were asked, *"About how often do you drink alcohol?"* For this, we fitted a linear regression between with the log2-transformed weekly alcohol intake and alcohol intake frequency in participants with both measures, and predicted weekly alcohol intake on the remaining individuals. The Townsend Deprivation Index, a proxy for socioeconomic status, was provided by the UK Biobank and inverse rank normalized because of a right-skewed distribution.[24]

Genotyping and Imputation in UK Biobank

UK Biobank participants were genotyped using custom Affymetrix Axiom (UK Biobank Lung Exome Variant Evaluation[27] or UK Biobank) arrays. The genotyping methods, arrays, and quality-control procedures have been described previously in detail[28,29] and are briefly described in Data S1.

Statistical Analysis

We performed multivariable Cox regression analyses to test the association of observational caffeine intake per 60 mg caffeine (equivalent to the caffeine content of 1 cup of instant coffee or 2 cups of tea) with new-onset CAD and T2DM in the UK Biobank. Hazard ratios with 95% CIs were calculated for 1 to 60, 61 to 120, 121 to 180, 181 to 240, 241 to 300, 301 to 360, or >360 mg of caffeine from coffee or combined, compared with individuals who drank 0 mg. Because of the lower caffeine content per cup of tea compared with caffeinated coffee, the hazard ratios and 95% CIs for caffeine from tea were calculated for 1 to 60, 61 to 120, 121 to 180, or >180 mg (equivalent to >6 cups of tea) of caffeine compared with individuals who had 0-mg intake from tea. The time scale for the Cox regression analyses was from inclusion in the UK Biobank until the outcome of interest, death or end of follow-up. Cox regression analyses were performed unadjusted and adjusted for age, sex, body mass index, active smoking, Townsend Deprivation Index, and weekly alcohol intake using Stata version 15 (StataCorp, College Station, TX).

All genetic analyses were adjusted for age, sex, genotyping array, and the first 30 genetic principal components to adjust for population stratification. We performed separate GWASs for inverse rank normalized combined caffeine intake, caffeine from coffee, and caffeine from tea in 19 400 838 SNPs using BOLT-LMM version 2.3.1 software (Broad Institute, Cambridge, MA).[30] A Bonferroni corrected $P<1.67\times10^{-8}$ (traditional GWAS significance threshold of $5\times10^{-8}/3$) was considered genome-wide significant. This significance threshold is conservative, considering that our phenotypes are correlated with Spearman's rank correlation coefficients between phenotype pairs ranging from $r=-0.33$ to 0.71 (Table S1). Details of the GWAS analyses, functional annotation of candidate genes,[31–35] and biological pathways are provided in Data S1.

We performed MR analyses using previously published summary statistics from the CARDIoGRAMplusC4D (Coronary Artery Disease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics) consortium (123 504 controls and 60 801 [33.0%] cases)[36] and the DIAGRAM Diabetes Genetics Replication And Meta-analysis)) consortium (132 532 controls and 26 676 [16.8%] cases)[37] to gain insight into potential causal relationships between caffeine intake and CAD or T2DM, respectively. Lead SNPs of each caffeine intake trait that reached $P<1.67\times10^{-8}$ were used to create a weighted genetic risk score and were also used as instrumental variables in the MR. Each genetic risk score was created using an additive model per GWAS, summing the number of effect alleles (0, 1, or 2) per individual after multiplying it with the effect size between the SNP and the GWAS phenotype. Statistical power for the MR with a binary outcome was calculated using an alpha of 0.05 and the explained variance of each genetic risk score, as described previously.[38] For the MR, SNPs that were not available in CARDIoGRAMplusC4D or DIAGRAM were replaced with proxies with R^2>0.8, and were otherwise excluded from the MR analyses if no eligible proxies were available. SNP effects were harmonized across studies using the built-in feature of the TwoSampleMR package in R (R Foundation for Statistical Computing, Vienna, Austria). The association between genetically determined higher caffeine intake and CAD or T2DM was assessed using fixed-effects inverse-variance weighted meta-analyses. Odds ratios (ORs) with 95% CIs are presented for the MR outcomes. To maximize the likelihood of reporting true findings, α was set at 0.005 instead of 0.05.[39] Associations with P<0.05 were considered suggestively significant. We assessed potential weak instrument bias per SNP using the F-statistic[40] and I^2_{GX}.[41] We determined the I^2 index.[42] Cochran's Q, Rücker's and thus potential pleiotropy. MR-Egger,[43] MR Pleiotropy Residual Sum and Outlier[44] and MR inverse-variance weighted random effects[43] were used as pleiotropy analyses. MR-Steiger filtering[45] was performed to remove variants more strongly associated with the outcome than the exposure. Weighted median and weighted mode-based estimator MR analyses[46] were performed as additional sensitivity analyses. Details of the MR analyses are provided in Data S1.

RESULTS

Cohort Characteristics

Of 502 525 UK Biobank individuals, 362 316 were available for the combined caffeine intake analyses, 373 522 for caffeine from coffee, and 395 866 for caffeine from tea (Figure S1). Baseline characteristics are shown in Table, per caffeine intake trait in Table S2, and stratified by caffeine intake in Tables S3 through S5. Median (interquartile range) combined caffeine intake was 205 (120–290) mg/day, from coffee 85 (3–180) mg/day, and from tea 90 (60–150) mg/day.

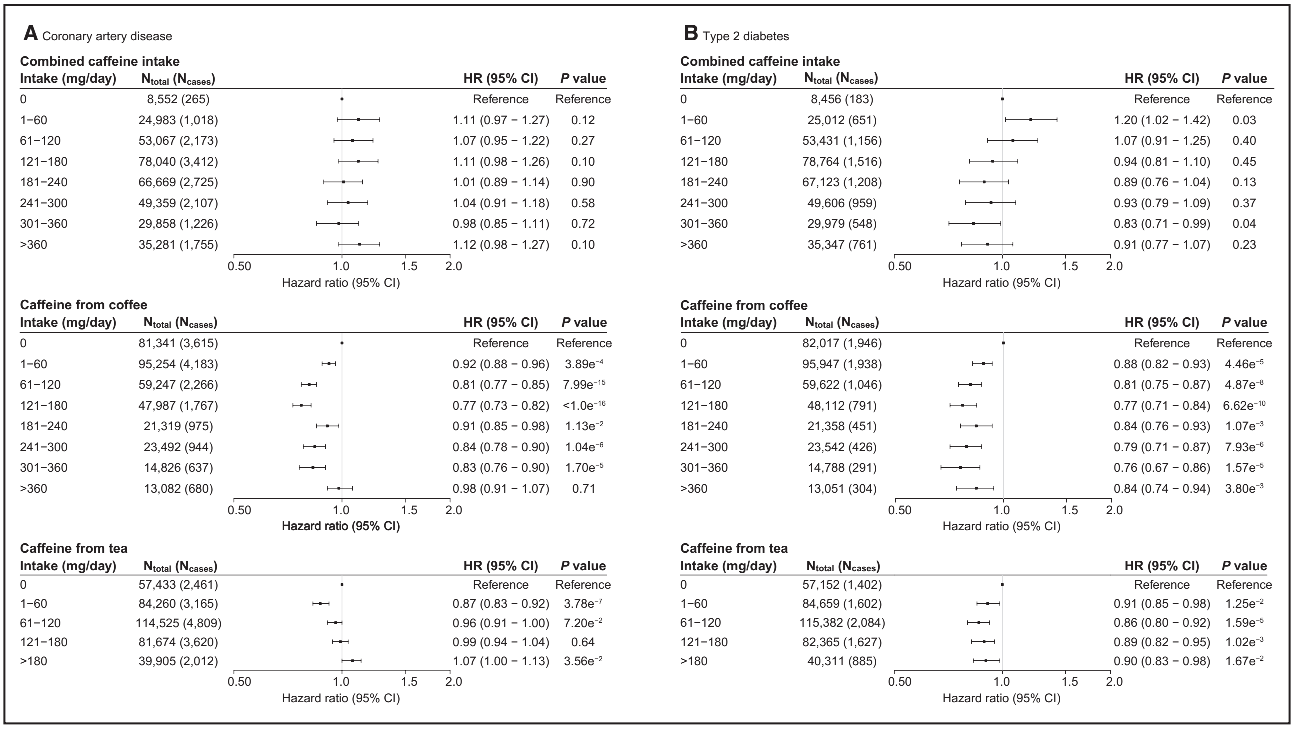
Associations of Observational Caffeine Intake With CAD and T2DM

During nearly 10 years (median, 8.1 years; interquartile range, 7.5–8.6) of follow-up in 345 809 participants without history of CAD and 347 718 participants without history of T2DM, 14 681 (4.2%) individuals developed CAD, and 6982 (2.0%) developed T2DM in the combined caffeine cohort. Results for unadjusted analyses are presented in Tables S6 and S7. In multivariable adjusted analyses (Tables S8 and S9), combined caffeine intake was very modestly or not associated with CAD or T2DM. However, the individual components, caffeine from coffee or tea, did show associations with lower risks of new-onset CAD and T2DM (Figure 1A and 1B, respectively). Overall, the associations between caffeine from coffee or tea with CAD and T2DM followed U-curve–type shapes, with the highest protective effects of caffeine intake from coffee on CAD at moderate intakes (121–180 mg/day), compared with no, lower, or higher intakes. Associations between caffeine from coffee with CAD or T2DM were not appreciably different when additionally adjusted for caffeine from tea, nor were the associations for caffeine from tea when additionally adjusted for caffeine from coffee (Table S10). Overall, caffeine intake from coffee was associated with lower risks of CAD and T2DM compared with caffeine from tea or combined. To determine whether this may be attributable to confounding by other, noncaffeine, substances, we stratified the

Table 1. Baseline Characteristics of All Included 407 072 UK Biobank Participants

Characteristics	Men	Women
Total, N	186 968	220 104
Age, y, mean (SD)	57.16 (8.08)	56.72 (7.92)
Daily caffeine intake, mg/d, median (IQR)		
Combined caffeine	210 (150–300)	180 (120–270)
Caffeine from coffee	85 (6–180)	60 (3–170)
Caffeine from tea	90 (60–150)	90 (60–150)
Blood pressure, mm Hg, mean (SD)		
Systolic	139.60 (16.15)	128.74 (17.88)
Diastolic	84.69 (8.22)	79.94 (8.20)
Active smoker, N (%)		
No	164 791 (88.1)	200 946 (91.3)
Yes	22 177 (11.9)	19 158 (8.7)
Body mass index , kg/m^2, mean (SD)	27.85 (4.23)	27.05 (5.13)
Weekly alcohol intake, UK units, median (IQR)	15.40 (5.50, 28.40)	6.40 (1.60, 13.20)
Hypertension, N (%)		
No	119 965 (64.2)	160 881 (73.1)
Yes	67 003 (35.8)	59 223 (26.9)
Hyperlipidemia, N (%)		
No	139 471 (74.6)	188 444 (85.6)
Yes	47 497 (25.4)	31 660 (14.4)

Combined caffeine intake was calculated as the sum of caffeine intake from coffee and tea. Body mass index was calculated as weight in kilograms divided by height in meters squared. Smoking status and weekly alcohol intake were self-reported at inclusion. IQR indicates interquartile range.



A Coronary artery disease

Combined caffeine intake

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	8,552 (265)	Reference	Reference
1–60	24,983 (1,018)	1.11 (0.97 − 1.27)	0.12
61–120	53,067 (2,173)	1.07 (0.95 − 1.22)	0.27
121–180	78,040 (3,412)	1.11 (0.98 − 1.26)	0.10
181–240	66,669 (2,725)	1.01 (0.89 − 1.14)	0.90
241–300	49,359 (2,107)	1.04 (0.91 − 1.18)	0.58
301–360	29,858 (1,226)	0.98 (0.85 − 1.11)	0.72
>360	35,281 (1,755)	1.12 (0.98 − 1.27)	0.10

Caffeine from coffee

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	81,341 (3,615)	Reference	Reference
1–60	95,254 (4,183)	0.92 (0.88 − 0.96)	3.89e^{-4}
61–120	59,247 (2,266)	0.81 (0.77 − 0.85)	7.99e^{-15}
121–180	47,987 (1,767)	0.77 (0.73 − 0.82)	<1.0e^{-16}
181–240	21,319 (975)	0.91 (0.85 − 0.98)	1.13e^{-2}
241–300	23,492 (944)	0.84 (0.78 − 0.90)	1.04e^{-6}
301–360	14,826 (637)	0.83 (0.76 − 0.90)	1.70e^{-5}
>360	13,082 (680)	0.98 (0.91 − 1.07)	0.71

Caffeine from tea

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	57,433 (2,461)	Reference	Reference
1–60	84,260 (3,165)	0.87 (0.83 − 0.92)	3.78e^{-7}
61–120	114,525 (4,809)	0.96 (0.91 − 1.00)	7.20e^{-2}
121–180	81,674 (3,620)	0.99 (0.94 − 1.04)	0.64
>180	39,905 (2,012)	1.07 (1.00 − 1.13)	3.56e^{-2}

B Type 2 diabetes

Combined caffeine intake

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	8,456 (183)	Reference	Reference
1–60	25,012 (651)	1.20 (1.02 − 1.42)	0.03
61–120	53,431 (1,156)	1.07 (0.91 − 1.25)	0.40
121–180	78,764 (1,516)	0.94 (0.81 − 1.10)	0.45
181–240	67,123 (1,208)	0.89 (0.76 − 1.04)	0.13
241–300	49,606 (959)	0.93 (0.79 − 1.09)	0.37
301–360	29,979 (548)	0.83 (0.71 − 0.99)	0.04
>360	35,347 (761)	0.91 (0.77 − 1.07)	0.23

Caffeine from coffee

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	82,017 (1,946)	Reference	Reference
1–60	95,947 (1,938)	0.88 (0.82 − 0.93)	4.46e^{-5}
61–120	59,622 (1,046)	0.81 (0.75 − 0.87)	4.87e^{-8}
121–180	48,112 (791)	0.77 (0.71 − 0.84)	6.62e^{-10}
181–240	21,358 (451)	0.84 (0.76 − 0.93)	1.07e^{-3}
241–300	23,542 (426)	0.79 (0.71 − 0.87)	7.93e^{-6}
301–360	14,788 (291)	0.76 (0.67 − 0.86)	1.57e^{-5}
>360	13,051 (304)	0.84 (0.74 − 0.94)	3.80e^{-3}

Caffeine from tea

Intake (mg/day)	N$_{total}$ (N$_{cases}$)	HR (95% CI)	*P* value
0	57,152 (1,402)	Reference	Reference
1–60	84,659 (1,602)	0.91 (0.85 − 0.98)	1.25e^{-2}
61–120	115,382 (2,084)	0.86 (0.80 − 0.92)	1.59e^{-5}
121–180	82,365 (1,627)	0.89 (0.82 − 0.95)	1.02e^{-3}
>180	40,311 (885)	0.90 (0.83 − 0.98)	1.67e^{-2}

Figure 1. Associations between observational caffeine intake with new-onset coronary artery disease (A) and type 2 diabetes mellitus (B).
Hazard ratios (HR) with 95% CIs were calculated using Cox regression analyses, adjusted for age, sex, active smoking, body mass index, and log-transformed weekly alcohol intake. Estimates <1 indicate a beneficial association between caffeine intake and outcome. Sixty milligrams of caffeine is equivalent to 1 cup of instant coffee or 2 cups of tea.

analyses by cups of decaffeinated or caffeinated coffee and found similar results. Both caffeinated and decaffeinated coffee were associated with lower risk of CAD and T2DM compared with no or high (>6 cups for caffeinated coffee; >3 for decaffeinated coffee) intake (Table S11).

GWAS on Caffeine Intake Traits

We identified 62 SNPs in 37 loci: 32 novel, associated with combined caffeine intake (Figure 2; Table S12); 27 SNPs in 24 loci (20 novel) with caffeine from coffee (Figure S2; Table S13); and 27 SNPs in 24 loci (21 novel) with caffeine from tea (Figure S3; Table S14).

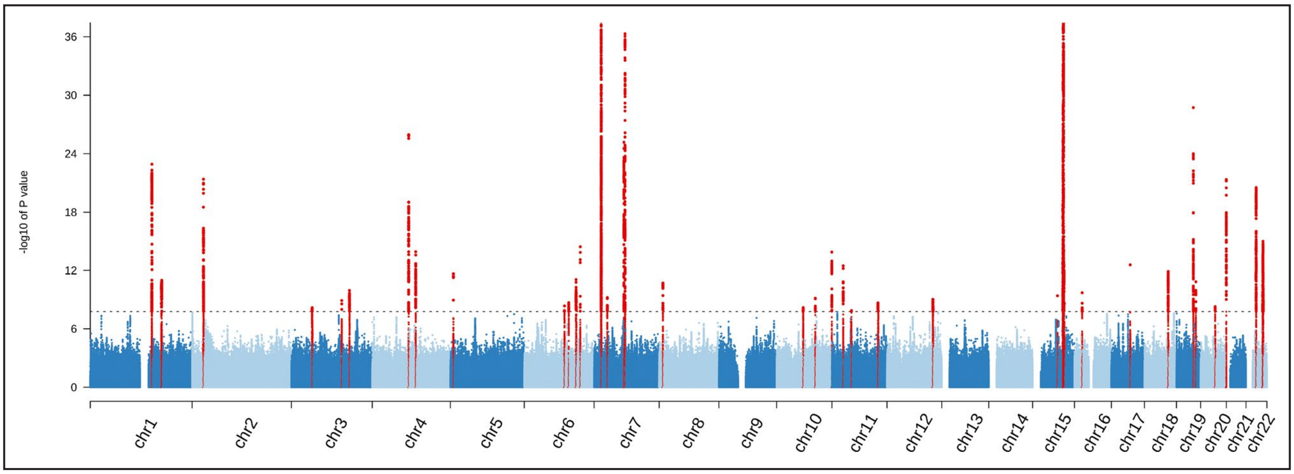


Figure 2. Manhattan plot for combined caffeine intake.
Manhattan plot showing the results for the genome-wide associations with combined caffeine intake in the UK Biobank with the −log10 *P* value on the vertical axis. The sentinel single nucleotide polymorphisms that reached genome-wide significance ($P<1.67\times10^{-8}$) are colored red.

When combined on the basis of the lowest *P* value over all traits, 73 unique SNPs in 5 known and 51 novel loci were associated with ≥1 caffeine trait (Figure S4, Table S15). In total, 15 of 20 previously reported SNPs were replicated within 1 MB of our sentinel SNPs (Table S16). Regional association plots for each independent locus per trait are presented in Figures S5 through S7 and QQ plots in Figures S8 through S10. The sentinel SNPs identified in the combined caffeine, caffeine from coffee, and caffeine from tea GWAS explained 1.32%, 0.59%, and 0.45% of variance in caffeine intake of their respective trait. The heritability rate (h_g^2) for all SNPs in the GWAS was 8.2% for combined caffeine intake, 6.1% for caffeine from coffee, and 7.1% for caffeine from tea.

Using the genetic risk score of each GWAS, each unit change in genetically determined caffeine intake was consistent with 131.6 mg combined caffeine intake, 134.5 mg caffeine intake from coffee, and 86.1 mg caffeine intake from tea. In coffee drinkers, depending on the type of coffee usually drunk, each unit related from 1.5 cup of decaffeinated coffee to 2.1 cups of instant coffee (Table S17).

Candidate Genes and Deeper Insights Into Biology

We explored the potential biology of the sentinel SNPs per GWAS by prioritizing potentially causal genes in these loci based on proximity, expression quantitative trait locus (eQTL) analyses, and data-driven expression-prioritized integration for complex traits. In total, we identified 48 candidate genes for combined caffeine intake, 27 for caffeine from coffee, and 40 for caffeine from tea (Figure 3). We identified the previously reported *AHR*, *CYP1A1*, and *POR* genes in all 3 GWASs. In addition, 2 novel genes, *GOLPH3L* and *HORMAD1,* were associated with all caffeine traits.

Across 209 tissue and cell types, central nervous system tissues were most enriched for SNPs associated

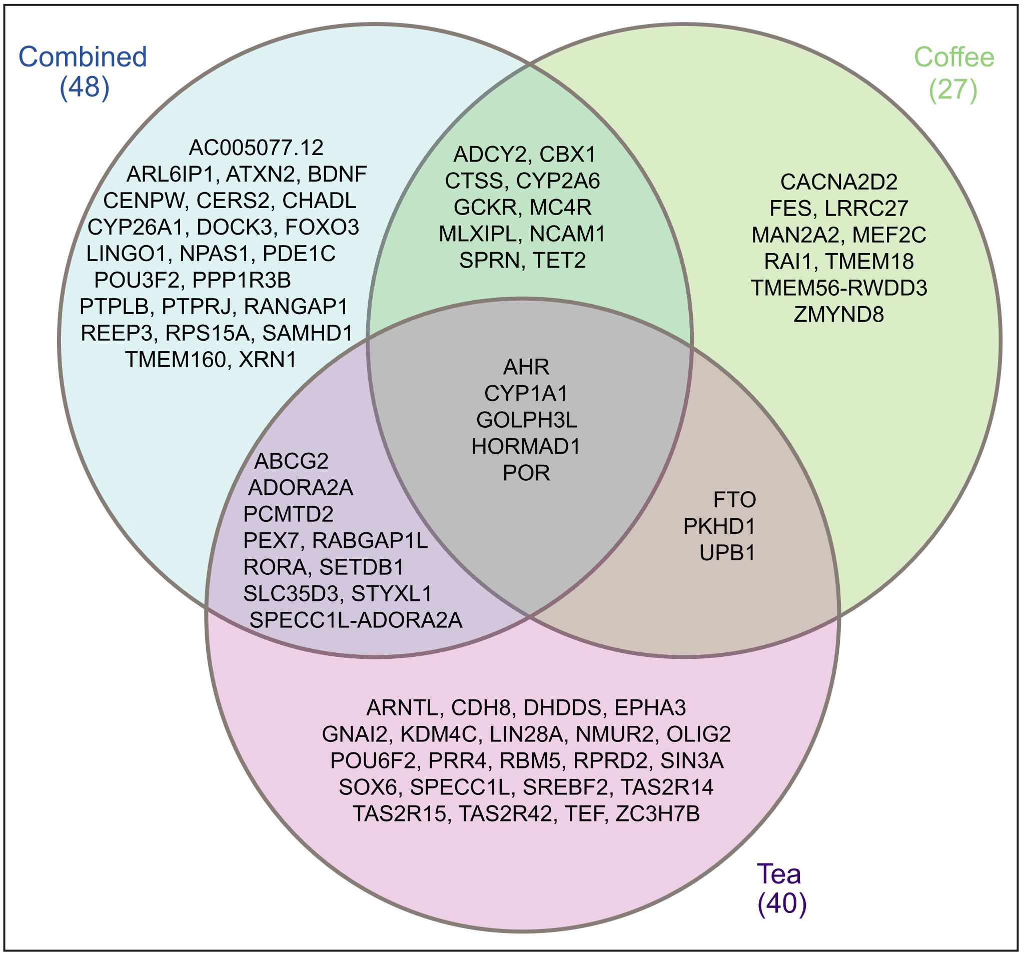


Figure 3. Venn diagram of candidate genes associated with caffeine intake.
Candidate genes were prioritized based on proximity, data-driven expression-prioritized integration for complex traits, and expression quantitative trait locus mapping for combined caffeine intake, caffeine from coffee, and caffeine from tea.

with caffeine from tea and combined, but none with caffeine from coffee (Table S18). Furthermore, 6 combined caffeine intake loci, and 3 loci each of caffeine from coffee or tea, contained variants with eQTLs in at least 1 tissue. The strongest associations were found for rs768283768 near *HORMAD1* and *GOLPH3L*, which tagged multiple tissues (Table S19).

Genetically Determined Caffeine Intake and CAD

The association between genetically determined caffeine intake and CAD was tested in the independent CARDIoGRAMplusC4D cohort (123 504 controls and 60 801 [33.0%] cases). In total, 35 SNPs from caffeine for combined caffeine intake, 22 for caffeine from coffee (rs2298527 excluded based on intermediate allele frequency in CARDIoGRAMplusC4D), and 24 for caffeine from tea (Table S20 through S22). F-statistics indicated low chances of weak instrument bias (Table S23) and I^2_{GX} indicated low chances of measurement error in MR-Egger (Table S24). However, I^2 and Cochran's Q indicated heterogeneity, and thus potential pleiotropy, for all caffeine traits (Table S24). Using the random effects inverse-variance weighted method as indicated by the nonsignificant Q-Q′ and MR-Egger intercepts, we found that genetically determined caffeine intake from combined or coffee were not associated with CAD (OR, 1.12 [95% CI, 0.80–1.40], *P*=0.31; OR 1.26 [95% CI, 0.82–1.93], *P*=0.28, respectively). MR-Egger was used for caffeine from tea because the Q-Q′ was significant; however, also for caffeine from tea, no association with CAD was indicated (OR, 1.60 [95% CI, 0.75–3.44], *P*=0.24). MR Pleiotropy Residual Sum and Outlier analyses corroborated these findings for all traits, with and without trimming outlier SNPs (Table S25). MR-Steiger filtering also did not attenuate the results for any caffeine trait (Table S26). Finally, weighted median and mode-based analyses also indicated no association between genetically determined caffeine intake and CAD. Individual SNP effects are shown in Figures S11 through S13 and the MR analyses in Figure 4A.

Genetically Determined Caffeine Intake and T2DM

The association between genetically determined caffeine intake and T2DM was investigated in the DIAGRAM cohort (132 532 controls and 26 676 [16.8%] cases). In DIAGRAM, 35 SNPs for combined caffeine intake, 23 SNPs for caffeine from coffee, and 24 SNPs for caffeine from tea were used (Tables S27 through S29). Also here, I^2 indices and Cochran's Q indicated pleiotropy for all traits, and the MR-Egger intercept was not significant. However, because the Q-Q′ was

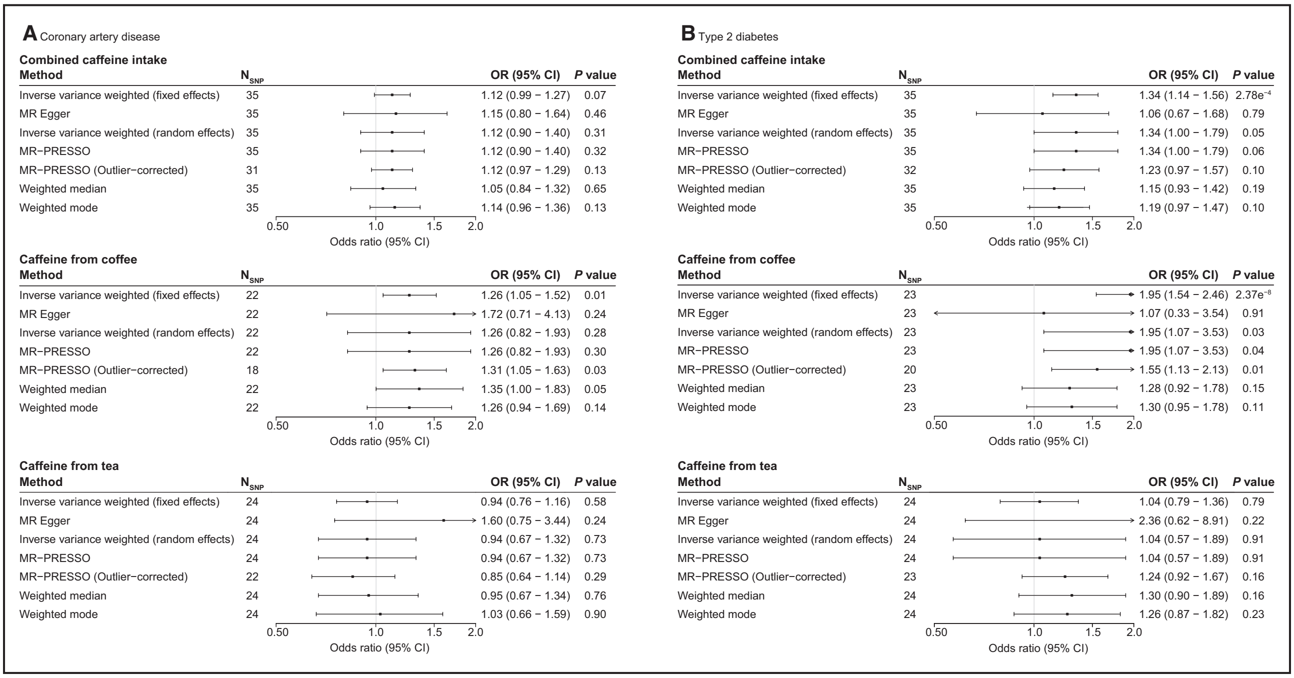


Figure 4. Mendelian randomization results for genetically determined higher caffeine intake (per SD) on coronary artery disease (A) and type 2 diabetes mellitus (B).

Odds ratios (OR) with 95% CIs are provided per standard deviation increase in genetically determined caffeine intake from combined, coffee, or tea. Number of single-nucleotide polymorphisms (SNPs) included are shown per method. Estimates <1.0 indicate a beneficial association between genetically determined caffeine intake and outcome. MR-PRESSO indicates Mendelian Randomization Pleiotropy Residual Sum and Outlier.

significant for all traits, we focused on the MR-Egger estimate for the causal effect. The MR-Egger analyses indicated no association between genetically determined higher caffeine intake from any trait with risk of T2DM (OR, 1.06 [95% CI, 0.67–1.68], P=0.79 for combined caffeine intake; OR, 1.07 [95% CI, 0.33–3.54], P=0.91 for caffeine from coffee; OR, 2.36 [95% CI, 0.62–8.91], P=0.22 for caffeine from tea; Figure 4B; estimates per SNP in Figures S14 through S16). Additional analyses using MR Pleiotropy Residual Sum and Outlier and MR-Steiger also found no associations between caffeine intake with T2DM after respectively trimming outliers and filtering (Tables S25 and S26). Finally, also weighted and mode-based estimator MR analyses were in line with these findings and indicated no association with T2DM.

Combined Caffeine Intake–Specific Variants

In total, 18 variants were associated with combined caffeine intake, of which the annotated genes do not overlap with those of caffeine from coffee or caffeine from tea. However, these variants were most strongly associated with combined caffeine intake compared with caffeine from tea or coffee and had concordant betas across all traits (Table S15). This suggests that these variants act on both caffeine from coffee and caffeine from tea. We repeated the MR analyses using these variants or their proxies available in CARDIoGRAMplusC4D and DIAGRAM. Similar to the MR using all combined caffeine intake variants, we found no associations with CAD or T2DM.

Moderate Versus Extreme Caffeine Intakes From Coffee or Tea

Because of the U-shaped curve observed in the observational analyses between caffeine from coffee and caffeine from tea with CAD or T2DM, we performed exploratory analyses to investigate variants associated with moderate caffeine intake from coffee or tea separately. Extremes of caffeine intake (0 and >360 mg/day for coffee and 0 and >120 mg/day for tea) were taken together and values between the extremes as moderate intake. A total of 373 522 individuals (99 427 [26.6%] with moderate intake) were included in the GWAS for moderate caffeine consumption from coffee, and 395 866 (188 013 [47.8%] with moderate intake) in the GWAS for moderate caffeine consumption from tea. However, GWAS on either phenotype found no variants at $P<1.67\times10^{-8}$ or $P<5\times10^{-8}$.

DISCUSSION

In this large prospective study, we observed U-type associations between observational caffeine intake with CAD and T2DM, although similar intakes from different sources had dissimilar effect sizes. In addition, we identified 51 novel genetic loci associated with caffeine intake, more than tripling the number of known loci.[11–17] In contrast to the observational analyses, genetic causal inference analyses indicated that genetically determined caffeine intake was not associated with CAD or T2DM.

Our observational findings are concordant with previous studies showing inverse or U-type associations between caffeine intake with CAD[2,47] and T2DM.[3,47,48] A meta-analysis in 1 283 685 individuals (28 347 CAD cases) estimated a relative risk of 0.89 (95% CI, 0.85–0.94) for CAD at 3 to 5 cups of coffee daily and a neutral effect at higher intakes (>360 mg or >6 cups of coffee) compared with no intake.[2] A plausible explanation for the U-type shape of the association is that coffee is a liquid extract of coffee beans and it contains a complex chemical mixture of biologically active compounds, some with beneficial and others with harmful effects.[49] At moderate intakes, the beneficial effects could outweigh or counteract the harmful effects, whereas at higher intakes the harmful effects may counterbalance this.[2] Our results for T2DM are in line with the most recent meta-analysis, which reported a relative risk of 0.70 (95% CI, 0.65–0.75) in individuals who consumed 5 cups of coffee per day compared with nondrinkers, although they reported no U-type associations.[50] The hypothesis that moderate caffeine intake may have beneficial effects compared with extreme intakes is also not supported by our findings for combined caffeine intake. The null findings of the observational analyses for combined caffeine intake indicate that caffeine by itself is unlikely to affect disease risk. The current study used the largest number of caffeine SNPs to date from different dietary sources, which is relevant for this UK population, where tea is the second-largest source of caffeine[1] and may confound the association. Using these SNPs in robust causal inference analyses, we found no associations between genetically determined higher or lower caffeine intake and CAD or T2DM. These findings are in line with previous MR studies of caffeine intake on CAD and T2DM.[7,18,19] The null findings of the combined caffeine intake SNPs can be considered a negative control for the observational findings. There is accumulating evidence that previous beneficial associations between caffeine intake with outcomes were attributable to residual confounding, most likely because of other compounds found in coffee[3,7,18,19] or smoking,[51] since no difference in outcomes is reported between decaffeinated and caffeinated coffee for CAD[8] or T2DM.[3] Also, in the current study, we found that observational decaffeinated coffee consumption was associated with similar effect sizes compared with caffeinated coffee. Caffeinated coffee was more robustly associated with outcomes, but this is likely attributable to the larger number of caffeinated coffee drinkers. Furthermore, caffeine from coffee was generally associated with lower estimates compared with caffeine from tea or combined, arguing against an independent effect of caffeine. In addition, both previous and the current MR analyses consistently lack evidence for causality, providing further argument against a protective effect of genetically determined higher caffeine intake.

To our knowledge, this is the largest study to date to investigate the association of both observational and genetically determined caffeine intake from multiple sources with CAD and T2DM. This study also reports the largest number of caffeine intake–associated SNPs, while also replicating previously reported SNPs. These newly identified variants were then used in independent disease-specific cohorts for both CAD and T2DM in 2-sample MR analyses. The explained variance of the sentinel SNPs is comparable with previously published GWASs on coffee[7,12] or alcohol[52] intake, which range between 0.6% and 1.3%. However, the explained variance was of little influence on the statistical power for the MR.

This study has some limitations. In the current analyses, caffeine intake was calculated on the basis of self-reported data at a single time point at baseline, which does not take into account possible changes in coffee- and tea-drinking habits. Furthermore, because the caffeine content of coffee may differ depending on the method of preparation,[53,54] use of filter,[55] and type of coffee bean,[1] and individuals may drink several types of coffee, the actual caffeine intake per day may differ from our calculation. We did not take into account caffeine intake from other sources such as cola or energy drinks, as this information was not available. In addition, the main MR analyses assume linear associations, whereas the causal associations might be nonlinear, with higher risks at low and high intakes, such as the U-shaped–curve associations observed in the observational analyses. However, it was not possible to examine nonlinear associations in the MR analyses because these require individual-level data in the outcome cohorts, which were not available. The MR analyses should therefore be interpreted with caution at the extremes of caffeine intake. It remains unclear which genetic variants are responsible for the specific parts of the potential U-shaped–curve association, and we cannot exclude the possibility that the variants associated with caffeine intake from coffee or tea could have bidirectional effects on the association. Exploratory analyses to investigate the nonlinear association within the UK Biobank, however, indicate that there may be no genetic variants solely associated with moderate or extreme caffeine intake from coffee or tea.

Also, despite our sensitivity analyses to test for and minimize bias, especially from genetic pleiotropy in which the instrumental variables may act on the outcome through other pathways than caffeine, this cannot be completely excluded. We found evidence for heterogeneity in the MR for CAD and T2DM for all caffeine traits, indicating that pleiotropy cannot be ruled out. We therefore report the correct model per degree of pleiotropy as the main results and performed several other sensitivity analyses to take this into account. Finally, the present analyses were performed in individuals of White British ancestry, which may limit the generalizability of the results to other populations.

In conclusion, this large prospective study showed inverse associations between observational caffeine intake with CAD and T2DM. However, effect sizes were similar between caffeinated and decaffeinated coffee; similar caffeine intakes from tea were associated with fewer inverse effects compared with caffeine from coffee. Furthermore, MR analyses in independent cohorts yielded no evidence for causality between genetically determined caffeine intake with CAD or T2DM. The main MR analysis results suggest that increasing caffeine intake may not be protective against the development of CAD or T2DM. However, these do not take into account the nonlinear association observed within the observational analyses. We therefore encourage reanalysis of the results when more advanced methods to study nonlinear associations within a summary-based 2-sample MR setting emerge, without individual-level exposure data in the outcome cohort.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S29
Figures S1–S16

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Supplemental Material

Data S1.

Supplemental Methods

UK Biobank participants

The study design and population of the UK Biobank study have been described in detail previously[20]. Briefly, between 2006 and 2010 over 500,000 participants aged 40-69 years from the general population were recruited at 22 assessment centers in the United Kingdom. Participants provided information on demographic, lifestyle, and other potentially health-related aspects through interviews, questionnaires, physical measurements as well as blood and urine samples[20]. All participants provided informed consent for the study at their first visit to the assessment center by agreeing to all individual statements of the consent form and providing their signature on an electronic pad[21]. The UK Biobank study has approval from the North West Multi-centre Research Ethics Committee for the UK, from the National information Governance Board for Health & Social Care for England and Wales, and from the Community health Index Advisory Group for Scotland[22].

Ascertainment of coffee and tea intake

During the first visit to the assessment center, daily coffee and tea intake were assessed by asking participants "*How many cups of coffee do you drink each day? (Include decaffeinated coffee)*" and "*How many cups of tea do you drink each day? (Include black and green tea)*".

Participants were asked to provide the average number of cups of either beverage they drink daily, based on their intake over the last year. We excluded participants who answered with "*Less than one*", "*Do not know*" or "*Prefer not to answer*". Participants who indicated to drink more than 10 cups of coffee or 20 cups of tea daily were asked to confirm their input. In addition, coffee drinkers were asked what type of coffee they usually drink, to which they could answer "*Decaffeinated coffee (any type)*", "*Instant coffee*", "*Ground coffee (include espresso, filter etc)*", "*Other type of coffee*", "*Do not know*" or "*Prefer not to answer*". Amongst coffee drinkers we additionally excluded those who did not provide information on the type of coffee they usually drink. Coffee and tea intake were truncated at 20 cups per day.

Decaffeinated coffee was considered to contain 3 mg of caffeine per cup, instant coffee 60 mg, ground coffee 85 mg, and tea 30 mg[23]. Combined caffeine intake from both coffee and tea was calculated as the sum of the daily caffeine intake from coffee and tea from individuals who provided data on both.

CAD and T2D prevalence and incidence in the UK Biobank

Prevalence and incidence of CAD and T2D within UK Biobank were captured using self-reported data collected using the baseline-questionnaires and verbal interviews as per prior analysis[24]. Diagnoses were additionally captured using the Hospital Episode Statistics "Spell and Episode" category, which contains data on diagnoses made during hospital in-patient stay. We used both main and secondary diagnoses, coded according to the International Classification of Diseases (ICD) versions 9 and 10[25]. For CAD, we used ICD-9 codes 410, 412 and 414, and ICD-10 codes I21-I25, Z951 and Z955. For T2D, we used ICD-9 code 250 and ICD-10 codes E10-E14. In addition we used surgical procedures that were recorded according to the Office of Population, Censuses and Surveys: Classification of interventions and Procedures (OPCS), version 4 coding[26]. For CAD, OPCS-4 codes K40-K46, K49, K50 and K75 were used. Incident cases that were based on self-reported diagnoses during follow-up visits were included only if there were no events recorded according to ICD-9/ICD-10/OPCS 4 and only if the participant did not report this in the previous visit. If the participant was the same age as the reported age of diagnosis, the median date between the visit and their birthday was taken as date of event, and if the age of diagnosis was before the participants current age we took the median date of the year of the reported age of diagnosis counted from the participants birthday. If age of diagnosis was not available we took the median date between the visit of the first self-reported diagnosis and the previous visit. Participants with CAD or T2D at inclusion were excluded for the observational analyses of the respective disease. Follow-up for incident CAD, T2D and death due to these conditions was from inclusion until March 31, 2017 for participants from England, February 29, 2016 for Wales, and October 31, 2016 for Scotland.

Genotyping and imputation in UK Biobank

The genotyping process and arrays used in UK Biobank have been described elsewhere in more detail. Briefly, participants were genotyped using the custom Affymetrix UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) Axiom^{TM} (N=49,950) or Affymetrix UK Biobank Axiom^{TM} array (N=438,427)[27,28]. The UK BiLEVE Axiom^{TM} and UK Biobank Axiom^{TM} arrays respectively have 807,411 and 820,927 single-nucleotide polymorphism (SNP), insertion and deletion markers with >95% common content[28]. Participants genotyped using the UK BiLEVE array were selected based on smoking behavior (heavy smokers with a mean 35 pack-years and never smokers)[27]. Genomic quality control of samples and variants, as well as imputation was performed by the Wellcome Trust Centre for Human Genetics, based on merged UK10K and 1000 Genomes phase 3 panels[27,29]. Participants were excluded if there was a mismatch between genetic and reported sex, if participants had high missingness or excess heterozygosity, or were not of white British descent. In total, from the 502,525 UK Biobank participants, 1,332 did not pass genomic quality control and 91,069 were not of white British descent.

Genetic analyses

All genetic analyses were adjusted for age, sex, genotyping array, and the first 30 principal components (PCs) to adjust for population stratification. We performed separate GWAS for inverse rank normalized combined caffeine intake, caffeine from coffee, and caffeine from tea. GWAS were performed using BOLT-LMM v2.3.1, which uses a linear mixed model that corrects for population structure and cryptic relatedness[30]. In total, 19,400,838 SNPs were included in the GWAS. To obtain a set of independent SNPs per phenotype, SNPs with $P<5\times10^{-8}$ were clumped together based on linkage disequilibrium (LD) $R^2>0.005$ and 5-Mb distance using the clumping procedure integrated in PLINK version 1.9. To account for multiple testing of the 3 GWAS, we considered only SNPs with Bonferroni corrected $P<1.67\text{x}10^{-8}$ (traditional GWAS significance threshold of $5\text{x}10^{-8}/3$) as statistically significant. This significance threshold is conservative, considering that our phenotypes are correlated with Spearman's rank correlation coefficients between phenotype pairs ranging from r=-0.33 to 0.71 (**Table S1**).

For each phenotype we consequently identified the sentinel SNP (defined as the most significant SNP in a 5-Mb region at either side of the SNP) at each locus. A locus was defined as a 1-Mb region at either side of the sentinel SNP. Similar to how the sentinel SNP per locus per phenotype was identified, a single sentinel SNP with the lowest *P* value per locus was identified across the sentinel SNPs of all three phenotypes for general caffeine intake. SNPs were excluded if the minor allele frequency (MAF) was <0.005 or the INFO score was below 0.3.

Identification of candidate genes

Candidate genes at each locus were prioritized based on 1) proximity, the nearest protein coding gene and any additional gene within 10kb of the sentinel SNP; 2) Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT); and 3) expression quantitative trait locus (eQTL) genes in cis analyses. Summary information about candidate causal genes was obtained through queries in GeneCards.

DEPICT analyses

DEPICT has been described in detail previously[31]. Briefly, DEPICT systematically prioritizes likely causal genes at associated loci, and identifies tissue and cell types where genes from associated loci are highly expressed. DEPICT.v1.beta version rel194 1KG imputed GWAS was obtained from https://data.broadinstitute.org/mpg/depict/. DEPICT was run with default settings, using all variants at $P<1.0\text{x}10^{-5}$. Tissue and cell type enrichment found by DEPICT at FDR <0.05 were considered significant.

eQTL analyses

We applied a summary-data-based MR (SMR) approach in cis-eQTL data repositories from Genotype-Tissue Expression (GTEx) version 7[32], Brain-eMeta eQTL[33], and blood eQTL from Westra[34] and CAGE[35]. SMR, by default, was performed only in cis-regions. eQTL genes were considered as candidate causal genes if the top associated eQTL SNP achieved $P<2.7\text{x}10^{-7}$ ($P = 0.05/n_{\text{SMRtests}}$ = [combined caffeine intake = 187,748; caffeine from coffee = 181,931; caffeine from tea = 182,971]), passed the HEterogeneity In Dependent Instruments (HEIDI) test with $P>0.05$, and were LD buddies ($R^2>0.8$) with the queried caffeine intake SNP. HEIDI distinguishes pleiotropy from linkage by testing for heterogeneity in SMR estimates of SNPs in LD with the top-associated cis-eQTL. In the case of pleiotropy, the gene expression and the trait of interest share the same SNP. Software for the SMR/HEIDI tests was downloaded from http://cnsgenomics.com/software/smr/#Download and eQTL catalogues from http://cnsgenomics.com/software/smr/#eQTLsummarydata.

Associations between genetics with outcomes

To gain insight in the potentially causal relationship between caffeine intake and CAD, we performed MR analyses on summary statistics data from the CARDIoGRAMplusC4D consortium as provided by Nikpay *et al.* in 123,504 controls and 60,801 (33.0%) cases[36]. The CARDIoGRAMplusC4D data was obtained through MR Base. To assess the potentially causal relationship with T2D, MR analyses were performed on summary statistics data from the DIAGRAM consortium as reported by Scott *et al.*, which included 132,532 controls and 26,676 cases (16.8%)[37]. Summary statistics data for DIAGRAM was downloaded from http://www.diagram-consortium.org/downloads.html. Analyses were performed per caffeine intake trait using the lead SNPs at $P<1.67\text{x}10^{-8}$. Proxies based on highest LD and position were used for SNPs that were not available in CARDIoGRAMplusC4D or DIAGRAM. SNPs were only replaced with proxies with $R^2>0.8$, and were otherwise excluded from the MR analyses if no eligible proxies were available. SNP effects were harmonized across the studies using the built-in function in the MR Base R package (*TwoSampleMR*). The association between genetically determined higher caffeine intake and CAD or T2D was assessed using a fixed-effects inverse-variance weighted (IVW) meta-analysis method which combines MR estimates for individual SNPs with the outcome. Odds ratios (OR) with 95%CI are presented for the MR outcomes. To maximize the likelihood of reporting true findings, α was set at 0.005 rather than 0.05[39]. Associations with $P<0.05$ were considered suggestively significant.

Weak instrument bias

The strength of the instruments (SNPs) per phenotype was assessed using the F-statistic, calculated as $F=R^2(n_{sample}-2)/(1-R^2)$, where R^2 is the proportion of variability in caffeine intake. An F-statistic >10 indicates relatively low risk of weak instrument bias in MR analyses[40], which is essential to prevent violation of the 'NO Measurement Error' assumption. Additionally, potential weak instrument bias in MR-Egger regression analyses was assessed by calculating I^2_{GX}, which is the true variance of the SNP-exposure association. I^2_{GX} >95% indicates small uncertainty in the SNP-exposure association estimates and was considered low risk of measurement error[41].

Analyses for pleiotropy in MR

In MR analyses, pleiotropy indicates multiple effects are exerted by a SNP, which could violate the assumption in MR analysis that the SNP only influences the outcome through the exposure of interest (here, caffeine). We applied multiple tests to investigate potential pleiotropy in our analyses. First, I^2 index and Cochran's Q statistic were determined. An I^2 index >25% and Cochran's Q $P<0.05$ were considered indicative of heterogeneity and thus pleiotropy[42]. In case of evidence of heterogeneity, each instrument can be allowed to have a (balanced) pleiotropic effect and a random effects IVW method can be applied[43]. MR-Egger, which in contrast to the IVW method assumes pleiotropic effects of the SNPs on the outcome are independent of their association with the exposure (caffeine), was performed as an additional test. If the MR-Egger intercept is zero, tested using $P>0.05$, this indicated there was evidence for absent pleiotropic bias, whereas deviations from zero indicate horizontal pleiotropy across the SNPs. If the InSIDE assumption, which assumes the association of SNPs with the exposure are independent of the direct pleiotropic effects of the SNP on the outcome, is satisfied, the coefficient from the MR-Egger regression is an estimate of the causal effect. We further assessed heterogeneity within the MR-Egger analysis using the Rücker's Q' statistic, and tested whether this differed ($P<0.05$) from Cochran's Q (Q-Q'). A significant difference indicates the MR-Egger is the preferred method to study the association between the exposure and the outcome[43]. Pleiotropy was further tested using the MR pleiotropy residual sum and outlier (MR-PRESSO) test[44], which compares the residuals for each SNP in the zero-intercept regression line of the SNP-outcome estimate with the SNP-exposure estimate in the absence of pleiotropy. Hereby, pleiotropic effects can be detected and outliers identified. MR-PRESSO then re-analyses the association without the outliers, correcting for potential pleiotropic effects[44]. MR-Steiger filtering was performed to remove variants which are stronger associated with the outcome than the exposure[45]. To this end, the R^2 for the exposure and outcome is calculated, after which variants with significantly lower R^2 for the exposure than for the outcome are removed.

Sensitivity analyses in MR

We additionally performed several sensitivity analyses. First, weighted median MR analysis was performed, which allows up to 50% of the instruments to be invalid, in contrast to regular IVW analysis where absence of pleiotropic effects of the instruments is assumed. Next, weighted mode-based estimator MR analyses were performed to allow even larger numbers of SNPs to be invalid, but rather takes the overall MR result from the greatest number of valid SNPs with similar MR estimates[46]. The R packages *TwoSampleMR* version 0.4.22 (https://mrcieu.github.io/TwoSampleMR/) and MR-PRESSO version 1.0 were used for the MR analyses.

Data sources

UK Biobank

This research has been conducted using the UK Biobank Resource under Application Number 12006 and 15031.

CARDIoGRAMplusC4D Consortium

We used summary statistics data available in MR Base from the Coronary Artery Disease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease (CARDIoGRAMplusC4D) consortium as published by Nikpay *et al.* in 2015[36]. The CARDIoGRAMplusC4D cohort consisted of 123,504 controls and 60,801 (33.0%) coronary artery disease cases.

DIAGRAM consortium

We used summary statistics data from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium as published by Scott *et al.* in 2017[37], downloaded from http://www.diagram-consortium.org/downloads.html. The DIAGRAM cohort consisted of 132,532 controls and 26,676 (16.8%) type 2 diabetes cases.

Table S1. Spearman's rank correlation between phenotypical caffeine intake traits

	Combined daily caffeine intake	**Daily caffeine intake from coffee**	**Daily caffeine intake from tea**
Combined daily caffeine intake	1		
Daily caffeine intake from coffee	0.7147	1	
Daily caffeine intake from tea	0.3071	-0.3319	1

Caffeine intake in mg/day

Table S2. Baseline characteristics for individuals included in the GWAS on combined caffeine intake, caffeine from coffee, or caffeine from tea

Characteristic	**Combined Caffeine**	**Caffeine from Coffee**	**Caffeine from Tea**
Total, n	362,316	373,522	395,866
Age, mean (SD), y	56.94 (8.00)	56.92 (8.01)	56.94 (7.99)
Female	195,754 (54.0%)	201,463 (53.9%)	214,395 (54.2%)
Daily caffeine intake, median (IQR), mg/day			
Combined caffeine	205 (120-290)	205 (120-290)	205 (120-290)
Caffeine from coffee	60 (3-180)	85 (3-180)	60 (3-180)
Caffeine from tea	90 (60-150)	90 (60-150)	90 (60-150)
Blood pressure, mean (SD), mm Hg			
Systolic	133.75 (17.94)	133.76 (17.93)	133.73 (17.95)
Diastolic	82.13 (8.54)	82.14 (8.54)	82.12 (8.54)
Active smoker			
No	325,226 (89.8%)	335,025 (89.7%)	355,938 (89.9%)
Yes	37,090 (10.2%)	38,497 (10.3%)	39,928 (10.1%)
BMI, mean (SD), kg/m^2	27.43 (4.74)	27.43 (4.75)	27.41 (4.75)
Weekly alcohol intake, median (IQR), UK units	9.60 (1.96-20.20)	9.60 (1.96-20.20)	9.60 (1.96-20.00)
Hypertension			
No	250,114 (69.0%)	257,966 (69.1%)	272,994 (69.0%)
Yes	112,202 (31.0%)	115,556 (30.9%)	122,872 (31.0%)
Hyperlipidemia			
No	291,798 (80.5%)	300,872 (80.6%)	318,841 (80.5%)
Yes	70,518 (19.5%)	72,650 (19.4%)	77,025 (19.5%)

Combined caffeine intake was calculated as the sum of caffeine intake from coffee and tea. Body mass index calculated as weight in kilograms divided by height in meters squared

Table S3. Baseline characteristics per 60 mg of combined caffeine intake

Characteristic	**0 mg**	**1-60 mg**	**61-120 mg**	**121-180 mg**	**181-240 mg**	**241-300 mg**	**301-360 mg**	**>360 mg**
Total, n	8,845	26,279	55,733	81,959	69,745	51,542	31,198	37,015
Age, mean (SD), y	53.61 (8.33)	56.05 (8.28)	56.91 (8.12)	57.33 (7.99)	57.52 (7.85)	57.20 (7.84)	56.87 (7.80)	56.19 (7.94)
Female	5,673 (64.1%)	16,185 (61.6%)	32,673 (58.6%)	46,430 (56.7%)	37,917 (54.4%)	26,289 (51.0%)	14,948 (47.9%)	15,639 (42.3%)
Daily caffeine intake, median (IQR), mg/day								
Combined caffeine	0 (0-0)	33 (15-60)	96 (90-120)	159 (150-180)	230 (210-240)	285 (270-300)	345 (330-360)	450 (420-540)
Caffeine from coffee	0 (0-0)	6 (0-15)	3 (0-60)	18 (0-85)	120 (60-170)	170 (120-240)	240 (170-300)	340 (255-425)
Caffeine from tea	0 (0-0)	30 (0-30)	90 (60-90)	120 (60-150)	120 (60-180)	120 (60-180)	90 (60-180)	120 (30-210)
Blood pressure, mean (SD), mm Hg								
Systolic	128.79 (17.62)	132.38 (18.11)	133.68 (18.19)	133.96 (18.18)	134.20 (17.91)	134.26 (17.72)	134.08 (17.56)	133.72 (17.44)
Diastolic	80.92 (8.87)	81.70 (8.70)	82.03 (8.58)	82.05 (8.56)	82.13 (8.47)	82.35 (8.44)	82.43 (8.50)	82.49 (8.50)
Active smoker								
No	8,235 (93.1%)	24,301 (92.5%)	52,154 (93.6%)	75,786 (92.5%)	63,530 (91.1%)	45,656 (88.6%)	26,631 (85.4%)	28,933 (78.2%)
Yes	610 (6.9%)	1,978 (7.5%)	3,579 (6.4%)	6,173 (7.5%)	6,215 (8.9%)	5,886 (11.4%)	4,567 (14.6%)	8,082 (21.8%)
BMI, mean (SD), kg/m^2	27.84 (5.77)	27.87 (5.23)	27.32 (4.82)	27.28 (4.69)	27.24 (4.57)	27.40 (4.53)	27.57 (4.65)	27.75 (4.75)
Weekly alcohol intake, median (IQR), UK units	1.96 (1.00-12.40)	6.90 (1.60-17.90)	8.70 (1.96-19.20)	9.60 (1.96-19.20)	9.60 (2.00-20.20)	10.80 (2.66-21.30)	11.20 (2.90-22.40)	11.20 (1.96-23.20)
Hypertension								
No	6,542 (74.0%)	17,598 (67.0%)	37,359 (67.0%)	55,634 (67.9%)	48,329 (69.3%)	36,266 (70.4%)	22,152 (71.0%)	26,234 (70.9%)
Yes	2,303 (26.0%)	8,681 (33.0%)	18,374 (33.0%)	26,325 (32.1%)	21,416 (30.7%)	15,276 (29.6%)	9,046 (29.0%)	10,781 (29.1%)
Hyperlipidemia								
No	7,646 (86.4%)	20,773 (79.0%)	44,522 (79.9%)	65,591 (80.0%)	56,254 (80.7%)	41,857 (81.2%)	25,345 (81.2%)	29,810 (80.5%)
Yes	1,199 (13.6%)	5,506 (21.0%)	11,211 (20.1%)	16,368 (20.0%)	13,491 (19.3%)	9,685 (18.8%)	5,853 (18.8%)	7,205 (19.5%)

Combined caffeine intake was calculated as the sum of caffeine intake from coffee and tea. Body mass index calculated as weight in kilograms divided by height in meters squared

Table S4. Baseline characteristics per 60 mg caffeine intake from coffee

Characteristic	**0 mg**	**1-60 mg**	**61-120 mg**	**121-180 mg**	**181-240 mg**	**24-300 mg1**	**301-360 mg**	**>360 mg**
Total, n	85,680	100,079	61,866	49,884	22,315	24,478	15,473	13,747
Age, mean (SD), y	55.88 (8.15)	57.95 (7.83)	57.25 (7.97)	57.15 (7.92)	56.85 (7.90)	56.36 (7.97)	56.31 (7.91)	55.35 (8.00)
Female	49,810 (58.1%)	59,014 (59.0%)	32,525 (52.6%)	25,331 (50.8%)	10,745 (48.2%)	11,382 (46.5%)	6,944 (44.9%)	5,712 (41.6%)
Daily caffeine intake, median (IQR), mg/day								
Combined caffeine	150 (90-180)	129 (72-183)	210 (175-240)	260 (210-300)	300 (240-360)	330 (300-375)	390 (360-450)	540 (480-630)
Caffeine from coffee	0 (0-0)	15 (6-60)	120 (85-120)	180 (170-180)	240 (240-240)	300 (255-300)	360 (340-360)	480 (425-595)
Caffeine from tea	150 (90-180)	90 (60-150)	90 (60-150)	90 (30-120)	60 (0-120)	60 (0-90)	30 (0-90)	30 (0-90)
Blood pressure, mean (SD), mm Hg								
Systolic	132.74 (18.30)	133.78 (17.99)	134.17 (17.93)	134.13 (17.80)	135.10 (17.70)	134.02 (17.43)	134.24 (17.26)	133.47 (17.36)
Diastolic	81.90 (8.68)	81.79 (8.46)	82.26 (8.53)	82.29 (8.45)	82.87 (8.58)	82.50 (8.48)	82.69 (8.46)	82.61 (8.58)
Active smoker								
No	77,385 (90.3%)	92,972 (92.9%)	56,678 (91.6%)	45,213 (90.6%)	19,289 (86.4%)	20,972 (85.7%)	12,607 (81.5%)	9,909 (72.1%)
Yes	8,295 (9.7%)	7,107 (7.1%)	5,188 (8.4%)	4,671 (9.4%)	3,026 (13.6%)	3,506 (14.3%)	2,866 (18.5%)	3,838 (27.9%)
BMI, mean (SD), kg/m^2	27.50 (5.01)	27.41 (4.70)	27.08 (4.58)	27.19 (4.54)	27.95 (4.69)	27.52 (4.64)	27.93 (4.87)	28.08 (4.98)
Weekly alcohol intake, median (IQR), UK units	6.40 (1.17-17.90)	8.00 (1.96-17.60)	11.20 (3.60-22.10)	12.00 (4.80-22.70)	11.50 (3.20-23.00)	12.60 (4.43-23.50)	12.30 (3.16-24.00)	11.00 (1.96-23.90)
Hypertension								
No	58,289 (68.0%)	66,870 (66.8%)	43,294 (70.0%)	35,409 (71.0%)	15,610 (70.0%)	17,743 (72.5%)	10,957 (70.8%)	9,794 (71.2%)
Yes	27,391 (32.0%)	33,209 (33.2%)	18,572 (30.0%)	14,475 (29.0%)	6,705 (30.0%)	6,735 (27.5%)	4,516 (29.2%)	3,953 (28.8%)
Hyperlipidemia								
No	69,397 (81.0%)	79,007 (78.9%)	50,233 (81.2%)	40,659 (81.5%)	18,025 (80.8%)	20,107 (82.1%)	12,464 (80.6%)	10,980 (79.9%)
Yes	16,283 (19.0%)	21,072 (21.1%)	11,633 (18.8%)	9,225 (18.5%)	4,290 (19.2%)	4,371 (17.9%)	3,009 (19.4%)	2,767 (20.1%)

Combined caffeine intake was calculated as the sum of caffeine intake from coffee and tea. Body mass index calculated as weight in kilograms divided by height in meters squared

Table S5. Baseline characteristics per 60 mg caffeine intake from tea

Characteristic	**0 mg**	**1-60 mg**	**61-120 mg**	**121-180 mg**	**>180 mg**
Total, n	60,199	87,981	119,872	85,705	42,109
Age, mean (SD), y	55.81 (8.18)	56.63 (8.16)	57.49 (7.90)	57.29 (7.83)	56.94 (7.79)
Female	33,935 (56.4%)	45,911 (52.2%)	65,987 (55.0%)	46,619 (54.4%)	21,943 (52.1%)
Daily caffeine intake, median (IQR), mg/day					
Combined caffeine	180 (12-300)	180 (72-270)	180 (120-270)	210 (162-270)	300 (240-385)
Caffeine from coffee	180 (12-300)	120 (15-240)	60 (3-170)	60 (0-120)	3 (0-85)
Caffeine from tea	0 (0-0)	60 (30-60)	90 (90-120)	150 (150-180)	240 (210-300)
Blood pressure, mean (SD), mm Hg					
Systolic	133.11 (17.83)	133.80 (17.94)	133.99 (17.99)	133.91 (18.03)	133.35 (17.84)
Diastolic	82.25 (8.68)	82.21 (8.60)	82.02 (8.48)	82.10 (8.50)	82.01 (8.48)
Active smoker					
No	52,157 (86.6%)	80,103 (91.0%)	110,804 (92.4%)	77,595 (90.5%)	35,279 (83.8%)
Yes	8,042 (13.4%)	7,878 (9.0%)	9,068 (7.6%)	8,110 (9.5%)	6,830 (16.2%)
BMI, mean (SD), kg/m^2	28.16 (5.27)	27.25 (4.69)	27.15 (4.55)	27.37 (4.63)	27.48 (4.73)
Weekly alcohol intake, log UK units	9.00 (1.96-20.60)	11.20 (3.20-22.40)	9.60 (2.06-19.80)	8.90 (1.96-19.20)	6.90 (1.17-18.40)
Hypertension					
No	41,492 (68.9%)	61,464 (69.9%)	82,497 (68.8%)	58,873 (68.7%)	28,668 (68.1%)
Yes	18,707 (31.1%)	26,517 (30.1%)	37,375 (31.2%)	26,832 (31.3%)	13,441 (31.9%)
Hyperlipidemia					
No	48,172 (80.0%)	71,307 (81.0%)	96,712 (80.7%)	68,990 (80.5%)	33,660 (79.9%)
Yes	12,027 (20.0%)	16,674 (19.0%)	23,160 (19.3%)	16,715 (19.5%)	8,449 (20.1%)

Combined caffeine intake was calculated as the sum of caffeine intake from coffee and tea. Body mass index calculated as weight in kilograms divided by height in meters squared

Table S6. Unadjusted associations of phenotypic caffeine intake with new-onset coronary artery disease

Caffeine Trait	**Caffeine intake (mg/day)**	**N total**	**N cases (%)**	**Person-time at risk (years)**	**Absolute risk**	**Hazard Ratio**	**95% Confidence interval**	***P* value**
Combined intake	0	8,552	265 (3.10)	68222.505	3.10	1	Reference	Reference
	1-60	24,983	1018 (4.07)	198905.92	4.07	1.32	(1.15-1.51)	6.27E-05
	61-120	53,067	2173 (4.09)	421662.78	4.09	1.33	(1.17-1.51)	1.22E-05
	121-180	78,040	3412 (4.37)	617136.57	4.37	1.43	(1.26-1.62)	2.52E-08
	181-240	66,669	2725 (4.09)	526813.63	4.09	1.34	(1.18-1.51)	7.05E-06
	241-300	49,359	2107 (4.27)	389466.51	4.27	1.40	(1.23-1.59)	2.89E-07
	301-360	29,858	1226 (4.11)	235711.7	4.11	1.34	(1.18-1.53)	1.40E-05
	>360	35,281	1755 (4.97)	277356.55	4.97	1.63	(1.44-1.86)	8.88E-14
Coffee	0	81,341	3615 (4.44)	644426.54	4.44	1	Reference	Reference
	1-60	95,254	4183 (4.39)	753153.67	4.39	0.99	(0.95-1.04)	0.67
	61-120	59,247	2266 (3.82)	468704.42	3.82	0.86	(0.82-0.91)	2.78E-08
	121-180	47,987	1767 (3.68)	380342.59	3.68	0.83	(0.78-0.88)	8.42E-11
	181-240	21,319	975 (4.57)	168465.82	4.57	1.03	(0.96-1.11)	0.39
	241-300	23,492	944 (4.02)	185517.36	4.02	0.91	(0.84-0.98)	8.00E-03
	301-360	14,826	637 (4.30)	117194.67	4.30	0.97	(0.89-1.06)	0.48
	>360	13,082	680 (5.20)	103020.73	5.20	1.18	(1.09-1.28)	8.54E-05
Tea	0	57,433	2461 (4.28)	454797.51	4.28	1	Reference	Reference
	1-60	84,260	3165 (3.76)	670336.26	3.76	0.87	(0.83-0.92)	3.38E-07
	61-120	114,525	4809 (4.20)	906479.66	4.20	0.98	(0.93-1.03)	0.43
	121-180	81,674	3620 (4.43)	643994.84	4.43	1.04	(0.99-1.09)	0.13
	>180	39,905	2012 (5.04)	313272.29	5.04	1.19	(1.12-1.26)	9.29E-09

Unadjusted Cox regression analyses. 60 mg caffeine is equivalent to the caffeine content of one cup of instant coffee or 2 cups of tea. Person-time follow up is provided per 1000 person-time years

Table S7. Unadjusted associations of phenotypic caffeine intake with new-onset type 2 diabetes

Caffeine Trait	**Caffeine intake (mg)**	**N total**	**N cases (%)**	**Person-time at risk (years)**	**Absolute risk**	**Hazard Ratio**	**95% Confidence interval**	***P* value**
Combined intake	0	8,456	183 (2.16)	67917.769	2.16	1	Reference	Reference
	1-60	25,012	651 (2.60)	200942.01	2.60	1.20	(1.02-1.42)	0.03
	61-120	53,431	1156 (2.16)	429276.93	2.16	1.00	(0.86-1.17)	0.99
	121-180	78,764	1516 (1.92)	631103.5	1.92	0.89	(0.77-1.04)	0.15
	181-240	67,123	1208 (1.80)	537016.45	1.80	0.84	(0.72-0.98)	0.02
	241-300	49,606	959 (1.93)	396529.11	1.93	0.90	(0.77-1.05)	0.19
	301-360	29,979	548 (1.83)	239606.07	1.83	0.85	(0.72-1.01)	0.06
	>360	35,347	761 (2.15)	282170.46	2.15	1.00	(0.85-1.18)	0.96
Coffee	0	82,017	1946 (2.37)	657588.3	2.37	1	Reference	Reference
	1-60	95,947	1938 (2.02)	768505.49	2.02	0.85	(0.80-0.91)	6.8E-07
	61-120	59,622	1046 (1.75)	477108.76	1.75	0.74	(0.69-0.80)	6.9E-15
	121-180	48,112	791 (1.64)	385341.27	1.64	0.69	(0.64-0.75)	<1.0E-16
	181-240	21,358	451 (2.11)	171104.9	2.11	0.89	(0.80-0.99)	0.03
	241-300	23,542	426 (1.81)	188172.08	1.81	0.77	(0.69-0.85)	6.7E-07
	301-360	14,788	291 (1.97)	118443.97	1.97	0.83	(0.73-0.94)	3.2E-03
	>360	13,051	304 (2.33)	104416.4	2.33	0.98	(0.87-1.11)	0.81
Tea	0	57,152	1402 (2.45)	457663.58	2.45	1	Reference	Reference
	1-60	84,659	1602 (1.89)	680333.52	1.89	0.77	(0.71-0.82)	4.77E-13
	61-120	115,382	2084 (1.81)	925272.64	1.81	0.74	(0.69-0.79)	<1.0E-16
	121-180	82,365	1627 (1.98)	658185.41	1.98	0.81	(0.75-0.87)	5.18E-09
	>180	40,311	885 (2.20)	321345.95	2.20	0.90	(0.83-0.98)	0.02

Unadjusted Cox regression analyses. 60 mg caffeine is equivalent to the caffeine content of one cup of instant coffee or 2 cups of tea. Person-time follow up is provided per 1000 person-time years

Table S8. Multivariable adjusted associations of phenotypic caffeine intake with new-onset coronary artery disease

Caffeine Trait	Caffeine intake (mg)	N total	N cases (%)	Person-time at risk (years)	Absolute risk	Hazard Ratio	95% Confidence interval	*P* value
Combined intake	0	8,552	265 (3.10)	68222.505	3.10	1	Reference	Reference
	1-60	24,983	1018 (4.07)	198905.92	4.07	1.11	(0.97-1.27)	0.12
	61-120	53,067	2173 (4.09)	421662.78	4.09	1.07	(0.95-1.22)	0.27
	121-180	78,040	3412 (4.37)	617136.57	4.37	1.11	(0.98-1.26)	0.10
	181-240	66,669	2725 (4.09)	526813.63	4.09	1.01	(0.89-1.14)	0.90
	241-300	49,359	2107 (4.27)	389466.51	4.27	1.04	(0.91-1.18)	0.58
	301-360	29,858	1226 (4.11)	235711.7	4.11	0.98	(0.85-1.11)	0.72
	>360	35,281	1755 (4.97)	277356.55	4.97	1.12	(0.98-1.27)	0.10
Coffee	0	81,341	3615 (4.44)	644426.54	4.44	1	Reference	Reference
	1-60	95,254	4183 (4.39)	753153.67	4.39	0.92	(0.88-0.96)	3.89E-04
	61-120	59,247	2266 (3.82)	468704.42	3.82	0.81	(0.77-0.85)	7.99E-15
	121-180	47,987	1767 (3.68)	380342.59	3.68	0.77	(0.73-0.82)	<1.0E-16
	181-240	21,319	975 (4.57)	168465.82	4.57	0.91	(0.85-0.98)	1.13E-02
	241-300	23,492	944 (4.02)	185517.36	4.02	0.84	(0.78-0.90)	1.04E-06
	301-360	14,826	637 (4.30)	117194.67	4.30	0.83	(0.76-0.90)	1.70E-05
	>360	13,082	680 (5.20)	103020.73	5.20	0.98	(0.91-1.07)	0.71
Tea	0	57,433	2461 (4.28)	454797.51	4.28	1	Reference	Reference
	1-60	84,260	3165 (3.76)	670336.26	3.76	0.87	(0.83-0.92)	3.78E-07
	61-120	114,525	4809 (4.20)	906479.66	4.20	0.96	(0.91-1.00)	7.20E-02
	121-180	81,674	3620 (4.43)	643994.84	4.43	0.99	(0.94-1.04)	0.64
	>180	39,905	2012 (5.04)	313272.29	5.04	1.07	(1.00-1.13)	3.56E-02

Cox regression analyses adjusted for age at inclusion, sex, body mass index (kg/m2) at inclusion, active smoking, log-transformed weekly alcohol intake (UK units), and Townsend Deprivation Index. 60 mg caffeine is equivalent to the caffeine content of one cup of instant coffee or 2 cups of tea. Person-time follow up is provided per 1000 person-time years

Table S9. Multivariable adjusted associations of phenotypic of caffeine intake with new-onset type 2 diabetes

Caffeine Trait	**Caffeine intake (mg)**	**N total**	**N cases (%)**	**Person-time at risk (years)**	**Absolute risk**	**Hazard Ratio**	**95% Confidence interval**	***P* value**
Combined intake	0	8,456	183 (2.16)	67917.769	2.16	1	Reference	Reference
	1-60	25,012	651 (2.60)	200942.01	2.60	1.20	(1.02-1.42)	0.03
	61-120	53,431	1156 (2.16)	429276.93	2.16	1.07	(0.91-1.25)	0.40
	121-180	78,764	1516 (1.92)	631103.5	1.92	0.94	(0.81-1.10)	0.45
	181-240	67,123	1208 (1.80)	537016.45	1.80	0.89	(0.76-1.04)	0.13
	241-300	49,606	959 (1.93)	396529.11	1.93	0.93	(0.79-1.09)	0.37
	301-360	29,979	548 (1.83)	239606.07	1.83	0.83	(0.71-0.99)	0.04
	>360	35,347	761 (2.15)	282170.46	2.15	0.91	(0.77-1.07)	0.23
Coffee	0	82,017	1946 (2.37)	657588.3	2.37	1	Reference	Reference
	1-60	95,947	1938 (2.02)	768505.49	2.02	0.88	(0.82-0.93)	4.46E-05
	61-120	59,622	1046 (1.75)	477108.76	1.75	0.81	(0.75-0.87)	4.87E-08
	121-180	48,112	791 (1.64)	385341.27	1.64	0.77	(0.71-0.84)	6.62E-10
	181-240	21,358	451 (2.11)	171104.9	2.11	0.84	(0.76-0.93)	1.07E-03
	241-300	23,542	426 (1.81)	188172.08	1.81	0.79	(0.71-0.87)	7.93E-06
	301-360	14,788	291 (1.97)	118443.97	1.97	0.76	(0.67-0.86)	1.57E-05
	>360	13,051	304 (2.33)	104416.4	2.33	0.84	(0.74-0.94)	3.80E-03
Tea	0	57,152	1402 (2.45)	457663.58	2.45	1	Reference	Reference
	1-60	84,659	1602 (1.89)	680333.52	1.89	0.91	(0.85-0.98)	1.25E-02
	61-120	115,382	2084 (1.81)	925272.64	1.81	0.86	(0.80-0.92)	1.59E-05
	121-180	82,365	1627 (1.98)	658185.41	1.98	0.89	(0.82-0.95)	1.02E-03
	>180	40,311	885 (2.20)	321345.95	2.20	0.90	(0.83-0.98)	1.67E-02

Cox regression analyses adjusted for age at inclusion, sex, body mass index (kg/m2) at inclusion, active smoking, log-transformed weekly alcohol intake (UK units), and Townsend Deprivation Index. 60 mg caffeine is equivalent to the caffeine content of one cup of instant coffee or 2 cups of tea. Person-time follow up is provided per 1000 person-time years

Table S10. Associations of caffeine from coffee or tea additionally adjusted for caffeine intake from tea or coffee respectively

Caffeine trait	Outcome	Caffeine intake (mg/day)	N total	N cases	Person-time at risk (years)	Hazard Ratio	95% Confidence interval	*P* value
Coffee	CAD	0	80,659	3585	638979.73	1	Reference	Reference
		1-60	93,173	4105	736562.39	0.93	0.89-0.98	3.49E-03
		61-120	57,946	2217	458418.04	0.82	0.78-0.87	4.92E-13
		121-180	46,065	1707	364964.26	0.79	0.75-0.84	1.33E-14
		181-240	20,183	939	159374.73	0.95	0.88-1.02	0.16
		241-300	21,967	898	173350.49	0.87	0.81-0.94	2.88E-04
		301-360	13,727	595	108434.36	0.86	0.78-0.94	7.88E-04
		>360	12,089	635	95192.156	1.03	0.94-1.12	0.58
Tea	CAD	0	55,825	2382	442052.98	1	Reference	Reference
		1-60	79,764	2978	634422.94	0.86	0.81-0.91	5.56E-08
		61-120	103,981	4370	822745.06	0.94	0.89-0.99	0.02
		121-180	71,617	3189	564449.23	0.97	0.91-1.02	0.22
		>180	34,622	1762	271605.95	1.04	0.98-1.11	0.19
Coffee	T2D	0	81,341	1929	652143.91	1	Reference	Reference
		1-60	93,878	1903	751852.25	0.86	0.81-0.92	4.79E-06
		61-120	58,318	1014	466693.64	0.79	0.73-0.85	1.29E-09
		121-180	46,186	758	369829.71	0.74	0.68-0.81	7.46E-12
		181-240	20,222	428	161941.97	0.80	0.72-0.89	4.48E-05
		241-300	22,000	388	175830.94	0.72	0.65-0.81	1.50E-08
		301-360	13,701	274	109674.18	0.72	0.63-0.82	9.16E-07
		>360	12,072	288	96595.711	0.80	0.71-0.91	8.75E-04
Tea	T2D	0	55,552	1357	444786.2	1	Reference	Reference
		1-60	80,118	1502	643704.93	0.88	0.82-0.95	7.49E-04
		61-120	104,793	1898	840005.24	0.82	0.76-0.88	5.82E-08
		121-180	72,247	1430	577158.15	0.82	0.76-0.89	6.32E-07
		>180	35,008	795	278907.78	0.85	0.78-0.93	4.70E-04

Adjusted for age at inclusion, sex, body mass index (kg/m2) at inclusion, active smoking, log-transformed weekly alcohol intake (UK units), and Townsend Deprivation Index. The analyses for caffeine from coffee were additionally adjusted for caffeine intake from tea, and the analyses for caffeine from tea were additionally adjusted for caffeine intake from coffee.

Table S11. Associations of decaffeinated and caffeinated cups of coffee with new-onset coronary artery disease and type 2 diabetes

Group	**Outcome**	**Cups of coffee**	**N total**	**N cases**	**Person-time at risk (years)**	**Hazard Ratio**	**95% Confidence interval**	***P* value**
Decaffeinated	CAD	0	85,257	6,222	662436.76	1	Reference	Reference
		1	16,340	1,116	127170.84	0.95	0.89-1.01	0.10
		2	14,932	928	116645.79	0.83	0.78-0.89	3.21E-07
		3	9,881	700	76817.509	0.96	0.89-1.04	0.28
		4	7,147	503	55563.823	0.92	0.84-1.01	0.07
		5	4,312	304	33483.425	0.93	0.83-1.05	0.24
		6	2,879	230	22278.00	1.02	0.90-1.17	0.75
		>6	2,351	176	18201.01	0.98	0.84-1.14	0.79
Caffeinated	CAD	0	85,257	6,222	662436.76	1	Reference	Reference
		1	62,144	4,025	482864.61	0.83	0.80-0.87	<1.0E-16
		2	60,858	3,718	474437.8	0.77	0.74-0.80	<1.0E-16
		3	40,666	2,562	317174.8	0.80	0.76-0.84	<1.0E-16
		4	28,098	1,891	218703.22	0.83	0.79-0.87	1.84E-12
		5	16,594	1,165	128721.25	0.86	0.81-0.92	5.62E-06
		6	11,122	825	86165.836	0.85	0.79-0.92	1.56E-05
		>6	9,411	803	72635.775	0.97	0.90-1.04	0.38
Decaffeinated	T2D	0	85,257	4,689	669744.72	1	Reference	Reference
		1	16,340	765	128765.31	0.94	0.87-1.01	0.10
		2	14,932	681	117636.71	0.89	0.82-0.96	0.00
		3	9,881	476	77887.652	0.92	0.83-1.01	0.08
		4	7,147	374	56086.719	0.93	0.84-1.04	0.20
		5	4,312	233	33805.93	0.92	0.80-1.05	0.20
		6	2,879	178	22489.786	1.04	0.89-1.20	0.63
		>6	2,351	149	18356.787	1.04	0.89-1.23	0.62
Caffeinated	T2D	0	85,257	4,689	669744.72	1	Reference	Reference
		1	62,144	2,813	488247.68	0.89	0.85-0.93	1.77E-06
		2	60,858	2,691	479099.39	0.87	0.83-0.91	1.40E-08
		3	40,666	1,844	320263.23	0.89	0.84-0.93	1.17E-05
		4	28,098	1,456	220558.29	0.94	0.88-1.00	0.04
		5	16,594	916	129881.67	0.96	0.89-1.03	0.23
		6	11,122	639	87104.843	0.91	0.84-0.99	0.03
		>6	9,411	635	73355.381	1.05	0.97-1.14	0.24

Adjusted for age at inclusion, sex, body mass index (kg/m2) at inclusion, active smoking, log-transformed weekly alcohol intake (UK units), and Townsend Deprivation Index. Results are provided for individuals who drank decaffeinated or decaffeinated coffee per cup of coffee.

Table S12. GWAS top SNP results for combined caffeine intake at $P<1.67x10^{-8}$

SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	P value	Genomic Band	Nearest genes	eQTL genes	DEPICT genes
rs2472297	15	75027880	C	T	0.731645	-0.10487	0.002616	2.4E-351	q24.1	CYP1A1		
rs4410790	7	17284577	T	C	0.364122	-0.08137	0.002412	1.50E-249	p21.1	AHR		
rs17685	7	75616105	G	A	0.721471	-0.0408	0.002584	3.80E-56	q11.23	POR, STYXL1	AC005077.12	
rs56113850	19	41353107	T	C	0.421755	-0.02649	0.002351	1.90E-29	q13.2	CYP2A6		
rs2231142	4	89052323	G	T	0.886707	0.03913	0.00366	1.10E-26	q22.1	ABCG2		
7:73042302_GCTTT_G	7	73042302	GCTTT	G	0.866226	-0.03591	0.003412	6.60E-26	q11.23	MLXIPL	MLXIPL	
rs768283768	1	150701510	A	AC	0.419751	0.024685	0.002462	1.20E-23	q21.3	HORMAD1, CTSS	CERS2, CTSS, GOLPH3L, HORMAD1, SETDB1	
rs1260326	2	27730940	T	C	0.391852	-0.02297	0.002377	4.20E-22	p23.3	GCKR		
rs6062679	20	62889991	T	C	0.534615	-0.02278	0.002358	4.50E-22	q13.33	PCMTD2	PCMTD2	
rs199612805	22	24843991	T	TGAAACCA	0.986403	0.095734	0.01012	3.10E-21	q11.23	SPECC1L-ADORA2A, ADORA2A		
rs9611527	22	41644428	G	A	0.664286	0.019792	0.002466	1.00E-15	q13.2	CHADL, RANGAP1	RANGAP1	
rs139797380	6	137244957	C	G	0.991601	0.106741	0.013575	3.70E-15	q23.3	PEX7, SLC35D3		
rs62332762	4	106143492	C	T	0.597585	0.01828	0.002368	1.20E-14	q24	TET2		
rs117810762	10	135315795	G	A	0.982023	-0.06827	0.008863	1.30E-14	q26.3	SPRN		
rs531431865	17	46165234	C	CA	0.678686	-0.01854	0.002537	2.70E-13	q21.32	CBX1		
rs6265	11	27679916	C	T	0.810755	0.021572	0.002964	3.40E-13	p14.1	BDNF		
rs489693	18	57882787	C	A	0.67465	-0.01759	0.002478	1.30E-12	q21.32	MC4R		
rs12514566	5	7391462	G	A	0.664698	0.017242	0.002456	2.20E-12	p15.31	ADCY2		
rs1490384	6	126851160	C	T	0.501467	-0.01587	0.002323	8.30E-12	q22.32	CENPW		
1:174856749_TG_T	1	174856749	TG	T	0.538714	0.016005	0.00235	9.70E-12	q25.1	RABGAP1L		
rs61141867	19	47556375	T	TG	0.253635	-0.01842	0.002725	1.40E-11	q13.32	NPAS1, TMEM160		
rs4240624	8	9184231	G	A	0.092461	0.02693	0.004012	1.90E-11	p23.1	PPP1R3B		
rs115454798	3	142092190	A	G	0.871965	-0.02252	0.003491	1.10E-10	q23	XRN1		
16:18776851_G_GA	16	18776851	G	GA	0.651439	0.017366	0.002727	1.90E-10	p12.3	RPS15A	ARL6IP1	
rs12591786	15	60902512	C	T	0.842038	0.020213	0.00323	3.90E-10	q22.2	RORA		
rs215601	7	32333921	A	C	0.372618	0.01488	0.002404	6.00E-10	p14.3	PDE1C		
rs4418728	10	94839724	G	T	0.550788	0.014384	0.002333	7.00E-10	q23.33	CYP26A1		
rs376877108	12	112020797	GTT	G	0.201051	0.01783	0.002912	9.10E-10	q24.12	ATXN2		
rs78456557	3	123300686	C	G	0.900201	-0.02364	0.00389	1.20E-09	q21.1	PTPLB		
6:108876096_CAAT_C	6	108876096	CAAT	C	0.838739	0.018991	0.003165	2.00E-09	q21	FOXO3		
rs7105462	11	112912048	G	A	0.40559	0.014163	0.002366	2.10E-09	q23.2	NCAM1		
rs2667773	15	77872191	A	G	0.686772	0.014947	0.002506	2.50E-09	q24.3	LINGO1		
rs754177720	6	98555544	CA	C	0.479652	-0.01384	0.002358	4.40E-09	q16.1	POU3F2		
20:35568001_AAAAG_A	20	35568001	AAAAG	A	0.68498	0.014682	0.002513	5.20E-09	q11.23	SAMHD1		
rs12785227	10	65262685	A	G	0.685798	0.014549	0.002507	6.50E-09	q21.3	REEP3		
3:50895869_ATAATAATAAT_A	3	50895869	ATAATAATAAT	A	0.915367	0.028214	0.004864	6.60E-09	p21.2	DOCK3		
rs1228024	11	47951353	C	A	0.340021	0.013965	0.002453	1.30E-08	p11.2	PTPRJ		

Sentinel SNPs per locus with P values $<1.67x10^{-8}$. Nearest genes were the nearest protein coding gene and any additional gene within 10kb of the sentinel SNP. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error; eQTL, expression quantitative locus; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits.

Table S13. GWAS top SNP results for caffeine intake from coffee at $P<1.67x10^{-8}$

SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	P value	Genomic Band	Nearest genes	eQTL genes	DEPICT genes
rs2472297	15	75027880	C	T	0.731859	-0.06521	0.002587	3.10E-140	q24.1	CYP1A1		
rs4410790	7	17284577	T	C	0.364412	-0.05171	0.002384	2.80E-104	p21.1	AHR		
rs1057868	7	75615006	C	T	0.714413	-0.02445	0.002536	5.50E-22	q11.23	POR		
rs201399553	16	53829963	T	TTC	0.594033	-0.02253	0.002377	2.60E-21	q12.2	FTO		
rs56113850	19	41353107	T	C	0.421821	-0.02071	0.002323	4.90E-19	q13.2	CYP2A6		
rs11127048	2	27752463	G	A	0.381191	-0.01997	0.002398	8.10E-17	p23.3	GCKR		
rs66723169	18	57808978	C	A	0.769043	-0.02249	0.002732	1.80E-16	q21.32	MC4R		
rs34060476	7	73037956	A	G	0.865581	-0.02519	0.003365	7.10E-14	q11.23	MLXIPL	MLXIPL	
rs181251778	22	24901968	A	G	0.986146	0.072648	0.009834	1.50E-13	q11.23	UPB1		
rs531431865	17	46165234	C	CA	0.678648	-0.0171	0.002507	9.00E-12	q21.32	CBX1		
rs7571970	2	646849	T	C	0.172823	-0.02076	0.003047	9.40E-12	p25.3	TMEM18		
rs1327259	6	51177811	A	G	0.614152	0.015707	0.002365	3.10E-11	p12.2	PKHD1		
rs6063085	20	45840459	A	C	0.625251	-0.01571	0.00237	3.40E-11	q13.12	ZMYND8		
rs2726513	4	106217358	G	T	0.587077	0.015301	0.002347	7.00E-11	q24	TET2		
rs4615895	1	96274668	G	A	0.259574	-0.01705	0.002627	8.60E-11	p21.3	TMEM56-RWDD3		
rs139937261	17	17585130	C	CG	0.487688	-0.01491	0.002304	9.80E-11	p11.2	RAI1		
rs2298527	11	112851961	G	C	0.405568	0.014947	0.002336	1.60E-10	q23.2	NCAM1		
rs35198275	3	50536092	A	G	0.865693	0.020797	0.003387	8.20E-10	p21.31	CACNA2D2		
rs12514566	5	7391462	G	A	0.664625	0.014831	0.002428	1.00E-09	p15.31	ADCY2		
rs6893807	5	87965021	A	G	0.843563	-0.01916	0.003159	1.30E-09	q14.3	MEF2C		
rs2521501	15	91437388	A	T	0.677316	0.014916	0.002472	1.60E-09	q26.1	FES, MAN2A2	FES	
rs768283768	1	150701510	A	AC	0.419823	0.014214	0.002434	5.20E-09	q21.3	HORMAD1, CTSS	CTSS, GOLPH3L, HORMAD1	
rs76881016	10	134196286	A	G	0.928496	-0.02584	0.004453	6.60E-09	q26.3	LRRC27		
rs117810762	10	135315795	G	A	0.982047	-0.05011	0.008765	1.10E-08	q26.3	SPRN		

Sentinel SNPs per locus with P values $<1.67x10^{-8}$. Nearest genes were the nearest protein coding gene and any additional gene within 10kb of the sentinel SNP. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error; eQTL, expression quantitative locus; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits.

Table S14. GWAS top SNP results for caffeine intake from tea at P<1.67x10^{-8}

SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	P value	Genomic Band	Nearest genes	eQTL genes	DEPICT genes
rs2472297	15	75027880	C	T	0.732806	-0.05411	0.002521	3.30E-102	q24.1	CYP1A1		SIN3A
rs4410790	7	17284577	T	C	0.36537	-0.04033	0.00232	1.10E-67	p21.1	AHR		
rs9624470	22	24820268	G	A	0.419254	-0.02534	0.002272	6.80E-29	q11.23	SPECC1L, SPECC1L-ADORA2A, ADORA2A	UPB1	
rs17685	7	75616105	G	A	0.721688	-0.02391	0.002488	7.20E-22	q11.23	POR,STYXL1		
rs2465018	6	51241140	G	A	0.769413	-0.02211	0.002666	1.10E-16	p12.2	PKHD1		
rs1481012	4	89039082	A	G	0.887297	0.026005	0.003536	1.90E-13	q22.1	ABCG2		
rs56188862	1	174189269	T	C	0.614947	0.016829	0.002297	2.40E-13	q25.1	RABGAP1L		
rs73053413	12	11329548	C	T	0.836535	0.021681	0.003021	7.10E-13	p13.2	PRR4, TAS2R14, TAS2R42	PRR4, TAS2R15	
rs140775622	20	62962869	C	T	0.830545	-0.02262	0.003207	1.80E-12	q13.33	PCMTD2		
rs4817505	21	34343828	T	C	0.607874	-0.01512	0.002292	4.20E-11	q22.11	OLIG2		OLIG2
rs192084998	5	152077481	G	A	0.703764	0.015836	0.002458	1.20E-10	q33.1	NMUR2		
rs10741694	11	16286183	T	C	0.372823	-0.01474	0.002312	1.80E-10	p15.1	SOX6		SOX6
rs132919	22	41809903	G	C	0.22639	-0.01708	0.002697	2.40E-10	q13.2	TEF		TEF, ZC3H7B, SREBF2
rs12591786	15	60902512	C	T	0.842256	0.019576	0.003109	3.00E-10	q22.2	RORA		
rs11204711	1	150682115	A	G	0.616497	-0.01444	0.002336	6.40E-10	q21.3	HORMAD1	GOLPH3L, HORMAD1	SETDB1, RPRD2
rs11022752	11	13307622	A	G	0.730907	-0.01535	0.002525	1.20E-09	p15.2	ARNTL		
rs141180025	7	39295736	CT	C	0.391273	-0.01399	0.002335	2.10E-09	p14.1	POU6F2		
rs2117137	3	89525505	A	G	0.594554	-0.01349	0.002273	2.90E-09	p11.1	EPHA3		
rs62534435	9	7042938	C	G	0.796528	-0.01629	0.002776	4.40E-09	p24.1	KDM4C		
rs28429148	16	53798319	G	A	0.565413	0.013189	0.002288	8.20E-09	q12.2	FTO		
rs139797380	6	137244957	C	G	0.991607	0.075145	0.013059	8.70E-09	q23.3	PEX7, SLC35D3		
rs199602679	16	63031361	G	GT	0.783938	-0.01603	0.0028	1.00E-08	q21	CDH8		
rs145755097	3	50254188	C	CTTTGT	0.852979	-0.01849	0.003258	1.40E-08	p21.31	GNAI2		RBM5
rs77476394	1	26757610	CTAAA	C	0.208732	-0.01572	0.002785	1.60E-08	p36.11	LIN28A, DHDDS		

Sentinel SNPs per locus with P values <1.67x10^{-8}. Nearest genes were the nearest protein coding gene and any additional gene within 10kb of the sentinel SNP. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error; eQTL, expression quantitative locus; DEPICT, Data-driven Expression-Prioritized Integration for Complex Traits

Table S15. GWAS SNP results over all caffeine traits at $P<1.67x10^{-8}$ based on the lowest P value

													Combined Caffeine intake					Caffeine from coffee					Caffeine from tea				
SNP	**CHR**	**hg19**	**EFAL**	**NEFAL**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**Origin**	**LOCUS**	**LOCUSID**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**
rs77476394	1	26757610	CTAAA	C	0.209	0.970	-0.016	0.003	1.60E-08	Tea	1	1	0.209	0.970	-0.005	0.003	6.30E-02	0.209	0.970	0.003	0.003	2.80E-01	0.209	0.970	-0.016	0.003	1.60E-08
rs1228024	11	47951353	C	A	0.340	0.986	0.014	0.002	1.30E-08	Combined	1	2	0.340	0.986	0.014	0.002	1.30E-08	0.340	0.986	0.007	0.002	2.60E-03	0.340	0.986	0.008	0.002	1.00E-03
rs199602679	16	63031361	G	GT	0.784	0.936	-0.016	0.003	1.00E-08	Tea	1	3	0.784	0.936	-0.008	0.003	3.80E-03	0.784	0.936	0.003	0.003	2.60E-01	0.784	0.936	-0.016	0.003	1.00E-08
rs76881016	10	134196286	A	G	0.928	1.000	-0.026	0.004	6.60E-09	Coffee	1	4	0.928	1.000	-0.017	0.005	1.30E-04	0.928	1.000	-0.026	0.004	6.60E-09	0.929	1.000	0.004	0.004	3.70E-01
rs12785227	10	65262685	A	G	0.686	0.997	0.015	0.003	6.50E-09	Combined	1	5	0.686	0.997	0.015	0.003	6.50E-09	0.686	0.997	0.006	0.002	1.30E-02	0.685	0.997	0.010	0.002	7.50E-05
20:35568001_AAAAG_A	20	35568001	AAAAG	A	0.685	0.989	0.015	0.003	5.20E-09	Combined	1	6	0.685	0.989	0.015	0.003	5.20E-09	0.685	0.989	0.011	0.002	4.60E-06	0.685	0.989	0.006	0.002	1.90E-02
rs62534435	9	7042938	C	G	0.797	0.997	-0.016	0.003	4.40E-09	Tea	1	7	0.797	0.997	-0.010	0.003	6.80E-04	0.797	0.997	0.003	0.003	3.70E-01	0.797	0.997	-0.016	0.003	4.40E-09
rs754177720	6	98555544	CA	C	0.480	0.972	-0.014	0.002	4.40E-09	Combined	1	8	0.480	0.972	-0.014	0.002	4.40E-09	0.479	0.972	-0.012	0.002	4.20E-07	0.480	0.972	-0.005	0.002	1.80E-02
rs2117137	3	89525505	A	G	0.595	1.000	-0.013	0.002	2.90E-09	Tea	1	9	0.595	1.000	-0.004	0.002	9.50E-02	0.595	1.000	0.005	0.002	2.40E-02	0.595	1.000	-0.013	0.002	2.90E-09
rs2667773	15	77872191	A	G	0.687	0.995	0.015	0.003	2.50E-09	Combined	1	10	0.687	0.995	0.015	0.003	2.50E-09	0.687	0.995	0.010	0.002	3.40E-05	0.687	0.995	0.001	0.002	6.40E-01
rs141180025	7	39295736	CT	C	0.391	0.956	-0.014	0.002	2.10E-09	Tea	1	11	0.391	0.956	-0.004	0.002	8.70E-02	0.391	0.956	0.005	0.002	2.40E-02	0.391	0.956	-0.014	0.002	2.10E-09
6:108876096_CAAT_C	6	108876096	CAAT	C	0.839	0.990	0.019	0.003	2.00E-09	Combined	1	12	0.839	0.990	0.019	0.003	2.00E-09	0.839	0.990	0.012	0.003	7.10E-05	0.839	0.990	0.009	0.003	2.70E-03
rs2521501	15	91437388	A	T	0.677	0.983	0.015	0.002	1.60E-09	Coffee	1	13	0.677	0.983	0.010	0.002	4.80E-05	0.677	0.983	0.015	0.002	1.60E-09	0.677	0.983	-0.005	0.002	4.40E-02
rs6893807	5	87965021	A	G	0.844	0.997	-0.019	0.003	1.30E-09	Coffee	1	14	0.844	0.997	-0.012	0.003	1.90E-04	0.844	0.997	-0.019	0.003	1.30E-09	0.844	0.997	0.007	0.003	2.60E-02
rs11022752	11	13307622	A	G	0.731	0.992	-0.015	0.003	1.20E-09	Tea	1	15	0.731	0.992	-0.014	0.003	5.00E-08	0.731	0.992	-0.003	0.003	2.30E-01	0.731	0.992	-0.015	0.003	1.20E-09
rs78456557	3	123300686	C	G	0.900	0.987	-0.024	0.004	1.20E-09	Combined	1	16	0.900	0.987	-0.024	0.004	1.20E-09	0.900	0.987	-0.016	0.004	4.40E-05	0.900	0.987	-0.011	0.004	3.10E-03
rs376877108	12	112020797	GTT	G	0.201	0.987	0.018	0.003	9.10E-10	Combined	1	17	0.201	0.987	0.018	0.003	9.10E-10	0.201	0.987	0.007	0.003	9.80E-03	0.201	0.987	0.013	0.003	3.00E-06
rs35198275	3	50536092	A	G	0.866	0.982	0.021	0.003	8.20E-10	Coffee	1	20	0.866	0.982	0.019	0.003	2.40E-08	0.866	0.982	0.021	0.003	8.20E-10	0.866	0.982	-0.010	0.003	3.70E-03
rs145755097	3	50254188	C	CTTTGT	0.853	0.935	-0.018	0.003	1.40E-08	Tea	0	20	0.853	0.935	0.000	0.003	8.90E-01	0.853	0.935	0.009	0.003	7.20E-03	0.853	0.935	-0.018	0.003	1.40E-08
3:50895869_ATAATAATAAT_A	3	50895869	ATAATAATAAT	A	0.915	0.735	0.028	0.005	6.60E-09	Combined	0	20	0.915	0.735	0.028	0.005	6.60E-09	0.915	0.735	0.022	0.005	5.10E-06	0.915	0.735	0.002	0.005	6.60E-01
rs4418728	10	94839724	G	T	0.551	0.999	0.014	0.002	7.00E-10	Combined	1	21	0.551	0.999	0.014	0.002	7.00E-10	0.551	0.999	0.006	0.002	1.10E-02	0.551	0.999	0.010	0.002	2.90E-06
rs215601	7	32333921	A	C	0.373	0.998	0.015	0.002	6.00E-10	Combined	1	22	0.373	0.998	0.015	0.002	6.00E-10	0.373	0.998	0.009	0.002	8.50E-05	0.373	0.998	0.007	0.002	1.20E-03
rs12591786	15	60902512	C	T	0.842	0.967	0.020	0.003	3.00E-10	Tea	1	24	0.842	0.967	0.020	0.003	3.90E-10	0.842	0.967	0.006	0.003	7.40E-02	0.842	0.967	0.020	0.003	3.00E-10
16:18776851_G_GA	16	18776851	G	GA	0.651	0.797	0.017	0.003	1.90E-10	Combined	1	25	0.651	0.797	0.017	0.003	1.90E-10	0.652	0.797	0.011	0.003	4.50E-05	0.651	0.797	0.008	0.003	2.20E-03
rs10741694	11	16286183	T	C	0.373	0.994	-0.015	0.002	1.80E-10	Tea	1	26	0.373	0.994	-0.008	0.002	4.60E-04	0.373	0.994	0.002	0.002	3.60E-01	0.373	0.994	-0.015	0.002	1.80E-10

													Combined Caffeine intake					**Caffeine from coffee**					**Caffeine from tea**				
SNP	**CHR**	**hg19**	**EFAL**	**NEFAL**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**Origin**	**LOCUS**	**LOCUSID**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**	**EF Freq**	**INFO**	**BETA**	**SE**	**P value**
rs2298527	11	112851961	G	C	0.406	0.996	0.015	0.002	1.60E-10	Coffee	1	28	0.406	0.996	0.014	0.002	2.40E-09	0.406	0.996	0.015	0.002	1.60E-10	0.405	0.996	-0.002	0.002	4.10E-01
rs7105462	11	112912048	G	A	0.406	0.993	0.014	0.002	2.10E-09	Combined	0	28	0.406	0.993	0.014	0.002	2.10E-09	0.406	0.993	0.015	0.002	1.90E-10	0.405	0.993	-0.002	0.002	4.30E-01
rs192084998	5	152077481	G	A	0.704	0.989	0.016	0.002	1.20E-10	Tea	1	29	0.704	0.989	0.009	0.003	4.40E-04	0.704	0.989	-0.002	0.003	5.30E-01	0.704	0.989	0.016	0.002	1.20E-10
rs115454798	3	142092190	A	G	0.872	0.990	-0.023	0.003	1.10E-10	Combined	1	30	0.872	0.990	-0.023	0.003	1.10E-10	0.872	0.990	-0.013	0.003	1.60E-04	0.872	0.990	-0.010	0.003	4.30E-03
rs139937261	17	17585130	C	CG	0.488	0.988	-0.015	0.002	9.80E-11	Coffee	1	31	0.488	0.988	-0.009	0.002	1.00E-04	0.488	0.988	-0.015	0.002	9.80E-11	0.488	0.988	0.006	0.002	7.60E-03
rs4615895	1	96274668	G	A	0.260	0.991	-0.017	0.003	8.60E-11	Coffee	1	32	0.260	0.991	-0.009	0.003	8.10E-04	0.260	0.991	-0.017	0.003	8.60E-11	0.260	0.991	0.005	0.003	5.00E-02
rs4817505	21	34343828	T	C	0.608	0.993	-0.015	0.002	4.20E-11	Tea	1	33	0.608	0.993	-0.003	0.002	1.80E-01	0.608	0.993	0.008	0.002	3.20E-04	0.608	0.993	-0.015	0.002	4.20E-11
rs6063085	20	45840459	A	C	0.625	1.000	-0.016	0.002	3.40E-11	Coffee	1	34	0.625	1.000	-0.007	0.002	3.20E-03	0.625	1.000	-0.016	0.002	3.40E-11	0.625	1.000	0.008	0.002	8.40E-04
rs4240624	8	9184231	G	A	0.092	0.999	0.027	0.004	1.90E-11	Combined	1	35	0.092	0.999	0.027	0.004	1.90E-11	0.092	0.999	0.016	0.004	6.40E-05	0.092	0.999	0.013	0.004	5.90E-04
rs61141867	19	47556375	T	TG	0.254	0.955	-0.018	0.003	1.40E-11	Combined	1	36	0.254	0.955	-0.018	0.003	1.40E-11	0.253	0.955	-0.011	0.003	4.20E-05	0.254	0.955	-0.008	0.003	1.70E-03
rs7571970	2	646849	T	C	0.173	0.990	-0.021	0.003	9.40E-12	Coffee	1	37	0.173	0.990	-0.017	0.003	4.10E-08	0.173	0.990	-0.021	0.003	9.40E-12	0.174	0.990	0.007	0.003	2.00E-02
rs1490384	6	126851160	C	T	0.501	1.000	-0.016	0.002	8.30E-12	Combined	1	38	0.501	1.000	-0.016	0.002	8.30E-12	0.502	1.000	-0.009	0.002	2.10E-04	0.502	1.000	-0.008	0.002	2.20E-04
rs12514566	5	7391462	G	A	0.665	0.998	0.017	0.002	2.20E-12	Combined	1	40	0.665	0.998	0.017	0.002	2.20E-12	0.665	0.998	0.015	0.002	1.00E-09	0.664	0.998	0.004	0.002	7.60E-02
rs73053413	12	11329548	C	T	0.837	0.997	0.022	0.003	7.10E-13	Tea	1	41	0.836	0.997	0.005	0.003	9.10E-02	0.836	0.997	-0.015	0.003	1.20E-06	0.837	0.997	0.022	0.003	7.10E-13
rs6265	11	27679916	C	T	0.811	1.000	0.022	0.003	3.40E-13	Combined	1	42	0.811	1.000	0.022	0.003	3.40E-13	0.811	1.000	0.015	0.003	5.60E-07	0.811	1.000	0.012	0.003	3.20E-05
rs531431865	17	46165234	C	CA	0.679	0.959	-0.019	0.003	2.70E-13	Combined	1	44	0.679	0.959	-0.019	0.003	2.70E-13	0.679	0.959	-0.017	0.003	9.00E-12	0.679	0.959	-0.003	0.002	2.70E-01
rs56188862	1	174189269	T	C	0.615	0.998	0.017	0.002	2.40E-13	Tea	1	46	0.615	0.998	0.015	0.002	5.10E-10	0.615	0.998	0.001	0.002	7.80E-01	0.615	0.998	0.017	0.002	2.40E-13
1:174856749_TG_T	1	174856749	TG	T	0.539	0.980	0.016	0.002	9.70E-12	Combined	0	46	0.539	0.980	0.016	0.002	9.70E-12	0.538	0.980	0.003	0.002	2.50E-01	0.539	0.980	0.015	0.002	5.90E-11
rs117810762	10	135315795	G	A	0.982	0.987	-0.068	0.009	1.30E-14	Combined	1	48	0.982	0.987	-0.068	0.009	1.30E-14	0.982	0.987	-0.050	0.009	1.10E-08	0.982	0.987	-0.025	0.009	3.10E-03
rs62332762	4	106143492	C	T	0.598	0.998	0.018	0.002	1.20E-14	Combined	1	50	0.598	0.998	0.018	0.002	1.20E-14	0.598	0.998	0.015	0.002	1.20E-10	0.598	0.998	0.005	0.002	3.80E-02
rs2726513	4	106217358	G	T	0.587	0.984	0.015	0.002	7.00E-11	Coffee	0	50	0.587	0.984	0.018	0.002	2.60E-14	0.587	0.984	0.015	0.002	7.00E-11	0.587	0.984	0.004	0.002	1.00E-01
rs139797380	6	137244957	C	G	0.992	0.867	0.107	0.014	3.70E-15	Combined	1	52	0.992	0.867	0.107	0.014	3.70E-15	0.992	0.867	0.056	0.013	2.60E-05	0.992	0.867	0.075	0.013	8.70E-09
rs9611527	22	41644428	G	A	0.664	0.994	0.020	0.002	1.00E-15	Combined	1	54	0.664	0.994	0.020	0.002	1.00E-15	0.664	0.994	0.009	0.002	1.70E-04	0.664	0.994	0.015	0.002	3.60E-10
rs132919	22	41809903	G	C	0.226	0.980	-0.017	0.003	2.40E-10	Tea	0	54	0.226	0.980	-0.019	0.003	3.90E-12	0.226	0.980	-0.006	0.003	4.60E-02	0.226	0.980	-0.017	0.003	2.40E-10
rs66723169	18	57808978	C	A	0.769	0.992	-0.022	0.003	1.80E-16	Coffee	1	56	0.769	0.992	-0.019	0.003	3.90E-12	0.769	0.992	-0.022	0.003	1.80E-16	0.769	0.992	0.002	0.003	3.60E-01
rs489693	18	57882787	C	A	0.675	1.000	-0.018	0.002	1.30E-12	Combined	0	56	0.675	1.000	-0.018	0.002	1.30E-12	0.674	1.000	-0.016	0.002	4.30E-11	0.674	1.000	-0.003	0.002	2.10E-01
rs2465018	6	51241140	G	A	0.769	0.987	-0.022	0.003	1.10E-16	Tea	1	58	0.770	0.987	-0.001	0.003	6.00E-01	0.770	0.987	0.016	0.003	2.20E-09	0.769	0.987	-0.022	0.003	1.10E-16

													Combined Caffeine intake					Caffeine from coffee					Caffeine from tea				
SNP	CHR	hg19	EFAL	NEFAL	EF Freq	INFO	BETA	SE	P value	Origin	LOCUS	LOCUSID	EF Freq	INFO	BETA	SE	P value	EF Freq	INFO	BETA	SE	P value	EF Freq	INFO	BETA	SE	P value
rs1327259	6	51177811	A	G	0.614	0.992	0.016	0.002	3.10E-11	Coffee	0	58	0.614	0.992	0.004	0.002	1.10E-01	0.614	0.992	0.016	0.002	3.10E-11	0.614	0.992	-0.013	0.002	5.50E-08
rs201399553	16	53829963	T	TTC	0.594	0.965	-0.023	0.002	2.60E-21	Coffee	1	60	0.594	0.965	-0.011	0.002	9.00E-06	0.594	0.965	-0.023	0.002	2.60E-21	0.594	0.965	0.011	0.002	4.30E-06
rs28429148	16	53798319	G	A	0.565	0.970	0.013	0.002	8.20E-09	Tea	0	60	0.565	0.970	-0.008	0.002	1.20E-03	0.565	0.970	-0.021	0.002	8.50E-19	0.565	0.970	0.013	0.002	8.20E-09
rs6062679	20	62889991	T	C	0.535	0.973	-0.023	0.002	4.50E-22	Combined	1	62	0.535	0.973	-0.023	0.002	4.50E-22	0.535	0.973	-0.013	0.002	2.00E-08	0.535	0.973	-0.014	0.002	2.60E-10
rs140775622	20	62962869	C	T	0.831	0.859	-0.023	0.003	1.80E-12	Tea	0	62	0.830	0.859	-0.025	0.003	1.20E-13	0.830	0.859	-0.012	0.003	4.70E-04	0.831	0.859	-0.023	0.003	1.80E-12
rs1260326	2	27730940	T	C	0.392	1.000	-0.023	0.002	4.20E-22	Combined	1	64	0.392	1.000	-0.023	0.002	4.20E-22	0.392	1.000	-0.020	0.002	1.00E-16	0.392	1.000	-0.006	0.002	1.30E-02
rs11127048	2	27752463	G	A	0.381	0.968	-0.020	0.002	8.10E-17	Coffee	0	64	0.381	0.968	-0.023	0.002	1.20E-20	0.381	0.968	-0.020	0.002	8.10E-17	0.382	0.968	-0.005	0.002	5.00E-02
rs768283768	1	150701510	A	AC	0.420	0.913	0.025	0.002	1.20E-23	Combined	1	67	0.420	0.913	0.025	0.002	1.20E-23	0.420	0.913	0.014	0.002	5.20E-09	0.420	0.913	0.014	0.002	2.80E-09
rs11204711	1	150682115	A	G	0.616	0.964	-0.014	0.002	6.40E-10	Tea	0	67	0.617	0.964	-0.023	0.002	9.00E-21	0.616	0.964	-0.012	0.002	2.30E-07	0.616	0.964	-0.014	0.002	6.40E-10
7:73042302_GCTTT_G	7	73042302	GCTTT	G	0.866	0.994	-0.036	0.003	6.60E-26	Combined	1	69	0.866	0.994	-0.036	0.003	6.60E-26	0.866	0.994	-0.025	0.003	8.70E-14	0.867	0.994	-0.011	0.003	1.20E-03
rs34060476	7	73037956	A	G	0.866	0.995	-0.025	0.003	7.10E-14	Coffee	0	69	0.866	0.995	-0.035	0.003	2.90E-25	0.866	0.995	-0.025	0.003	7.10E-14	0.866	0.995	-0.010	0.003	2.30E-03
rs2231142	4	89052323	G	T	0.887	1.000	0.039	0.004	1.10E-26	Combined	1	71	0.887	1.000	0.039	0.004	1.10E-26	0.887	1.000	0.019	0.004	1.10E-07	0.886	1.000	0.026	0.004	2.40E-13
rs1481012	4	89039082	A	G	0.887	0.994	0.026	0.004	1.90E-13	Tea	0	71	0.888	0.994	0.039	0.004	2.70E-26	0.888	0.994	0.019	0.004	2.00E-07	0.887	0.994	0.026	0.004	1.90E-13
rs9624470	22	24820268	G	A	0.419	0.989	-0.025	0.002	6.80E-29	Tea	1	74	0.419	0.989	-0.019	0.002	3.40E-16	0.419	0.989	0.003	0.002	2.20E-01	0.419	0.989	-0.025	0.002	6.80E-29
rs199612805	22	24843991	T	TGAAACCA	0.986	0.984	0.096	0.010	3.10E-21	Combined	0	74	0.986	0.984	0.096	0.010	3.10E-21	0.986	0.984	0.073	0.010	2.40E-13	0.986	0.984	0.035	0.010	3.10E-04
rs181251778	22	24901968	A	G	0.986	0.992	0.073	0.010	1.50E-13	Coffee	0	74	0.986	0.992	0.093	0.010	7.00E-21	0.986	0.992	0.073	0.010	1.50E-13	0.986	0.992	0.034	0.010	3.30E-04
rs56113850	19	41353107	T	C	0.422	0.994	-0.026	0.002	1.90E-29	Combined	1	76	0.422	0.994	-0.026	0.002	1.90E-29	0.422	0.994	-0.021	0.002	4.90E-19	0.422	0.994	-0.008	0.002	3.50E-04
rs17685	7	75616105	G	A	0.721	1.000	-0.041	0.003	3.80E-56	Combined	1	79	0.721	1.000	-0.041	0.003	3.80E-56	0.721	1.000	-0.024	0.003	9.20E-22	0.722	1.000	-0.024	0.002	7.20E-22
rs1057868	7	75615006	C	T	0.714	1.000	-0.024	0.003	5.50E-22	Coffee	0	79	0.714	1.000	-0.040	0.003	9.00E-56	0.714	1.000	-0.024	0.003	5.50E-22	0.715	1.000	-0.023	0.002	2.70E-21
rs4410790	7	17284577	T	C	0.364	1.000	-0.081	0.002	1.50E-249	Combined	1	82	0.364	1.000	-0.081	0.002	1.50E-249	0.364	1.000	-0.052	0.002	2.80E-104	0.365	1.000	-0.040	0.002	1.10E-67
rs2472297	15	75027880	C	T	0.732	1.000	-0.105	0.003	2.4E-351	Combined	1	85	0.732	1.000	-0.105	0.003	2.4E-351	0.732	1.000	-0.065	0.003	3.10E-140	0.733	1.000	-0.054	0.003	3.30E-102

Sentinel SNPs at each locus over all traits combined based on lowest P value are indicated by a 1 in the LOCUS column. Non-sentinel SNPs are indicated by a 0 in the LOCUS column. The trait corresponding with the SNP's lowest P value is indicated in the Origin column. Details for each SNP are provided for all three traits.
Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error

Table S16. Previously reported SNPs associated with caffeine intake or coffee consumption

Study	Author	Year	PMID	Population	SNPs	Chr	hg19	EFAL/NEFAL	Beta (SE)	P value	Comment	Within 1MB of sentinel SNP	Sentinel SNP	Sentinel SNP GWAS
Non-additive genome-wide association scan reveals a new gene associated with habitual coffee consumption.	Pirastu	2016	27561104	Italian	rs2216084	6	107553312	T/C	0.082 (0.014)	9.25E-09	Only significant in discovery stage	No		
					rs6942255	6	107555018	A/G	0.082 (0.014)	9.79E-09	Only significant in discovery stage	No		
					rs7745311	6	107565060	C/T	0.082 (0.014)	1.23E-08	Only significant in discovery stage	No		
					rs7754744	6	107551281	G/A	0.082 (0.014)	8.80E-09	Only significant in discovery stage	No		
					rs9386630	6	107562914	G/T	0.082 (0.014)	1.07E-08	Only significant in discovery stage	No		
Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption.	Coffee and Caffeine Genetics Consortium	2015	25288136	European/African	rs6968554	7	17287106	A/G	-0.07 (0.01)	2.78E-10	Significant in stage 2	Yes, not sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2470893	15	75019449	T/C	0.09 (0.01)	9.92E-11	Significant in stage 2	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2472297	15	75027880	T/C	0.11 (0.01)	3.26E-16	Significant in stage 2	Yes, sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs4410790	7	17284577	T/C	-0.14 (0.01)	1.48E-57	Significant in stage 1	Yes, sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs7800944	7	73035857	T/C	-0.05 (0.01)	7.82E-09	Significant in stage 1	Yes, not sentinel SNP	7:73042302_GCTTT_G	Caffeine combined, Caffeine from Coffee
					rs17685	7	75616105	A/G	0.07 (0.01)	9.06E-14	Significant in stage 1	Yes, sentinel SNP	rs17685	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
Genome-wide association analysis of coffee drinking suggests association with CYP1A1/CYP1A2 and NRCAM	Amin	2012	21876539	Northern European	rs2470893	15	75019449	T/C	0.0675 (0.010)	2.39E-08	Meta-analysis results	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2472297	15	75027880	T/C	0.076 (0.011)	2.70E-11	Meta-analysis results	Yes, sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs6495122	15	75125645	C/A	-0.05 (0.008)	7.10E-09	Meta-analysis results	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs382140	7	107782200	A/G	0.079 (0.014)	3.90E-09	Meta-analysis results	No		
Sequence variants at CYP1A1–CYP1A2 and AHR associate with coffee consumption	Sulem	2011	21357676	European	rs2472297	15	75027880	T/C	NA	5.40E-14	No effect size reported in combined analysis	Yes, sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs6968865	7	17287269	T/A	NA	2.30E-11	No effect size reported in combined analysis	Yes, not sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
A genome-wide association study in the Japanese population identifies the 12q24 locus for habitual coffee consumption: The J-MICC Study.	Nakagawa-Senda	2018	29367735	Japanese	rs2074356	12	112645401	A/G	0.1920 (0.0234)	2.20E-16	NA	Yes, not sentinel SNP	rs376877108	Caffeine combined

Study	**Author**	**Year**	**PMID**	**Population**	**SNPs**	**Chr**	**hg19**	**EFAL/ NEFAL**	**Beta (SE)**	**P value**	**Comment**	**Within 1MB of sentinel SNP**	**Sentinel SNP**	**Sentinel SNP GWAS**
Genome-wide meta-analysis identifies regions on 7p21 (AHR) and 15q24 (CYP1A2) as determinants of habitual caffeine consumption.	Cornelis	2011	21490707	European descent in the US	rs4410790	7	17284577	T/C	-0.15 (0.02)	2.40E-19	NA	Yes, sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2470893	15	75019449	T/C	0.12 (0.02)	5.20E-14	NA	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior	Cornelis	2016	27702941	European ancestry	rs4410790	7	17284577	T/C	NA	1.80E-13	Significant for caffeine	Yes, sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs6968554	7	17287106	A/G	NA	5.40E-13	Significant for caffeine	Yes, not sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs10275488	7	17303778	T/C	NA	4.80E-09	Significant for caffeine	Yes, not sentinel SNP	rs4410790	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs12909047	15	74782356	A/G	NA	1.30E-11	Significant for caffeine	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs35107470	15	74817689	A/G	NA	2.40E-16	Significant for caffeine	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs62005807	15	74890981	C/G	NA	3.20E-09	Significant for caffeine	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2470893	15	75019449	T/C	NA	5.30E-18	Significant for caffeine	Yes, not sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea
					rs2472297	15	75027880	T/C	NA	1.00E-20	Significant for caffeine	Yes, sentinel SNP	rs2472297	Caffeine combined, Caffeine from Coffee, Caffeine from Tea

Previously reported SNPs associated with caffeine intake or coffee consumption. Only SNPs that reached $P<5x10^{-8}$ were included. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error

Table S17. Cups of different coffee type relating to one unit change in genetically determined caffeine intake from coffee

Type of coffee usually drunk	N	Median caffeine intake (IQR)	Beta	SE	95% confidence interval	P value
Decaffeinated coffee	58,060	6 (3-12)	1.47	0.10	1.26-1.67	<0.001
Instant coffee	167,923	180 (60-240)	2.10	0.06	1.97-2.22	<0.001
Ground coffee	61,859	170 (85-255)	1.73	0.08	1.57-1.90	<0.001

Linear regression estimates adjusted for genotyping chip, age at inclusion, sex, and the first 30 principal components

Table S18. DEPICT tissue and cell type enrichment results for caffeine intake SNPs

				Combined Caffeine intake		**Caffeine from Coffee**		**Caffeine from Tea**	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A08.186.211.132	Brain Stem	Nervous System	Central Nervous System	2.78E-03	<0.05	8.96E-03	>=0.20	9.64E-04	<0.01
A08.186.211.132.810.428.200	Cerebellum	Nervous System	Central Nervous System	4.60E-04	<0.05	6.13E-03	>=0.20	3.65E-04	<0.01
A08.186.211.865.428	Metencephalon	Nervous System	Central Nervous System	7.06E-04	<0.05	5.21E-03	>=0.20	3.87E-04	<0.01
A09.371.729	Retina	Sense Organs	Eye	3.40E-03	<0.05	4.12E-03	>=0.20	5.80E-04	<0.01
A08.186.211.865	Rhombencephalon	Nervous System	Central Nervous System	7.06E-04	<0.05	5.21E-03	>=0.20	3.87E-04	<0.01
A08.186.211	Brain	Nervous System	Central Nervous System	0.04	>=0.20	6.83E-03	>=0.20	8.76E-04	<0.01
A08.186	Central Nervous System	Nervous System	Central Nervous System	0.04	>=0.20	6.53E-03	>=0.20	8.67E-04	<0.01
A08.186.211.464.405	Hippocampus	Nervous System	Central Nervous System	8.37E-03	<0.20	2.96E-03	>=0.20	1.28E-03	<0.05
A08.186.211.464	Limbic System	Nervous System	Central Nervous System	0.02	>=0.20	3.22E-03	>=0.20	2.40E-03	<0.05
A08.186.211.730.885.287.500.571.735	Visual Cortex	Nervous System	Central Nervous System	0.01	<0.20	0.01	>=0.20	8.99E-03	<0.20
A08.186.211.730.885.287.500	Cerebral Cortex	Nervous System	Central Nervous System	0.02	>=0.20	4.25E-03	>=0.20	3.26E-03	<0.20
A08.186.211.730.885.287	Cerebrum	Nervous System	Central Nervous System	0.02	>=0.20	6.24E-03	>=0.20	3.78E-03	<0.20
A08.186.211.464.710.225	Entorhinal Cortex	Nervous System	Central Nervous System	0.03	>=0.20	4.03E-03	>=0.20	3.14E-03	<0.20
A10.272.497	Epidermis	Tissues	Epithelium	0.27	>=0.20	0.84	>=0.20	0.01	<0.20
A11.872.653	Neural Stem Cells	Cells	Stem Cells	0.22	>=0.20	0.18	>=0.20	3.63E-03	<0.20
A08.186.211.730.885.287.500.571	Occipital Lobe	Nervous System	Central Nervous System	0.01	>=0.20	0.01	>=0.20	7.79E-03	<0.20
A08.186.211.464.710	Parahippocampal Gyrus	Nervous System	Central Nervous System	0.03	>=0.20	4.03E-03	>=0.20	3.14E-03	<0.20
A08.186.211.730	Prosencephalon	Nervous System	Central Nervous System	0.03	>=0.20	8.28E-03	>=0.20	6.68E-03	<0.20
A08.186.211.730.885	Telencephalon	Nervous System	Central Nervous System	0.02	>=0.20	6.47E-03	>=0.20	3.80E-03	<0.20
A08.186.211.730.885.287.500.863	Temporal Lobe	Nervous System	Central Nervous System	0.04	>=0.20	5.27E-03	>=0.20	4.01E-03	<0.20
A06.407.071	Adrenal Glands	Endocrine System	Endocrine Glands	2.35E-03	<0.05	0.16	>=0.20	0.35	>=0.20
A06.407.071.140	Adrenal Cortex	Endocrine System	Endocrine Glands	4.35E-03	<0.20	0.25	>=0.20	0.4	>=0.20
A10.165.114.830.500	Abdominal Fat	Tissues	Connective Tissue	0.68	>=0.20	0.56	>=0.20	0.26	>=0.20
A11.329.114	Adipocytes	Cells	Connective Tissue Cells	0.45	>=0.20	0.81	>=0.20	0.66	>=0.20
A10.165.114	Adipose Tissue	Tissues	Connective Tissue	0.61	>=0.20	0.59	>=0.20	0.28	>=0.20
A10.165.114.830	Adipose Tissue White	Tissues	Connective Tissue	0.6	>=0.20	0.55	>=0.20	0.23	>=0.20
A05.360.319.114	Adnexa Uteri	Urogenital System	Genitalia	0.14	>=0.20	0.37	>=0.20	0.24	>=0.20
A11.872.040	Adult Stem Cells	Cells	Stem Cells	0.44	>=0.20	0.88	>=0.20	0.62	>=0.20
A09.371.060	Anterior Eye Segment	Sense Organs	Eye	0.78	>=0.20	0.98	>=0.20	0.36	>=0.20
A11.063	Antibody Producing Cells	Cells	Antibody-Producing Cells	0.79	>=0.20	0.08	>=0.20	0.98	>=0.20
A11.066	Antigen Presenting Cells	Cells	Antigen-Presenting Cells	0.99	>=0.20	0.43	>=0.20	0.64	>=0.20

				Combined Caffeine intake		Caffeine from Coffee		Caffeine from Tea	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A07.541.510.110	Aortic Valve	Cardiovascular System	Heart	0.14	>=0.20	0.35	>=0.20	0.11	>=0.20
A07.231.114	Arteries	Cardiovascular System	Blood Vessels	0.86	>=0.20	0.99	>=0.20	0.53	>=0.20
A07.541.358.100	Atrial Appendage	Cardiovascular System	Heart	0.3	>=0.20	0.13	>=0.20	0.58	>=0.20
A11.118.637.555.567.562	B Lymphocytes	Cells	Blood Cells	0.79	>=0.20	0.08	>=0.20	0.98	>=0.20
A08.186.211.730.885.287.249	Basal Ganglia	Nervous System	Central Nervous System	0.13	>=0.20	0.35	>=0.20	0.1	>=0.20
A15.145	Blood	Hemic and Immune Systems	Blood	0.92	>=0.20	0.08	>=0.20	0.93	>=0.20
A15.145.229	Blood Cells	Hemic and Immune Systems	Blood	0.97	>=0.20	0.08	>=0.20	0.94	>=0.20
A15.145.229.188	Blood Platelets	Hemic and Immune Systems	Blood	0.86	>=0.20	0.13	>=0.20	1	>=0.20
A07.231	Blood Vessels	Cardiovascular System	Blood Vessels	0.95	>=0.20	0.98	>=0.20	0.87	>=0.20
A02.835.232	Bone and Bones	Musculoskeletal System	Skeleton	0.98	>=0.20	0.21	>=0.20	0.95	>=0.20
A15.382.216	Bone Marrow	Hemic and Immune Systems	Immune System	0.97	>=0.20	0.18	>=0.20	0.95	>=0.20
A15.378.316	Bone Marrow Cells	Hemic and Immune Systems	Hematopoietic System	1	>=0.20	0.48	>=0.20	0.93	>=0.20
A02.835.232.043	Bones of Lower Extremity	Musculoskeletal System	Skeleton	0.76	>=0.20	0.97	>=0.20	0.41	>=0.20
A02.165	Cartilage	Musculoskeletal System	Cartilage	0.2	>=0.20	0.73	>=0.20	0.62	>=0.20
A15.145.229.637.555.567.569.200	CD4 Positive T Lymphocytes	Hemic and Immune Systems	Blood	0.29	>=0.20	0.11	>=0.20	0.41	>=0.20
A03.556.249.249.209	Cecum	Digestive System	Gastrointestinal Tract	0.31	>=0.20	0.57	>=0.20	0.71	>=0.20
A02.835.232.834.151	Cervical Vertebrae	Musculoskeletal System	Skeleton	0.36	>=0.20	0.75	>=0.20	0.46	>=0.20
A05.360.319.679.256	Cervix Uteri	Urogenital System	Genitalia	0.74	>=0.20	0.46	>=0.20	0.96	>=0.20
A11.329.171	Chondrocytes	Cells	Connective Tissue Cells	0.53	>=0.20	0.9	>=0.20	0.89	>=0.20
A10.615.284.473	Chorion	Tissues	Membranes	0.64	>=0.20	0.97	>=0.20	0.93	>=0.20
A10.165.450.300	Cicatrix	Tissues	Connective Tissue	0.86	>=0.20	0.81	>=0.20	0.66	>=0.20
A03.556.249.249.356	Colon	Digestive System	Gastrointestinal Tract	0.28	>=0.20	0.78	>=0.20	0.69	>=0.20
A03.556.249.249.356.668	Colon Sigmoid	Digestive System	Gastrointestinal Tract	0.31	>=0.20	0.45	>=0.20	0.56	>=0.20
A09.371.337.168	Conjunctiva	Sense Organs	Eye	0.76	>=0.20	0.98	>=0.20	0.36	>=0.20
A10.165	Connective Tissue	Tissues	Connective Tissue	0.98	>=0.20	0.22	>=0.20	0.95	>=0.20
A11.329	Connective Tissue Cells	Cells	Connective Tissue Cells	0.98	>=0.20	0.98	>=0.20	0.84	>=0.20
A08.186.211.730.885.287.249.487	Corpus Striatum	Nervous System	Central Nervous System	0.09	>=0.20	0.47	>=0.20	0.09	>=0.20
A06.407.312.497.535.300.500	Cumulus Cells	Endocrine System	Endocrine Glands	0.09	>=0.20	0.36	>=0.20	0.99	>=0.20
A15.382.812.260	Dendritic Cells	Hemic and Immune Systems	Immune System	0.99	>=0.20	0.43	>=0.20	0.64	>=0.20
A14.549.167	Dentition	Stomatognathic System	Mouth	0.97	>=0.20	0.92	>=0.20	0.85	>=0.20
A08.186.211.730.317	Diencephalon	Nervous System	Central Nervous System	0.55	>=0.20	0.21	>=0.20	0.5	>=0.20
A11.872.190.260	Embryoid Bodies	Cells	Stem Cells	0.87	>=0.20	0.99	>=0.20	0.98	>=0.20
A11.872.190	Embryonic Stem Cells	Cells	Stem Cells	0.45	>=0.20	0.82	>=0.20	0.25	>=0.20
A11.382	Endocrine Cells	Cells	Endocrine Cells	0.07	>=0.20	0.69	>=0.20	0.92	>=0.20
A06.407	Endocrine Glands	Endocrine System	Endocrine Glands	0.05	>=0.20	0.38	>=0.20	0.24	>=0.20
A05.360.319.679.490	Endometrium	Urogenital System	Genitalia	0.13	>=0.20	0.55	>=0.20	0.26	>=0.20
A11.436.275	Endothelial Cells	Cells	Epithelial Cells	0.9	>=0.20	0.98	>=0.20	0.69	>=0.20
A11.382.625	Enteroendocrine Cells	Cells	Endocrine Cells	0.28	>=0.20	0.95	>=0.20	0.39	>=0.20

				Combined Caffeine intake		Caffeine from Coffee		Caffeine from Tea	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A11.436	Epithelial Cells	Cells	Epithelial Cells	0.86	>=0.20	1	>=0.20	0.77	>=0.20
A10.272	Epithelium	Tissues	Epithelium	0.21	>=0.20	0.92	>=0.20	0.09	>=0.20
A15.145.229.334	Erythrocytes	Hemic and Immune Systems	Blood	0.91	>=0.20	0.56	>=0.20	0.96	>=0.20
A11.443	Erythroid Cells	Cells	Erythroid Cells	0.92	>=0.20	0.57	>=0.20	0.96	>=0.20
A15.378.316.378.590.837.250	Erythroid Precursor Cells	Hemic and Immune Systems	Hematopoietic System	0.79	>=0.20	0.82	>=0.20	0.37	>=0.20
A03.556.875.500	Esophagus	Digestive System	Gastrointestinal Tract	0.31	>=0.20	0.89	>=0.20	0.67	>=0.20
A10.336	Exocrine Glands	Tissues	Exocrine Glands	0.11	>=0.20	0.97	>=0.20	0.58	>=0.20
A10.615.284	Extraembryonic Membranes	Tissues	Membranes	0.64	>=0.20	0.97	>=0.20	0.93	>=0.20
A09.371	Eye	Sense Organs	Eye	0.29	>=0.20	0.23	>=0.20	0.05	>=0.20
A09.371.337	Eyelids	Sense Organs	Eye	0.76	>=0.20	0.98	>=0.20	0.36	>=0.20
A05.360.319.114.373	Fallopian Tubes	Urogenital System	Genitalia	0.19	>=0.20	0.36	>=0.20	0.12	>=0.20
A15.145.300	Fetal Blood	Hemic and Immune Systems	Blood	0.98	>=0.20	0.18	>=0.20	0.96	>=0.20
A11.329.228	Fibroblasts	Cells	Connective Tissue Cells	0.27	>=0.20	0.94	>=0.20	0.83	>=0.20
A02.835.232.043.300	Foot Bones	Musculoskeletal System	Skeleton	0.76	>=0.20	0.97	>=0.20	0.41	>=0.20
A05.360.444.492.362	Foreskin	Urogenital System	Genitalia	0.35	>=0.20	1	>=0.20	0.75	>=0.20
A08.186.211.730.885.287.500.270	Frontal Lobe	Nervous System	Central Nervous System	0.39	>=0.20	0.12	>=0.20	0.29	>=0.20
A03.556	Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.47	>=0.20	0.93	>=0.20	0.81	>=0.20
A05.360	Genitalia	Urogenital System	Genitalia	0.08	>=0.20	0.82	>=0.20	0.37	>=0.20
A05.360.319	Genitalia Female	Urogenital System	Genitalia	0.13	>=0.20	0.45	>=0.20	0.24	>=0.20
A05.360.444	Genitalia Male	Urogenital System	Genitalia	0.1	>=0.20	0.98	>=0.20	0.57	>=0.20
A05.360.490	Germ Cells	Urogenital System	Genitalia	0.32	>=0.20	0.99	>=0.20	0.91	>=0.20
A11.436.294.064	Glucagon Secreting Cells	Cells	Epithelial Cells	0.28	>=0.20	0.95	>=0.20	0.39	>=0.20
A06.407.312	Gonads	Endocrine System	Endocrine Glands	0.13	>=0.20	0.44	>=0.20	0.26	>=0.20
A10.165.450	Granulation Tissue	Tissues	Connective Tissue	0.86	>=0.20	0.81	>=0.20	0.66	>=0.20
A11.872.378.590.635	Granulocyte Macrophage Progenitor Cells	Cells	Stem Cells	1	>=0.20	0.76	>=0.20	0.99	>=0.20
A11.627.340.360	Granulocyte Precursor Cells	Cells	Myeloid Cells	0.98	>=0.20	0.55	>=0.20	0.6	>=0.20
A11.118.637.415	Granulocytes	Cells	Blood Cells	0.96	>=0.20	0.42	>=0.20	0.77	>=0.20
A11.436.329	Granulosa Cells	Cells	Epithelial Cells	0.09	>=0.20	0.36	>=0.20	0.99	>=0.20
A07.541	Heart	Cardiovascular System	Heart	0.77	>=0.20	0.55	>=0.20	0.78	>=0.20
A07.541.358	Heart Atria	Cardiovascular System	Heart	0.35	>=0.20	0.16	>=0.20	0.65	>=0.20
A07.541.510	Heart Valves	Cardiovascular System	Heart	0.14	>=0.20	0.35	>=0.20	0.11	>=0.20
A07.541.560	Heart Ventricles	Cardiovascular System	Heart	0.83	>=0.20	0.6	>=0.20	0.83	>=0.20
A11.872.378	Hematopoietic Stem Cells	Cells	Stem Cells	0.99	>=0.20	0.7	>=0.20	0.85	>=0.20
A15.378	Hematopoietic System	Hemic and Immune Systems	Hematopoietic System	1	>=0.20	0.48	>=0.20	0.93	>=0.20
A11.436.348	Hepatocytes	Cells	Epithelial Cells	0.48	>=0.20	0.87	>=0.20	0.82	>=0.20
A08.186.211.730.317.357.352.435	Hypothalamo Hypophyseal System	Nervous System	Central Nervous System	0.27	>=0.20	0.17	>=0.20	0.54	>=0.20
A08.186.211.730.317.357	Hypothalamus	Nervous System	Central Nervous System	0.34	>=0.20	0.18	>=0.20	0.53	>=0.20
A08.186.211.730.317.357.352	Hypothalamus Middle	Nervous System	Central Nervous System	0.27	>=0.20	0.17	>=0.20	0.54	>=0.20
A03.556.249.124	Ileum	Digestive System	Gastrointestinal Tract	0.3	>=0.20	0.76	>=0.20	0.69	>=0.20

				Combined Caffeine intake		Caffeine from Coffee		Caffeine from Tea	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A15.382	Immune System	Hemic and Immune Systems	Immune System	0.99	>=0.20	0.13	>=0.20	0.96	>=0.20
A11.872.700.500	Induced Pluripotent Stem Cells	Cells	Stem Cells	0.41	>=0.20	0.83	>=0.20	0.35	>=0.20
A03.556.124.369	Intestinal Mucosa	Digestive System	Gastrointestinal Tract	0.63	>=0.20	0.99	>=0.20	0.71	>=0.20
A03.556.249.249	Intestine Large	Digestive System	Gastrointestinal Tract	0.3	>=0.20	0.76	>=0.20	0.74	>=0.20
A03.556.124.684	Intestine Small	Digestive System	Gastrointestinal Tract	0.52	>=0.20	0.62	>=0.20	0.95	>=0.20
A03.556.124	Intestines	Digestive System	Gastrointestinal Tract	0.37	>=0.20	0.86	>=0.20	0.76	>=0.20
A03.734.414	Islets of Langerhans	Digestive System	Pancreas	0.32	>=0.20	0.97	>=0.20	0.47	>=0.20
A02.835.583.443	Joint Capsule	Musculoskeletal System	Skeleton	0.38	>=0.20	0.65	>=0.20	0.98	>=0.20
A02.835.583	Joints	Musculoskeletal System	Skeleton	0.38	>=0.20	0.65	>=0.20	0.98	>=0.20
A10.165.450.300.425	Keloid	Tissues	Connective Tissue	0.89	>=0.20	0.86	>=0.20	0.53	>=0.20
A11.436.397	Keratinocytes	Cells	Epithelial Cells	0.99	>=0.20	1	>=0.20	0.83	>=0.20
A05.810.453	Kidney	Urogenital System	Urinary Tract	0.15	>=0.20	0.31	>=0.20	0.52	>=0.20
A05.810.453.324	Kidney Cortex	Urogenital System	Urinary Tract	0.2	>=0.20	0.39	>=0.20	0.89	>=0.20
A15.382.490.555.567.537	Killer Cells Natural	Hemic and Immune Systems	Immune System	0.47	>=0.20	0.22	>=0.20	0.67	>=0.20
A11.118.637	Leukocytes	Cells	Blood Cells	0.98	>=0.20	0.13	>=0.20	0.97	>=0.20
A15.145.229.637.555	Leukocytes Mononuclear	Hemic and Immune Systems	Blood	0.96	>=0.20	0.09	>=0.20	0.98	>=0.20
A03.620	Liver	Digestive System	Liver	0.05	>=0.20	0.37	>=0.20	0.4	>=0.20
A03.556.249	Lower Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.3	>=0.20	0.76	>=0.20	0.75	>=0.20
A04.411	Lung	Respiratory System	Lung	0.15	>=0.20	0.74	>=0.20	0.42	>=0.20
A10.549.400	Lymph Nodes	Tissues	Lymphoid Tissue	0.84	>=0.20	0.04	>=0.20	0.8	>=0.20
A15.382.520	Lymphatic System	Hemic and Immune Systems	Immune System	0.76	>=0.20	0.04	>=0.20	0.74	>=0.20
A15.382.490.555.567	Lymphocytes	Hemic and Immune Systems	Immune System	0.76	>=0.20	0.04	>=0.20	0.95	>=0.20
A15.382.490.555.567.622	Lymphocytes Null	Hemic and Immune Systems	Immune System	0.91	>=0.20	0.58	>=0.20	0.49	>=0.20
A11.872.378.294	Lymphoid Progenitor Cells	Cells	Stem Cells	0.29	>=0.20	0.06	>=0.20	0.23	>=0.20
A10.549	Lymphoid Tissue	Tissues	Lymphoid Tissue	0.76	>=0.20	0.04	>=0.20	0.74	>=0.20
A15.382.812.522	Macrophages	Hemic and Immune Systems	Immune System	1	>=0.20	0.88	>=0.20	0.66	>=0.20
A11.329.372.600	Macrophages Alveolar	Cells	Connective Tissue Cells	1	>=0.20	0.79	>=0.20	0.13	>=0.20
A11.872.378.590.817	Megakaryocyte Erythroid Progenitor Cells	Cells	Stem Cells	0.79	>=0.20	0.82	>=0.20	0.37	>=0.20
A10.615	Membranes	Tissues	Membranes	0.45	>=0.20	1	>=0.20	0.54	>=0.20
A08.186.211.653	Mesencephalon	Nervous System	Central Nervous System	0.49	>=0.20	0.32	>=0.20	0.26	>=0.20
A11.872.580	Mesenchymal Stem Cells	Cells	Stem Cells	0.37	>=0.20	0.78	>=0.20	0.87	>=0.20
A11.627.624.249	Monocyte Macrophage Precursor Cells	Cells	Myeloid Cells	1	>=0.20	0.78	>=0.20	1	>=0.20
A15.378.316.580	Monocytes	Hemic and Immune Systems	Hematopoietic System	1	>=0.20	0.55	>=0.20	0.97	>=0.20
A15.382.812	Mononuclear Phagocyte System	Hemic and Immune Systems	Immune System	1	>=0.20	0.62	>=0.20	0.84	>=0.20
A14.549	Mouth	Stomatognathic System	Mouth	0.8	>=0.20	0.99	>=0.20	0.81	>=0.20
A10.615.550.599	Mouth Mucosa	Tissues	Membranes	0.46	>=0.20	0.96	>=0.20	0.38	>=0.20
A10.615.550	Mucous Membrane	Tissues	Membranes	0.47	>=0.20	0.99	>=0.20	0.4	>=0.20
A10.690.552.500	Muscle Skeletal	Tissues	Muscles	0.84	>=0.20	0.27	>=0.20	0.92	>=0.20

				Combined Caffeine intake		Caffeine from Coffee		Caffeine from Tea	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A10.690.467	Muscle Smooth	Tissues	Muscles	0.99	>=0.20	0.99	>=0.20	0.95	>=0.20
A10.690.552	Muscle Striated	Tissues	Muscles	0.84	>=0.20	0.27	>=0.20	0.92	>=0.20
A11.620	Muscle Cells	Cells	Muscle Cells	1	>=0.20	1	>=0.20	0.99	>=0.20
A10.690	Muscles	Tissues	Muscles	0.93	>=0.20	0.49	>=0.20	0.96	>=0.20
A11.627	Myeloid Cells	Cells	Myeloid Cells	1	>=0.20	0.61	>=0.20	0.87	>=0.20
A11.627.635	Myeloid Progenitor Cells	Cells	Myeloid Cells	0.99	>=0.20	0.82	>=0.20	0.92	>=0.20
A11.620.520	Myocytes Smooth Muscle	Cells	Muscle Cells	1	>=0.20	1	>=0.20	0.99	>=0.20
A05.360.319.679.690	Myometrium	Urogenital System	Genitalia	0.04	>=0.20	0.26	>=0.20	0.16	>=0.20
A04.531.520	Nasal Mucosa	Respiratory System	Nose	0.22	>=0.20	0.84	>=0.20	0.23	>=0.20
A14.724.557	Nasopharynx	Stomatognathic System	Pharynx	1	>=0.20	0.8	>=0.20	0.51	>=0.20
A08.713	Neurosecretory Systems	Nervous System	Neurosecretory Systems	0.27	>=0.20	0.17	>=0.20	0.54	>=0.20
A15.382.490.315.583	Neutrophils	Hemic and Immune Systems	Immune System	0.95	>=0.20	0.41	>=0.20	0.76	>=0.20
A09.531	Nose	Sense Organs	Nose	0.22	>=0.20	0.84	>=0.20	0.23	>=0.20
A11.497.497.600	Oocytes	Cells	Germ Cells	0.12	>=0.20	0.95	>=0.20	0.75	>=0.20
A04.623.603	Oropharynx	Respiratory System	Pharynx	0.75	>=0.20	0.1	>=0.20	0.61	>=0.20
A11.329.629	Osteoblasts	Cells	Connective Tissue Cells	0.54	>=0.20	0.63	>=0.20	0.55	>=0.20
A05.360.319.114.630.535	Ovarian Follicle	Urogenital System	Genitalia	0.09	>=0.20	0.36	>=0.20	0.99	>=0.20
A05.360.319.114.630	Ovary	Urogenital System	Genitalia	0.14	>=0.20	0.37	>=0.20	0.24	>=0.20
A05.360.490.690	Ovum	Urogenital System	Genitalia	0.12	>=0.20	0.95	>=0.20	0.75	>=0.20
A15.382.520.604.800	Palatine Tonsil	Hemic and Immune Systems	Immune System	0.75	>=0.20	0.1	>=0.20	0.61	>=0.20
A03.734	Pancreas	Digestive System	Pancreas	0.19	>=0.20	0.75	>=0.20	0.28	>=0.20
A08.186.211.730.885.287.500.670	Parietal Lobe	Nervous System	Central Nervous System	0.08	>=0.20	9.67E-03	>=0.20	0.12	>=0.20
A03.556.500.760.464	Parotid Gland	Digestive System	Gastrointestinal Tract	0.52	>=0.20	0.73	>=0.20	0.97	>=0.20
A05.360.444.492	Penis	Urogenital System	Genitalia	0.34	>=0.20	1	>=0.20	0.75	>=0.20
A14.549.167.646	Periodontium	Stomatognathic System	Mouth	0.92	>=0.20	0.89	>=0.20	0.8	>=0.20
A15.382.680	Phagocytes	Hemic and Immune Systems	Immune System	1	>=0.20	0.59	>=0.20	0.87	>=0.20
A14.724	Pharynx	Stomatognathic System	Pharynx	1	>=0.20	0.54	>=0.20	0.57	>=0.20
A15.145.693	Plasma	Hemic and Immune Systems	Blood	0.87	>=0.20	0.15	>=0.20	0.99	>=0.20
A15.145.229.637.555.567.562.725	Plasma Cells	Hemic and Immune Systems	Blood	0.87	>=0.20	0.16	>=0.20	0.99	>=0.20
A11.872.700	Pluripotent Stem Cells	Cells	Stem Cells	0.41	>=0.20	0.83	>=0.20	0.35	>=0.20
A07.231.908.670	Portal System	Cardiovascular System	Blood Vessels	0.89	>=0.20	0.95	>=0.20	0.53	>=0.20
A11.118.637.555.567.562.440	Precursor Cells B Lymphoid	Cells	Blood Cells	0.29	>=0.20	0.06	>=0.20	0.23	>=0.20
A10.336.707	Prostate	Tissues	Exocrine Glands	0.11	>=0.20	0.96	>=0.20	0.53	>=0.20
A02.633.567.850	Quadriceps Muscle	Musculoskeletal System	Muscles	0.85	>=0.20	0.26	>=0.20	0.93	>=0.20
A03.556.124.526.767	Rectum	Digestive System	Gastrointestinal Tract	0.58	>=0.20	0.51	>=0.20	0.98	>=0.20
A10.615.550.760	Respiratory Mucosa	Tissues	Membranes	0.22	>=0.20	0.84	>=0.20	0.23	>=0.20
A03.556.500.760	Salivary Glands	Digestive System	Gastrointestinal Tract	0.6	>=0.20	0.73	>=0.20	0.98	>=0.20
A10.615.789	Serous Membrane	Tissues	Membranes	0.39	>=0.20	0.69	>=0.20	0.61	>=0.20
A15.145.846	Serum	Hemic and Immune Systems	Blood	0.92	>=0.20	0.95	>=0.20	0.85	>=0.20

				Combined Caffeine intake		**Caffeine from Coffee**		**Caffeine from Tea**	
MeSH term	**Name**	**MeSH first level term**	**MeSH second level term**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**	**Nominal P value**	**False discovery rate**
A02.835	Skeleton	Musculoskeletal System	Skeleton	0.98	>=0.20	0.21	>=0.20	0.96	>=0.20
A17.815	Skin	Integumentary System	Skin	0.28	>=0.20	0.99	>=0.20	0.25	>=0.20
A02.835.232.834	Spine	Musculoskeletal System	Skeleton	0.36	>=0.20	0.75	>=0.20	0.48	>=0.20
A15.382.520.604.700	Spleen	Hemic and Immune Systems	Immune System	0.1	>=0.20	0.19	>=0.20	0.4	>=0.20
A11.872	Stem Cells	Cells	Stem Cells	0.81	>=0.20	0.79	>=0.20	0.66	>=0.20
A03.556.875.875	Stomach	Digestive System	Gastrointestinal Tract	0.35	>=0.20	0.64	>=0.20	0.71	>=0.20
A11.329.830	Stromal Cells	Cells	Connective Tissue Cells	0.49	>=0.20	0.94	>=0.20	0.87	>=0.20
A10.165.114.830.750	Subcutaneous Fat	Tissues	Connective Tissue	0.6	>=0.20	0.55	>=0.20	0.23	>=0.20
A10.165.114.830.500.750	Subcutaneous Fat Abdominal	Tissues	Connective Tissue	0.68	>=0.20	0.56	>=0.20	0.26	>=0.20
A02.835.583.443.800.800	Synovial Fluid	Musculoskeletal System	Skeleton	0.72	>=0.20	0.2	>=0.20	0.84	>=0.20
A02.835.583.443.800	Synovial Membrane	Musculoskeletal System	Skeleton	0.38	>=0.20	0.65	>=0.20	0.98	>=0.20
A11.118.637.555.567.569	T Lymphocytes	Cells	Blood Cells	0.6	>=0.20	0.08	>=0.20	0.68	>=0.20
A11.118.637.555.567.569.200.700	T Lymphocytes Regulatory	Cells	Blood Cells	0.23	>=0.20	0.1	>=0.20	0.24	>=0.20
A02.835.232.043.300.710	Tarsal Bones	Musculoskeletal System	Skeleton	0.76	>=0.20	0.97	>=0.20	0.41	>=0.20
A06.407.312.782	Testis	Endocrine System	Endocrine Glands	0.31	>=0.20	0.93	>=0.20	0.57	>=0.20
A06.407.900	Thyroid Gland	Endocrine System	Endocrine Glands	0.16	>=0.20	0.23	>=0.20	0.41	>=0.20
A14.549.885	Tongue	Stomatognathic System	Mouth	0.98	>=0.20	0.99	>=0.20	0.98	>=0.20
A07.231.908.670.874	Umbilical Veins	Cardiovascular System	Blood Vessels	0.89	>=0.20	0.95	>=0.20	0.53	>=0.20
A03.556.875	Upper Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	0.39	>=0.20	0.75	>=0.20	0.77	>=0.20
A05.810.890	Urinary Bladder	Urogenital System	Urinary Tract	0.65	>=0.20	0.47	>=0.20	0.83	>=0.20
A05.810	Urinary Tract	Urogenital System	Urinary Tract	0.16	>=0.20	0.32	>=0.20	0.54	>=0.20
A05.360.319.679	Uterus	Urogenital System	Genitalia	0.16	>=0.20	0.53	>=0.20	0.37	>=0.20
A07.231.908	Veins	Cardiovascular System	Blood Vessels	0.92	>=0.20	0.95	>=0.20	0.65	>=0.20
A05.360.319.887	Vulva	Urogenital System	Genitalia	0.83	>=0.20	0.99	>=0.20	0.56	>=0.20

Table S19. Functional eQTL genes associated with caffeine intake

GWAS SNP	Caffeine Trait	probe ID	Probe Chr	Gene	Probe postion	eQTL SNP	eQTL SNP Chr	eQTL SNP position	EF AL	NE FAL	EF Freq	Beta GWAS	SE GWAS	*P* GWAS	Beta eQTL	SE eQTL	*P* eQTL	Beta SMR	SE SMR	*P* SMR	*P* HEIDI	eQTL repository
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11587444	1	150722844	G	A	0.396321	0.0234978	0.00237896	5.20E-23	1.1957	0.0565677	3.60E-99	0.0196519	0.0021961	3.60E-19	0.1070597	GTEx - Nerve Tibial
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11204717	1	150709129	A	T	0.394263	0.0231968	0.00237641	1.70E-22	1.10797	0.0508788	3.86E-105	0.0209363	0.00235045	5.23E-19	0.2278421	GTEx - Skin Sun Exposed Lower leg
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11204718	1	150709785	G	C	0.394263	0.0231956	0.00237643	1.70E-22	1.12726	0.0529239	1.14E-100	0.020577	0.00231896	7.10E-19	0.1377202	GTEx - Esophagus Mucosa
rs768283768	Combined Caffeine	ENSG00000143457.6	1	GOLPH3L	150644165	rs11587444	1	150722844	G	A	0.396321	0.0234978	0.00237896	5.20E-23	0.88578	0.0470777	5.66E-79	0.0265278	0.00303331	2.22E-18	0.1119635	GTEx - Nerve Tibial
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs7529194	1	150622620	A	T	0.394	0.0230701	0.00237586	2.70E-22	1.06836	0.0572195	8.48E-78	0.0215939	0.0025066	7.00E-18	0.147406	GTEx - Skin Not Sun Exposed Suprapubic
rs768283768	Combined Caffeine	ENSG00000143457.6	1	GOLPH3L	150644165	rs1134067	1	150721175	T	G	0.39639	0.0235077	0.00237826	4.90E-23	0.788672	0.0455441	3.52E-67	0.0298067	0.0034722	9.13E-18	0.1489021	GTEx - Skin Sun Exposed Lower leg
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs111842513	1	150712926	A	G	0.394263	0.0232029	0.0023766	1.60E-22	0.921119	0.0574382	7.08E-58	0.0251899	0.00302065	7.48E-17	0.3795036	GTEx - Adipose Subcutaneous
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs72704603	1	150707992	T	C	0.394263	0.0232622	0.00237665	1.30E-22	0.950796	0.0623663	1.77E-52	0.024466	0.00297046	1.77E-16	0.2328227	GTEx - Cells Transformed fibroblasts
7:73042302_GCTTT_G	Combined Caffeine	ENSG00000009950.11	7	MLXIPL	73023198	rs34060476	7	73037956	G	A	0.146685	0.0353479	0.00340377	2.90E-25	0.796108	0.0658142	1.10E-33	0.0444009	0.00563502	3.29E-15	0.07818656	GTEx - Skin Sun Exposed Lower leg
7:73042302_GCTTT_G	Combined Caffeine	ENSG00000009950.11	7	MLXIPL	73023198	rs34060476	7	73037956	G	A	0.146685	0.0353479	0.00340377	2.90E-25	0.753091	0.0680875	1.95E-28	0.0469371	0.0061997	3.71E-14	0.1286897	GTEx - Thyroid
rs6062679	Combined Caffeine	ENSG00000203880.7	20	PCMTD2	62906974	rs1808056	20	62890932	A	G	0.457023	0.0227612	0.00235819	4.80E-22	-0.27819	0.0258003	4.17E-27	-0.0818189	0.0113771	6.41E-13	0.6371555	GTEx - Thyroid
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11204698	1	150659545	A	G	0.394	0.0230793	0.00237565	2.60E-22	0.756408	0.0835393	1.37E-19	0.0305117	0.00460645	3.50E-11	0.3133836	GTEx - Breast Mammary Tissue
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs7533678	1	150699586	C	T	0.40527	0.0227913	0.00236385	5.30E-22	0.550309	0.0612163	2.48E-19	0.0414155	0.00629891	4.86E-11	0.05189475	GTEx - Thyroid
rs768283768	Combined Caffeine	ENSG00000143457.6	1	GOLPH3L	150644165	rs6685702	1	150656307	G	A	0.405	0.0227773	0.00236378	5.60E-22	0.250716	0.0279988	3.41E-19	0.090849	0.01385	5.40E-11	0.07505418	GTEx - Esophagus Mucosa
7:73042302_GCTTT_G	Combined Caffeine	ENSG00000009950.11	7	MLXIPL	73023198	rs34763247	7	72866616	T	A	0.139333	0.0340615	0.0035132	3.20E-22	0.666216	0.0777223	1.02E-17	0.0511268	0.00796144	1.35E-10	0.2345691	GTEx - Pancreas
rs768283768	Combined Caffeine	ENSG00000163131.6	1	CTSS	150720552	rs868751	1	150669414	G	T	0.394	0.023091	0.00237564	2.50E-22	0.416326	0.0487067	1.26E-17	0.0554637	0.00864091	1.37E-10	0.1221481	GTEx - Liver
rs34060476	Caffeine from Coffee	ENSG00000009950.11	7	MLXIPL	73023198	rs34060476	7	73037956	G	A	0.146685	0.0251884	0.00336487	7.10E-14	0.796108	0.0658142	1.10E-33	0.0316394	0.00497052	1.95E-10	0.120355	GTEx - Skin Sun Exposed Lower leg
7:73042302_GCTTT_G	Combined Caffeine	ENSG00000009950.11	7	MLXIPL	73023198	rs13235543	7	73013901	T	C	0.141667	0.0343207	0.00344971	2.60E-23	0.541017	0.0662661	3.23E-16	0.0634374	0.0100515	2.77E-10	0.09963132	GTEx - Esophagus Muscularis
rs6062679	Combined Caffeine	ENSG00000203880.7	20	PCMTD2	62906974	rs1808056	20	62890932	A	G	0.457023	0.0227612	0.00235819	4.80E-22	-0.263918	0.0320418	1.77E-16	-0.0862435	0.013765	3.72E-10	0.3796367	GTEx - Esophagus Muscularis
rs9624470	Caffeine from Tea	ENSG00000100024	22	UPB1	24893782	rs1041750	22	24847606	A	T	0.611333	0.0235842	0.00228676	6.10E-25	-0.550949	0.0698889	3.19E-15	-0.0428065	0.0068347	3.77E-10	0.1232167	Brain-eMeta
rs9624470	Caffeine from Tea	ENSG00000100024.10	22	UPB1	24893782	rs1041750	22	24847606	A	T	0.611333	0.0235842	0.00228676	6.10E-25	-0.550949	0.0698889	3.19E-15	-0.0428065	0.0068347	3.77E-10	0.1232167	GTEx Brain
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs7524620	1	150616699	G	A	0.406774	0.0229777	0.00236672	2.80E-22	1.00072	0.123587	5.62E-16	0.0229612	0.00369246	5.02E-10	0.0695423	GTEx - Vagina
rs34060476	Caffeine from Coffee	ENSG00000009950.11	7	MLXIPL	73023198	rs34060476	7	73037956	G	A	0.146685	0.0251884	0.00336487	7.10E-14	0.753091	0.0680875	1.95E-28	0.0334467	0.00539518	5.67E-10	0.1378098	GTEx - Thyroid
rs6062679	Combined Caffeine	ENSG00000203880.7	20	PCMTD2	62906974	rs1808056	20	62890932	A	G	0.457023	0.0227612	0.00235819	4.80E-22	-0.229143	0.0286915	1.39E-15	-0.0993319	0.0161433	7.60E-10	0.3140653	GTEx - Adipose Subcutaneous

GWAS SNP	Caffeine Trait	probe ID	Probe Chr	Gene	Probe postion	eQTL SNP	eQTL SNP Chr	eQTL SNP position	EF AL	NE FAL	EF Freq	Beta GWAS	SE GWAS	*P* GWAS	Beta eQTL	SE eQTL	*P* eQTL	Beta SMR	SE SMR	*P* SMR	*P* HEIDI	eQTL repository
rs768283768	Combined Caffeine	ENSG00000143418.15	1	CERS2	150941903	rs2867300	1	150666990	C	G	0.405	0.0227913	0.0023639	5.30E-22	0.46562	0.0585626	1.85E-15	0.0489483	0.00797972	8.57E-10	0.1157918	GTEx - Brain Cerebellum
rs6062679	Combined Caffeine	ENSG00000203880.7	20	PCMTD2	62906974	rs1808056	20	62890932	A	G	0.457023	0.0227612	0.00235819	4.80E-22	-0.326626	0.0435156	6.10E-14	-0.0696858	0.011761	3.12E-09	0.3331977	GTEx - Esophagus Gastroesophageal Junction
rs2521501	Caffeine from Coffee	ILMN_1693650	15	FES	91438855	rs2521501	15	91437388	T	A	0.339029	-0.0149164	0.002472	1.60E-09	-0.457456	0.0196169	2.81E-120	0.0326073	0.00558178	5.17E-09	0.8210296	Westra
rs768283768	Combined Caffeine	ENSG00000143418.15	1	CERS2	150941903	rs17658705	1	150678071	T	G	0.405	0.022792	0.00236378	5.30E-22	0.169654	0.0232326	2.83E-13	0.134344	0.0230778	5.84E-09	0.0773745	GTEx - Adipose Subcutaneous
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11204705	1	150672223	T	G	0.405	0.0227919	0.00236378	5.30E-22	0.393616	0.0547792	6.70E-13	0.0579039	0.01005	8.33E-09	0.06568804	GTEx - Muscle Skeletal
rs9624470	Caffeine from Tea	ENSG00000100024.10	22	UPB1	24893782	rs1008932	22	24855182	T	C	0.613	0.0234215	0.00228758	1.30E-24	-0.282294	0.0411528	6.90E-12	-0.0829685	0.0145588	1.21E-08	0.1022363	GTEx - Lung
rs11204711	Caffeine from Tea	ENSG00000143452.11	1	HORMAD1	150681950	rs7529194	1	150622620	A	T	0.394	0.0136362	0.00228609	2.40E-09	1.06836	0.0572195	8.48E-78	0.0127637	0.00224635	1.33E-08	0.06575839	GTEx - Skin Not Sun Exposed Suprapubic
rs11204711	Caffeine from Tea	ENSG00000143452.11	1	HORMAD1	150681950	rs11204717	1	150709129	A	T	0.394263	0.0134274	0.00228667	4.30E-09	1.10797	0.0508788	3.86E-105	0.0121189	0.00213755	1.43E-08	0.1723868	GTEx - Skin Sun Exposed Lower leg
rs11204711	Caffeine from Tea	ENSG00000143452.11	1	HORMAD1	150681950	rs11204718	1	150709785	G	C	0.394263	0.0134292	0.00228668	4.30E-09	1.12726	0.0529239	1.14E-100	0.0119131	0.00210422	1.50E-08	0.07798458	GTEx - Esophagus Mucosa
rs11204711	Caffeine from Tea	ENSG00000143457.6	1	GOLPH3L	150644165	rs1134067	1	150721175	T	G	0.39639	0.0136748	0.00228844	2.30E-09	0.788672	0.0455441	3.52E-67	0.017339	0.00306954	1.62E-08	0.09304391	GTEx - Skin Sun Exposed Lower leg
rs9624470	Caffeine from Tea	ENSG00000100024.10	22	UPB1	24893782	rs9624470	22	24820268	A	G	0.579127	0.0253437	0.00227204	6.80E-29	-0.300833	0.0459905	6.10E-11	-0.0842451	0.0149303	1.68E-08	0.2396185	GTEx - Muscle Skeletal
rs9611527	Combined Caffeine	ENSG00000100401.15	22	RANGAP1	41661935	rs6002310	22	41675126	G	A	0.344043	-0.0193024	0.00246584	5.00E-15	-0.219437	0.0269815	4.19E-16	0.0879633	0.0155966	1.70E-08	0.2792009	GTEx - Esophagus Mucosa
rs9624470	Caffeine from Tea	ENSG00000100024.10	22	UPB1	24893782	rs11703648	22	24843886	G	C	0.584	0.0249661	0.00226437	2.90E-28	-0.603932	0.0936659	1.14E-10	-0.0413393	0.00742728	2.61E-08	0.2119155	GTEx - Brain Putamen basal ganglia
rs11204711	Caffeine from Tea	ENSG00000143452.11	1	HORMAD1	150681950	rs111842513	1	150712926	A	G	0.394263	0.0134291	0.00228685	4.30E-09	0.921119	0.0574382	7.08E-58	0.0145791	0.0026439	3.50E-08	0.1929549	GTEx - Adipose Subcutaneous
16:18776851_G_GA	Combined Caffeine	ILMN_1708416	16	ARL6IP1	18803495	rs11640850	16	18823607	A	G	0.378333	-0.013592	0.0023763	1.10E-08	-0.568952	0.0282008	1.62E-90	0.0238895	0.00434124	3.74E-08	0.7615016	CAGE
rs11204711	Caffeine from Tea	ENSG00000143452.11	1	HORMAD1	150681950	rs72704603	1	150707992	T	C	0.394263	0.0134578	0.00228692	4.00E-09	0.950796	0.0623663	1.77E-52	0.0141542	0.00257824	4.02E-08	0.1913184	GTEx - Cells Transformed fibroblasts
rs768283768	Caffeine from Coffee	ILMN_1743032	1	CTSS	150702935	rs2867301	1	150653795	T	C	0.405	0.0129773	0.00233671	2.80E-08	0.496667	0.0185951	3.64E-157	0.0261288	0.00480541	5.41E-08	0.367449	Westra
rs6062679	Combined Caffeine	ENSG00000203880.7	20	PCMTD2	62906974	rs6062679	20	62889991	C	T	0.456993	0.0227779	0.00235823	4.50E-22	-0.344557	0.05249	5.23E-11	-0.0661078	0.0121765	5.66E-08	0.6792679	GTEx - Pancreas
rs768283768	Caffeine from Coffee	ILMN_1743032	1	CTSS	150702936	rs1977715	1	150675147	G	A	0.405	0.0129724	0.00233671	2.80E-08	0.630879	0.0283742	1.60E-109	0.0205624	0.00381761	7.20E-08	0.06656519	CAGE
rs34060476	Caffeine from Coffee	ENSG00000009950.11	7	MLXIPL	73023198	rs34763247	7	72866616	T	A	0.139333	0.0240415	0.00347404	4.50E-12	0.666216	0.0777223	1.02E-17	0.0360866	0.00670191	7.26E-08	0.2448739	GTEx - Pancreas
rs73053413	Caffeine from Tea	ENSG00000111215.7	12	PRR4	11150885	rs10772395	12	11128666	T	C	0.831333	0.0206226	0.00299459	5.70E-12	-0.710679	0.0829164	1.03E-17	-0.0290182	0.00540533	7.94E-08	0.1335246	GTEx - Cells Transformed fibroblasts
rs73053413	Caffeine from Tea	ENSG00000212125.2	12	TAS2R15	11117487	rs1669411	12	11338614	G	A	0.833667	0.0215404	0.0030102	8.30E-13	-0.583853	0.0720713	5.45E-16	-0.0368935	0.00687911	8.18E-08	0.2270893	GTEx - Nerve Tibial

GWAS SNP	**Caffeine Trait**	**probe ID**	**Probe Chr**	**Gene**	**Probe postion**	**eQTL SNP**	**eQTL SNP Chr**	**eQTL SNP position**	**EFAL**	**NEFAL**	**EF Freq**	**Beta GWAS**	**SE GWAS**	***P* GWAS**	**Beta eQTL**	**SE eQTL**	***P* eQTL**	**Beta SMR**	**SE SMR**	***P* SMR**	***P* HEIDI**	**eQTL repository**
rs73053413	Caffeine from Tea	ENSG00000212125.2	12	TAS2R15	11117487	rs187328	12	11331479	C	T	0.833889	0.0215481	0.00301052	8.20E-13	-0.570406	0.0713309	1.28E-15	-0.0377768	0.00708328	9.65E-08	0.1048308	GTEx - Lung
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11204694	1	150653391	A	G	0.394	0.0231206	0.00237574	2.20E-22	0.593578	0.0935545	2.23E-10	0.0389512	0.0073286	1.07E-07	0.07874566	GTEx - Colon Sigmoid
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs6685702	1	150656307	G	A	0.405	0.0227773	0.00236378	5.60E-22	0.462113	0.0725196	1.86E-10	0.0492895	0.00927337	1.07E-07	0.2066777	GTEx - Esophagus Muscularis
rs34060476	Caffeine from Coffee	ENSG00000009950.11	7	MLXIPL	73023198	rs13235543	7	73013901	T	C	0.141667	0.0238165	0.00341046	2.90E-12	0.541017	0.0662661	3.23E-16	0.0440217	0.00829525	1.12E-07	0.09238904	GTEx - Esophagus Muscularis
rs768283768	Caffeine from Coffee	ENSG00000143457.6	1	GOLPH3L	150644165	rs1134067	1	150721175	T	G	0.39639	0.0131067	0.00235125	2.50E-08	0.788672	0.0455441	3.52E-67	0.0166187	0.00313194	1.12E-07	0.6084519	GTEx - Skin Sun Exposed Lower leg
7:73042302_GCTTT_G	Combined Caffeine	ENSG00000009950.11	7	MLXIPL	73023198	rs13246993	7	73022746	A	G	0.142667	0.0347445	0.00345425	8.40E-24	0.506704	0.0815321	5.14E-10	0.0685696	0.0129695	1.24E-07	0.265909	GTEx - Esophagus Gastroesophageal Junction
rs768283768	Caffeine from Coffee	ENSG00000143452.11	1	HORMAD1	150681950	rs11204717	1	150709129	A	T	0.394263	0.0127784	0.00234937	5.40E-08	1.10797	0.0508788	3.86E-105	0.0115332	0.00218557	1.31E-07	0.5859677	GTEx - Skin Sun Exposed Lower leg
rs768283768	Caffeine from Coffee	ENSG00000143452.11	1	HORMAD1	150681950	rs11204718	1	150709785	G	C	0.394263	0.0127732	0.00234939	5.40E-08	1.12726	0.0529239	1.14E-100	0.0113312	0.00215098	1.38E-07	0.6964135	GTEx - Esophagus Mucosa
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs11583636	1	150694777	G	A	0.405	0.0227894	0.0023638	5.40E-22	0.732626	0.117162	4.02E-10	0.0311065	0.00592929	1.55E-07	0.07462922	GTEx - Cells EBV-transformed lymphocytes
rs768283768	Combined Caffeine	ENSG00000143379.8	1	SETDB1	150917976	rs17658705	1	150678071	T	G	0.405	0.022792	0.00236378	5.30E-22	-0.243504	0.038968	4.14E-10	-0.0936001	0.0178493	1.57E-07	0.2054016	GTEx - Skin Not Sun Exposed Suprapubic
rs2521501	Caffeine from Coffee	ENSG00000182511.7	15	FES	91432965	rs7497304	15	91429176	T	G	0.343	-0.0142403	0.00244464	5.70E-09	-0.5141	0.0436416	4.95E-32	0.0276995	0.00530479	1.77E-07	0.5628922	GTEx - Thyroid
rs768283768	Combined Caffeine	ENSG00000143452.11	1	HORMAD1	150681950	rs17658705	1	150678071	T	G	0.405	0.022792	0.00236378	5.30E-22	0.580348	0.0935432	5.50E-10	0.039273	0.00752736	1.81E-07	0.2153355	GTEx - Esophagus Gastroesophageal Junction
rs17685	Combined Caffeine	ENSG00000227038.2	7	AC005077.12	75728923	rs1057868	7	75615006	T	C	0.305333	0.0403552	0.00256502	9.00E-56	0.290964	0.0530468	4.13E-08	0.138695	0.0267787	2.23E-07	0.8782062	GTEx - Testis
rs768283768	Caffeine from Coffee	ENSG00000143457.6	1	GOLPH3L	150644165	rs1134067	1	150721175	T	G	0.39639	0.0131067	0.00235125	2.50E-08	0.621831	0.0458045	5.58E-42	0.0210776	0.00408752	2.52E-07	0.6080412	GTEx - Skin Not Sun Exposed Suprapubic
rs768283768	Caffeine from Coffee	ENSG00000143452.11	1	HORMAD1	150681950	rs7529194	1	150622620	A	T	0.394	0.0125987	0.00234883	8.10E-08	1.06836	0.0572195	8.48E-78	0.0117926	0.00228746	2.53E-07	0.5178539	GTEx - Skin Not Sun Exposed Suprapubic
rs768283768	Caffeine from Coffee	ENSG00000143452.11	1	HORMAD1	150681950	rs111842513	1	150712926	A	G	0.394263	0.0127876	0.00234956	5.30E-08	0.921119	0.0574382	7.08E-58	0.0138827	0.00269366	2.55E-07	0.6394203	GTEx - Adipose Subcutaneous
rs768283768	Caffeine from Coffee	ENSG00000143452.11	1	HORMAD1	150681950	rs72704603	1	150707992	T	C	0.394263	0.0128283	0.00234961	4.80E-08	0.950796	0.0623663	1.77E-52	0.0134922	0.00262489	2.75E-07	0.5119789	GTEx - Cells Transformed fibroblasts

eQTL gene mapping was performed using a SMR approach in data repositories from GTEx V7, GTEx brain, Brain-eMeta eQTL and blood eQTL (Westra and CAGE). eQTL genes were considered candidate causal genes if they passed the SMR test with Bonferroni-corrected P value <2.7×10^{-7}, passed the HEIDI test with P>0.05, and if the lead SNP of the eQTL gene was in LD ($R^2>0.8$) with the queried caffeine intake SNPs. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error; eQTL, expression quantitative trait locus; SMR, summary-data-based MR; HEIDI, Heterogeneity in Dependent Instruments test; GTEx, Genotype-Tissue Expression

Table S20. SNPs and proxies for Mendelian Randomization analyses for combined caffeine intake on coronary artery disease

SNP	CHR	BP	ALLELE1	ALLELE0	A1FREQ	BETA	SE	P value	Proxy for	R^2
rs7412396	1	150666797	G	A	0.597491	-0.02279	0.002364	5.50E-22	rs768283768	0.930744
rs2987869	1	174789407	G	T	0.458638	-0.01562	0.002332	2.10E-11	1:174856749_TG_T	0.998626
rs1260326	2	27730940	T	C	0.391852	-0.02297	0.002377	4.20E-22		
rs78456557	3	123300686	C	G	0.900201	-0.02364	0.00389	1.20E-09		
rs114066728	3	142022265	T	C	0.870043	-0.02127	0.003456	7.50E-10	rs115454798	0.991139
rs2231142	4	89052323	G	T	0.886707	0.03913	0.00366	1.10E-26		
rs62332762	4	106143492	C	T	0.597585	0.01828	0.002368	1.20E-14		
rs12514566	5	7391462	G	A	0.664698	0.017242	0.002456	2.20E-12		
rs1872841	6	98576688	C	A	0.483724	-0.01316	0.002328	1.60E-08	rs754177720	0.902704
rs9486902	6	108878052	C	T	0.837869	0.018849	0.00315	2.20E-09	6:108876096_CAAT_C	0.997488
rs1490384	6	126851160	C	T	0.501467	-0.01587	0.002323	8.30E-12		
rs139797380	6	137244957	C	G	0.991601	0.106741	0.013575	3.70E-15		
rs4410790	7	17284577	T	C	0.364122	-0.08137	0.002412	1.50E-249		
rs215601	7	32333921	A	C	0.372618	0.01488	0.002404	6.00E-10		
rs34060476	7	73037956	A	G	0.865587	-0.03535	0.003404	2.90E-25	7:73042302_GCTTT_G	0.99198
rs17685	7	75616105	G	A	0.721471	-0.0408	0.002584	3.80E-56		
rs4240624	8	9184231	G	A	0.092461	0.02693	0.004012	1.90E-11		
rs12785227	10	65262685	A	G	0.685798	0.014549	0.002507	6.50E-09		
rs4418728	10	94839724	G	T	0.550788	0.014384	0.002333	7.00E-10		
rs117810762	10	135315795	G	A	0.982023	-0.06827	0.008863	1.30E-14		
rs6265	11	27679916	C	T	0.810755	0.021572	0.002964	3.40E-13		
rs1228024	11	47951353	C	A	0.340021	0.013965	0.002453	1.30E-08		
rs7105462	11	112912048	G	A	0.40559	0.014163	0.002366	2.10E-09		
rs595529	12	112000648	A	T	0.796265	-0.01662	0.002882	8.10E-09	rs376877108	0.993627
rs12591786	15	60902512	C	T	0.842038	0.020213	0.00323	3.90E-10		
rs2472297	15	75027880	C	T	0.731645	-0.10487	0.002616	2.4E-351		
rs2667773	15	77872191	A	G	0.686772	0.014947	0.002506	2.50E-09		
rs59681738	16	18788186	A	G	0.618174	0.013733	0.002417	1.30E-08	16:18776851_G_GA	0.934833
rs489693	18	57882787	C	A	0.67465	-0.01759	0.002478	1.30E-12		
rs56113850	19	41353107	T	C	0.421755	-0.02649	0.002351	1.90E-29		
rs138761767	19	47559089	T	C	0.25755	-0.01627	0.002695	1.60E-09	rs61141867	0.90578
rs1291145	20	35528475	T	C	0.313259	-0.01456	0.002506	6.30E-09	20:35568001_AAAAG_A	0.998402
rs6062679	20	62889991	T	C	0.534615	-0.02278	0.002358	4.50E-22		
rs190800998	22	24666292	T	C	0.985779	0.090577	0.009889	5.20E-20	rs199612805	1
rs9611527	22	41644428	G	A	0.664286	0.019792	0.002466	1.00E-15		

Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column. No proxy with $R^2>0.8$ was available for 3:50895869_ATAATAATAAT_A and rs531431865, which were therefore excluded from analyses.

Table S21. SNPs and proxies for Mendelian Randomization analyses for caffeine from coffee on coronary artery disease

SNP	CHR	BP	ALLELE1	ALLELE0	A1FREQ	BETA	SE	P value	Proxy for	R^2
rs4615895	1	96274668	G	A	0.259574	-0.01705	0.002627	8.60E-11		
rs7412396	1	150666797	G	A	0.597371	-0.01297	0.002337	2.90E-08	rs768283768	0.930744
rs7571957	2	646803	T	C	0.170688	-0.02056	0.003047	1.50E-11	rs7571970	0.99315
rs11127048	2	27752463	G	A	0.381191	-0.01997	0.002398	8.10E-17		
rs35198275	3	50536092	A	G	0.865693	0.020797	0.003387	8.20E-10		
rs2726513	4	106217358	G	T	0.587077	0.015301	0.002347	7.00E-11		
rs12514566	5	7391462	G	A	0.664625	0.014831	0.002428	1.00E-09		
rs6893807	5	87965021	A	G	0.843563	-0.01916	0.003159	1.30E-09		
rs1327259	6	51177811	A	G	0.614152	0.015707	0.002365	3.10E-11		
rs4410790	7	17284577	T	C	0.364412	-0.05171	0.002384	2.80E-104		
rs34060476	7	73037956	A	G	0.865581	-0.02519	0.003365	7.10E-14		
rs1057868	7	75615006	C	T	0.714413	-0.02445	0.002536	5.50E-22		
rs76881016	10	134196286	A	G	0.928496	-0.02584	0.004453	6.60E-09		
rs117810762	10	135315795	G	A	0.982047	-0.05011	0.008765	1.10E-08		
rs2298527	11	112851961	G	C	0.405568	0.014947	0.002336	1.60E-10		
rs2472297	15	75027880	C	T	0.731859	-0.06521	0.002587	3.10E-140		
rs2521501	15	91437388	A	T	0.677316	0.014916	0.002472	1.60E-09		
rs28567725	16	53826028	T	C	0.5877	-0.02172	0.002331	1.20E-20	rs201399553	0.945928
rs2350633	17	17587395	A	G	0.486877	-0.01469	0.002296	1.60E-10	rs139937261	0.997277
rs66723169	18	57808978	C	A	0.769043	-0.02249	0.002732	1.80E-16		
rs56113850	19	41353107	T	C	0.421821	-0.02071	0.002323	4.90E-19		
rs6063085	20	45840459	A	C	0.625251	-0.01571	0.00237	3.40E-11		
rs181251778	22	24901968	A	G	0.986146	0.072648	0.009834	1.50E-13		

Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column. No proxy with $R^2>0.8$ was available for rs1962201, which was therefore excluded from analyses.

Table S22. SNPs and proxies for Mendelian Randomization analyses for caffeine from tea on coronary artery disease

SNP	**CHR**	**BP**	**ALLELE1**	**ALLELE0**	**A1FREQ**	**BETA**	**SE**	**P value**	**Proxy for**	**R^2**
rs9438624	1	26758044	C	T	0.19273	-0.01535	0.002844	6.70E-08	rs77476394	0.887444
rs11204708	1	150682095	C	G	0.619872	-0.01428	0.002349	1.20E-09	rs11204711	0.998421
rs56188862	1	174189269	T	C	0.614947	0.016829	0.002297	2.40E-13		
rs78020607	3	50254624	A	G	0.887096	-0.01866	0.003527	1.20E-07	rs145755097	0.869438
rs2117137	3	89525505	A	G	0.594554	-0.01349	0.002273	2.90E-09		
rs1481012	4	89039082	A	G	0.887297	0.026005	0.003536	1.90E-13		
rs192084998	5	152077481	G	A	0.703764	0.015836	0.002458	1.20E-10		
rs2465018	6	51241140	G	A	0.769413	-0.02211	0.002666	1.10E-16		
rs139797380	6	137244957	C	G	0.991607	0.075145	0.013059	8.70E-09		
rs4410790	7	17284577	T	C	0.36537	-0.04033	0.00232	1.10E-67		
rs6462899	7	39296489	T	A	0.375354	-0.01259	0.002312	5.10E-08	rs141180025	0.943469
rs17685	7	75616105	G	A	0.721688	-0.02391	0.002488	7.20E-22		
rs62534435	9	7042938	C	G	0.796528	-0.01629	0.002776	4.40E-09		
rs11022752	11	13307622	A	G	0.730907	-0.01535	0.002525	1.20E-09		
rs10741694	11	16286183	T	C	0.372823	-0.01474	0.002312	1.80E-10		
rs73053413	12	11329548	C	T	0.836535	0.021681	0.003021	7.10E-13		
rs12591786	15	60902512	C	T	0.842256	0.019576	0.003109	3.00E-10		
rs2472297	15	75027880	C	T	0.732806	-0.05411	0.002521	3.30E-102		
rs28429148	16	53798319	G	A	0.565413	0.013189	0.002288	8.20E-09		
rs153328	16	63025865	C	G	0.782673	-0.01445	0.002718	1.10E-07	rs199602679	0.976937
rs140775622	20	62962869	C	T	0.830545	-0.02262	0.003207	1.80E-12		
rs4817505	21	34343828	T	C	0.607874	-0.01512	0.002292	4.20E-11		
rs9624470	22	24820268	G	A	0.419254	-0.02534	0.002272	6.80E-29		
rs132919	22	41809903	G	C	0.22639	-0.01708	0.002697	2.40E-10		

Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column.

Table S23. F-statistics of all instruments for the Mendelian Randomization analyses between caffeine intake and CAD or T2D

GWAS trait	SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	R^2	N	F Statistic	P STATA	P GWAS	MR
Combined caffeine intake	rs7412396	1	150666797	G	A	0.597491	-0.02279	0.002364	0.014067	362316	5169.384	1.73E-21	5.50E-22	CAD
Combined caffeine intake	rs2987869	1	174789407	G	T	0.458638	-0.01562	0.002332	0.013936	362316	5120.384	3.91E-11	2.10E-11	CAD
Combined caffeine intake	rs1260326	2	27730940	T	C	0.391852	-0.02297	0.002377	0.014068	362316	5169.591	8.45E-22	4.20E-22	CAD
Combined caffeine intake	rs78456557	3	123300686	C	G	0.900201	-0.02364	0.00389	0.013912	362316	5111.729	3.18E-09	1.20E-09	CAD
Combined caffeine intake	rs114066728	3	142022265	T	C	0.870043	-0.02127	0.003456	0.013924	362316	5115.983	4.60E-10	7.50E-10	CAD
Combined caffeine intake	rs2231142	4	89052323	G	T	0.886707	0.03913	0.00366	0.014118	362316	5188.382	4.78E-26	1.10E-26	CAD
Combined caffeine intake	rs62332762	4	106143492	C	T	0.597585	0.01828	0.002368	0.013985	362316	5138.959	6.20E-15	1.20E-14	CAD
Combined caffeine intake	rs12514566	5	7391462	G	A	0.664698	0.017242	0.002456	0.013963	362316	5130.563	2.59E-13	2.20E-12	CAD
Combined caffeine intake	rs1872841	6	98576688	C	A	0.483724	-0.01316	0.002328	0.013899	362316	5106.653	4.52E-08	1.60E-08	CAD
Combined caffeine intake	rs9486902	6	108878052	C	T	0.837869	0.018849	0.00315	0.013912	362316	5111.45	4.20E-09	2.20E-09	CAD
Combined caffeine intake	rs1490384	6	126851160	C	T	0.501467	-0.01587	0.002323	0.013936	362316	5120.626	3.76E-11	8.30E-12	CAD
Combined caffeine intake	rs139797380	6	137244957	C	G	0.991601	0.106741	0.013575	0.013989	362316	5140.392	5.51E-16	3.70E-15	CAD
Combined caffeine intake	rs4410790	7	17284577	T	C	0.364122	-0.08137	0.002412	0.016873	362316	6218.187	4.90E-248	1.50E-249	CAD
Combined caffeine intake	rs215601	7	32333921	A	C	0.372618	0.01488	0.002404	0.013919	362316	5114.316	9.96E-10	6.00E-10	CAD
Combined caffeine intake	rs34060476	7	73037956	A	G	0.865587	-0.03535	0.003404	0.014101	362316	5182.065	7.21E-24	2.90E-25	CAD
Combined caffeine intake	rs17685	7	75616105	G	A	0.721471	-0.0408	0.002584	0.014481	362316	5323.936	2.32E-54	3.80E-56	CAD
Combined caffeine intake	rs4240624	8	9184231	G	A	0.092461	0.02693	0.004012	0.01394	362316	5122.161	2.03E-11	1.90E-11	CAD
Combined caffeine intake	rs12785227	10	65262685	A	G	0.685798	0.014549	0.002507	0.0139	362316	5107.326	3.26E-08	6.50E-09	CAD
Combined caffeine intake	rs4418728	10	94839724	G	T	0.550788	0.014384	0.002333	0.013924	362316	5116.012	3.88E-10	7.00E-10	CAD
Combined caffeine intake	rs117810762	10	135315795	G	A	0.982023	-0.06827	0.008863	0.013972	362316	5134.15	4.37E-14	1.30E-14	CAD
Combined caffeine intake	rs6265	11	27679916	C	T	0.810755	0.021572	0.002964	0.013957	362316	5128.536	7.83E-13	3.40E-13	CAD
Combined caffeine intake	rs1228024	11	47951353	C	A	0.340021	0.013965	0.002453	0.013901	362316	5107.388	3.28E-08	1.30E-08	CAD
Combined caffeine intake	rs7105462	11	112912048	G	A	0.40559	0.014163	0.002366	0.013919	362316	5114.38	9.50E-10	2.10E-09	CAD
Combined caffeine intake	rs595529	12	112000648	A	T	0.796265	-0.01662	0.002882	0.013909	362316	5110.631	5.94E-09	8.10E-09	CAD
Combined caffeine intake	rs12591786	15	60902512	C	T	0.842038	0.020213	0.00323	0.013914	362316	5112.39	2.27E-09	3.90E-10	CAD
Combined caffeine intake	rs2472297	15	75027880	C	T	0.731645	-0.10487	0.002616	0.01816	362316	6701.501	0	2.4E-351	CAD
Combined caffeine intake	rs2667773	15	77872191	A	G	0.686772	0.014947	0.002506	0.013912	362316	5111.556	3.88E-09	2.50E-09	CAD
Combined caffeine intake	rs59681738	16	18788186	A	G	0.618174	0.013733	0.002417	0.013904	362316	5108.777	1.57E-08	1.30E-08	CAD
Combined caffeine intake	rs489693	18	57882787	C	A	0.67465	-0.01759	0.002478	0.013947	362316	5124.483	6.86E-12	1.30E-12	CAD
Combined caffeine intake	rs56113850	19	41353107	T	C	0.421755	-0.02649	0.002351	0.01416	362316	5203.96	3.48E-29	1.90E-29	CAD
Combined caffeine intake	rs138761767	19	47559089	T	C	0.25755	-0.01627	0.002695	0.013915	362316	5112.586	2.17E-09	1.60E-09	CAD
Combined caffeine intake	rs1291145	20	35528475	T	C	0.313259	-0.01456	0.002506	0.013905	362316	5108.846	1.53E-08	6.30E-09	CAD
Combined caffeine intake	rs6062679	20	62889991	T	C	0.534615	-0.02278	0.002358	0.014074	362316	5172.107	3.00E-22	4.50E-22	CAD
Combined caffeine intake	rs190800998	22	24666292	T	C	0.985779	0.090577	0.009889	0.014057	362316	5165.523	3.22E-20	5.20E-20	CAD
Combined caffeine intake	rs9611527	22	41644428	G	A	0.664286	0.019792	0.002466	0.013997	362316	5143.193	6.20E-16	1.00E-15	CAD
Combined caffeine intake	rs7412396	1	150666797	G	A	0.597491	-0.02279	0.002364	0.014067	362316	5169.384	1.73E-21	5.50E-22	T2D
Combined caffeine intake	rs2987869	1	174789407	G	T	0.458638	-0.01562	0.002332	0.013936	362316	5120.384	3.91E-11	2.10E-11	T2D
Combined caffeine intake	rs1260326	2	27730940	T	C	0.391852	-0.02297	0.002377	0.014068	362316	5169.591	8.45E-22	4.20E-22	T2D
Combined caffeine intake	rs78456557	3	123300686	C	G	0.900201	-0.02364	0.00389	0.013912	362316	5111.729	3.18E-09	1.20E-09	T2D
Combined caffeine intake	rs114066728	3	142022265	T	C	0.870043	-0.02127	0.003456	0.013924	362316	5115.983	4.60E-10	7.50E-10	T2D
Combined caffeine intake	rs2231142	4	89052323	G	T	0.886707	0.03913	0.00366	0.014118	362316	5188.382	4.78E-26	1.10E-26	T2D
Combined caffeine intake	rs62332762	4	106143492	C	T	0.597585	0.01828	0.002368	0.013985	362316	5138.959	6.20E-15	1.20E-14	T2D
Combined caffeine intake	rs12514566	5	7391462	G	A	0.664698	0.017242	0.002456	0.013963	362316	5130.563	2.59E-13	2.20E-12	T2D
Combined caffeine intake	rs1872841	6	98576688	C	A	0.483724	-0.01316	0.002328	0.013899	362316	5106.653	4.52E-08	1.60E-08	T2D

GWAS trait	SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	R^2	N	F Statistic	P STATA	P GWAS	MR
Combined caffeine intake	rs9486902	6	108878052	C	T	0.837869	0.018849	0.00315	0.013912	362316	5111.45	4.20E-09	2.20E-09	T2D
Combined caffeine intake	rs1490384	6	126851160	C	T	0.501467	-0.01587	0.002323	0.013936	362316	5120.626	3.76E-11	8.30E-12	T2D
Combined caffeine intake	rs139797380	6	137244957	C	G	0.991601	0.106741	0.013575	0.013989	362316	5140.392	5.51E-16	3.70E-15	T2D
Combined caffeine intake	rs4410790	7	17284577	T	C	0.364122	-0.08137	0.002412	0.016873	362316	6218.187	4.90E-248	1.50E-249	T2D
Combined caffeine intake	rs215601	7	32333921	A	C	0.372618	0.01488	0.002404	0.013919	362316	5114.316	9.96E-10	6.00E-10	T2D
Combined caffeine intake	rs34060476	7	73037956	A	G	0.865587	-0.03535	0.003404	0.014101	362316	5182.065	7.21E-24	2.90E-25	T2D
Combined caffeine intake	rs17685	7	75616105	G	A	0.721471	-0.0408	0.002584	0.014481	362316	5323.936	2.32E-54	3.80E-56	T2D
Combined caffeine intake	rs4240624	8	9184231	G	A	0.092461	0.02693	0.004012	0.01394	362316	5122.161	2.03E-11	1.90E-11	T2D
Combined caffeine intake	rs12785227	10	65262685	A	G	0.685798	0.014549	0.002507	0.0139	362316	5107.326	3.26E-08	6.50E-09	T2D
Combined caffeine intake	rs4418728	10	94839724	G	T	0.550788	0.014384	0.002333	0.013924	362316	5116.012	3.88E-10	7.00E-10	T2D
Combined caffeine intake	rs117810762	10	135315795	G	A	0.982023	-0.06827	0.008863	0.013972	362316	5134.15	4.37E-14	1.30E-14	T2D
Combined caffeine intake	rs6265	11	27679916	C	T	0.810755	0.021572	0.002964	0.013957	362316	5128.536	7.83E-13	3.40E-13	T2D
Combined caffeine intake	rs1228024	11	47951353	C	A	0.340021	0.013965	0.002453	0.013901	362316	5107.388	3.28E-08	1.30E-08	T2D
Combined caffeine intake	rs7105462	11	112912048	G	A	0.40559	0.014163	0.002366	0.013919	362316	5114.38	9.50E-10	2.10E-09	T2D
Combined caffeine intake	rs607316	12	111969448	C	T	0.795666	-0.01678	0.002878	0.013911	362316	5111.429	3.96E-09	5.50E-09	T2D
Combined caffeine intake	rs12591786	15	60902512	C	T	0.842038	0.020213	0.00323	0.013914	362316	5112.39	2.27E-09	3.90E-10	T2D
Combined caffeine intake	rs2472297	15	75027880	C	T	0.731645	-0.10487	0.002616	0.01816	362316	6701.501	0	2.4E-351	T2D
Combined caffeine intake	rs2667773	15	77872191	A	G	0.686772	0.014947	0.002506	0.013912	362316	5111.556	3.88E-09	2.50E-09	T2D
Combined caffeine intake	rs3965574	16	18789966	A	G	0.61805	0.013716	0.002416	0.013904	362316	5108.739	1.60E-08	1.40E-08	T2D
Combined caffeine intake	rs489693	18	57882787	C	A	0.67465	-0.01759	0.002478	0.013947	362316	5124.483	6.86E-12	1.30E-12	T2D
Combined caffeine intake	rs56113850	19	41353107	T	C	0.421755	-0.02649	0.002351	0.01416	362316	5203.96	3.48E-29	1.90E-29	T2D
Combined caffeine intake	rs61599759	19	47557472	A	G	0.245811	-0.01741	0.002732	0.013926	362316	5116.85	2.45E-10	1.80E-10	T2D
Combined caffeine intake	rs1291145	20	35528475	T	C	0.313259	-0.01456	0.002506	0.013905	362316	5108.846	1.53E-08	6.30E-09	T2D
Combined caffeine intake	rs6062679	20	62889991	T	C	0.534615	-0.02278	0.002358	0.014074	362316	5172.107	3.00E-22	4.50E-22	T2D
Combined caffeine intake	rs138019862	22	24821154	G	T	0.986106	0.093407	0.009925	0.014071	362316	5171.046	2.18E-21	4.90E-21	T2D
Combined caffeine intake	rs9611527	22	41644428	G	A	0.664286	0.019792	0.002466	0.013997	362316	5143.193	6.20E-16	1.00E-15	T2D
Caffeine from coffee	rs4615895	1	96274668	G	A	0.259574	-0.01705	0.002627	0.011992	373522	4533.705	1.92E-10	8.60E-11	CAD
Caffeine from coffee	rs7412396	1	150666797	G	A	0.597371	-0.01297	0.002337	0.01197	373522	4525.166	1.35E-08	2.90E-08	CAD
Caffeine from coffee	rs7571957	2	646803	T	C	0.170688	-0.02056	0.003047	0.01201	373522	4540.678	4.81E-12	1.50E-11	CAD
Caffeine from coffee	rs11127048	2	27752463	G	A	0.381191	-0.01997	0.002398	0.012081	373522	4567.802	6.74E-18	8.10E-17	CAD
Caffeine from coffee	rs35198275	3	50536092	A	G	0.865693	0.020797	0.003387	0.011987	373522	4531.599	4.48E-10	8.20E-10	CAD
Caffeine from coffee	rs2726513	4	106217358	G	T	0.587077	0.015301	0.002347	0.011987	373522	4531.666	5.18E-10	7.00E-11	CAD
Caffeine from coffee	rs12514566	5	7391462	G	A	0.664625	0.014831	0.002428	0.011991	373522	4533.052	2.31E-10	1.00E-09	CAD
Caffeine from coffee	rs6893807	5	87965021	A	G	0.843563	-0.01916	0.003159	0.011983	373522	4530.283	9.38E-10	1.30E-09	CAD
Caffeine from coffee	rs1327259	6	51177811	A	G	0.614152	0.015707	0.002365	0.011995	373522	4534.635	1.14E-10	3.10E-11	CAD
Caffeine from coffee	rs4410790	7	17284577	T	C	0.364412	-0.05171	0.002384	0.013193	373522	4993.793	6.01E-110	2.80E-104	CAD
Caffeine from coffee	rs34060476	7	73037956	A	G	0.865581	-0.02519	0.003365	0.012032	373522	4549.021	1.47E-13	7.10E-14	CAD
Caffeine from coffee	rs1057868	7	75615006	C	T	0.714413	-0.02445	0.002536	0.012128	373522	4585.517	9.77E-22	5.50E-22	CAD
Caffeine from coffee	rs76881016	10	134196286	A	G	0.928496	-0.02584	0.004453	0.011957	373522	4520.214	1.39E-07	6.60E-09	CAD
Caffeine from coffee	rs117810762	10	135315795	G	A	0.982047	-0.05011	0.008765	0.011989	373522	4532.505	3.50E-10	1.10E-08	CAD
Caffeine from coffee	rs2298527	11	112851961	G	C	0.405568	0.014947	0.002336	0.011978	373522	4528.319	2.77E-09	1.60E-10	CAD
Caffeine from coffee	rs2472297	15	75027880	C	T	0.731859	-0.06521	0.002587	0.013586	373522	5144.517	1.83E-138	3.10E-140	CAD
Caffeine from coffee	rs2521501	15	91437388	A	T	0.677316	0.014916	0.002472	0.011971	373522	4525.774	1.02E-08	1.60E-09	CAD
Caffeine from coffee	rs28567725	16	53826028	T	C	0.5877	-0.02172	0.002331	0.012113	373522	4579.932	1.89E-20	1.20E-20	CAD
Caffeine from coffee	rs2350633	17	17587395	A	G	0.486877	-0.01469	0.002296	0.012003	373522	4537.946	1.77E-11	1.60E-10	CAD

GWAS trait	SNP	CHR	hg19	EFAL	NEFAL	EF Freq	BETA	SE	R^2	N	F Statistic	P STATA	P GWAS	MR
Caffeine from coffee	rs66723169	18	57808978	C	A	0.769043	-0.02249	0.002732	0.012045	373522	4553.886	1.26E-14	1.80E-16	CAD
Caffeine from coffee	rs56113850	19	41353107	T	C	0.421821	-0.02071	0.002323	0.012076	373522	4565.758	1.95E-17	4.90E-19	CAD
Caffeine from coffee	rs6063085	20	45840459	A	C	0.625251	-0.01571	0.00237	0.011992	373522	4533.476	1.88E-10	3.40E-11	CAD
Caffeine from coffee	rs181251778	22	24901968	A	G	0.986146	0.072648	0.009834	0.012039	373522	4551.664	1.53E-14	1.50E-13	CAD
Caffeine from coffee	rs4615895	1	96274668	G	A	0.259574	-0.01705	0.002627	0.011992	373522	4533.705	1.92E-10	8.60E-11	T2D
Caffeine from coffee	rs7412396	1	150666797	G	A	0.597371	-0.01297	0.002337	0.01197	373522	4525.166	1.35E-08	2.90E-08	T2D
Caffeine from coffee	rs7561317	2	644953	A	G	0.171158	-0.02037	0.003043	0.01201	373522	4540.321	5.84E-12	2.20E-11	T2D
Caffeine from coffee	rs11127048	2	27752463	G	A	0.381191	-0.01997	0.002398	0.012081	373522	4567.802	6.74E-18	8.10E-17	T2D
Caffeine from coffee	rs35198275	3	50536092	A	G	0.865693	0.020797	0.003387	0.011987	373522	4531.599	4.48E-10	8.20E-10	T2D
Caffeine from coffee	rs2726513	4	106217358	G	T	0.587077	0.015301	0.002347	0.011987	373522	4531.666	5.18E-10	7.00E-11	T2D
Caffeine from coffee	rs12514566	5	7391462	G	A	0.664625	0.014831	0.002428	0.011991	373522	4533.052	2.31E-10	1.00E-09	T2D
Caffeine from coffee	rs6893807	5	87965021	A	G	0.843563	-0.01916	0.003159	0.011983	373522	4530.283	9.38E-10	1.30E-09	T2D
Caffeine from coffee	rs1327259	6	51177811	A	G	0.614152	0.015707	0.002365	0.011995	373522	4534.635	1.14E-10	3.10E-11	T2D
Caffeine from coffee	rs4410790	7	17284577	T	C	0.364412	-0.05171	0.002384	0.013193	373522	4993.793	6.01E-110	2.80E-104	T2D
Caffeine from coffee	rs34060476	7	73037956	A	G	0.865581	-0.02519	0.003365	0.012032	373522	4549.021	1.47E-13	7.10E-14	T2D
Caffeine from coffee	rs1057868	7	75615006	C	T	0.714413	-0.02445	0.002536	0.012128	373522	4585.517	9.77E-22	5.50E-22	T2D
Caffeine from coffee	rs76881016	10	134196286	A	G	0.928496	-0.02584	0.004453	0.011957	373522	4520.214	1.39E-07	6.60E-09	T2D
Caffeine from coffee	rs117810762	10	135315795	G	A	0.982047	-0.05011	0.008765	0.011989	373522	4532.505	3.50E-10	1.10E-08	T2D
Caffeine from coffee	rs2298527	11	112851961	G	C	0.405568	0.014947	0.002336	0.011978	373522	4528.319	2.77E-09	1.60E-10	T2D
Caffeine from coffee	rs2472297	15	75027880	C	T	0.731859	-0.06521	0.002587	0.013586	373522	5144.517	1.83E-138	3.10E-140	T2D
Caffeine from coffee	rs2521501	15	91437388	A	T	0.677316	0.014916	0.002472	0.011971	373522	4525.774	1.02E-08	1.60E-09	T2D
Caffeine from coffee	rs28567725	16	53826028	T	C	0.5877	-0.02172	0.002331	0.012113	373522	4579.932	1.89E-20	1.20E-20	T2D
Caffeine from coffee	rs2350633	17	17587395	A	G	0.486877	-0.01469	0.002296	0.012003	373522	4537.946	1.77E-11	1.60E-10	T2D
Caffeine from coffee	rs66723169	18	57808978	C	A	0.769043	-0.02249	0.002732	0.012045	373522	4553.886	1.26E-14	1.80E-16	T2D
Caffeine from coffee	rs56113850	19	41353107	T	C	0.421821	-0.02071	0.002323	0.012076	373522	4565.758	1.95E-17	4.90E-19	T2D
Caffeine from coffee	rs6063085	20	45840459	A	C	0.625251	-0.01571	0.00237	0.011992	373522	4533.476	1.88E-10	3.40E-11	T2D
Caffeine from coffee	rs181251778	22	24901968	A	G	0.986146	0.072648	0.009834	0.012039	373522	4551.664	1.53E-14	1.50E-13	T2D
Caffeine from tea	rs9438624	1	26758044	C	T	0.19273	-0.01535	0.002844	0.011885	373522	4492.773	4.63E-01	6.70E-08	CAD
Caffeine from tea	rs11204708	1	150682095	C	G	0.619872	-0.01428	0.002349	0.011959	373522	4521.126	1.04E-07	1.20E-09	CAD
Caffeine from tea	rs56188862	1	174189269	T	C	0.614947	0.016829	0.002297	0.011884	373522	4492.339	7.38E-01	2.40E-13	CAD
Caffeine from tea	rs78020607	3	50254624	A	G	0.887096	-0.01866	0.003527	0.011906	373522	4500.895	3.64E-03	1.20E-07	CAD
Caffeine from tea	rs2117137	3	89525505	A	G	0.594554	-0.01349	0.002273	0.011896	373522	4497.011	2.98E-02	2.90E-09	CAD
Caffeine from tea	rs1481012	4	89039082	A	G	0.887297	0.026005	0.003536	0.011945	373522	4515.799	1.13E-06	1.90E-13	CAD
Caffeine from tea	rs192084998	5	152077481	G	A	0.703764	0.015836	0.002458	0.011885	373522	4492.581	5.55E-01	1.20E-10	CAD
Caffeine from tea	rs2465018	6	51241140	G	A	0.769413	-0.02211	0.002666	0.011975	373522	4527.092	4.55E-09	1.10E-16	CAD
Caffeine from tea	rs139797380	6	137244957	C	G	0.991607	0.075145	0.013059	0.011926	373522	4508.398	4.72E-05	8.70E-09	CAD
Caffeine from tea	rs4410790	7	17284577	T	C	0.36537	-0.04033	0.00232	0.013193	373522	4993.793	6.01E-110	1.10E-67	CAD
Caffeine from tea	rs6462899	7	39296489	T	A	0.375354	-0.01259	0.002312	0.011893	373522	4495.738	6.31E-02	5.10E-08	CAD
Caffeine from tea	rs17685	7	75616105	G	A	0.721688	-0.02391	0.002488	0.012123	373522	4583.926	2.17E-21	7.20E-22	CAD
Caffeine from tea	rs62534435	9	7042938	C	G	0.796528	-0.01629	0.002776	0.011885	373522	4492.788	4.57E-01	4.40E-09	CAD
Caffeine from tea	rs11022752	11	13307622	A	G	0.730907	-0.01535	0.002525	0.011888	373522	4493.73	2.24E-01	1.20E-09	CAD
Caffeine from tea	rs10741694	11	16286183	T	C	0.372823	-0.01474	0.002312	0.011885	373522	4492.73	4.82E-01	1.80E-10	CAD
Caffeine from tea	rs73053413	12	11329548	C	T	0.836535	0.021681	0.003021	0.011946	373522	4516.148	1.15E-06	7.10E-13	CAD
Caffeine from tea	rs12591786	15	60902512	C	T	0.842256	0.019576	0.003109	0.011894	373522	4495.968	5.41E-02	3.00E-10	CAD
Caffeine from tea	rs2472297	15	75027880	C	T	0.732806	-0.05411	0.002521	0.013586	373522	5144.517	1.83E-138	3.30E-102	CAD

GWAS trait	**SNP**	**CHR**	**hg19**	**EFAL**	**NEFAL**	**EF Freq**	**BETA**	**SE**	**R^2**	**N**	**F Statistic**	**P STATA**	**P GWAS**	**MR**
Caffeine from tea	rs28429148	16	53798319	G	A	0.565413	0.013189	0.002288	0.012094	373522	4572.593	6.52E-19	8.20E-09	CAD
Caffeine from tea	rs153328	16	63025865	C	G	0.782673	-0.01445	0.002718	0.011884	373522	4492.32	7.60E-01	1.10E-07	CAD
Caffeine from tea	rs140775622	20	62962869	C	T	0.830545	-0.02262	0.003207	0.011916	373522	4504.501	5.30E-04	1.80E-12	CAD
Caffeine from tea	rs4817505	21	34343828	T	C	0.607874	-0.01512	0.002292	0.01192	373522	4506.003	2.31E-04	4.20E-11	CAD
Caffeine from tea	rs9624470	22	24820268	G	A	0.419254	-0.02534	0.002272	0.011889	373522	4494.15	1.69E-01	6.80E-29	CAD
Caffeine from tea	rs132919	22	41809903	G	C	0.22639	-0.01708	0.002697	0.011893	373522	4495.762	6.25E-02	2.40E-10	CAD
Caffeine from tea	rs9438624	1	26758044	C	T	0.19273	-0.01535	0.002844	0.011885	373522	4492.773	4.63E-01	6.70E-08	T2D
Caffeine from tea	rs11204710	1	150682110	A	G	0.619798	-0.01427	0.002348	0.01196	373522	4521.319	9.45E-08	1.20E-09	T2D
Caffeine from tea	rs56188862	1	174189269	T	C	0.614947	0.016829	0.002297	0.011884	373522	4492.339	7.38E-01	2.40E-13	T2D
Caffeine from tea	rs78020607	3	50254624	A	G	0.887096	-0.01866	0.003527	0.011906	373522	4500.895	3.64E-03	1.20E-07	T2D
Caffeine from tea	rs2117137	3	89525505	A	G	0.594554	-0.01349	0.002273	0.011896	373522	4497.011	2.98E-02	2.90E-09	T2D
Caffeine from tea	rs1481012	4	89039082	A	G	0.887297	0.026005	0.003536	0.011945	373522	4515.799	1.13E-06	1.90E-13	T2D
Caffeine from tea	rs192084998	5	152077481	G	A	0.703764	0.015836	0.002458	0.011885	373522	4492.581	5.55E-01	1.20E-10	T2D
Caffeine from tea	rs2465018	6	51241140	G	A	0.769413	-0.02211	0.002666	0.011975	373522	4527.092	4.55E-09	1.10E-16	T2D
Caffeine from tea	rs139797380	6	137244957	C	G	0.991607	0.075145	0.013059	0.011926	373522	4508.398	4.72E-05	8.70E-09	T2D
Caffeine from tea	rs4410790	7	17284577	T	C	0.36537	-0.04033	0.00232	0.013193	373522	4993.793	6.01E-110	1.10E-67	T2D
Caffeine from tea	rs6462899	7	39296489	T	A	0.375354	-0.01259	0.002312	0.011893	373522	4495.738	6.31E-02	5.10E-08	T2D
Caffeine from tea	rs17685	7	75616105	G	A	0.721688	-0.02391	0.002488	0.012123	373522	4583.926	2.17E-21	7.20E-22	T2D
Caffeine from tea	rs62534435	9	7042938	C	G	0.796528	-0.01629	0.002776	0.011885	373522	4492.788	4.57E-01	4.40E-09	T2D
Caffeine from tea	rs11022752	11	13307622	A	G	0.730907	-0.01535	0.002525	0.011888	373522	4493.73	2.24E-01	1.20E-09	T2D
Caffeine from tea	rs10741694	11	16286183	T	C	0.372823	-0.01474	0.002312	0.011885	373522	4492.73	4.82E-01	1.80E-10	T2D
Caffeine from tea	rs73053413	12	11329548	C	T	0.836535	0.021681	0.003021	0.011946	373522	4516.148	1.15E-06	7.10E-13	T2D
Caffeine from tea	rs12591786	15	60902512	C	T	0.842256	0.019576	0.003109	0.011894	373522	4495.968	5.41E-02	3.00E-10	T2D
Caffeine from tea	rs2472297	15	75027880	C	T	0.732806	-0.05411	0.002521	0.013586	373522	5144.517	1.83E-138	3.30E-102	T2D
Caffeine from tea	rs28429148	16	53798319	G	A	0.565413	0.013189	0.002288	0.012094	373522	4572.593	6.52E-19	8.20E-09	T2D
Caffeine from tea	rs153328	16	63025865	C	G	0.782673	-0.01445	0.002718	0.011884	373522	4492.32	7.60E-01	1.10E-07	T2D
Caffeine from tea	rs140775622	20	62962869	C	T	0.830545	-0.02262	0.003207	0.011916	373522	4504.501	5.30E-04	1.80E-12	T2D
Caffeine from tea	rs4817505	21	34343828	T	C	0.607874	-0.01512	0.002292	0.01192	373522	4506.003	2.31E-04	4.20E-11	T2D
Caffeine from tea	rs9624470	22	24820268	G	A	0.419254	-0.02534	0.002272	0.011889	373522	4494.15	1.69E-01	6.80E-29	T2D
Caffeine from tea	rs132919	22	41809903	G	C	0.22639	-0.01708	0.002697	0.011893	373522	4495.762	6.25E-02	2.40E-10	T2D

P values from the linear regression in STATA may differ from the GWAS P value since BOLT-LMM assumes a slightly different model. An F-statistic >10 indicates low risk of weak instrument bias in Mendelian randomization analyses. F-statistics were calculated as $F=R^2*(n-2)/(1-R^2)$ where R^2 is the proportion of variability in caffeine intake explained by the SNP. The outcome of the MR for which the SNPs are included is indicated by CAD or MR. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; EFAL, effect allele; NEFAL, non-effect allele; EF Freq, effect allele frequency; SE, standard error; CAD, coronary artery disease; T2D, type 2 diabetes; MR, Mendelian randomization.

Table S24. Heterogeneity (I^2, Cochran's Q, Rücker's Q', and Q-Q'), pleiotropy (MR-Egger intercept) and weak instrument statistics (I^2_{GX}) in Mendelian randomization analyses between caffeine intake and CAD or T2D

Exposure	**Outcome**	**I^2 index**	**I^2 95%CI min**	**I^2 95%CI max**	**Cochran's Q**	**df Cochran's Q**	**P value Cochran's Q**	**Rücker's Q'**	**df Rücker's Q'**	**P value Rücker's Q'**	**Q-Q'**	**df Q-Q'**	**P value Q-Q'**	**MR-Egger intercept**	**SE MR-Egger intercept**	**P value MR-Egger intercept**	**I^2_{GX}**
Combined caffeine intake	CAD	0.68722	0.55735	0.77899	110	34	9.70E-10	110	33	5.40E-10	8.70E-02	1	0.77	-0.00091	0.00559	0.87	0.99
Caffeine from coffee	CAD	0.80856	0.71856	0.86978	110	21	5.40E-14	110	20	8.90E-14	3.3	1	0.069	-0.00900	0.01140	0.44	0.99
Caffeine from tea	CAD	0.60638	0.38546	0.74788	58	23	6.40E-05	53	22	2.30E-04	5.5	1	0.019	-0.01290	0.00854	0.15	0.98
Combined caffeine intake	T2D	0.71038	0.59298	0.79391	120	34	4.20E-11	110	33	1.50E-10	5.3	1	0.021	0.00911	0.00726	0.22	0.99
Caffeine from coffee	T2D	0.84599	0.78048	0.89195	140	22	1.10E-19	130	21	1.30E-18	8.1	1	0.004	0.01744	0.01550	0.27	0.99
Caffeine from tea	T2D	0.79760	0.70575	0.86078	110	23	5.70E-14	100	22	8.70E-13	8.7	1	0.003	-0.02059	0.01527	0.19	0.98

Abbreviations: CAD, coronary artery disease; T2D, type 2 diabetes; MR, Mendelian randomization; df, degrees of freedom

Table S25. Excluded variants in MR-PRESSO analyses on CAD and T2D

Combined caffeine intake SNPs				**Caffeine from coffee SNPs**				**Caffeine from tea SNPs**			
Outlier SNP	**RSS$_{obs}$**	**P value**	**Outcome**	**Outlier SNP**	**RS$_{Sobs}$**	**P value**	**Outcome**	**Outlier SNP**	**RSS$_{obs}$**	**P value**	**Outcome**
rs1490384	0.001195111	0.05	CAD	rs2350633	0.001956	<0.05	CAD	rs11022752	0.002	<0.05	CAD
rs4418728	0.001363837	<0.05	CAD	rs2521501	0.00415	<0.05	CAD	rs4410790	0.0014	<0.05	CAD
rs489693	0.002065843	<0.05	CAD	rs66723169	0.003039	<0.05	CAD	rs28429148	0.0151	<0.05	T2D
rs595529	0.002935062	<0.05	CAD	rs7412396	0.000736	0.05	CAD				
rs1490384	0.003607685	<0.05	T2D	rs2350633	0.00191	<0.05	T2D				
rs2667773	0.001851194	<0.05	T2D	rs28567725	0.012255	<0.05	T2D				
rs489693	0.002973746	<0.05	T2D	rs66723169	0.002487	<0.05	T2D				

Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) outlier information for the excluded variants per outcome. Abbreviations: CAD, coronary artery disease; T2D, type 2 diabetes; SNP, single nucleotide polymorphism, RSS$_{obs}$, observed residual sum of squares

Table S26. Mendelian randomization analyses results after MR-Steiger filtering

MR Method	n SNPs	Beta	SE	P value	Outcome	Filtered SNPs	Exposure
Inverse variance weighted (fixed effects)	32	0.09	0.06	0.166	CAD	rs4418728 rs489693 rs595529	Combined caffeine
MR Egger	32	0.18	0.13	0.182			
Weighted median	32	0.05	0.11	0.653			
Inverse variance weighted (multiplicative random effects)	32	0.09	0.08	0.274			
Weighted mode	32	0.14	0.09	0.121			
Inverse variance weighted (fixed effects)	19	0.27	0.10	0.01	CAD	rs2350633 rs2521501 rs66723169	Caffeine from coffee
MR Egger	19	0.27	0.28	0.35			
Weighted median	19	0.29	0.15	0.05			
Inverse variance weighted (multiplicative random effects)	19	0.27	0.14	0.05			
Weighted mode	19	0.06	0.18	0.76			
Inverse variance weighted (fixed effects)	23	0.01	0.11	0.91	CAD	rs11022752	Caffeine from tea
MR Egger	23	0.37	0.34	0.30			
Weighted median	23	-0.05	0.19	0.78			
Inverse variance weighted (multiplicative random effects)	23	0.01	0.15	0.93			
Weighted mode	23	0.03	0.25	0.92			
Inverse variance weighted (fixed effects)	34	0.25	0.08	2.01E-03	T2D	rs1490384	Combined caffeine
MR Egger	34	0.12	0.21	0.59			
Weighted median	34	0.14	0.11	0.21			
Inverse variance weighted (multiplicative random effects)	34	0.25	0.13	0.07			
Weighted mode	34	0.16	0.11	0.13			
Inverse variance weighted (fixed effects)	22	0.43	0.12	4.51E-04	T2D	rs28567725	Caffeine from coffee
MR Egger	22	0.09	0.41	0.83			

MR Method	n SNPs	Beta	SE	P value	Outcome	Filtered SNPs	Exposure
Weighted median	22	0.24	0.17	0.17			
Inverse variance weighted (multiplicative random effects)	22	0.43	0.21	0.04			
Weighted mode	22	0.24	0.16	0.15			
Inverse variance weighted (fixed effects)	23	0.22	0.14	0.12	T2D	rs28429148	Caffeine from tea
MR Egger	23	0.37	0.35	0.30			
Weighted median	23	0.27	0.20	0.18			
Inverse variance weighted (multiplicative random effects)	23	0.22	0.15	0.15			
Weighted mode	23	0.23	0.21	0.29			

Mendelian randomization (MR) analysis method results for the association between genetically determined higher caffeine intake on coronary artery disease or type 2 diabetes after filtering of SNPs more strongly associated (R2) with the outcome than the exposure. Beta's are per standard deviation increase in genetically determined caffeine intake.

Table S27. SNPs and proxies for Mendelian Randomization analyses for combined caffeine intake on type 2 diabetes

SNP	**CHR**	**BP**	**ALLELE1**	**ALLELE0**	**A1FREQ**	**BETA**	**SE**	**P value**	**Proxy for**	**R^2**
rs7412396	1	150666797	G	A	0.597491	-0.02279	0.002364	5.50E-22	rs768283768	0.930744
rs2987869	1	174789407	G	T	0.458638	-0.01562	0.002332	2.10E-11	1:174856749_TG_T	0.998626
rs1260326	2	27730940	T	C	0.391852	-0.02297	0.002377	4.20E-22		
rs78456557	3	123300686	C	G	0.900201	-0.02364	0.00389	1.20E-09		
rs114066728	3	142022265	T	C	0.870043	-0.02127	0.003456	7.50E-10	rs115454798	0.991139
rs2231142	4	89052323	G	T	0.886707	0.03913	0.00366	1.10E-26		
rs62332762	4	106143492	C	T	0.597585	0.01828	0.002368	1.20E-14		
rs12514566	5	7391462	G	A	0.664698	0.017242	0.002456	2.20E-12		
rs1872841	6	98576688	C	A	0.483724	-0.01316	0.002328	1.60E-08	rs754177720	0.902704
rs9486902	6	108878052	C	T	0.837869	0.018849	0.00315	2.20E-09	6:108876096_CAAT_C	0.997488
rs1490384	6	126851160	C	T	0.501467	-0.01587	0.002323	8.30E-12		
rs139797380	6	137244957	C	G	0.991601	0.106741	0.013575	3.70E-15		
rs4410790	7	17284577	T	C	0.364122	-0.08137	0.002412	1.50E-249		
rs215601	7	32333921	A	C	0.372618	0.01488	0.002404	6.00E-10		
rs34060476	7	73037956	A	G	0.865587	-0.03535	0.003404	2.90E-25	7:73042302_GCTTT_G	0.99198
rs17685	7	75616105	G	A	0.721471	-0.0408	0.002584	3.80E-56		
rs4240624	8	9184231	G	A	0.092461	0.02693	0.004012	1.90E-11		
rs12785227	10	65262685	A	G	0.685798	0.014549	0.002507	6.50E-09		
rs4418728	10	94839724	G	T	0.550788	0.014384	0.002333	7.00E-10		
rs117810762	10	135315795	G	A	0.982023	-0.06827	0.008863	1.30E-14		
rs6265	11	27679916	C	T	0.810755	0.021572	0.002964	3.40E-13		
rs1228024	11	47951353	C	A	0.340021	0.013965	0.002453	1.30E-08		
rs7105462	11	112912048	G	A	0.40559	0.014163	0.002366	2.10E-09		
rs607316	12	111969448	C	T	0.795666	-0.01678	0.002878	5.50E-09	rs376877108	0.993627
rs12591786	15	60902512	C	T	0.842038	0.020213	0.00323	3.90E-10		
rs2472297	15	75027880	C	T	0.731645	-0.10487	0.002616	2.4E-351		
rs2667773	15	77872191	A	G	0.686772	0.014947	0.002506	2.50E-09		

SNP	**CHR**	**BP**	**ALLELE1**	**ALLELE0**	**A1FREQ**	**BETA**	**SE**	**P value**	**Proxy for**	**R^2**
rs3965574	16	18789966	A	G	0.61805	0.013716	0.002416	1.40E-08	16:18776851_G_GA	0.934833
rs489693	18	57882787	C	A	0.67465	-0.01759	0.002478	1.30E-12		
rs56113850	19	41353107	T	C	0.421755	-0.02649	0.002351	1.90E-29		
rs61599759	19	47557472	A	G	0.245811	-0.01741	0.002732	1.80E-10	rs61141867	0.984394
rs1291145	20	35528475	T	C	0.313259	-0.01456	0.002506	6.30E-09	20:35568001_AAAAG_A	0.998402
rs6062679	20	62889991	T	C	0.534615	-0.02278	0.002358	4.50E-22		
rs138019862	22	24821154	G	T	0.986106	0.093407	0.009925	4.90E-21	rs199612805	1
rs9611527	22	41644428	G	A	0.664286	0.019792	0.002466	1.00E-15		

Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column. No proxy with $R^2>0.8$ was available for 3:50895869_ATAATAATAAT_A and rs531431865, which were therefore excluded from analyses.

Table S28. SNPs and proxies for Mendelian Randomization analyses for caffeine from coffee on type 2 diabetes

SNP	CHR	BP	ALLELE1	ALLELE0	A1FREQ	BETA	SE	P value	Proxy for	R^2
rs4615895	1	96274668	G	A	0.259574	-0.01705	0.002627	8.60E-11		
rs7412396	1	150666797	G	A	0.597371	-0.01297	0.002337	2.90E-08	rs768283768	0.930744
rs7561317	2	644953	A	G	0.171158	-0.02037	0.003043	2.20E-11	rs7571970	0.99315
rs11127048	2	27752463	G	A	0.381191	-0.01997	0.002398	8.10E-17		
rs35198275	3	50536092	A	G	0.865693	0.020797	0.003387	8.20E-10		
rs2726513	4	106217358	G	T	0.587077	0.015301	0.002347	7.00E-11		
rs12514566	5	7391462	G	A	0.664625	0.014831	0.002428	1.00E-09		
rs6893807	5	87965021	A	G	0.843563	-0.01916	0.003159	1.30E-09		
rs1327259	6	51177811	A	G	0.614152	0.015707	0.002365	3.10E-11		
rs4410790	7	17284577	T	C	0.364412	-0.05171	0.002384	2.80E-104		
rs34060476	7	73037956	A	G	0.865581	-0.02519	0.003365	7.10E-14		
rs1057868	7	75615006	C	T	0.714413	-0.02445	0.002536	5.50E-22		
rs76881016	10	134196286	A	G	0.928496	-0.02584	0.004453	6.60E-09		
rs117810762	10	135315795	G	A	0.982047	-0.05011	0.008765	1.10E-08		
rs2298527	11	112851961	G	C	0.405568	0.014947	0.002336	1.60E-10		
rs2472297	15	75027880	C	T	0.731859	-0.06521	0.002587	3.10E-140		
rs2521501	15	91437388	A	T	0.677316	0.014916	0.002472	1.60E-09		
rs28567725	16	53826028	T	C	0.5877	-0.02172	0.002331	1.20E-20	rs201399553	0.945928
rs2350633	17	17587395	A	G	0.486877	-0.01469	0.002296	1.60E-10	rs139937261	0.997277
rs66723169	18	57808978	C	A	0.769043	-0.02249	0.002732	1.80E-16		
rs56113850	19	41353107	T	C	0.421821	-0.02071	0.002323	4.90E-19		
rs6063085	20	45840459	A	C	0.625251	-0.01571	0.00237	3.40E-11		
rs181251778	22	24901968	A	G	0.986146	0.072648	0.009834	1.50E-13		

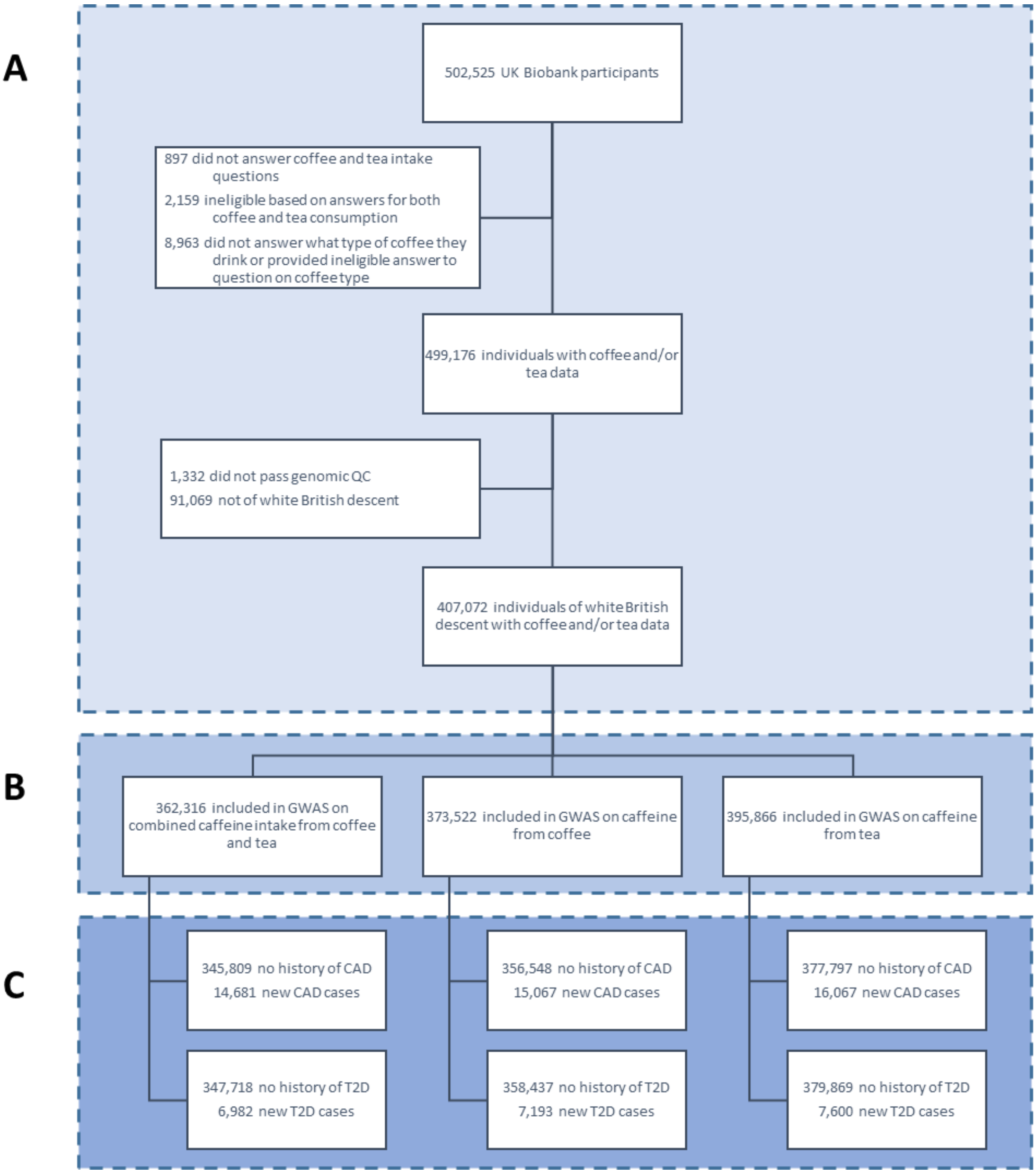
Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column. No proxy with $R^2>0.8$ was available for rs531431865, which was therefore excluded from analyses.

Table S29. SNPs and proxies for Mendelian Randomization analyses for caffeine from tea on type 2 diabetes

SNP	CHR	BP	ALLELE1	ALLELE0	A1FREQ	BETA	SE	P value	Proxy for	R^2
rs9438624	1	26758044	C	T	0.19273	-0.01535	0.002844	6.70E-08	rs77476394	0.887444
rs11204710	1	150682110	A	G	0.619798	-0.01427	0.002348	1.20E-09	rs11204711	0.998421
rs56188862	1	174189269	T	C	0.614947	0.016829	0.002297	2.40E-13		
rs78020607	3	50254624	A	G	0.887096	-0.01866	0.003527	1.20E-07	rs145755097	0.869438
rs2117137	3	89525505	A	G	0.594554	-0.01349	0.002273	2.90E-09		
rs1481012	4	89039082	A	G	0.887297	0.026005	0.003536	1.90E-13		
rs192084998	5	152077481	G	A	0.703764	0.015836	0.002458	1.20E-10		
rs2465018	6	51241140	G	A	0.769413	-0.02211	0.002666	1.10E-16		
rs139797380	6	137244957	C	G	0.991607	0.075145	0.013059	8.70E-09		
rs4410790	7	17284577	T	C	0.36537	-0.04033	0.00232	1.10E-67		
rs6462899	7	39296489	T	A	0.375354	-0.01259	0.002312	5.10E-08	rs141180025	0.943469
rs17685	7	75616105	G	A	0.721688	-0.02391	0.002488	7.20E-22		
rs62534435	9	7042938	C	G	0.796528	-0.01629	0.002776	4.40E-09		
rs11022752	11	13307622	A	G	0.730907	-0.01535	0.002525	1.20E-09		
rs10741694	11	16286183	T	C	0.372823	-0.01474	0.002312	1.80E-10		
rs73053413	12	11329548	C	T	0.836535	0.021681	0.003021	7.10E-13		
rs12591786	15	60902512	C	T	0.842256	0.019576	0.003109	3.00E-10		
rs2472297	15	75027880	C	T	0.732806	-0.05411	0.002521	3.30E-102		
rs28429148	16	53798319	G	A	0.565413	0.013189	0.002288	8.20E-09		
rs153328	16	63025865	C	G	0.782673	-0.01445	0.002718	1.10E-07	rs199602679	0.976937
rs140775622	20	62962869	C	T	0.830545	-0.02262	0.003207	1.80E-12		
rs4817505	21	34343828	T	C	0.607874	-0.01512	0.002292	4.20E-11		
rs9624470	22	24820268	G	A	0.419254	-0.02534	0.002272	6.80E-29		
rs132919	22	41809903	G	C	0.22639	-0.01708	0.002697	2.40E-10		

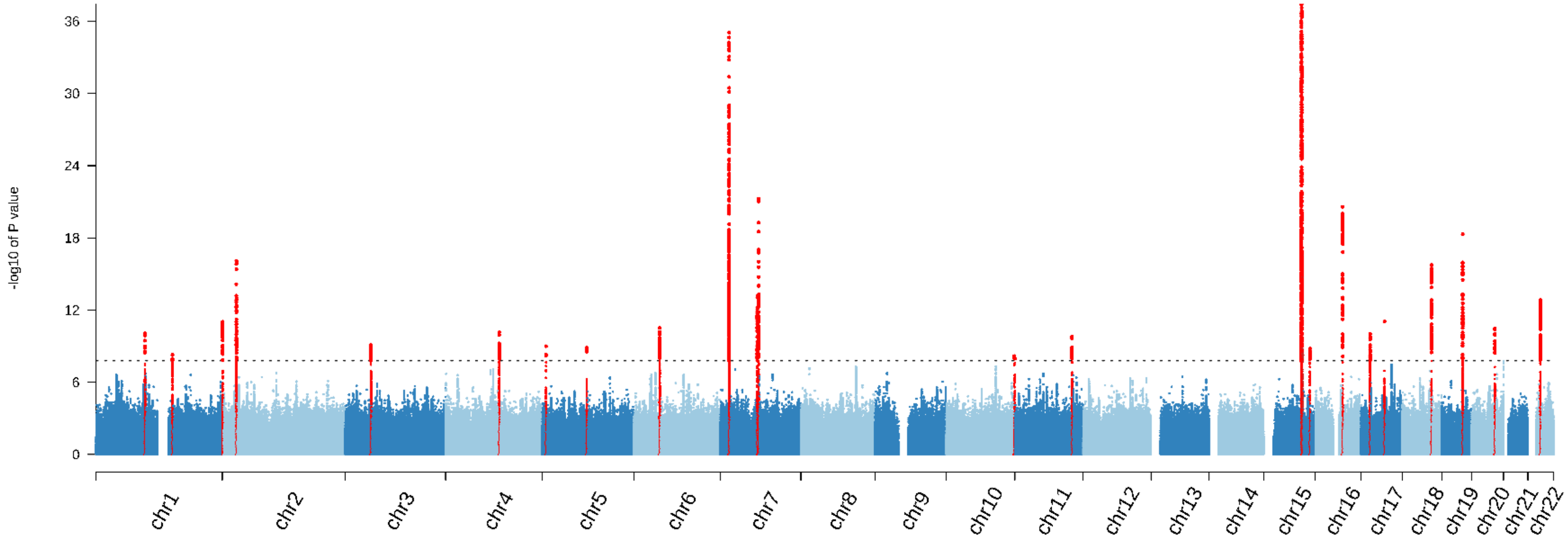
Sentinel single nucleotide polymorphisms (SNPs) and proxies used are provided for the Mendelian randomization analyses. In case a proxy was used, the original sentinel SNP is provided in the "Proxy for" column and the R^2 between them in the "R^2" column

Figure S1. UK Biobank study population selection



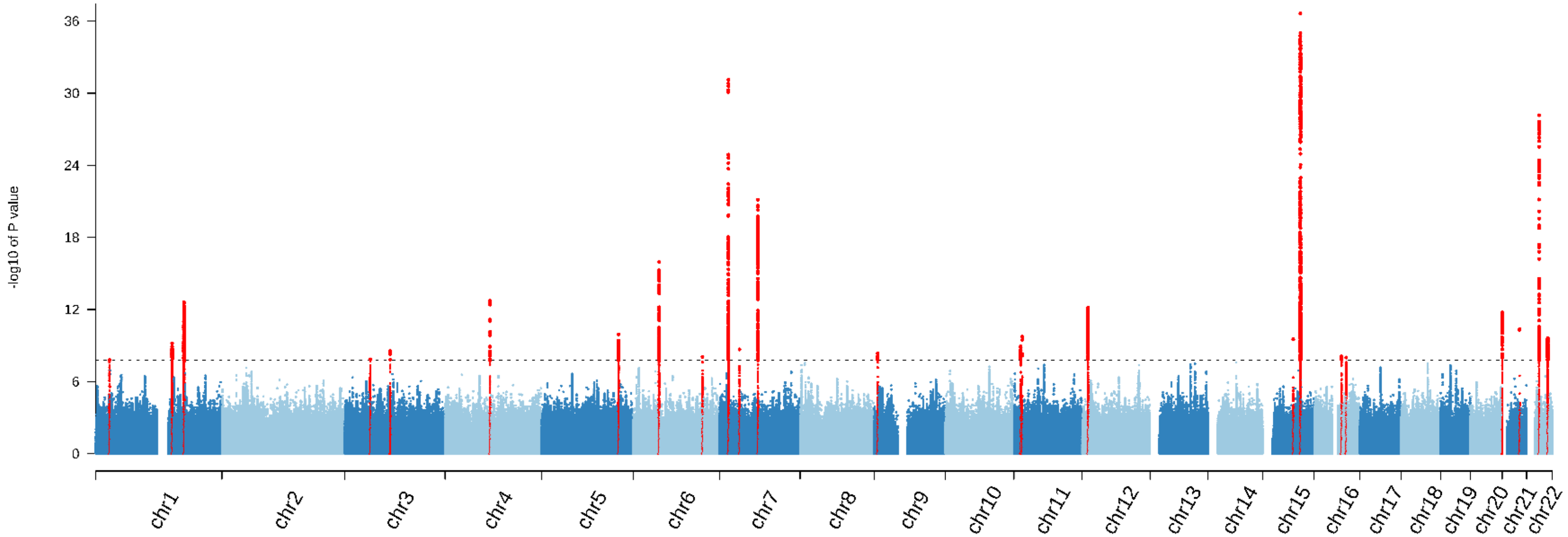
Study sample selection flowchart. Section A depicts the selection procedure leading up to the total number of participants included in one or more genome wide association study (B) and the number of new-onset cases and controls within each genetic cohort that were included in observational analyses. Abbreviations: CAD, coronary artery disease; GWAS, genome wide association study; T2D, type 2 diabetes; QC, quality control

Figure S2. Manhattan plot for caffeine from coffee



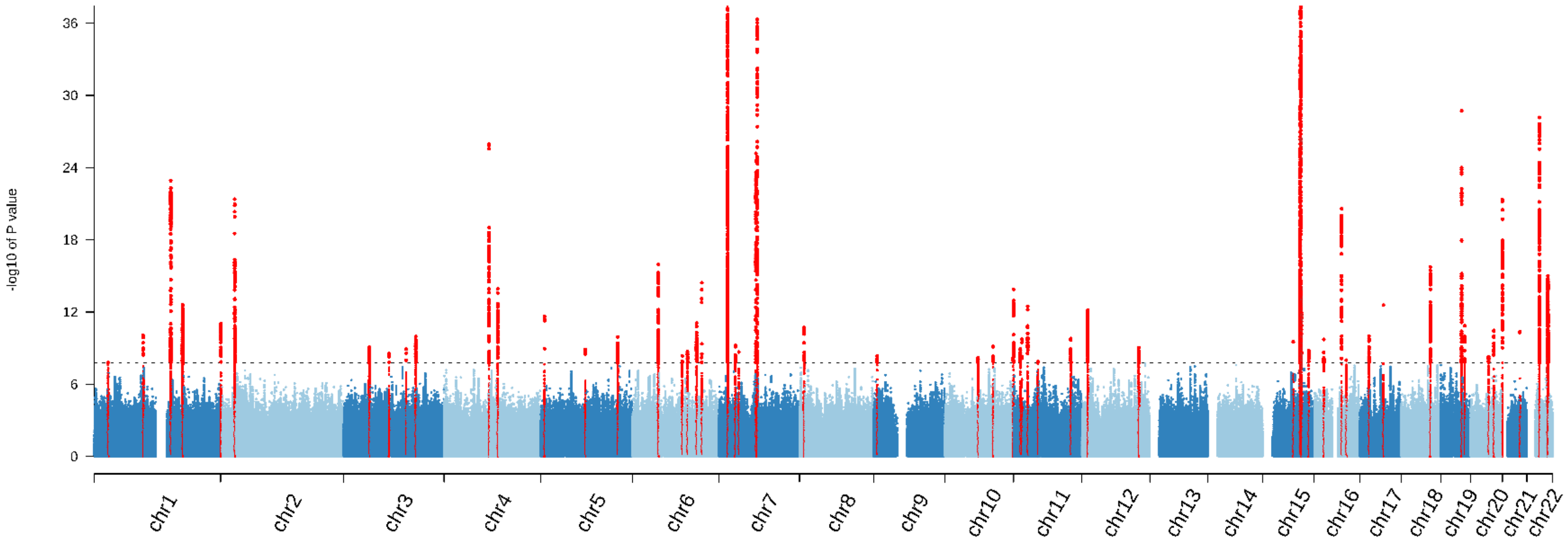
Manhattan plot showing the results for the genome-wide associations with caffeine from coffee in the UK Biobank with the –log10 *P* value on the vertical axis. The sentinel single nucleotide polymorphisms that reached genome-wide significance ($P<1.67x10^{-8}$) are colored red.

Figure S3. Manhattan plot for caffeine from tea



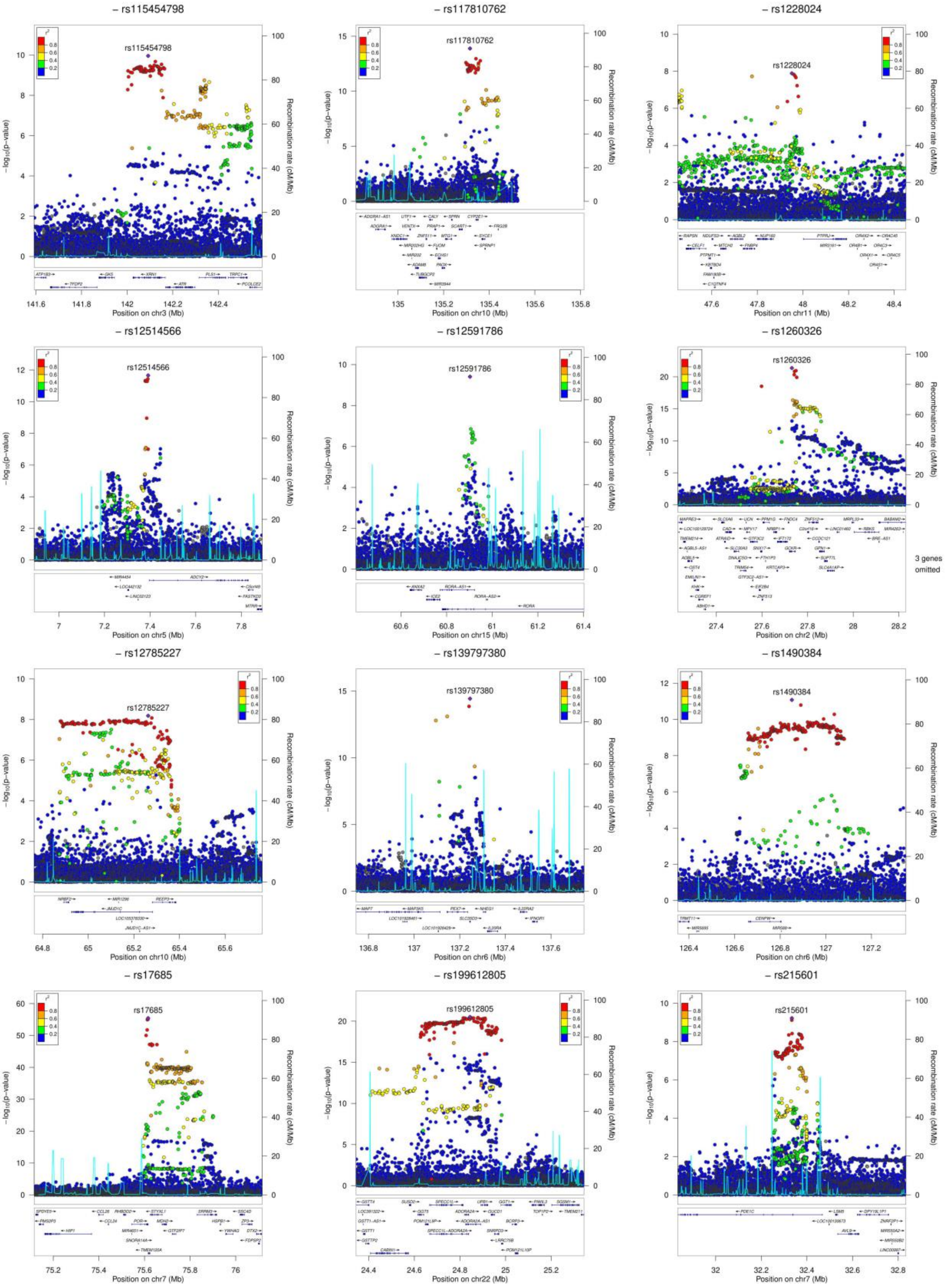
Manhattan plot showing the results for the genome-wide associations with caffeine from tea in the UK Biobank with the –log10 *P* value on the vertical axis. The sentinel single nucleotide polymorphisms that reached genome-wide significance ($P<1.67x10^{-8}$) are colored red.

Figure S4. Overlay Manhattan plot based on lowest P value for all caffeine intake traits

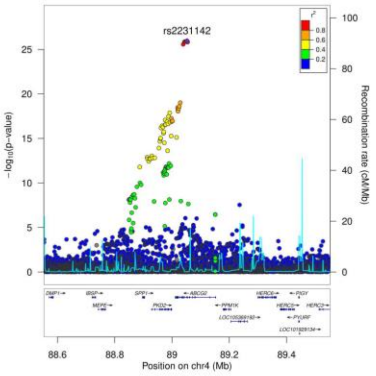


Overlay Manhattan plot showing the results for the genome-wide associations with caffeine intake over all traits based on the lowest P value within the UK Biobank with the –log10 *P* value on the vertical axis. The sentinel single nucleotide polymorphisms that reached genome-wide significance ($P<1.67x10^{-8}$) are colored red.

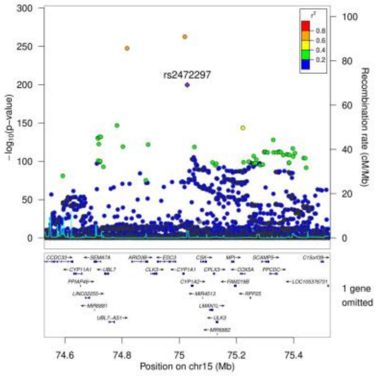
Figure S5. Locus plots for combined caffeine intake



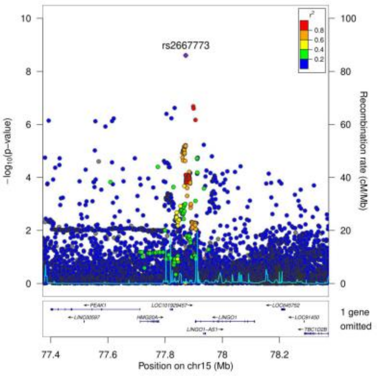
– rs2231142



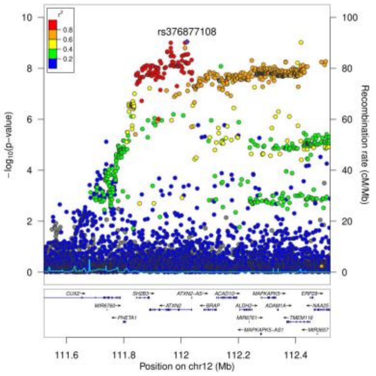
– rs2472297



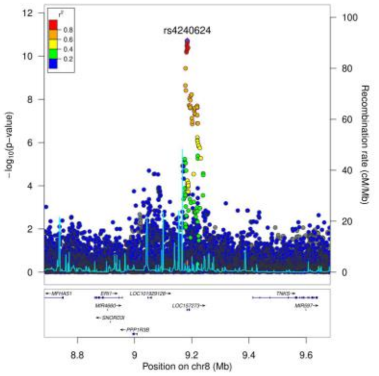
– rs2667773



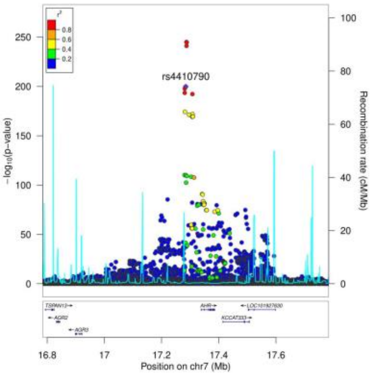
– rs376877108



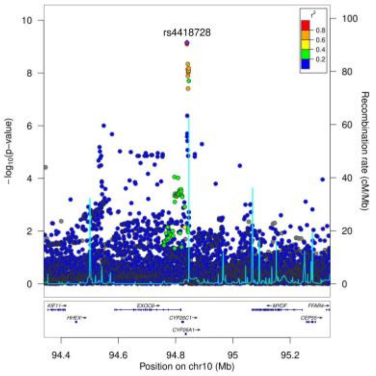
– rs4240624



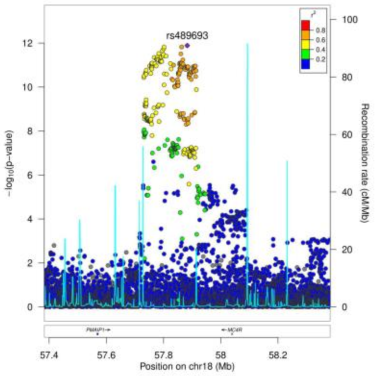
– rs4410790



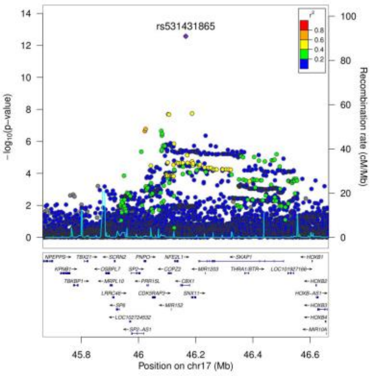
– rs4418728



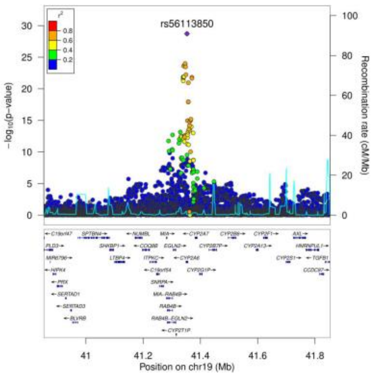
– rs489693



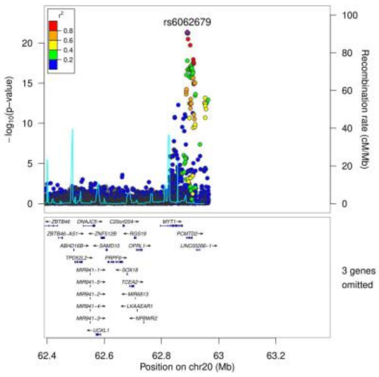
– rs531431865



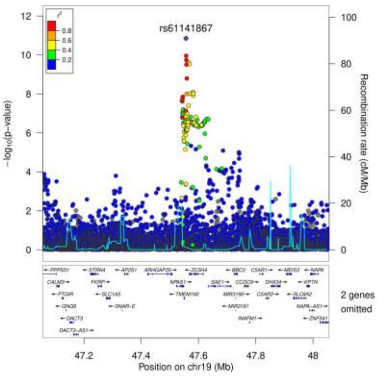
– rs56113850



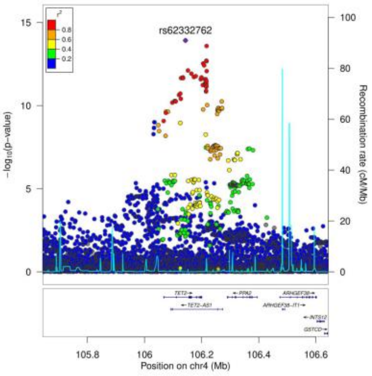
– rs6062679



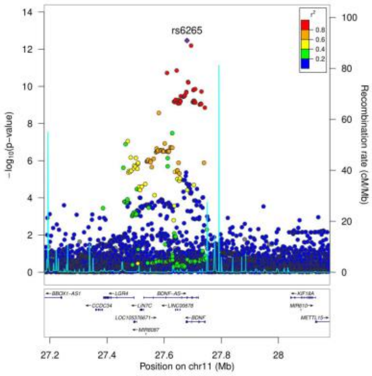
– rs61141867



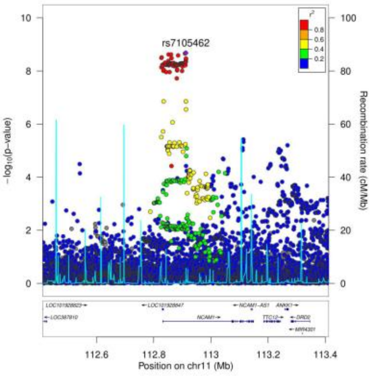
– rs62332762



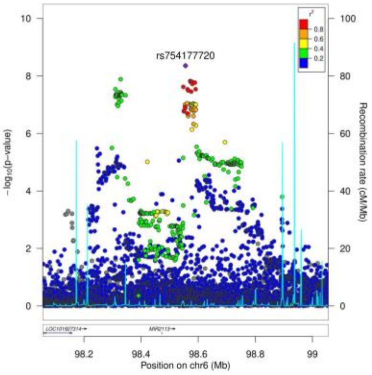
– rs6265



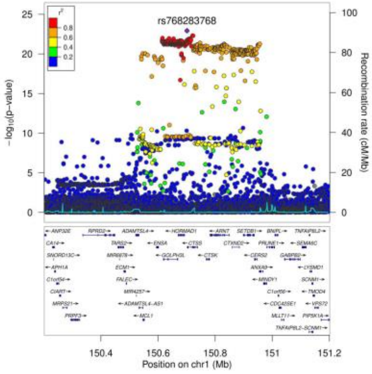
– rs7105462



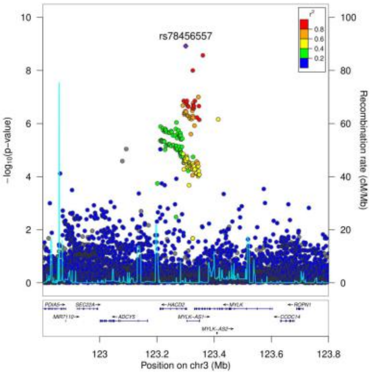
– rs754177720



– rs768283768



– rs78456557



– rs9611527

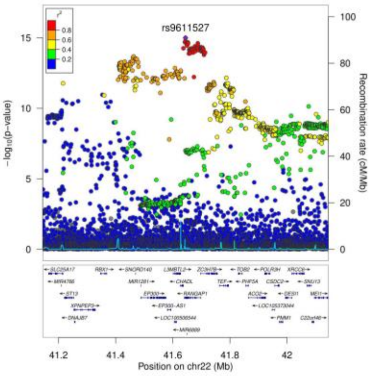
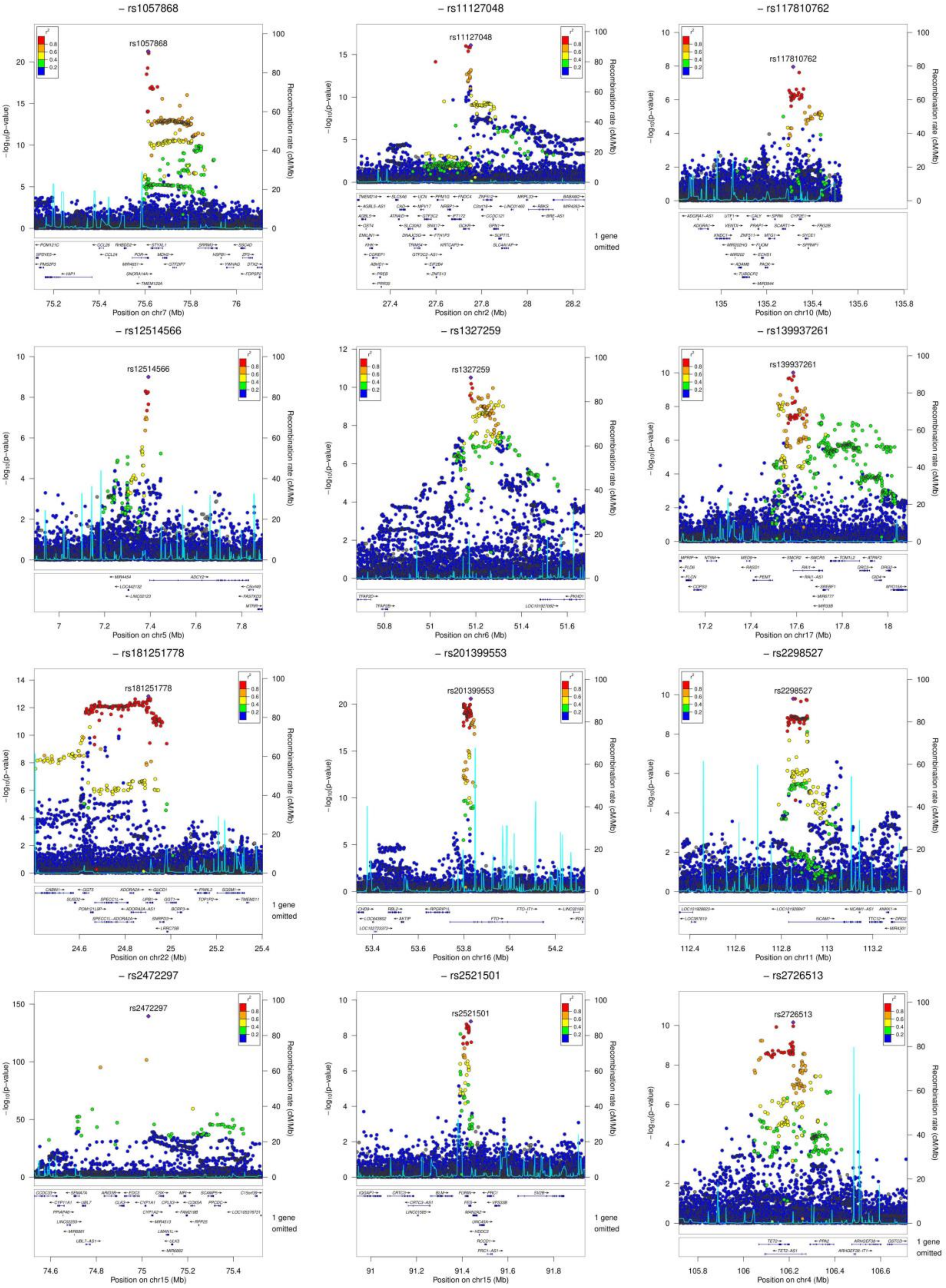
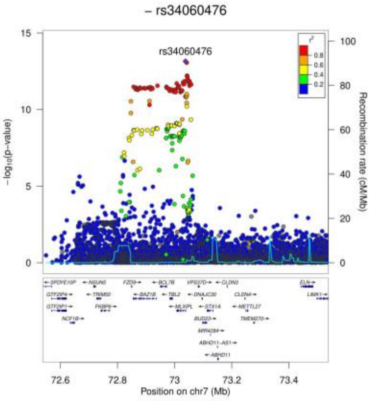
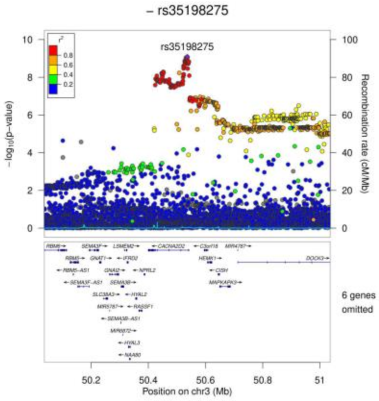
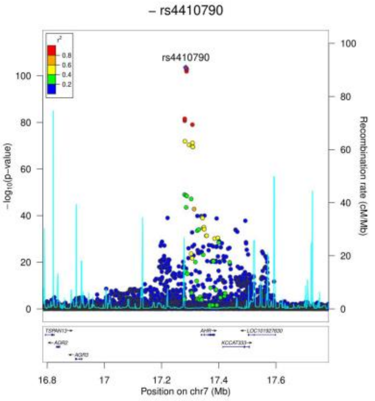


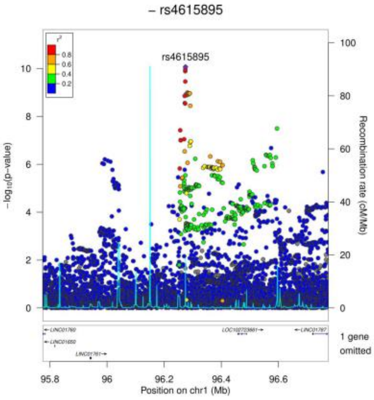
Figure S6. Locus plots for caffeine from coffee

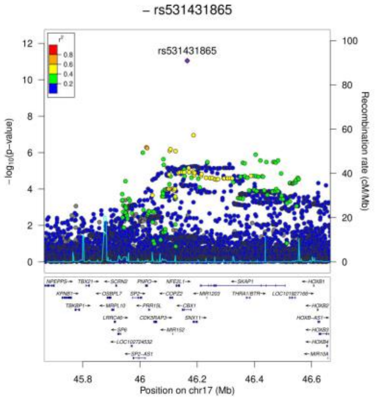


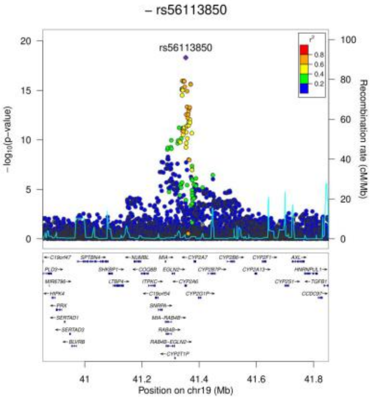

– rs34060476
rs34060476
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
5
10
15
0
20
40
60
80
100
72.6
72.8
73
73.2
73.4
Position on chr7 (Mb)

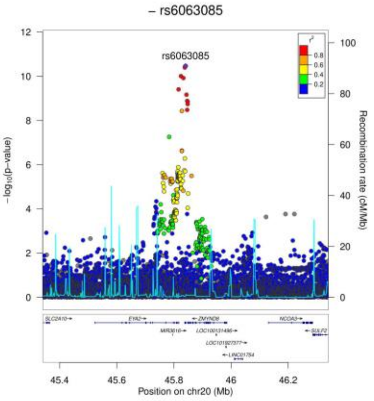

– rs35198275
rs35198275
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
6 genes omitted
50.2
50.4
50.6
50.8
51
Position on chr3 (Mb)

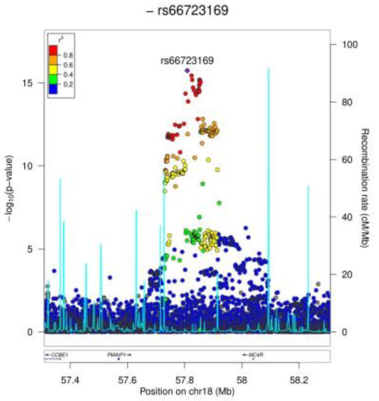

– rs4410790
rs4410790
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
20
40
60
80
100
0
20
40
60
80
100
16.8
17
17.2
17.4
17.6
Position on chr7 (Mb)

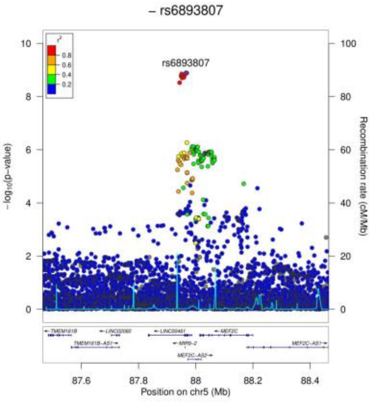

– rs4615895
rs4615895
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
1 gene omitted
95.8
96
96.2
96.4
96.6
Position on chr1 (Mb)

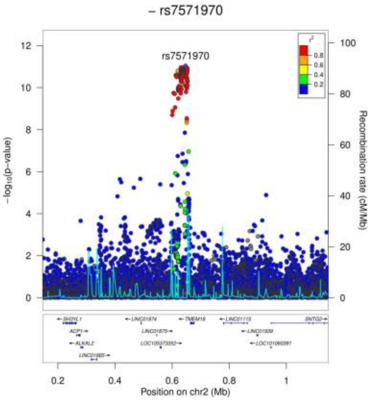

– rs531431865
rs531431865
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
12
0
20
40
60
80
100
45.8
46
46.2
46.4
46.6
Position on chr17 (Mb)

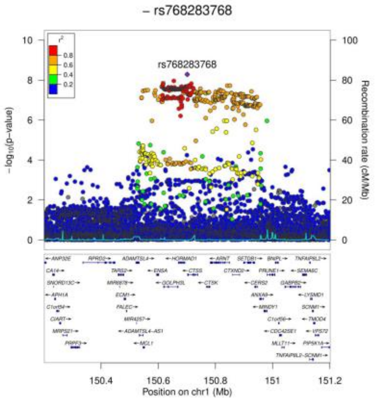

– rs56113850
rs56113850
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
5
10
15
20
0
20
40
60
80
100
41
41.2
41.4
41.6
41.8
Position on chr19 (Mb)


– rs6063085
rs6063085
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
12
0
20
40
60
80
100
45.4
45.6
45.8
46
46.2
Position on chr20 (Mb)


– rs66723169
rs66723169
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
5
10
15
0
20
40
60
80
100
57.4
57.6
57.8
58
58.2
Position on chr18 (Mb)


– rs6893807
rs6893807
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
87.6
87.8
88
88.2
88.4
Position on chr5 (Mb)


– rs7571970
rs7571970
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
12
0
20
40
60
80
100
0.2
0.4
0.6
0.8
1
Position on chr2 (Mb)


– rs768283768
rs768283768
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
150.4
150.6
150.8
151
151.2
Position on chr1 (Mb)

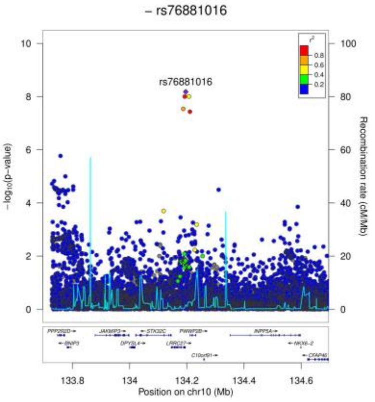
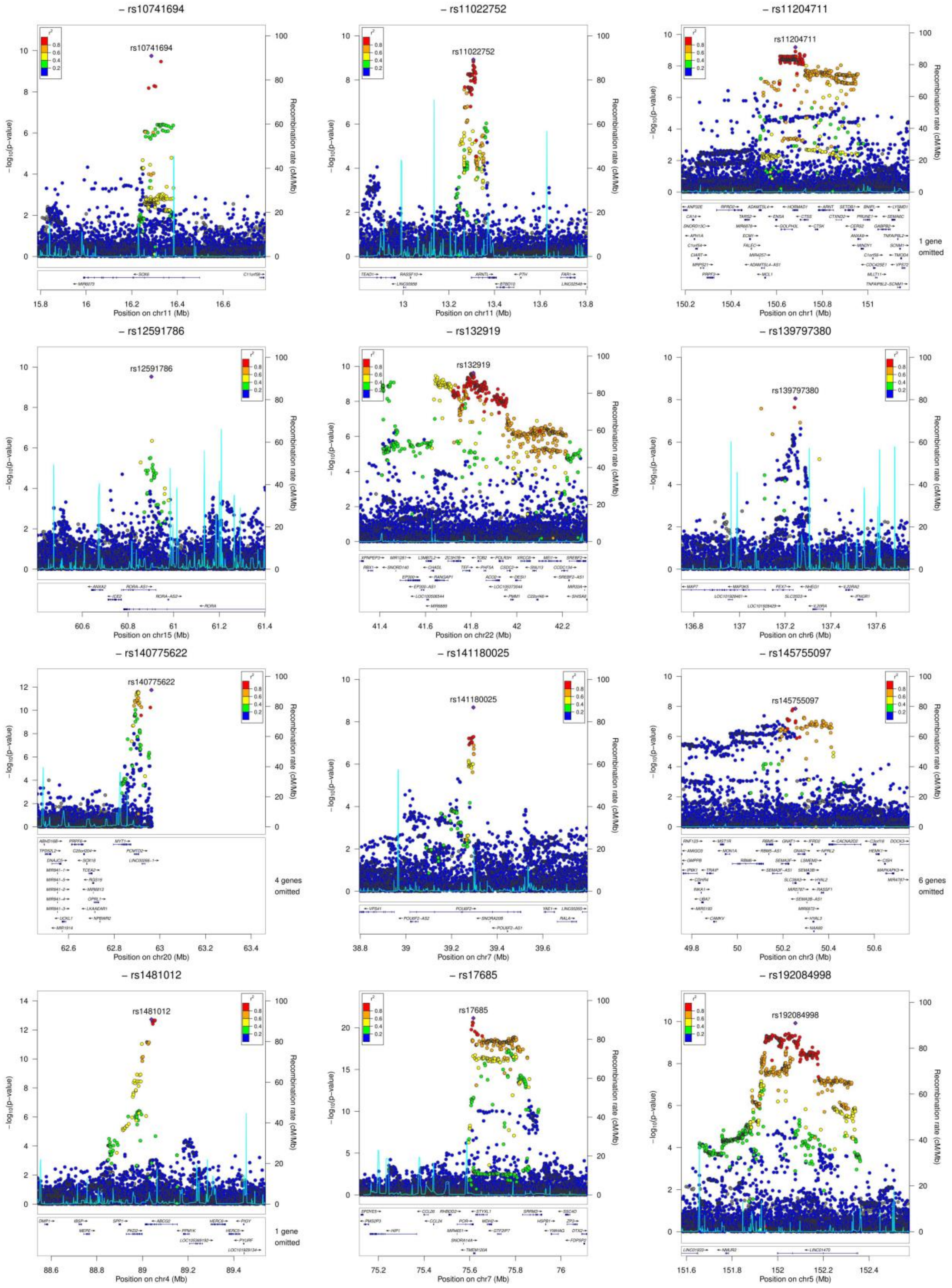
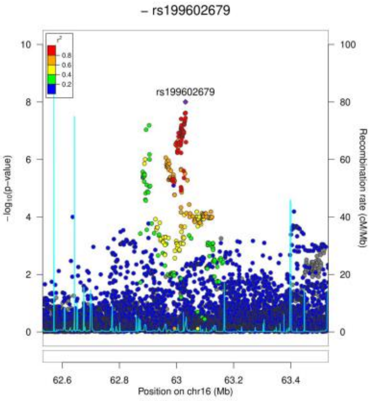
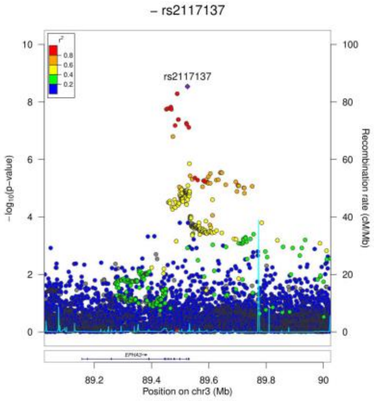
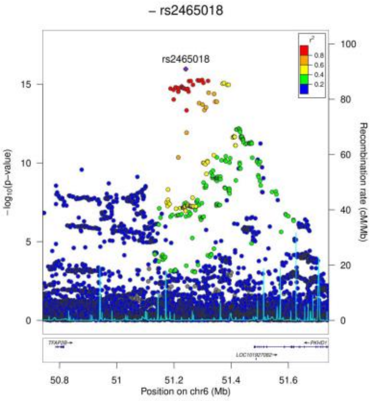

– rs76881016
rs76881016
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
133.8
134
134.2
134.4
134.6
Position on chr10 (Mb)

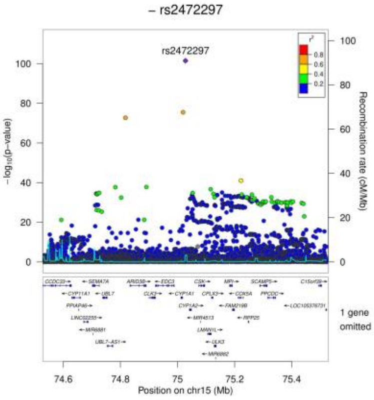
Figure S7. Locus plots for caffeine from tea

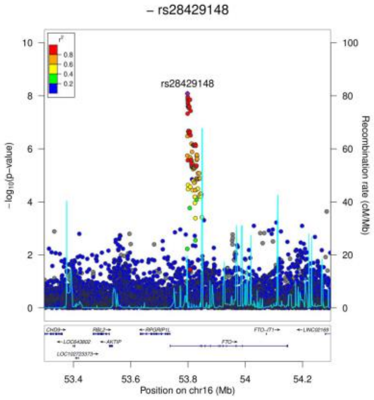


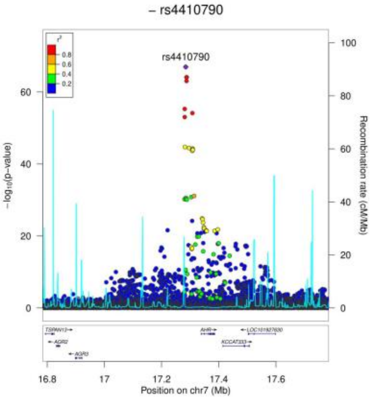

– rs199602679
rs199602679
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr16 (Mb)
62.6
62.8
63
63.2
63.4

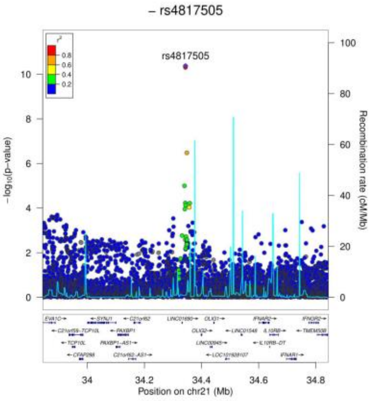

– rs2117137
rs2117137
−log10(p−value)
Recombination rate (cM/Mb)
EPHA3
Position on chr3 (Mb)
89.2
89.4
89.6
89.8
90

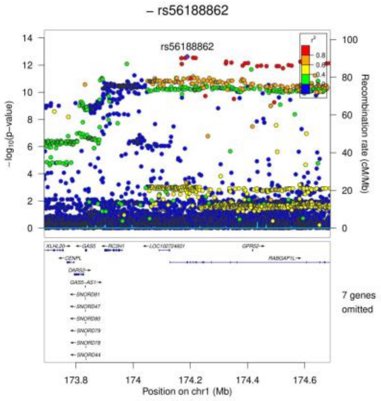

– rs2465018
rs2465018
−log10(p−value)
Recombination rate (cM/Mb)
TFAP2B
PKHD1
LOC101927260
Position on chr6 (Mb)
50.8
51
51.2
51.4
51.6

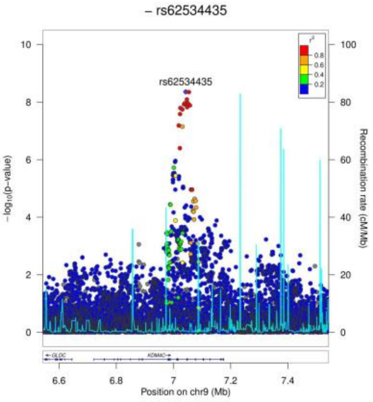

– rs2472297
rs2472297
−log10(p−value)
Recombination rate (cM/Mb)
CYP1A1
CYP1A2
1 gene omitted
Position on chr15 (Mb)
74.6
74.8
75
75.2
75.4

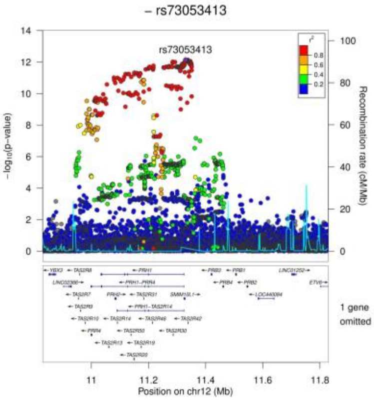

– rs28429148
rs28429148
−log10(p−value)
Recombination rate (cM/Mb)
FTO
Position on chr16 (Mb)
53.4
53.6
53.8
54
54.2

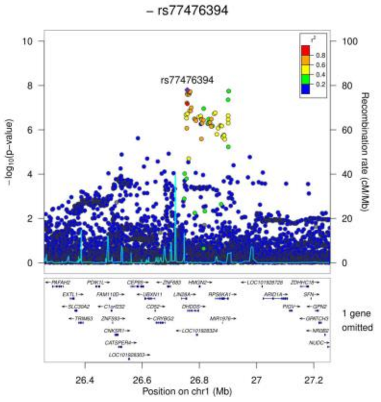

– rs4410790
rs4410790
−log10(p−value)
Recombination rate (cM/Mb)
AHR
Position on chr7 (Mb)
16.8
17
17.2
17.4
17.6


– rs4817505
rs4817505
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr21 (Mb)
34
34.2
34.4
34.6
34.8


– rs56188862
rs56188862
−log10(p−value)
Recombination rate (cM/Mb)
7 genes omitted
Position on chr1 (Mb)
173.8
174
174.2
174.4
174.6


– rs62534435
rs62534435
−log10(p−value)
Recombination rate (cM/Mb)
GLDC
KDM4C
Position on chr9 (Mb)
6.6
6.8
7
7.2
7.4


– rs73053413
rs73053413
−log10(p−value)
Recombination rate (cM/Mb)
1 gene omitted
Position on chr12 (Mb)
11
11.2
11.4
11.6
11.8


– rs77476394
rs77476394
−log10(p−value)
Recombination rate (cM/Mb)
1 gene omitted
Position on chr1 (Mb)
26.4
26.6
26.8
27
27.2

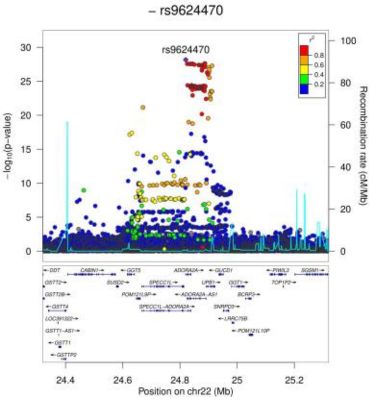

– rs9624470
rs9624470
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr22 (Mb)
24.4
24.6
24.8
25
25.2

Figure S8. QQ plot for combined caffeine intake

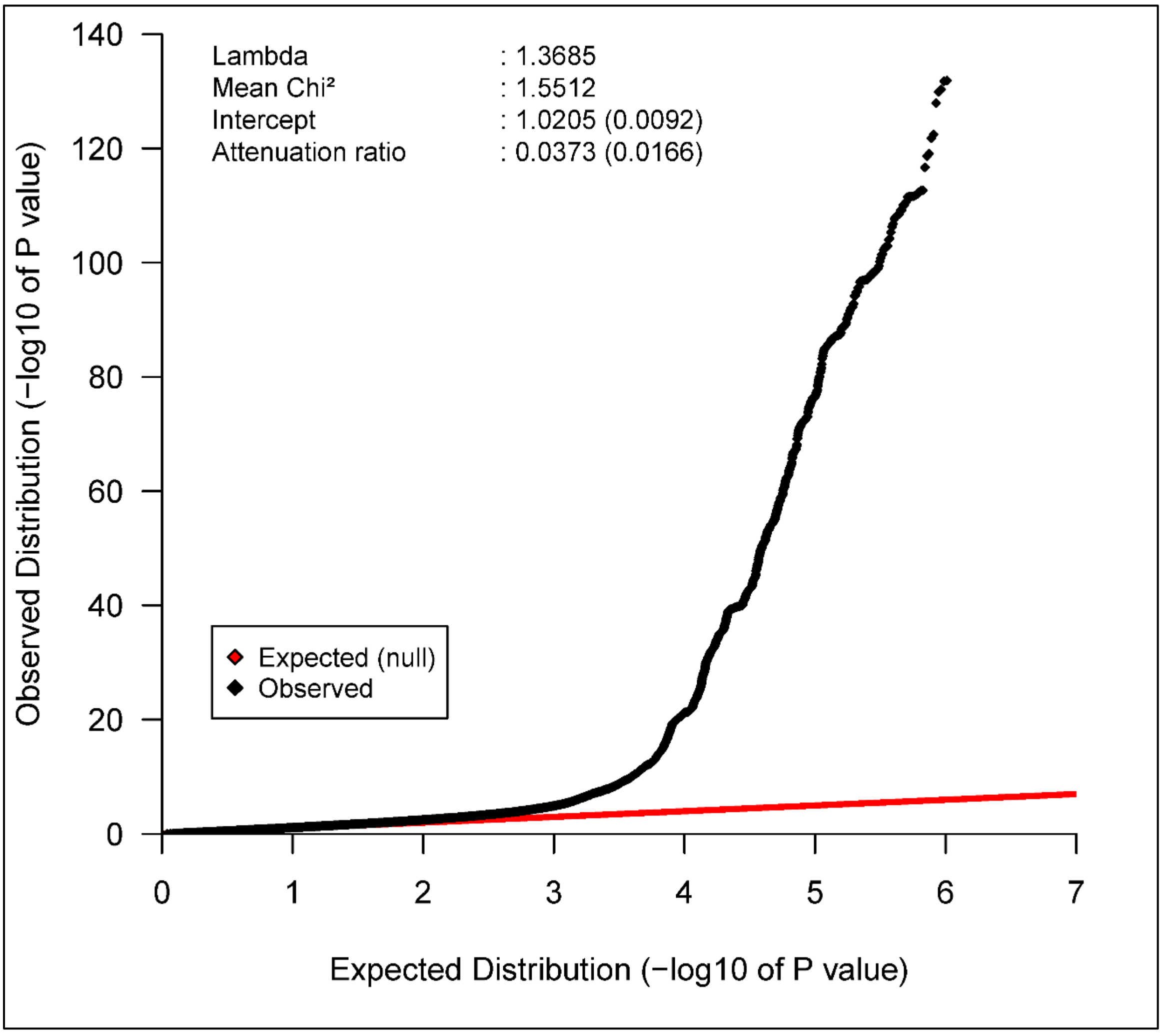


Figure S9. QQ plot for caffeine from coffee

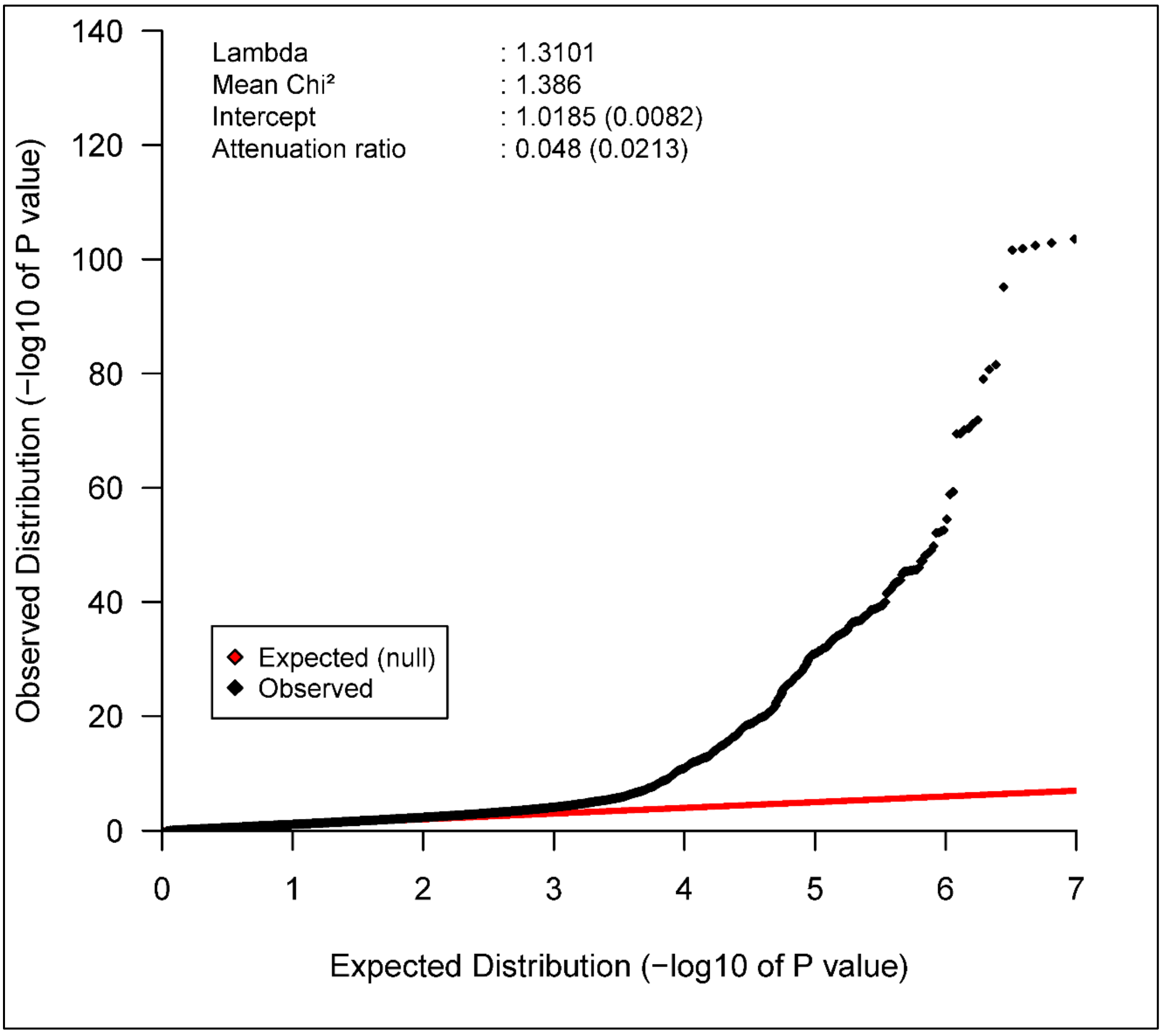


Figure S10. QQ plot for caffeine from tea

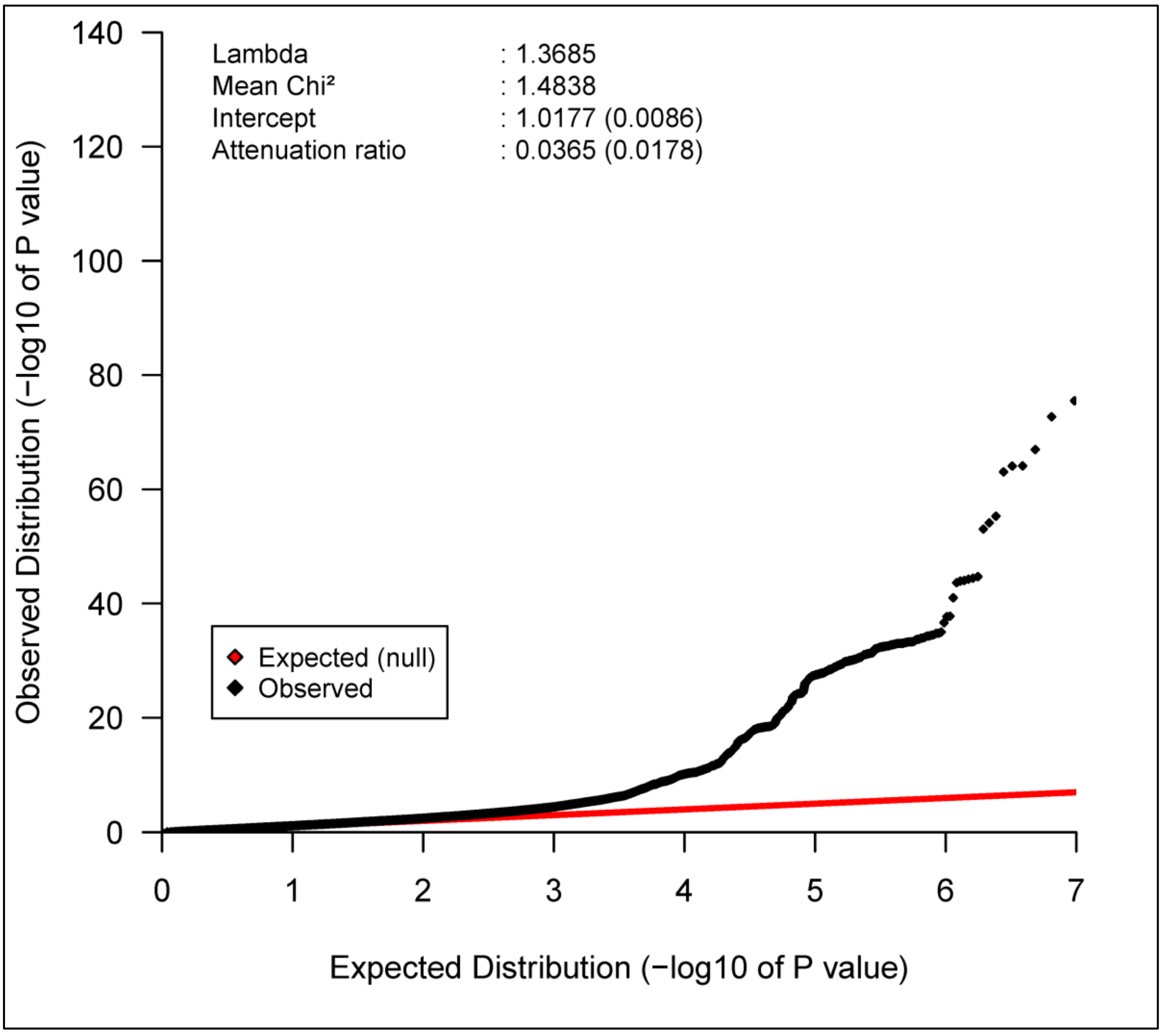


Figure S11. Forest plot showing individual SNP estimates with CAD for combined caffeine intake

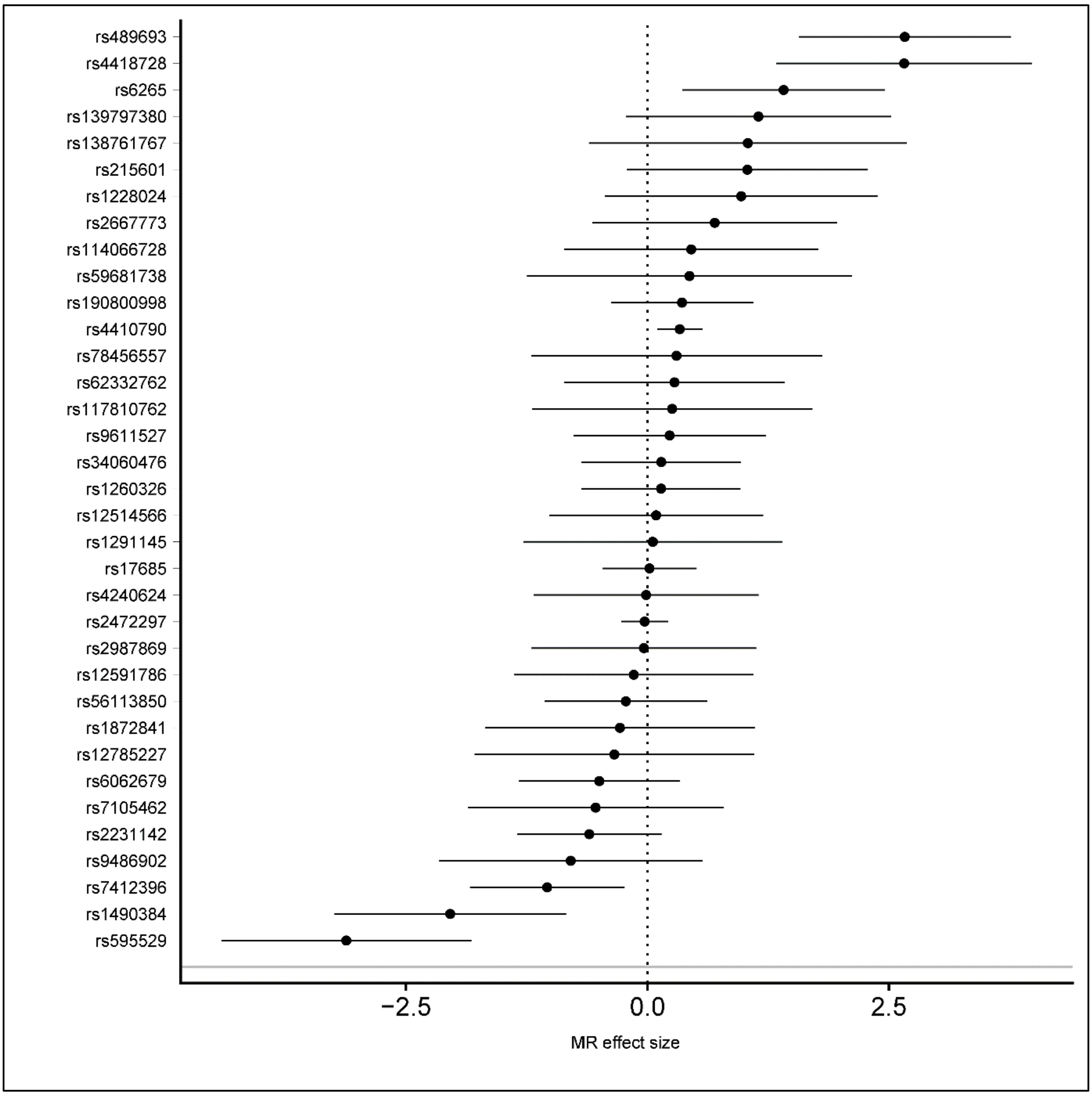


Figure S12. Forest plot showing individual SNP estimates with CAD for caffeine from coffee

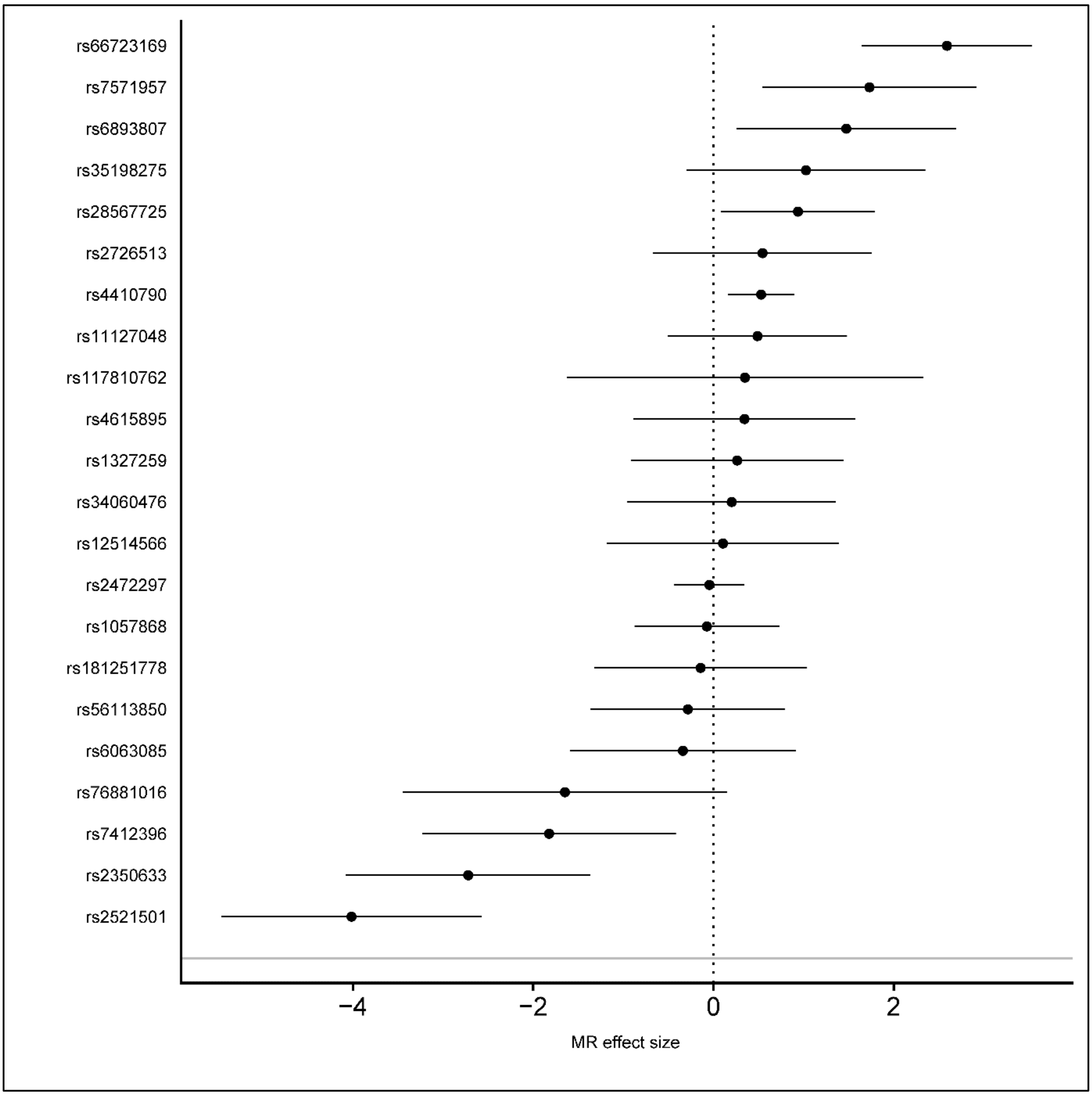


Figure S13. Forest plot showing individual SNP estimates with CAD for caffeine from tea

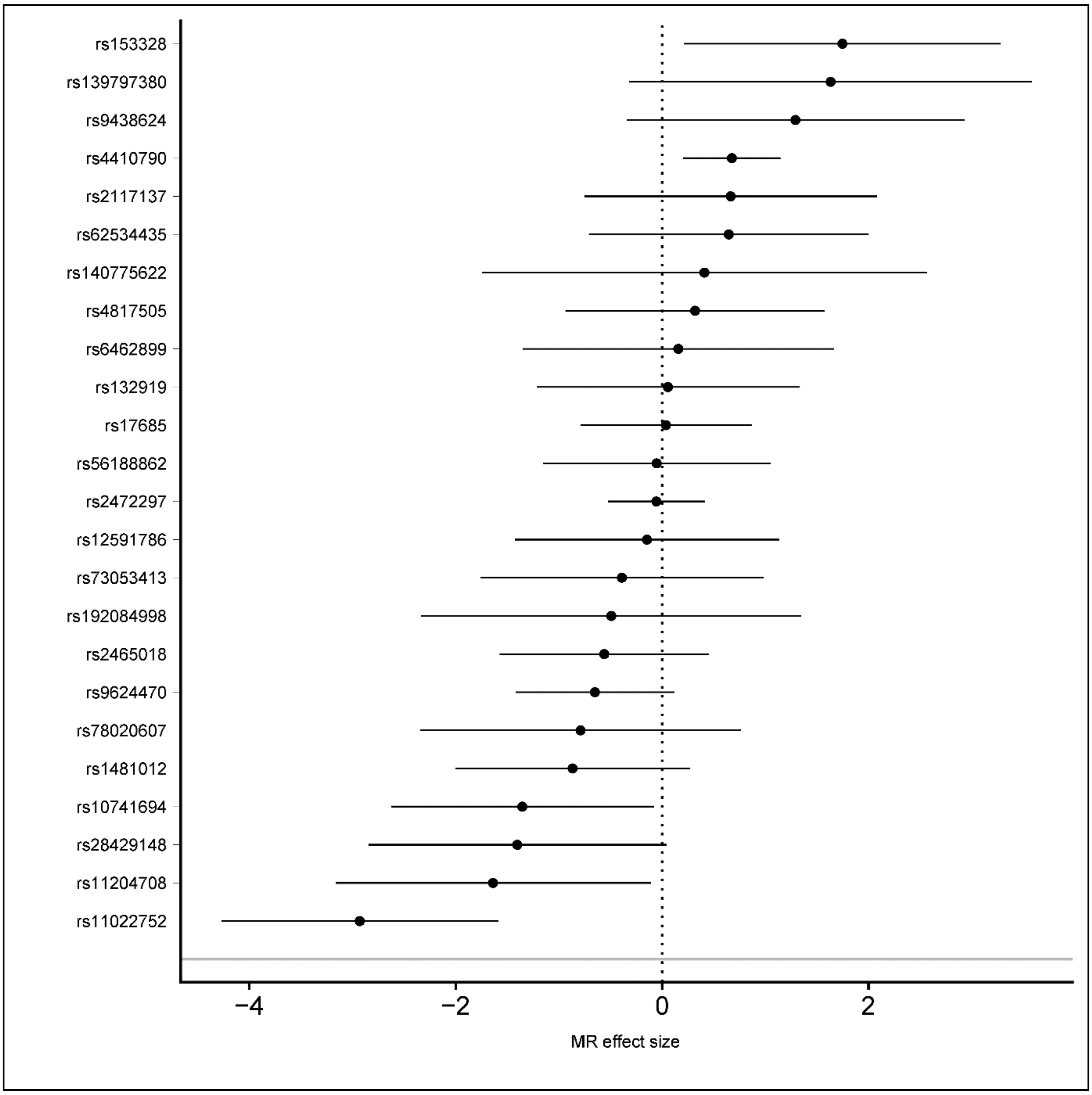


Figure S14. Forest plot showing individual SNP estimates with T2D for combined caffeine intake

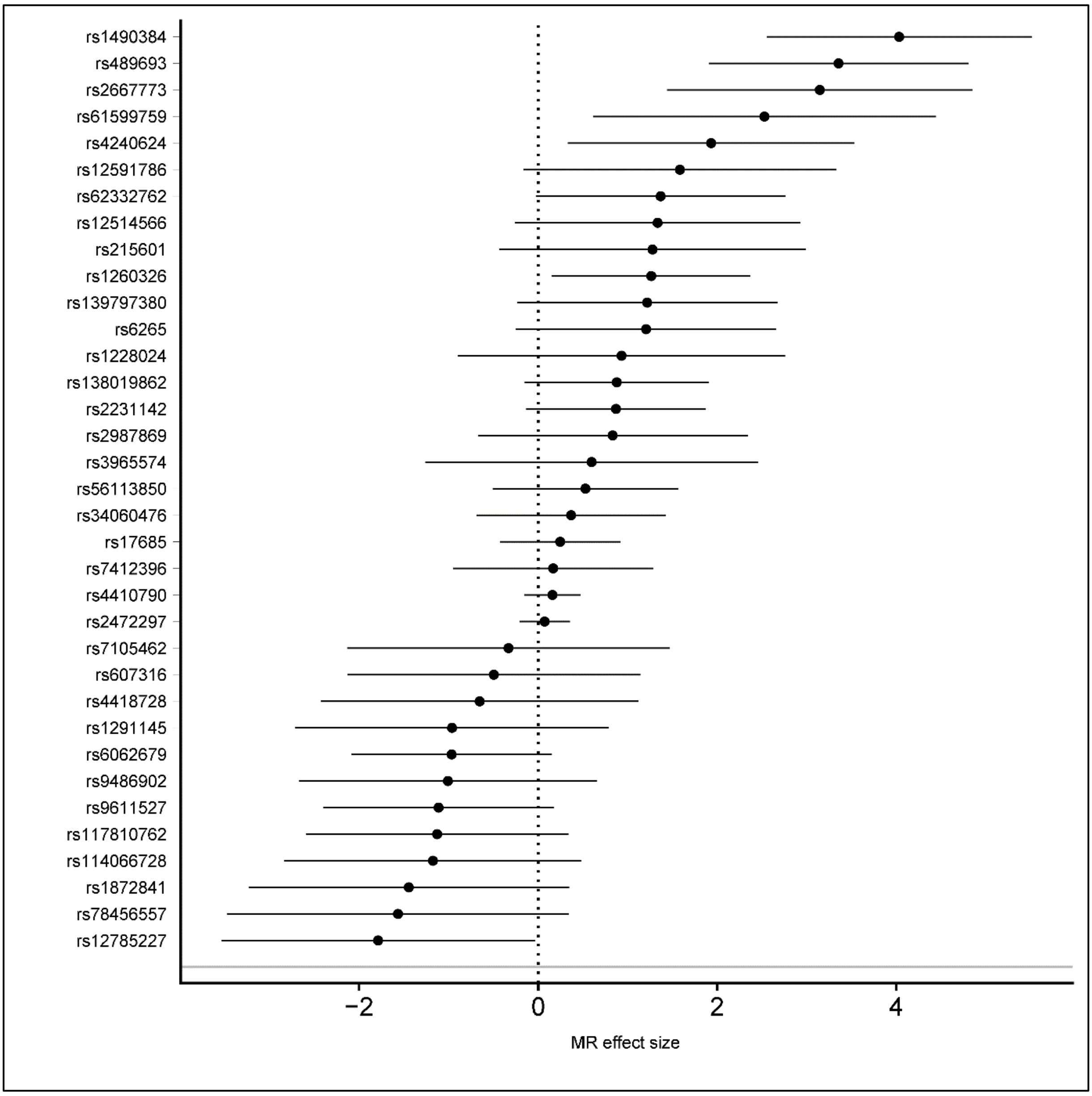


Figure S15. Forest plot showing individual SNP estimates with T2D for caffeine from coffee

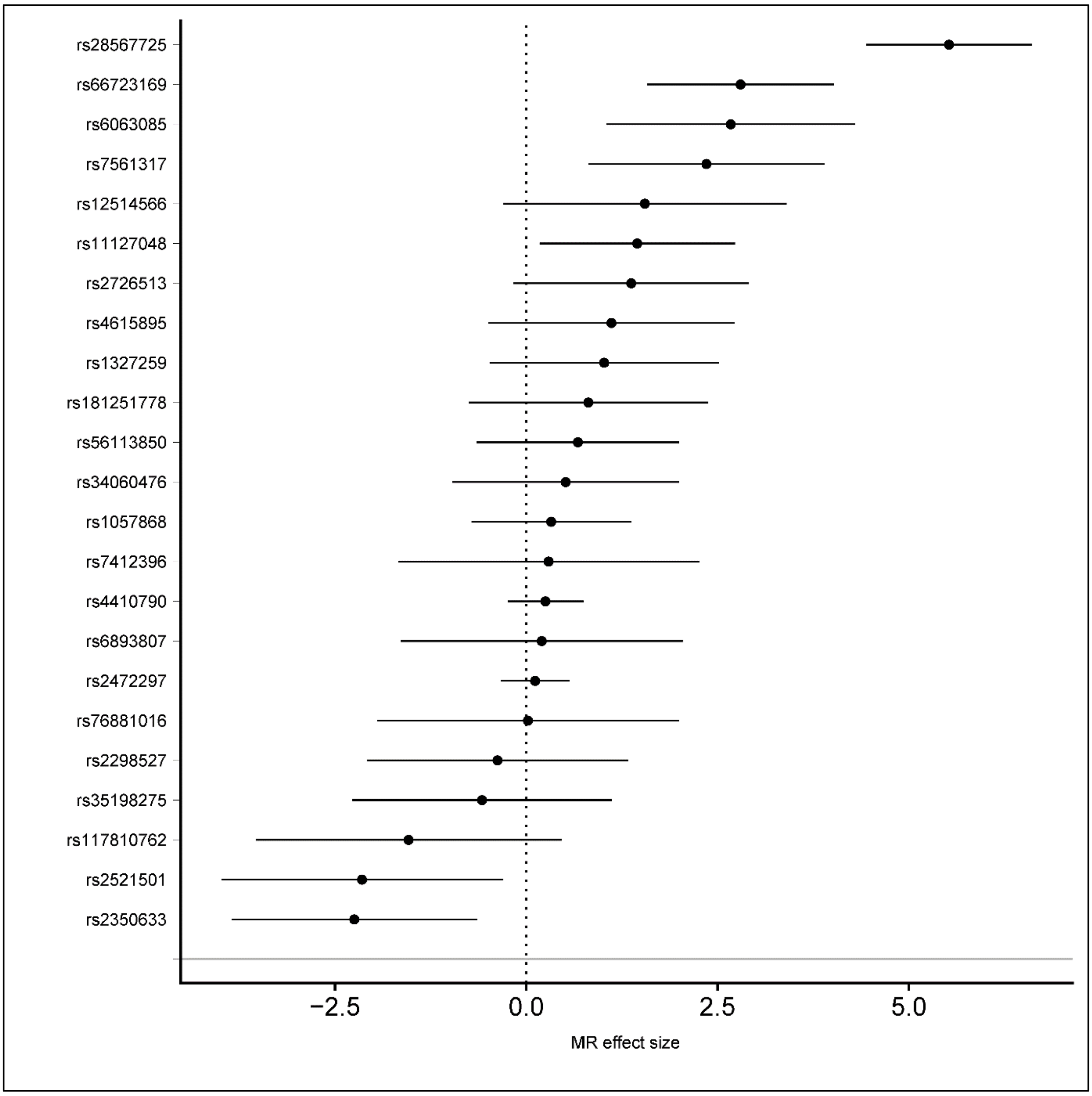


Figure S16. Forest plot showing individual SNP estimates with T2D for caffeine from tea