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Mendelian Randomisation Study of Smoking, Alcohol, and Coffee Drinking in Relation to Parkinson's Disease

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Mendelian randomisation study of smoking, alcohol, and coffee drinking in relation to Parkinson's disease

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Abstract

Background: Previous studies showed that lifestyle behaviors (cigarette smoking, alcohol, coffee) are inversely associated with Parkinson's disease (PD). The prodromal phase of PD raises the possibility that these associations may be explained by reverse causation.

Objective: To examine associations of lifestyle behaviors with PD using two-sample Mendelian randomisation (MR) and the potential for survival and incidence-prevalence biases.

Methods: We used summary statistics from publicly available studies to estimate the association of genetic polymorphisms with lifestyle behaviors, and from Courage-PD (7,369 cases, 7,018 controls; European ancestry) to estimate the association of these variants with PD. We used the inverse-variance weighted method to compute odds ratios (OR_{IVW}) of PD and 95% confidence intervals (CI). Significance was determined using a Bonferroni-corrected significance threshold ($p=0.017$).

Results: We found a significant inverse association between smoking initiation and PD (OR_{IVW} per 1-SD increase in the prevalence of ever smoking=0.74, 95%CI=0.60-0.93, $p=0.009$) without significant directional pleiotropy. Associations in participants ≤ 67 y and cases with disease duration ≤ 7 y were of a similar size. No significant associations were observed for alcohol and coffee drinking. In reverse MR, genetic liability toward PD was not associated with smoking or coffee drinking, but was positively associated with alcohol drinking.

Conclusion: Our findings are in favor of an inverse association between smoking and PD that is not explained by reverse causation, confounding, and survival or incidence-prevalence biases. Genetic liability toward PD was positively associated with alcohol drinking. Conclusions on the association of alcohol and coffee drinking with PD are hampered by insufficient statistical power.

Keywords: Smoking, alcohol, coffee, Parkinson's disease, Mendelian randomisation.

Introduction

PD is considered as a multifactorial disease, involving genetic susceptibility and environmental factors.[1] Epidemiologic studies have revealed a striking pattern, whereby several lifestyle behaviours, including cigarette smoking, alcohol, and coffee drinking, are inversely associated with PD.[2] It remains debated whether these inverse associations are causal. The existence of a long prodromal phase in PD[3, 4] raises the possibility that they may be explained by reverse causation defined as situations where the outcome precedes and influences the exposure. For instance, the prodromal phase of PD may be characterized by a loss of appetite for cigarettes,[5] and patients who later develop PD may be more successful in their attempts to quit smoking during the prodromal phase due to reduced dopamine reward.[6]

Mendelian randomisation (MR) is a form of instrumental variable analysis that uses genetic variants associated with an exposure as instruments to estimate its causal association with a disease.[7] Unlike traditional epidemiologic approaches, MR analyses are not biased by confounding or reverse causation if a set of assumptions are met.[8] However, MR analyses in elderly populations may be biased due to survival bias, a form of selection bias that may arise as older persons consist of a non-random subset of the general population who have survived long enough to be included into the study.[9] This bias is a particular threat for MR studies investigating exposures that strongly affect survival,[10] and is more pronounced for two-sample than one-sample MR studies.[9] MR studies that include prevalent cases may also be biased by incidence-prevalence bias, if the genetic instrument is associated with survival after disease onset.[11]

As part of the COmprehensive Unbiased Risk factor Assessment for Genetics and Environment in PD (COurage-PD) consortium, we used two-sample MR to examine the association of three lifestyle behaviours (smoking, alcohol drinking, coffee drinking) with PD, and assessed whether MR findings are robust in analyses addressing the potential for survival and incidence-prevalence biases.

Material and methods

Study design: two-sample Mendelian randomisation

MR uses genetic variants, mainly single nucleotide polymorphisms (SNPs), associated with an exposure to estimate its causal effect on an outcome. For SNPs to be valid instruments, three assumptions must be verified: (i) SNPs should be associated with the exposure (IV1 assumption); (ii) SNPs should not be directly associated with the outcome except through the exposure (IV2 assumption); (iii) SNPs should not be associated with unmeasured confounders of the exposure-outcome association (i.e., no horizontal pleiotropy, IV3 assumption).[7]

In two-sample MR, summary statistics (effect size estimates and standard errors [SE]) for the SNP-exposure and SNP-outcome associations, required to estimate the causal exposure-disease association, come from two independent samples.

PD GWAS: Courage-PD consortium

We used summary statistics from a GWAS (NeuroChip)[12] in 23 out of 35 studies from the Courage-PD consortium (Supplementary methods). We excluded from the analyses: samples overlapping with the international Parkinson Disease Genomics Consortium (iPDGC); Asian studies (so that estimates for SNP-exposure and SNP-PD associations come from Caucasian populations); studies that included cases only; studies with less than 50 cases and 50 controls. As the role of environmental factors may be different in carriers of Mendelian PD mutations, we also excluded participants with *GBA/LRRK2* mutations or with positive family history of PD. Participants' characteristics are shown in Supplementary table 1.

In each study, the frequency of SNPs was compared in cases and controls under an additive model using logistic regression adjusted for sex and the first four principal components. We meta-analysed summary statistics from the 23 GWAS (European ancestry: 7,369 cases, 7,018 controls) using a fixed ($I^2 \leq 25\%$) or random ($I^2 > 25\%$) effects model (Supplementary methods).

Individual studies within each genome-wide association study had received approval from a relevant institutional review board from their country, and informed consent was obtained from participants or from a caregiver, legal guardian, or other proxy.

GWAS of exposures

We used summary statistics (betas, SEs) from published GWAS in individuals of European descent to select SNPs associated with exposures of interest at a genome-wide significant threshold ($p < 5 \times 10^{-8}$) and with a minor allele frequency (MAF) ≥ 0.01 . To retain independent SNPs, we clumped them based on European ancestry reference data (1000 Genomes Project, $r^2 > 0.001$, genomic region = 10,000 kb). For SNPs not available in Courage-PD, we selected proxies in high linkage disequilibrium (LD) with the index SNP ($r^2 > 0.8$) according to LDlink[13] or SNIPA.[14] Summary statistics were harmonised on alleles positively associated with exposures. Ambiguous palindromic SNPs (A/T, C/G) with a MAF > 0.42 were discarded.[15]

Smoking initiation and alcohol drinking: the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) provided summary statistics for smoking initiation ($n = 1,232,091$, 203 SNPs) and for the number of alcohol drinks per week ($n = 941,280$, 71 SNPs) in participants of European descent.[16] The proxy rs117495226 in high LD ($r^2 = 0.90$) with the index SNP rs6050446 was used.

Information on smoking status was missing in several studies from Courage-PD; therefore, we were not able to run analyses stratified by smoking status and to examine the role of SNPs associated with smoking heaviness or age at smoking cessation or initiation in smokers.[17] To overcome this limitation, we used a lifetime smoking exposure index developed using UK Biobank data (in 462,690 European descent) that allows to perform MR using summary data from samples unstratified by smoking status. Briefly, this lifetime smoking index combines several aspects of smoking, including smoking status and, among ever smokers, duration, heaviness, and cessation, and was validated using positive outcomes (e.g., lung cancer). We selected 126 SNPs associated with this index.[17]

Coffee drinking: we used a GWAS on self-reported bitter and sweet beverage consumption, including coffee (European ancestry, n=370,000, 11 SNPs).[18]

Statistical analyses

Statistical analyses were performed using the *TwoSampleMR*, *MRPRESSO*, and *simex* R packages (R Foundation for Statistical Computing, Vienna, Austria). P-values are two-sided. We examined three main exposures (smoking initiation, alcohol drinking, coffee drinking). To account for multiple testing, we used a conservative approach and applied a Bonferroni corrected significance level of 0.017 (i.e., 0.05/3). P-values ≤ 0.05 but > 0.017 were considered as suggestive statistical evidence for an association.[19]

Only SNPs available in 75% (n=17) of the studies or more were retained for our analyses. For each SNP, we computed the proportion of the variance of the exposure explained by the SNP (R^2).[8]

For MR analyses of individual SNPs, we used the Wald ratio estimate (exponentiated ratio of the SNP-outcome association to the SNP-exposure association).

Our primary MR analyses based on multiple SNPs were conducted using the random-effects inverse-variance weighted (IVW) method that provides accurate estimates for SNPs that verify IV assumptions. Heterogeneity between genetic instruments was tested using the Cochran's Q-statistic.[7]

In sensitivity MR analyses, we used other approaches that relax some IV assumptions. The *MR-Egger method* can detect directional pleiotropy and provides corrected effect estimates but has low power and requires the InSIDE (INstrument Strength Independent of Direct Effect) assumption.[20] We used the I^2_{GX} statistic to quantify the strength of regression dilution bias in SNP-exposure association estimates, with values $< 90\%$ indicating violation of the NOME (No Measurement Error) assumption, in which case we used the SIMEX method to correct MR-Egger estimates.[21] The *weighted median-method* provides consistent estimates if at least 50% of the SNPs are valid instruments.[22] The *weighted mode-based method* uses the causal estimate from each SNP to calculate the modal estimate. The largest group of

variants with the same causal estimate in the asymptotic limit are considered valid instruments.[23] *MR-PRESSO* allows to detect outliers (global test), to compute an estimate corrected for horizontal pleiotropy after removing them (if $p\text{-global test} < 0.05$), and to test the difference between the original and updated estimates (distortion test).[24] In addition, as two SNPs were associated with both alcohol and coffee drinking, we repeated analyses for these phenotypes after excluding them.

PD is typically a disease of old age, and survival bias may bias genetic associations and MR estimates in any direction in studies in older populations for exposures that are associated with survival into old age (Supplementary figure 1).[9, 10] In some situations, increasing age is associated with increasing bias; in addition, bias is likely to be more pronounced in two-sample than one-sample MR studies. As smoking and alcohol drinking are strongly associated with survival, we performed analyses stratified by median age at study of cases and controls (67 years) and examined whether MR estimates observed overall were consistent with those seen in younger participants in whom survival bias is unlikely as mortality rates are low in this group.[25-27]

The consortium included prevalent and incident patients. If genetic variants have a stronger effect on survival in PD patients than controls, genetic associations may be biased.[11] We examined whether MR estimates in cases with shorter disease duration (median ≤ 7 years) compared to controls were consistent with those obtained overall.

Finally, we tested for reverse causation by performing a reverse MR analysis where the exposure was PD genetic susceptibility and the outcome was smoking initiation, alcohol, or coffee drinking. We identified top SNPs (and corresponding association estimates) from the largest PD iPDGC GWAS as exposure instrumental variables,[28] and extracted summary statistics for these SNPs from the GWAS for lifestyle behaviours [16-18]. For smoking initiation, we used summary statistics without 23andMe ($N=599,289$). In this analysis, we estimated the effect of genetic liability toward PD on lifestyle behaviours in order to examine whether genetic liability toward PD is associated with smoking initiation, alcohol drinking, or coffee drinking. ORs are scaled to 1-unit increase in log odds of liability to PD.[29]

Statistical power

For each exposure, we computed the proportion of variance explained by the SNPs, the F-statistic as a measure of instrument strength,[15] and statistical power for a type-I error rate of 5% and 1.7% (Supplementary table 2).[30]

Data availability

Results can be reproduced using Supplementary tables 3 and 4; no additional data available.

Results

The associations of SNPs with exposures and PD are shown in Supplementary table 3. Supplementary table 5 shows the number of SNPs retained for each exposure and F-statistics.

Smoking and PD

Of the SNPs positively associated with smoking traits, two (1.1%) were positively associated with PD at $p < 0.05$ for smoking initiation, and five (4.4%) for the lifetime smoking index; six (3.3%) were inversely associated with PD for smoking initiation, and five (4.4%) for the lifetime smoking index (Supplementary table 3).

Smoking initiation was significantly and inversely associated with PD ($OR_{IVW}=0.74$, 95% CI=0.60-0.93, $p=0.009$; Table 1, Supplementary figure 2). The weighted median approach also showed a significant inverse association ($p=0.008$) while the weighted mode approach yielded slightly lower point estimates with wider CIs. The MR-Egger method did not show significant directional pleiotropy.

In sensitivity analyses, there was a suggestive inverse association for the lifetime smoking index ($OR_{IVW}=0.54$, 95% CI=0.29-1.00, $p=0.050$; Table 1, Supplementary figure 2) that became more significant after excluding two outliers identified by MR-PRESSO ($OR_{MR-PRESSO}=0.51$, 95% CI=0.29-0.89, $p=0.021$). The weighted median method yielded an inverse association that was statistically significant ($p=0.017$). MR-Egger did not show significant directional pleiotropy.

Both for smoking initiation and the lifetime smoking index, associations tended to be stronger in younger individuals (smoking initiation: $OR_{IVW}=0.68$, 95% CI=0.48-0.97; lifetime smoking index: $OR_{IVW}=0.46$, 95% CI=0.19-1.09) than in older ones (smoking initiation: $OR_{IVW}=0.83$, 95% CI=0.58-1.18; lifetime smoking index: $OR_{IVW}=0.88$, 95% CI=0.37-2.07) and were consistent with those seen overall (Figure 1, Supplementary table 6). Associations were of a similar size in patients with shorter and longer disease duration and comparable to associations seen overall (Figure 1, Supplementary table 7).

Alcohol drinking and PD

Of the SNPs positively associated with alcohol drinking, two (3.2%) were positively and three (4.8%) were inversely associated with PD at $p < 0.05$ (Supplementary table 3).

There was no significant association between alcohol drinking and PD ($OR_{IVW}=0.68$, 95% CI=0.39-1.18, $p=0.17$; Table 2, Supplementary figure 2). Exclusion of two SNPs associated with coffee drinking led to similar conclusions. In stratified analyses, there was no significant association between alcohol drinking and PD in younger individuals and patients with shorter disease duration (Supplementary tables 6-7). There was a trend towards an inverse association only in prevalent PD cases ($OR_{IVW}=0.53$, 95% CI=0.27-1.02, $p=0.057$).

MR analyses using a single SNP in the *ADH1B* gene (rs1229984) showed no association with PD ($OR_{Wald\ ratio}=0.93$, 95% CI=0.45-1.91, $p=0.85$; Supplementary table 3); this gene plays an important role in explaining alcohol drinking variance and analyses based on this gene are less likely to be biased by pleiotropy due to the known role of alcohol dehydrogenase in alcohol metabolism.

Coffee drinking and PD

Of the SNPs positively associated with coffee drinking, one (9.1%) was positively, and another (9.1%) was inversely associated with PD at $p < 0.05$ (Supplementary table 3).

There was a positive and non-statistically significant association of genetically-predicted coffee drinking with PD ($OR_{IVW}=1.69$, 95% CI=0.51-5.63, $p=0.40$; Table 3, Supplementary figure 2). However, after excluding two SNPs associated with alcohol drinking, the association decreased ($OR_{IVW}=1.09$, 95% CI=0.26-4.45, $p=0.91$). Stratified analyses showed no associations (Supplementary tables 6-7).

MR analyses based on SNPs in two genes that are known to play an important role in caffeine metabolism (*AHR*-rs4410790, *CYP1A2*-rs2472297) showed no association with PD (rs4410790: $OR_{Wald\ ratio}=0.79$, 95% CI=0.21-2.98, $p=0.72$; rs2472297: $OR_{Wald\ ratio}=2.09$, 95% CI=0.47-9.16, $p=0.33$; Supplementary table 3).

Reverse MR

Supplementary table 8 shows the SNPs and association estimates used for reverse MR analyses. Table 4 shows the results of reverse MR analyses. There was no association between genetic liability toward PD and smoking or coffee drinking. For alcohol drinking, genetic liability toward PD was positively associated with alcohol drinking using the IVW method. MR-PRESSO identified 5 outliers; the corrected MR estimate after excluding these outliers was still in favour of a positive association.

Discussion

Based on data from the Courage-PD consortium and after exclusion of samples overlapping with iPDGC, our findings **add further evidence in favour of** an inverse association between smoking initiation and PD but not for alcohol and coffee drinking.

Smoking

According to observational studies, ever smokers have a ~40% reduced risk of developing PD.[31] It has been argued, however, that this association may be due to reverse causation[5] as PD patients may stop smoking more easily during the PD prodromal phase than other persons due to reduced responsiveness to nicotine.[32] Others argued that the association seen in long-term ex-smokers[1] and the dose-effect relationship seen both in ex- and current-smokers are not in favour of this hypothesis.[33]

Previous MR studies examined the association between smoking and PD using iPDGC data. One study (9,581 cases, 33,245 controls) assessed several risky behaviours in relation with PD,[34] and reported a significant inverse association for smoking initiation (213 SNPs; OR per log odds of ever smoking=0.71, 95% CI=0.57-0.90). In another study (37,688 cases with some overlap with the previous study, 18,618 UK Biobank proxy-cases, 1.4 million controls), there was a trend towards an inverse association between ever-smoking and PD that was not statistically significant (OR per log odds of ever-smoking=0.94, 95% CI=0.88-1.01).[28] **Recently, another MR study used the same dataset to assess the role of several tobacco behaviours (smoking initiation, continuation, heaviness, and age at initiation). They showed that smoking continuation (current versus former smokers) was inversely associated with PD (OR per doubling of odds for smoking continuation=0.64, 95%CI=0.46-0.89, p=0.008) but smoking initiation, heaviness, or age at initiation were not. However, they used only 87 SNPs for smoking initiation and analyses were not stratified by smoking status for analyses of smoking characteristics among smokers.[35]** The iPDGC PD MR Portal, a platform which offers MR analyses for a total of 5,839 GWAS versus the largest iPDGC GWAS available with some overlap with the two previous studies, also reports some evidence to support a protective effect of current smoking using a genetic instrument that included 12 SNPs.[36] These studies

are not independent as they relied on overlapping datasets and did not examine associations in younger subjects or in those with shorter disease duration to assess whether survival or incidence-prevalence bias may have distorted MR estimates.

Our study replicates these findings and **add further evidence in favour of an association** between smoking initiation and lower PD risk; in addition, our findings show that genetic liability toward PD is not associated with smoking initiation which does not support the hypothesis of reverse causation for smoking. We further show that survival into old age and incidence-prevalence bias are unlikely explanations for the inverse association between smoking and PD. Since smoking is a major risk factor of mortality, differential survival could potentially bias the association between smoking-related SNP and PD; however, the observation that associations in younger participants were consistent with those seen overall is against this hypothesis and supports **an association between smoking and PD**. [9, 25-27] In addition, the finding that associations tended to be weaker in older participants than in younger ones is in agreement with some previous observational studies that showed age-dependent associations between smoking and PD with no association in the oldest age groups. [37, 38] This pattern could be interpreted in two different ways: (i) survival bias may have diluted association estimates in older subjects; (ii) alternatively, there may exist age-related etiologic heterogeneity in PD, and smoking may play a weaker role in PD at older ages where other factors may be more important. There was no marked difference in ORs according to disease duration, thus suggesting that incidence-prevalence bias is unlikely.

The consistency of MR findings with those from traditional epidemiologic studies and reports of smoking-by-gene interactions [39, 40] **support a causal association** between smoking and PD. However, the underlying mechanisms remain poorly understood. Although cigarette smoke includes a wide range of chemical components, a role for nicotine in PD was suggested by studies showing that it reduced neuronal damage in culture systems and protected against nigrostriatal dopaminergic damage in parkinsonian animal models. [41] In addition, among five compounds present in cigarette smoke (anabasine, cotinine, hydroquinone, nicotine, nor nicotine), nicotine and hydroquinone inhibited alpha-synuclein aggregation. [42]

Previous randomised clinical trials of nicotine for motor symptoms in PD failed to show an effect,[43-45] but their design may have been hampered by small sizes and short follow-up. In addition, these trials were conducted in PD patients and examined disease progression rather than prevention. Additional well-designed neuroprotection trials are needed.

Alcohol drinking

A meta-analysis of the relation between alcohol and PD reported an inverse association in case-control studies but not in cohort studies, with marked heterogeneity across studies.[46] Two of the cohort studies reported positive associations, while three reported inverse associations, but none of them was statistically significant.

A previous MR study that examined several risky behaviours in relation with PD using iPDGC data (9,581 cases, 33,245 controls) did not provide evidence in favour of an association for the number of drinks per week (70 SNPs; OR=1.15, 95% CI=0.87-1.53) or alcohol consumption (7 SNPs; OR=1.39, 95% CI=0.11-17.56).[34] In contrast, another MR study that used the most recent iPDGC dataset showed an inverse and significant association with the number of drinks per weeks (OR=0.79, 95%CI=0.65-0.96, p=0.021; 33 SNPs).[28] We did not find a significant association with alcohol; however, given the low power of the study to detect an association with this exposure, we cannot draw firm conclusions.

Alternatively, reverse MR showed that genetic liability toward PD is positively associated with alcohol drinking, thus suggesting that persons at higher PD risk are more prone to drink alcohol, independently of whether they actually develop PD. This finding warrants further investigation and replication in further studies.

Coffee drinking

Previous studies, both case-control and cohort, have shown an inverse association between coffee drinking or caffeine intake and PD, with a dose-effect relationship, that was present after adjustment for smoking or in never-smokers.[47]

A previous MR study that assessed several risky behaviours in relation with PD using iPDGC data (9,581 cases, 33,245 controls) did not provide evidence in favour of an association for the number of coffee cups per day (4 SNPs; OR=1.03, 95% CI=0.65-1.63). We did not find

a significant association with coffee drinking, but given the low power of the study to detect an association with this exposure, we cannot draw firm conclusions. However, we did find that genetic liability toward PD was not associated with coffee drinking which does not support the hypothesis of reverse causation for coffee drinking.

Strengths and weaknesses of the study

Strengths of this study include the assessment of several lifestyle behaviours and use of data from a large consortium in which PD cases were carefully assessed by experienced movement disorders specialists. The MR design represents another strength as it avoids bias from reverse causation and confounding.[8] This approach, however, relies on a number of assumptions. We cannot exclude that our findings might have been affected by weak instrument bias. However, in MR analyses, the F-statistic was >10 for all exposures and bias from weak instruments is expected to be towards the null in a two-sample setting.[48] Pleiotropy is an important concern for MR analyses, and recent guidelines recommend using multiple methods that make different assumptions to assess the robustness of findings.[15] We used a number of approaches developed to address this issue, including the weighted median and mode, MR-Egger, and MR-PRESSO. Population stratification is unlikely to be a major concern for our analyses, as we restricted analyses within the Courage-PD consortium to individuals of European descent, cases were compared to controls from each site, and analyses were adjusted for principal components. Another strength of our study is that individual data on age at study and disease duration were available, which allowed us to run stratified analyses. Although stratification inevitably leads to a loss of statistical power, we were able to examine whether associations were consistent in younger participants and in those with shorter disease duration. As PD is a disease of old age, it is possible that genetic associations are biased by survival bias, but analyses in younger participants are unlikely to be biased as they did not reach the age where mortality rates are high.[9]

The main limitation of our study pertains to its statistical power. Our power calculations showed that our sample size was sufficient to detect ORs in the range of 0.4-0.6 for a type-1 error rate of 1.7% to 5%, for smoking and alcohol but not for coffee drinking. The highest power

was noted for smoking initiation; the study was underpowered to detect weaker associations for coffee and alcohol drinking, hence limiting our ability to draw firm conclusions for these exposures. Please note that our study examined a limited number of exposures (selected *a priori* based on existing literature) and is not exploratory, and that the Bonferroni correction is conservative. Our aim was to assess whether MR findings were consistent with those from observational studies using different sets of genetic instruments and methods, and to perform subgroup sensitivity analyses to examine the robustness of our findings. One limitation of our analyses for smoking is that we were not able to stratify analyses by smoking status and to compare results in ever and never smokers using genetic instruments for smoking intensity or cessation.[49] We addressed this issue by using a lifetime smoking exposure index that takes into account several aspects of smoking and was developed in order to allow two-sample MR using data unstratified by smoking status.[17]

Conclusions and future research

Using an independent dataset, our study confirms previous MR findings **adds further evidence** in favour of a protective effect of smoking on PD and shows that this association is not explained by survival or incidence-prevalence bias. For alcohol and coffee drinking, larger studies and stronger genetic instruments are needed.

The number of PD cases is predicted to double between 2015-2040,[50] and the identification of neuroprotective strategies is a major goal. Our findings may help prioritise neuroprotective approaches for PD. Further research is necessary to improve genetic instruments for some of the exposures examined here, to understand the pathways involved in these associations, to determine whether these findings are corroborated in non-European populations, whether PD patients subgroups should be more specifically targeted, and whether there are critical periods of exposure.

Appendix

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Conflict of interest

- PM reports grants from Fonds National de Recherche (FNR), grants from German Research Council (DFG), during the conduct of the study; and Patrick May is co-founder of MeGeno S.A., Esch-sur-Alzette, Luxembourg, a company for personal genomics.
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Table 1: Effect of genetically-predicted smoking on PD.

Exposure	Odds ratio (95% CI)	P-value
Smoking initiation (per 1-SD increase in the prevalence of ever smoking)		
IVW (p-heterogeneity=0.39)	0.74 (0.60-0.93)	0.009
Weighted median	0.64 (0.47-0.89)	0.008
Weighted mode	0.58 (0.24-1.42)	0.23
MR Egger (p-pleiotropy=0.59; I^2_{GX} =0.66)	0.59 (0.24-1.45)	0.25
Corrected MR Egger	0.56 (0.22-1.39)	0.26
MR-PRESSO (p-pleiotropy=0.24)	-	-
Lifetime smoking index (per 1-unit)^a		
IVW (p-heterogeneity=0.007)	0.54 (0.29-1.00)	0.050
Weighted median	0.37 (0.16-0.84)	0.017
Weighted mode	0.29 (0.06-1.34)	0.12
MR Egger (p-pleiotropy=0.93; I^2_{GX} =0.64)	0.60 (0.05-6.77)	0.68
Corrected MR Egger	0.60 (0.06-6.47)	0.68
MR-PRESSO (p-pleiotropy=0.010, p-distortion=0.77) ^b	0.51 (0.29-0.89)	0.021

CI, confidence interval; IVW, inverse variance weighted.

^a In the UK Biobank, the lifetime smoking index had a mean of 0.359 and a standard deviation (SD) of 0.694; a 1-SD increase in the lifetime smoking index is equivalent to an individual smoking 20 cigarettes a day for 15 years and stopping 17 years ago or an individual smoking 60 cigarettes a day for 13 years and stopping 22 years ago. The OR_{IVW} for a 1-SD increase is $0.67^{0.694}=0.76$.

^b Outliers: rs202645.

Table 2: Effect of genetically-predicted alcohol drinking on PD.

Exposure	Odds ratio (95% CI)	P-value
Alcohol drinking (per 1-SD increase of ln(drinks per week))		
IVW (p-heterogeneity=0.062)	0.68 (0.39-1.18)	0.17
Weighted median	0.86 (0.42-1.75)	0.67
Weighted mode	0.86 (0.41-1.77)	0.68
MR Egger (p-pleiotropy=0.94; I^2_{GX} =0.96)	0.70 (0.30-1.61)	0.40
MR-PRESSO (p-pleiotropy=0.042, p-distortion=0.73 ^a)	0.77 (0.46-1.29)	0.33
Alcohol drinking: after exclusion of 2 SNPs associated with coffee drinking: rs1260326 and rs2472297 (per 1-SD increase of ln(drinks per week))		
IVW (p-heterogeneity=0.11)	0.78 (0.45-1.35)	0.37
Weighted median	0.88 (0.44-1.76)	0.72
Weighted mode	0.85 (0.46-1.58)	0.61
MR Egger (p-pleiotropy=0.98; I^2_{GX} =0.96)	0.78 (0.34-1.78)	0.56
MR-PRESSO (p-pleiotropy=0.089)	-	-

CI, confidence interval; IVW, inverse variance weighted.

^a Outliers: rs9607814.

Table 3: Effect of genetically-predicted coffee drinking on PD.

Exposure	Odds ratio (95% CI)	P-value
Coffee drinking (per ln(cups per day))		
IVW (p-heterogeneity=0.017)	1.69 (0.51-5.63)	0.40
Weighted median	1.51 (0.50-4.51)	0.47
Weighted mode	1.45 (0.52-4.03)	0.50
MR Egger (p-pleiotropy=0.73; $I^2_{GX}=0.97$)	2.50 (0.21-29.59)	0.49
MR-PRESSO (p-pleiotropy=0.035, p-distortion=0.86) ^a	1.86 (0.67-5.11)	0.26
Coffee drinking: after exclusion of 2 SNPs associated with alcohol drinking: rs1260326 and rs2472297 (per ln(cups per day))		
IVW (p-heterogeneity=0.053)	1.09 (0.26-4.45)	0.91
Weighted median	1.06 (0.32-3.53)	0.93
Weighted mode	1.11 (0.31-4.01)	0.88
MR Egger (p-pleiotropy=0.35; $I^2_{GX}=0.96$)	3.86 (0.22-66.63)	0.38
MR-PRESSO (p-pleiotropy=0.12)	-	-

CI, confidence interval; IVW, inverse variance weighted.

^a Outlier: rs574367.

Table 4: Reverse Mendelian randomisation using PD-associated SNPs from iPDGC (Nalls et al. 2019)[28] as genetic instruments.

Method	OR (95%CI)	P-value	P-het.	P-pleio.
Smoking initiation 64 SNPs				
IVW	1.01 (0.99-1.02)	0.18	<0.001	
Weighted median	1.01 (0.99-1.02)	0.36		
Weighted mode	1.01 (0.99-1.03)	0.35		
MR-Egger	1.02 (0.99-1.05)	0.15		0.36
MR-PRESSO	-	-		<0.001 ^a
Lifetime smoking index 65 SNPs				
IVW	1.00 (0.99-1.01)	0.83	<0.001	
Weighted median	1.00 (0.99-1.01)	0.38		
Weighted mode	0.99 (0.98-1.01)	0.092		
MR-Egger	1.01 (0.99-1.02)	0.34		0.23
MR-PRESSO	1.00 (0.99-1.01)	0.56		<0.001 ^b
Alcohol drinking 64 SNPs				
IVW	1.02 (1.01-1.03)	0.002	<.001	
Weighted median	1.01 (0.99-1.02)	0.14		
Weighted mode	1.01 (0.99-1.02)	0.21		
MR-Egger	1.02 (0.99-1.04)	0.097		0.85
MR-PRESSO	1.01 (1.00-1.02)	0.042		<.001 ^c
Coffee drinking 65 SNPs				
IVW	1.00 (0.99-1.01)	0.15	<0.001	
Weighted median	1.00 (0.99-1.01)	0.82		
Weighted mode	1.00 (0.99-1.01)	0.65		
MR-Egger	1.00 (0.99-1.01)	0.69		0.21
MR-PRESSO	1.00 (0.99-1.01)	0.25		<0.001 ^d

OR, odds ratio per 1-unit increase in log odds of liability to PD; IVW, inverse-variance weighted (random-effect); CI, confidence interval; p-het., p for heterogeneity (IVW); p-pleio., p for pleiotropy (MR-Egger and MR-PRESSO).

^aNo outlier detected.

^bOutliers: rs12497850, rs12600861, and rs62053943; p-distortion=NS.

^cOutliers: rs62053943, rs6476434, rs6854006, rs7134559, and rs823118; p-distortion=0.041.

^dOutliers: rs2248244 and rs61169879; p-distortion=NS.

Figure 1

Title Forest plot showing MR estimates for the association of smoking initiation and a lifetime smoking index with PD, overall and after stratification by age at study and disease duration in cases.

OR = odds ratio; CI = confidence interval.

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Supplementary methods

Courage-PD international consortium

The Courage-PD (COMprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease) international consortium pooled individual-level data from 35 studies on Parkinson's disease (PD) from different populations worldwide and used the same array to genotype their participants.

The Geo-PD (Genetic Epidemiology Of Parkinson's disease; <https://geopd.biomedinfo.org/>) consortium represents one of the components of Courage-PD. This consortium aims at conducting collaborative studies on genetic susceptibility in PD; one of its main features is that participating sites are distributed in the five continents, therefore representing a highly diverse population. In addition, several other studies from Europe contributed to Courage-PD. PD was diagnosed using standard criteria (United Kingdom Parkinson's Disease Society Brain Bank - UKPDSBB, Gelb, Bower).¹⁻³

All studies were approved by local ethical committees following the procedures of each country, and material transfer agreements were set up between participating sites and the University of Tübingen (Germany).

According to the study's consortium agreement, participating sites contributed DNA and demographic/environmental data. DNAs (25µl of DNA at a concentration of 50 to 100 ng/µl) were shipped for quality control to University of Tübingen (Germany) and genotyped in a central laboratory in Munich (Institute of Human Genetics, Helmholtz Zentrum, Germany). The samples from two sites (Gasser, Morris/Wood) were genotyped at the Laboratory of Neurogenetics (National Institute on Aging, National Institutes of Health, Bethesda, USA). Demographic data were harmonized and collected using a standardized form and cleaned at Inserm U1018 (Villejuif, France).

Genotyping

The Neurochip chip was used to genotype all the samples.⁴ Briefly, this chip is a custom-designed array containing a tagging variant backbone with good genome-wide resolution of about 306,670, complemented with a manually curated custom content comprised of 179,467 variants implicated in diverse neurological diseases, including PD.

Genotyping was performed with an automated protocol according to the manufacturer's instructions (Illumina, San Diego, CA, USA). All arrays were scanned with an Illumina iScan and raw data were analyzed with the Illumina Beeline and GenomeStudio software packages using the manifest file Neuro_Consortium_20013217_A1.bpm. Clustering was performed in GenomeStudio with the GenTrain

cluster 2.0 algorithm. Genotypes were post-processed with zCall (DOI: 10.1093/bioinformatics/bts479) to improve detection of rare alleles.

Quality control

Genotyped data exported from Genome Studio to PLINK format were used for quality control and downstream analysis. The pooled dataset from the 35 sites consists of 27,538 subjects. Phenotypic data were missing for 245 subjects and three sites were removed as they only included cases, leaving 26,535 subjects (14,859 cases, 11,431 controls) for quality control using “COMRARE” an automated pipeline under development at the University of Tübingen. The pipeline uses PLINK (<https://www.cog-genomics.org/plink>) and R scripts (R Foundation for Statistical Computing, Vienna, Austria) and the following steps were implemented separately for each site:

1- Per individual quality control:

- Identification of individuals with elevated missing genotyping rates or outlying heterozygosity rate: individuals with a genotype failure rate $\geq 4\%$ or heterozygosity rate ± 4 standard deviations from the mean were excluded.
- Identification of Individuals with discordant sex information: the homozygosity rate was calculated for X-linked SNPs for each individual and compared to the expected rate. Participants for whom phenotypic and genotypic sex were discordant were removed.
- Identification of duplicated or related Individuals: pairs of individuals with an identity by descent (IBD) greater than 0.185 were removed.
- Eigensoft software was used to compute principal components in order to correct for population stratification by merging our dataset with HapMap.^{5 6} A scatter plot of the first two principal components was used to identify outliers in each study.

2- Per marker quality control:

- Identification of markers with high missing data rate: a call-rate threshold of 4% was used and SNPs with a lower rate were removed.
- SNPs with a significant ($P < 10^{-5}$) difference in rates of missing values between cases and controls were removed.
- We excluded variants with a minor allele frequency (MAF) $< 5 \times 10^{-8}$ and those in Hardy-Weinberg disequilibrium ($P < 5 \times 10^{-8}$).

Imputation

After QC, we used the HRC/1000G imputation preparation and checking tool (<https://www.well.ox.ac.uk/~wrayner/tools/HRC-1000G-check-bim-v4.3.0.zip>) to check for Ref/Alt allele assignments, incorrect strands, deviation from allele frequency, and palindromic SNPs. Imputation of autosomal variants was performed separately for each dataset based on based on 271,398 to 373,664 SNPs in each study, through the Michigan Imputation server using the HRC reference panel and the GRCh37/hg19 assembly with a R^2 filter of 0.3. The mean of the number of SNPs available in each study after imputation was 13,710,549 (SD=2,986,478).

Association analysis and meta-analysis

We excluded from our analyses samples overlapping with the international Parkinson Disease Genomics Consortium (iPDGC) which included all the samples from three sites (Pastor/Diez-Fairen, Spain; Toft, Norway; Morris/Wood, UK) as well as 1,000 samples from the Gasser/Sharma (Germany) site (642 cases, 358 controls) and 137 samples of PD cases from the Tolosa site (Spain). Analyses are also restricted to sites that provided samples for both cases and controls and to participants of Caucasian ancestry; only sites with at least 50 cases or 50 controls were included. In addition, as the role of environmental factors may be different in carriers of Mendelian PD mutations, we excluded participants with GBA/LRRK2 mutations or positive family history of PD. The main characteristics of 7,369 cases and 7,018 controls from 23 sites included in the analyses are shown in Supplementary table 1.

We excluded SNPs with a MAF <1%, in Hardy-Weinberg disequilibrium ($P < 5 \times 10^{-8}$), and those with low imputation quality ($r^2 < 0.8$). The final number of SNPs available for analysis in each study was comprised between 5,934,239 and 7,168,307. Only SNPs available in 75% ($n=17$) of the studies or more were retained for further analyses.

For our MR analyses, we selected a total of 411 SNPs, of which 6 were not available and 37 excluded (Supplementary table 5). Therefore, the final number of SNPs used in the analyses was of 368 SNPs, of which 93% were available in all studies. Of these SNPs, 27 were genotyped and 341 were imputed; when genotyped SNPs were available, we selected them in priority.

For each site, logistic regression adjusted for sex and the first four principal components was performed for each SNP under an additive genetic model (number of alleles for genotyped SNPs, dosage for imputed SNPs) using PLINK software (version 1.9).⁷

Summary statistics from the GWAS of the 23 studies were meta-analysed using the GWAMA software.⁸ To assess heterogeneity of genetic associations with each SNP in Courage-PD, we used the I^2

statistic; I^2 values of 0 to 24% suggest little heterogeneity, 25 to 49% reflect moderate heterogeneity, 50 to 74% reflect large heterogeneity, and >75% reflect very large heterogeneity. Effects size and standard errors of SNPs with little heterogeneity across studies ($I^2 \leq 25\%$) were combined using a fixed-effect model, while we used a random-effects model for SNPs with higher heterogeneity ($I^2 > 25\%$). Of 368 SNPs used in our MR analyses, 324 (88%) displayed little heterogeneity and 44 (12%) had moderate heterogeneity; there were no SNPs with I^2 above 50%.

Analyses were first performed overall. We then repeated our analyses: (i) in two groups defined by median age at study (≤ 67 years, > 67 years; 6,086 cases and 5,672 controls from 19 studies); (ii) in two groups defined by median disease duration in PD cases (≤ 7 years, $N=3,633$; > 7 years, $N=3,271$) from 22 studies (cases from each group were compared to all controls).

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Supplementary table 1: Characteristics of cases and controls from the Courage-PD consortium by study site (after quality control).

Continent	Principal investigators	Country	Status	N	Sex (%)		Age at study			Age at PD onset			Age at PD diagnosis			Disease duration ^b	
					Male	Female	Mean	SD	MD	Mean	SD	MD	Mean	SD	MD	Mean	SD
Africa	Bardien/Carr ^a	South Africa	Cases	117	59.8	40.2	68.2	11.2		59.6	12.6		59.6	12.6		8.5	6.7
			Controls	80	57.5	42.5	50.8	12.6		-	-		-	-		-	-
North America	Farrer ^a	United States	Cases	262	66.4	33.6	66.9	10.4	1	55.8	11.5	1	58.6	11.5	96	11.0	6.5
			Controls	394	31.0	69.0	69.4	12.2		-	-		-	-		-	-
	Rogaeva/Lang ^a	Canada	Cases	159	66.0	34.0	62.6	13.0	5	52.8	12.8	5			159	9.8	5.9
			Controls	149	38.9	61.1	74.0	8.6		-	-		-	-		-	-
Australia	Mellick ^a	Australia	Cases	399	64.9	35.1	68.2	9.3		59.1	11.5		60.7	10.8	8	9.2	7.1
			Controls	399	48.4	51.6	67.7	9.0		-	-		-	-		-	-
Europe	Aasly ^a	Norway	Cases	463	59.6	40.4	78.2	11.2		61.1	10.8				463	17.1	5.4
			Controls	487	54.2	45.8	73.2	14.1	74	-	-		-	-		-	-
	Annesi ^a	Italy	Cases	89	65.2	34.8	66.8	9.0		59.6	10.1		66.8	9.0		7.2	5.6
			Controls	93	46.2	53.8	58.6	20.1		-	-		-	-		-	-
	Brice/Corvol/Lesage ^a	France	Cases	745	59.6	40.4	61.1	10.8	25	52.1	11.0	25			745	8.9	6.3
			Controls	275	56.4	43.6	62.4	10.6		-	-		-	-		-	-
	Carmine Belin/Ran ^a	Sweden	Cases	214	63.6	36.4	67.2	10.3		58.6	11.0				214	8.6	6.2
			Controls	611	54.8	45.2	66.3	9.8	583	-	-		-	-		-	-
	Chartier-Harlin/Muttez ^a	France	Cases	285	55.8	44.2	64.3	9.0		52.3	10.3		53.3	10.1		12	5.9
			Controls	217	38.7	61.3	59.8	12.5		-	-		-	-		-	-
	Deutschländer ^a	Germany	Cases	264	61.7	38.3	69.6	9.9		60.7	11.4		59.6	10.7	199	8.9	6.6
			Controls	40	32.5	67.5	66.3	10.2		-	-		-	-		-	-
	Elbaz ^a	France	Cases	387	60.5	39.5	70.1	7.3		65	7.6		65.9	7.4	1	5.2	4.1
			Controls	998	59.0	41.0	69.8	7.6		-	-		-	-		-	-
	Ferreira	Portugal	Cases	313	58.5	41.5	69.1	10.1		58.5	11.7		60.2	11.8		10.6	7.2
			Controls	53	26.4	73.6	46.9	18.7		-	-		-	-		-	-
	Gasser/Sharma ^c	Germany	Cases	432	65.0	35.0	65.8	10.8		60.4	11.2		60.4	11.2	129	5.3	5.1
			Controls	388	43.0	57.0	62.9	7.3		-	-		-	-		-	-
	Duga/Cilia ^a	Italy	Cases	1340	59.3	40.7	65.9	10.9		59.1	11.3		60.7	11.1		6.8	5.6
			Controls	1328	34.3	65.7	61.9	10.9		-	-		-	-		-	-
	Hadjigeorgiou ^a	Greece	Cases	256	48.4	51.6	67.6	10.4		62.8	10.3		63.7	10.4		4.8	4.4
			Controls	310	47.4	52.6	69.8	8.7		-	-		-	-		-	-
	Koks/Taba ^a	Estonia	Cases	210	40.0	60.0	73.0	8.2		66.7	9.8				210	6.3	5.4
			Controls	163	41.1	58.9	72.6	10.1		-	-		-	-		-	-

	Principal investigators	Country	Status	N	Sex (%)		Age at study			Age at PD onset			Age at PD diagnosis			Disease duration ^b		
Continent					Male	Female	Mean	SD	MD	Mean	SD	MD	Mean	SD	MD	Mean	SD	
	Kruger ^a	Luxembourg	Cases	285	69.5	30.5	67.7	11.3		60.1	12.8		62.3	12.0	10	7.2	6.2	
			Controls	283	57.2	42.8	58.5	12.1		-	-		-	-		-	-	
	Puschmann ^a	Sweden	Cases	50	70.0	30.0	69.0	10.4		61.5	11.3				49	7.4	4.8	
			Controls	105	29.5	70.5	66.7	8.9		-	-		-	-		-	-	
	Stefanis/Simitsi ^a	Greece	Cases	174	62.1	37.9	67.7	13.3		61.5	13.6		61.9	12.7	44	6.2	6.3	
			Controls	178	36.0	64.0	67.0	9.6		-	-		-	-		-	-	
	Tolosa ^d	Spain	Cases	141	62.4	37.6	67.4	10.3		60.4	11.1				141	7.0	5.9	
			Controls	66	16.7	83.3	61.9	12.1	8	-	-		-	-		-	-	
	Valente	Italy	Cases	223	60.1	39.9	67.1	12.7	4	54.3	10.8	4	59.1	7.8	144	12.7	8.2	
			Controls	54	38.9	61.1	78.4	9.6		-	-		-	-		-	-	
	Wirdefeldt ^a	Sweden	Cases	61	55.7	44.3	75.9	8.1		66.8	9.9				61	8.6	5.6	
			Controls	165	46.1	53.9	73.9	9.6		-	-		-	-		-	-	
	Zimprich	Austria	Cases	500	63.0	37.0				500	59.1	11.2				500		
			Controls	182	40.1	59.9				182	-	-		-	-		-	-
	Total			Cases	7,369													
				Controls	7,018													

MD, missing data; SD, standard deviation.

^a Sites from the Geo-PD consortium.

^b Duration disease = age at study - age at PD onset. Missing values are the same as those for age at study.

^c For the Gasser/Sharma site, we excluded 1,000 samples overlapping with iPDGC (642 cases, 358 controls).

^d For the Tolosa site, we excluded 137 samples of PD cases overlapping with iPDGC.

Supplementary table 2: Statistical power to detect odds ratios comprised between 0.3 and 0.9 for two values of type-1 error in Mendelian randomization analyses in the Courage-PD consortium (7,369 cases, 7,018 controls).

Exposure	R ²	Type-1 error=1.7%							Type-1 error=5%						
		Odds ratio							Odds ratio						
		0.30	0.40	0.50	0.60	0.70	0.80	0.90	0.30	0.40	0.50	0.60	0.70	0.80	0.90
Smoking initiation	2.95%	1.00	1.00	1.00	1.00	0.91	0.47	0.10	1.00	1.00	1.00	1.00	0.96	0.64	0.19
Lifetime smoking index	0.49%	1.00	0.95	0.73	0.42	0.19	0.07	0.03	1.00	0.98	0.85	0.59	0.33	0.16	0.07
Alcohol drinking	0.48%	1.00	0.94	0.72	0.41	0.19	0.07	0.03	1.00	0.98	0.84	0.58	0.32	0.15	0.07
Coffee drinking	0.21%	0.88	0.60	0.33	0.17	0.08	0.04	0.02	0.95	0.75	0.50	0.30	0.17	0.09	0.06

R² is the sum of the proportion of the variance of the exposure explained by each individual genetic variants (Supplementary table 3).

Bold values are ≥ 0.80 .

Statistical power was computed according to Brion MJ et al. (Int J Epidemiol 2013;42:1497-1501).

Supplementary table 3: SNPs used for Mendelian randomization analyses: individual associations with exposures and PD.

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							R ²
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I ² (%)	
Alcohol drinking (per 1-SD increase of ln(drinks per week))														
rs705687	1:4548453	G/A	0.22	0.011	0.002	8.15E-10	23	14387	0.79	0.031	0.032	3.28E-01	0	4.01E-05
rs58107686	1:33837334	A/C	0.67	0.010	0.002	7.79E-10	23	14387	0.34	0.020	0.027	4.59E-01	11.1	4.19E-05
rs12088813	1:66407700	C/A	0.73	0.009	0.002	1.58E-08	23	14387	0.26	0.044	0.029	1.26E-01	0	3.41E-05
rs5024204	1:71491890	A/T	0.28	0.010	0.002	2.55E-09	23	14387	0.28	0.045	0.028	1.16E-01	0	3.78E-05
rs10753661	1:165119792	A/G	0.32	0.009	0.002	3.76E-08	23	14387	0.68	0.033	0.028	2.40E-01	0	3.23E-05
rs28680958	1:173848808	A/G	0.78	0.011	0.002	5.13E-10	23	14387	0.22	0.004	0.031	8.96E-01	0	4.11E-05
rs823114	1:205719532	G/A	0.55	0.009	0.001	2.31E-09	23	14387	0.42	-0.032	0.026	2.22E-01	0	3.80E-05
rs77165542	2:430975	T/C	0.97	0.026	0.004	5.63E-11	3	1179	Excluded for MR					
rs1260326 ^b	2:27730940	T/C	0.60	0.021	0.001	8.05E-45	23	14387	0.46	-0.069	0.026	8.41E-03	0	2.09E-04
rs13383034	2:45155276	C/T	0.33	0.015	0.002	6.31E-22	23	14387	0.68	-0.061	0.035	8.17E-02	28.4	9.84E-05
rs13032049	2:63581507	A/G	0.28	0.010	0.002	3.00E-10	23	14387	0.70	0.055	0.038	1.47E-01	32.8	4.22E-05
rs828867	2:74334462	G/A	0.54	0.009	0.001	2.15E-09	16	9769	Excluded for MR					
rs11692435	2:98275354	G/A	0.09	0.017	0.003	2.53E-11	NA in COURAGE-PD							
rs13024996	2:144225215	A/C	0.64	0.011	0.002	5.72E-13	23	14387	0.37	0.009	0.027	7.43E-01	14.9	5.51E-05
rs72859280	2:147956293	G/T	0.04	0.023	0.004	4.44E-09	20	11260	0.96	-0.131	0.081	1.06E-01	0	3.65E-05
rs56337305	2:225475560	C/T	0.62	0.010	0.001	1.63E-10	23	14387	0.38	-0.014	0.026	5.83E-01	24.8	4.35E-05
rs13094887	3:70968431	T/A	0.70	0.010	0.002	8.57E-11	23	14387	0.69	-0.037	0.028	1.77E-01	0	4.47E-05
rs62250685	3:85457240	G/A	0.39	0.014	0.002	1.05E-21	23	14387	0.61	-0.017	0.026	5.09E-01	0	9.77E-05
rs9838144	3:131576287	C/G	0.79	0.010	0.002	2.65E-08	23	14387	0.80	-0.050	0.032	1.26E-01	15.8	3.28E-05
rs2011092	3:141124607	C/T	0.66	0.009	0.002	7.35E-09	23	14387	0.30	-0.006	0.028	8.19E-01	0	3.55E-05
rs6787172	3:158187811	G/T	0.45	0.008	0.001	4.27E-08	23	14387	0.54	0.022	0.025	3.77E-01	0	3.19E-05
rs3748034	4:3446091	T/G	0.86	0.012	0.002	1.67E-08	23	14387	0.14	-0.009	0.037	8.16E-01	23.3	3.38E-05
rs11940694 ^a	4:39414993	A/G	0.60	0.026	0.001	3.03E-68	23	14387	0.43	-0.031	0.028	2.70E-01	6.3	3.24E-04
rs4501255	4:42151306	C/G	0.23	0.011	0.002	4.83E-10	23	14387	0.23	-0.030	0.031	3.30E-01	0	4.11E-05
rs1229984 ^a	4:100239319	T/C	0.96	0.151	0.004	<1.00E-300	21	14004	0.06	-0.011	0.055	8.49E-01	0	1.61E-03
rs2165670	4:100286085	G/A	0.11	0.023	0.002	1.67E-22	22	14205	0.91	0.047	0.061	4.37E-01	36.6	1.01E-04
rs13107325 ^a	4:103188709	T/C	0.93	0.028	0.003	1.53E-22	23	14387	0.07	-0.104	0.051	4.04E-02	0	1.01E-04
rs4690727	4:143648579	C/G	0.72	0.011	0.002	2.43E-11	23	14387	0.70	-0.009	0.028	7.63E-01	0	4.74E-05
rs12651313	4:171086393	G/C	0.56	0.009	0.001	3.79E-09	23	14387	0.56	Excluded for MR				
rs4916723	5:87854395	C/A	0.58	0.010	0.001	1.72E-11	23	14387	0.40	-0.044	0.027	1.06E-01	0	4.81E-05
rs12655091	5:144412335	A/G	0.47	0.008	0.001	1.25E-08	23	14387	0.52	-0.021	0.026	4.13E-01	6.1	3.44E-05
rs55872084	5:155902003	G/T	0.23	0.010	0.002	6.32E-09	23	14387	0.78	0.012	0.031	7.03E-01	0	3.58E-05
rs6460047	7:73042443	T/C	0.21	0.012	0.002	9.69E-11	23	14387	0.81	-0.021	0.041	6.08E-01	26.8	4.45E-05
rs10236149	7:98977515	G/A	0.88	0.013	0.002	1.18E-09	23	14387	0.13	0.032	0.038	4.00E-01	9.7	3.93E-05
rs35034355	7:103840115	A/G	0.48	0.008	0.001	2.87E-08	23	14387	0.49	-0.013	0.026	6.24E-01	0	3.27E-05
rs6951574	7:153489744	T/C	0.46	0.013	0.001	1.58E-19	23	14387	0.53	0.010	0.026	6.99E-01	0	8.68E-05
rs13250583	8:20949917	T/C	0.79	0.010	0.002	4.70E-08	23	14387	0.20	-0.011	0.033	7.34E-01	15.1	3.17E-05
rs1217091	8:64527399	T/C	0.81	0.012	0.002	7.05E-11	23	14387	0.20	0.073	0.033	2.53E-02	0	4.52E-05
rs28601761	8:126500031	C/G	0.42	0.009	0.001	7.17E-10	23	14387	0.42	Excluded for MR				
rs55932213	9:108755622	A/G	0.74	0.009	0.002	9.55E-09	21	13853	0.30	-0.019	0.030	5.29E-01	13.5	3.50E-05
rs10978550 ^a	9:109345993	C/T	0.79	0.012	0.002	7.15E-11	23	14387	0.20	0.014	0.032	6.64E-01	0	4.52E-05
rs7074871	10:110507806	A/G	0.74	0.009	0.002	1.86E-08	23	14387	0.25	0.009	0.029	7.48E-01	0	3.36E-05
rs17665139	10:125093880	T/C	0.85	0.012	0.002	1.59E-08	23	14387	0.14	-0.007	0.037	8.45E-01	14.3	3.39E-05
rs7950166	11:8642218	T/C	0.36	0.010	0.002	9.89E-11	23	14387	0.60	-0.019	0.027	4.76E-01	13.6	4.44E-05

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²
rs11030084	11:27643725	T/C	0.82	0.011	0.002	1.72E-08	23	14387	0.20	-0.035	0.032	2.82E-01	0	3.38E-05
rs56030824	11:47397353	A/G	0.68	0.012	0.002	1.15E-13	23	14387	0.32	0.006	0.027	8.26E-01	24.9	5.88E-05
rs10750025 ^a	11:113424042	C/T	0.69	0.010	0.002	4.89E-11	23	14387	0.34	-0.004	0.027	8.85E-01	0	4.59E-05
rs4938230	11:116075001	C/A	0.84	0.013	0.002	1.48E-10	14	6683	Excluded for MR					
rs682011 ^a	11:121544285	T/C	0.56	0.008	0.001	2.22E-08	23	14387	0.46	-0.021	0.026	4.21E-01	0	3.33E-05
rs12795042	11:133658168	C/A	0.38	0.008	0.002	3.25E-08	23	14387	0.58	-0.012	0.036	7.33E-01	31.3	3.25E-05
rs3809162	12:54674235	A/G	0.40	0.009	0.001	1.19E-09	23	14387	0.64	-0.014	0.027	6.00E-01	8.5	3.93E-05
rs10506274	12:81601464	T/G	0.52	0.009	0.001	5.78E-10	23	14387	0.48	0.017	0.025	5.13E-01	19.7	4.08E-05
rs4842786	12:92170791	A/G	0.42	0.009	0.001	2.73E-09	23	14387	0.56	0.000	0.027	9.99E-01	22.8	3.76E-05
rs500321	13:27124360	T/A	0.26	0.010	0.002	4.92E-09	23	14387	0.28	0.009	0.029	7.70E-01	11.5	3.63E-05
rs1123285	14:57274519	G/C	0.66	0.009	0.002	8.14E-09	23	14387	0.66	-0.041	0.027	1.35E-01	10.4	3.53E-05
rs28929474	14:94844947	T/C	0.98	0.037	0.005	1.34E-11	16	9567	Excluded for MR					
rs2472297 ^{a,b}	15:75027880	C/T	0.25	0.011	0.002	3.10E-10	23	14387	0.81	-0.032	0.033	3.30E-01	0	4.21E-05
rs12907323	15:86796012	A/G	0.41	0.008	0.001	9.93E-09	23	14387	0.56	0.010	0.026	7.11E-01	2	3.50E-05
rs17177078 ^a	16:24810681	T/C	0.94	0.022	0.003	1.27E-13	23	14387	0.08	-0.027	0.048	5.78E-01	0	5.84E-05
rs378421	16:28754684	A/G	0.60	0.011	0.001	4.83E-14	23	14387	0.38	-0.030	0.027	2.56E-01	8.6	6.05E-05
rs62044525	16:64872590	G/C	0.82	0.012	0.002	1.03E-10	23	14387	0.82	0.079	0.033	1.77E-02	0	4.45E-05
rs1104608	16:73912588	C/G	0.58	0.011	0.001	1.05E-13	11	5990	Excluded for MR					
rs4548913	17:2209888	A/G	0.37	0.008	0.002	3.11E-08	23	14387	0.60	-0.014	0.027	5.91E-01	9.7	3.25E-05
rs3803800 ^a	17:7462969	A/G	0.79	0.011	0.002	1.50E-10	23	14387	0.20	0.005	0.032	8.82E-01	0	4.36E-05
rs2854334	17:29715500	A/G	0.62	0.009	0.001	7.51E-10	20	13362	0.39	0.035	0.030	2.38E-01	0	4.03E-05
rs10438820	17:78524597	C/T	0.70	0.009	0.002	1.76E-08	23	14387	0.30	0.029	0.028	3.03E-01	6.3	3.37E-05
rs9950000	18:53052169	T/C	0.60	0.009	0.001	9.38E-10	23	14387	0.40	-0.009	0.026	7.41E-01	0	3.97E-05
rs4092465	18:55080437	G/A	0.36	0.008	0.002	4.39E-08	NA in COURAGE-PD							
rs281379	19:49214274	G/A	0.51	0.014	0.001	4.91E-21	23	14387	0.54	0.016	0.026	5.43E-01	0	9.41E-05
rs4815364	20:25035711	G/A	0.62	0.009	0.001	1.02E-08	23	14387	0.37	0.044	0.027	1.04E-01	6.3	3.48E-05
rs9607814	22:41946519	A/C	0.80	0.010	0.002	4.31E-08	23	14387	0.21	-0.121	0.032	1.83E-04	4.2	3.32E-05
Coffee drinking (per ln(cups per day))														
rs574367	1:177873210	T/G	0.21	0.010	0.002	8.06E-09	23	14387	0.18	-0.139	0.051	6.63E-03	47	3.32E-05
rs10865548	2:631606	G/A	0.83	0.015	0.002	4.46E-15	23	14387	0.80	0.014	0.033	6.77E-01	10.4	6.35E-05
rs1260326 ^b	2:27730940	C/T	0.61	0.014	0.002	2.62E-19	23	14387	0.54	0.069	0.026	8.41E-03	0	9.33E-05
rs4410790	7:17284577	C/T	0.63	0.039	0.002	5.59E-141	23	14387	0.61	-0.009	0.027	7.22E-01	3.6	7.09E-04
rs34060476	7:73037956	G/A	0.13	0.019	0.002	5.06E-18	23	14387	0.11	0.045	0.041	2.72E-01	15.6	8.17E-05
rs1057868	7:75615006	T/C	0.29	0.020	0.002	5.26E-33	23	14387	0.28	0.041	0.028	1.48E-01	0	1.65E-04
rs597045	11:56272114	A/T	0.70	0.011	0.002	6.62E-11	23	14387	0.70	-0.035	0.037	3.42E-01	33.2	5.08E-05
rs1956218	14:33075243	G/A	0.56	0.008	0.002	3.62E-08	23	14387	0.53	-0.027	0.026	2.96E-01	0	3.15E-05
rs2472297 ^{a,b}	15:75027880	T/C	0.26	0.044	0.002	5.19E-155	23	14387	0.19	0.032	0.033	3.30E-01	0	7.45E-04
rs66723169	18:57808978	A/C	0.23	0.015	0.002	9.88E-17	23	14387	0.23	-0.019	0.031	5.47E-01	9.5	7.97E-05
rs2330783	22:24747031	G/T	0.99	0.044	0.006	1.57E-12	18	11562	0.98	0.168	0.119	1.57E-01	4.6	3.83E-05
Lifetime smoking index														
rs1193237	1:7526486	C/G	0.56	0.008	0.001	2.80E-08	23	14387	0.57	Excluded for MR				
rs4949465	1:32178489	C/T	0.13	0.012	0.002	1.70E-08	23	14387	0.12	0.002	0.040	9.59E-01	0	3.06E-05
rs549845	1:44076469	G/A	0.30	0.011	0.002	8.30E-14	23	14387	0.33	-0.054	0.028	5.20E-02	23.8	5.34E-05
rs1933270	1:49977965	T/G	0.36	0.009	0.001	1.50E-10	23	14387	0.37	0.057	0.027	3.23E-02	0	3.93E-05
rs7528604	1:66407352	G/A	0.57	0.010	0.001	5.70E-12	23	14387	0.56	-0.002	0.026	9.32E-01	0.4	4.58E-05
rs11210229	1:73860028	A/G	0.38	0.012	0.001	2.00E-16	23	14387	0.45	-0.025	0.026	3.48E-01	17.4	6.48E-05

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I ² (%)	R ²
rs7553348	1:75005067	G/A	0.44	0.010	0.001	5.20E-12	23	14387	0.44	0.009	0.026	7.44E-01	4.8	4.57E-05
rs10922907	1:91193049	A/T	0.45	0.010	0.001	3.00E-13	23	14387	0.48			Excluded for MR		
rs1931263	1:96175101	T/G	0.49	0.008	0.001	4.00E-08	23	14387	0.50	-0.026	0.026	3.16E-01	2.8	2.89E-05
rs7519626	1:99514554	C/T	0.32	0.008	0.001	1.20E-08	23	14387	0.36	0.005	0.028	8.64E-01	12	3.10E-05
rs9435340	1:107593201	T/A	0.34	0.008	0.001	1.20E-08	23	14387	0.35	0.013	0.028	6.37E-01	0	3.15E-05
rs10918701	1:162090536	G/A	0.37	0.008	0.001	2.10E-08	23	14387	0.40	-0.017	0.026	5.25E-01	17	3.01E-05
rs2867112	2:651349	T/G	0.83	0.015	0.002	4.80E-15	23	14387	0.82	0.015	0.034	6.59E-01	5.9	6.03E-05
rs6741228	2:22548774	T/C	0.43	0.008	0.001	1.60E-08	23	14387	0.44	-0.015	0.026	5.56E-01	10.9	3.09E-05
rs62135536	2:44326028	C/T	0.97	0.024	0.004	8.00E-10	18	13065	0.97	-0.006	0.086	9.49E-01	13.6	3.64E-05
rs7569203	2:45154418	C/A	0.31	0.011	0.002	7.40E-13	23	14387	0.32	0.058	0.035	9.40E-02	27.7	4.96E-05
rs13016665	2:57995348	A/C	0.42	0.008	0.001	1.80E-09	23	14387	0.42	0.041	0.027	1.19E-01	0	3.52E-05
rs4671357 ^a	2:60136176	C/T	0.48	0.009	0.001	1.10E-11	23	14386	0.47	-0.018	0.026	4.82E-01	0	4.45E-05
rs359243	2:60475509	C/T	0.61	0.009	0.001	9.50E-10	23	14387	0.57	-0.013	0.035	7.03E-01	32.1	3.63E-05
rs2678670	2:104469564	A/T	0.49	0.009	0.001	3.10E-10	23	14387	0.50			Excluded for MR		
rs62155874	2:105973094	G/A	0.13	0.017	0.002	5.20E-16	23	14387	0.12	-0.023	0.039	5.63E-01	0	6.32E-05
rs3811038	2:113240183	C/T	0.28	0.010	0.002	8.90E-10	23	14387	0.28	-0.004	0.029	8.90E-01	9.1	3.64E-05
rs2890772	2:146175106	T/G	0.59	0.014	0.001	2.10E-22	23	14387	0.55	0.009	0.026	7.20E-01	0	9.10E-05
rs62175972	2:161362830	T/C	0.97	0.022	0.004	1.70E-08	23	14387	0.96	0.050	0.069	4.66E-01	0	3.11E-05
rs3769949	2:166199284	A/T	0.47	0.008	0.001	2.50E-09	23	14387	0.47			Excluded for MR		
rs13009008	2:174043233	A/G	0.33	0.009	0.001	4.60E-09	23	14387	0.35	0.045	0.027	9.27E-02	0	3.28E-05
rs4473348	2:182073742	T/A	0.75	0.010	0.002	6.40E-11	23	14387	0.76	-0.037	0.030	2.21E-01	13.6	4.08E-05
rs12623702	2:202885506	G/A	0.39	0.010	0.001	7.70E-12	23	14387	0.37	-0.048	0.027	6.88E-02	0	4.53E-05
rs6779302	3:16859710	T/G	0.37	0.009	0.001	1.20E-09	23	14387	0.35	0.041	0.027	1.25E-01	0	3.56E-05
rs6778080 ^a	3:49317338	T/C	0.27	0.011	0.002	1.30E-12	23	14387	0.27	-0.018	0.030	5.39E-01	2.8	4.84E-05
rs775758	3:77582005	A/T	0.43	0.008	0.001	1.10E-08	23	14387	0.43			Excluded for MR		
rs421983	3:84892866	T/C	0.52	0.009	0.001	3.30E-10	23	14387	0.50	0.004	0.025	8.64E-01	14.2	3.79E-05
rs326341	3:107811142	G/A	0.52	0.009	0.001	1.20E-11	23	14387	0.55	-0.012	0.026	6.48E-01	0	4.44E-05
rs73220544	3:131074511	C/A	0.16	0.011	0.002	1.50E-08	21	13998	0.18	-0.062	0.037	9.73E-02	0	3.11E-05
rs9842947	3:157412246	T/C	0.67	0.009	0.001	3.10E-09	23	14387	0.70	0.033	0.029	2.51E-01	0	3.38E-05
rs624833 ^a	4:2881256	T/G	0.69	0.009	0.002	6.60E-10	23	14387	0.69	-0.076	0.031	1.30E-02	10.7	3.66E-05
rs61796681	4:23678196	T/A	0.09	0.013	0.002	4.20E-08	23	14387	0.07	0.025	0.049	6.17E-01	6.7	2.88E-05
rs317021	4:35418368	A/T	0.19	0.012	0.002	1.10E-10	23	14387	0.16	0.030	0.035	3.96E-01	15.1	4.05E-05
rs72678864	4:112422145	G/A	0.83	0.012	0.002	1.60E-11	23	14387	0.85	0.025	0.037	4.88E-01	0	4.36E-05
rs17576594	4:147952241	G/A	0.72	0.011	0.002	1.70E-12	23	14387	0.74	-0.044	0.029	1.27E-01	0	4.80E-05
rs11948770	5:13246336	C/T	0.23	0.010	0.002	4.90E-10	23	14387	0.23	-0.045	0.030	1.38E-01	23.6	3.73E-05
rs71627581	5:43161351	G/A	0.89	0.013	0.002	1.60E-09	15	8384				Excluded for MR		
rs10052591	5:50812738	T/C	0.57	0.008	0.001	2.10E-09	23	14387	0.57	0.026	0.026	3.10E-01	0	3.45E-05
rs2080870	5:60388313	A/T	0.26	0.009	0.002	4.90E-08	23	14387	0.25	0.062	0.030	3.68E-02	0	2.85E-05
rs4571506 ^a	5:87756918	C/T	0.54	0.008	0.001	1.50E-08	23	14385	0.51	-0.053	0.026	4.10E-02	0	3.08E-05
rs4957528	5:106420589	C/A	0.79	0.010	0.002	4.20E-09	10	5308				Excluded for MR		
rs329120 ^a	5:133861756	C/T	0.58	0.010	0.001	6.30E-12	23	14387	0.57	-0.045	0.026	8.41E-02	0	4.54E-05
rs986391	5:166993972	G/A	0.37	0.011	0.001	9.40E-15	23	14387	0.38	-0.020	0.027	4.73E-01	0	5.76E-05
rs13153393	5:167604213	G/A	0.12	0.014	0.002	2.50E-10	23	14387	0.11	0.054	0.041	1.88E-01	10.7	3.88E-05
rs245774	5:170530930	G/A	0.73	0.009	0.002	7.40E-09	23	14387	0.71	-0.053	0.029	6.81E-02	0	3.22E-05
rs6935954	6:26255451	A/G	0.42	0.010	0.001	8.20E-12	23	14387	0.39	0.028	0.033	4.01E-01	25.5	4.48E-05
rs2254710	6:37477000	C/A	0.24	0.009	0.002	3.50E-08	23	14387	0.23	0.028	0.042	5.05E-01	33.1	2.92E-05
rs2894808	6:52861990	A/T	0.08	0.015	0.003	3.50E-09	23	14387	0.10	0.007	0.044	8.70E-01	0	3.36E-05
rs12202536	6:67475273	G/A	0.49	0.008	0.001	2.80E-09	23	14387	0.46	-0.068	0.026	8.41E-03	20.2	3.39E-05

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²
rs7766610	6:111707821	C/A	0.18	0.013	0.002	2.20E-12	23	14387	0.19	-0.058	0.043	1.84E-01	29.6	4.73E-05
rs1922018	7:3560401	C/T	0.36	0.010	0.001	3.00E-12	23	14387	0.35	-0.014	0.027	6.11E-01	0	4.66E-05
rs10226228	7:32315613	G/A	0.37	0.011	0.001	2.00E-15	23	14387	0.36	-0.034	0.027	2.04E-01	0	6.07E-05
rs11768481	7:96629103	C/A	0.67	0.009	0.001	9.90E-10	5	3107	Excluded for MR					
rs6962772	7:99081730	A/G	0.85	0.011	0.002	7.80E-09	23	14387	0.85	-0.012	0.036	7.28E-01	0	3.20E-05
rs10282292 ^a	7:111092478	C/T	0.36	0.009	0.001	5.90E-10	23	14386	0.37	0.019	0.027	4.73E-01	0	3.71E-05
rs2401924	7:115057862	G/C	0.50	0.011	0.001	2.70E-14	23	14387	0.51	Excluded for MR				
rs7807019	7:117543063	G/A	0.46	0.010	0.001	6.70E-14	23	14387	0.45	0.020	0.026	4.32E-01	5.5	5.39E-05
rs6957896 ^a	7:132309592	T/C	0.50	0.008	0.001	4.50E-08	22	13529	0.50	-0.039	0.035	2.67E-01	32	2.88E-05
rs4731925	7:132664757	T/C	0.68	0.008	0.001	2.60E-08	23	14387	0.69	-0.035	0.028	2.06E-01	0	2.97E-05
rs35169606	8:9604066	T/G	0.61	0.009	0.001	1.20E-09	16	9769	Excluded for MR					
rs11783093	8:27425349	C/T	0.84	0.016	0.002	1.20E-16	23	14387	0.84	-0.021	0.035	5.46E-01	21.5	6.67E-05
rs2062882 ^a	8:91839576	A/G	0.41	0.008	0.001	1.10E-08	23	14387	0.43	-0.022	0.026	3.87E-01	0	3.19E-05
rs72674867	8:95578201	A/T	0.76	0.009	0.002	3.80E-08	23	14387	0.73	0.015	0.029	6.04E-01	15.3	2.91E-05
rs4543592	9:3014254	C/T	0.48	0.009	0.001	4.50E-10	23	14387	0.48	-0.026	0.026	3.25E-01	17.6	3.75E-05
rs7039819	9:82430418	G/A	0.43	0.009	0.001	5.10E-10	23	14387	0.42	-0.009	0.027	7.52E-01	0	3.73E-05
rs1246265	9:86761745	C/T	0.70	0.009	0.002	4.20E-09	23	14387	0.69	-0.020	0.035	5.77E-01	26.2	3.33E-05
rs1221148	9:122046875	C/G	0.59	0.009	0.001	7.30E-11	23	14387	0.61	0.026	0.027	3.38E-01	0	4.07E-05
rs13296519	9:128471924	T/G	0.39	0.010	0.001	8.10E-12	23	14387	0.39	-0.024	0.027	3.56E-01	10	4.49E-05
rs113382419	9:136463019	A/C	0.11	0.028	0.002	3.00E-37	23	14387	0.10	-0.017	0.044	6.92E-01	0	1.57E-04
rs11255908	10:8802912	G/T	0.26	0.010	0.002	2.30E-10	23	14387	0.26	-0.015	0.029	6.13E-01	0	3.87E-05
rs2675638 ^a	10:63576286	G/A	0.58	0.008	0.001	1.30E-09	23	14385	0.61	-0.021	0.026	4.22E-01	0	3.52E-05
rs10823968	10:74738269	A/T	0.63	0.008	0.001	2.10E-08	23	14387	0.65	0.009	0.027	7.29E-01	3.1	3.08E-05
rs17553262 ^c	10:92912773	C/A	0.12	0.013	0.002	5.30E-09	9	4488	Excluded for MR					
rs7077678	10:104438565	C/T	0.62	0.009	0.001	2.60E-09	23	14387	0.62	0.000	0.026	9.93E-01	0	3.43E-05
rs12244388	10:104640052	A/G	0.34	0.013	0.001	1.40E-19	23	14387	0.37	-0.055	0.026	3.57E-02	0	7.87E-05
rs3896224 ^a	10:106467853	A/G	0.59	0.010	0.001	1.10E-11	23	14387	0.54	-0.008	0.026	7.52E-01	0	4.50E-05
rs34866095	11:16377356	G/A	0.31	0.009	0.002	1.20E-08	23	14387	0.33	-0.044	0.028	1.11E-01	12.6	3.16E-05
rs75742406	11:17070365	G/A	0.74	0.010	0.002	1.30E-09	23	14387	0.77	-0.024	0.039	5.50E-01	29.7	3.57E-05
rs17309874	11:27667236	A/G	0.26	0.011	0.002	9.70E-13	23	14387	0.22	-0.037	0.031	2.33E-01	0	4.90E-05
rs4391802	11:28674592	A/G	0.71	0.010	0.002	1.40E-11	23	14387	0.71	0.057	0.029	4.64E-02	0	4.41E-05
rs112282219	11:46632809	A/G	0.04	0.023	0.004	3.80E-11	22	14205	0.04	0.023	0.069	7.38E-01	0	4.23E-05
rs9919670	11:112877304	A/G	0.39	0.015	0.001	7.60E-27	23	14387	0.39	-0.013	0.026	6.26E-01	0	1.10E-04
rs74086911	12:50015942	G/A	0.93	0.015	0.003	2.10E-08	23	14387	0.93	-0.045	0.050	3.73E-01	0	3.02E-05
rs7297175	12:56473808	C/T	0.57	0.008	0.001	6.60E-09	23	14387	0.58	0.011	0.027	6.96E-01	0	3.23E-05
rs10879871	12:75380511	G/T	0.66	0.010	0.001	5.00E-11	23	14387	0.60	-0.012	0.027	6.69E-01	0	4.14E-05
rs12831617	12:84758368	T/C	0.24	0.009	0.002	1.90E-08	23	14387	0.25	0.023	0.029	4.42E-01	0	3.04E-05
rs6562474	13:67332812	C/G	0.65	0.008	0.001	1.00E-08	23	14387	0.65	-0.004	0.027	8.86E-01	0	3.18E-05
rs7333559	13:100546450	G/A	0.21	0.011	0.002	3.20E-10	21	13839	0.24	-0.034	0.033	2.96E-01	7.9	3.85E-05
rs860326	14:57342912	C/T	0.43	0.008	0.001	2.70E-09	23	14387	0.42	0.011	0.026	6.83E-01	18	3.40E-05
rs7155595	14:77502546	C/A	0.33	0.009	0.001	2.50E-09	23	14387	0.32	-0.012	0.028	6.75E-01	0	3.44E-05
rs3742365	14:104198251	C/T	0.40	0.011	0.001	2.50E-14	23	14387	0.37	0.001	0.027	9.77E-01	0	5.61E-05
rs35175834	15:47680815	A/G	0.21	0.016	0.002	4.60E-22	23	14387	0.22	-0.043	0.031	1.62E-01	10.2	8.98E-05
rs28485305	15:74044197	C/T	0.63	0.008	0.001	2.60E-08	23	14387	0.60	0.015	0.026	5.61E-01	0	2.98E-05
rs8042849	15:78817929	C/T	0.34	0.019	0.001	1.80E-39	23	14387	0.39	-0.019	0.027	4.81E-01	0	1.66E-04
rs8042134	15:97514404	G/T	0.46	0.010	0.001	1.30E-12	23	14387	0.44	0.047	0.026	7.40E-02	0	4.91E-05
rs6598539	15:99204483	C/T	0.51	0.008	0.001	4.50E-09	23	14387	0.49	-0.019	0.026	4.64E-01	23.9	3.32E-05
rs11861214	16:746611	G/T	0.78	0.009	0.002	2.00E-08	22	14161	0.79	0.046	0.032	1.49E-01	17.8	3.03E-05

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I ² (%)	R ²
rs12708665	16:24728227	G/A	0.72	0.009	0.002	3.50E-09	23	14387	0.68	-0.013	0.028	6.36E-01	0	3.36E-05
rs57611503	16:31165795	G/A	0.48	0.008	0.001	4.00E-08	20	13192	0.46	-0.100	0.029	4.95E-04	12.5	3.00E-05
rs889398	16:69556715	C/T	0.59	0.009	0.001	6.30E-11	18	10342	0.59	0.013	0.048	7.86E-01	45.4	4.14E-05
rs60952428	16:75640521	T/C	0.91	0.013	0.002	3.00E-08	14	6978	Excluded for MR					
rs1050847	16:87443734	C/T	0.43	0.008	0.001	1.40E-08	23	14387	0.49	-0.013	0.026	6.21E-01	11.3	3.11E-05
rs369230	16:89645437	T/G	0.69	0.009	0.002	1.80E-09	22	14161	0.74	-0.043	0.030	1.55E-01	3	3.52E-05
rs8614	17:27588806	A/C	0.18	0.011	0.002	1.80E-10	22	13821	0.17	0.084	0.037	2.24E-02	0	3.92E-05
rs732083	17:37834367	G/A	0.33	0.008	0.001	1.50E-08	23	14387	0.36	-0.028	0.028	3.23E-01	15.4	3.10E-05
rs9904288	17:47031973	T/C	0.71	0.008	0.002	3.10E-08	23	14387	0.71	-0.018	0.028	5.38E-01	0	2.94E-05
rs67596067	17:50333733	A/G	0.35	0.009	0.001	1.20E-09	23	14387	0.33	0.009	0.027	7.47E-01	0	3.59E-05
rs12967855	18:35138245	A/G	0.33	0.008	0.001	3.10E-08	23	14387	0.35	-0.040	0.028	1.52E-01	1.3	2.97E-05
rs62098013	18:50863861	A/G	0.36	0.009	0.001	4.10E-09	23	14387	0.36	0.043	0.027	1.14E-01	23.6	3.38E-05
rs71367545	18:77576337	A/G	0.21	0.010	0.002	1.40E-09	23	14387	0.17	0.023	0.034	4.98E-01	0	3.53E-05
rs76608582	19:4474725	C/A	0.95	0.022	0.003	3.20E-10	NA in COURAGE-PD							
rs35343344	19:18471610	C/A	0.73	0.009	0.002	8.80E-09	23	14387	0.75	0.056	0.031	7.27E-02	0	3.30E-05
rs4814873	20:19616429	C/T	0.77	0.010	0.002	2.90E-09	23	14387	0.75	-0.013	0.030	6.68E-01	0	3.38E-05
rs6119897	20:31145415	A/G	0.24	0.013	0.002	3.60E-15	23	14387	0.21	-0.018	0.032	5.89E-01	0	5.95E-05
rs12481282	20:44761377	C/G	0.28	0.009	0.002	7.80E-09	23	14387	0.26	-0.020	0.030	5.15E-01	0	3.21E-05
rs348809	20:59032097	G/A	0.65	0.008	0.001	1.30E-08	23	14387	0.62	-0.012	0.027	6.62E-01	0	3.11E-05
rs6011779	20:61984317	C/T	0.19	0.019	0.002	2.30E-27	22	14161	0.22	-0.017	0.032	6.00E-01	0	1.13E-04
rs147412694	21:40702786	A/G	0.15	0.012	0.002	2.90E-09	23	14387	0.14	-0.024	0.038	5.22E-01	0	3.41E-05
rs2838834	21:46665208	T/C	0.30	0.009	0.002	6.30E-10	23	14387	0.29	0.016	0.028	5.61E-01	19.7	3.69E-05
rs136233	22:31212410	G/A	0.19	0.010	0.002	1.80E-08	23	14387	0.19	-0.037	0.032	2.50E-01	0	3.06E-05
rs202645	22:41798520	G/A	0.80	0.010	0.002	3.90E-09	23	14387	0.77	0.122	0.032	1.47E-04	3.5	3.34E-05
Smoking initiation (per 1-SD increase in the prevalence of ever smoking)														
rs12130857	1:7791461	G/A	0.68	0.018	0.003	3.65E-11	23	14387	0.69	-0.027	0.028	3.34E-01	0	1.42E-04
rs3820277	1:18436657	G/T	0.47	0.019	0.003	1.57E-13	23	14387	0.50	-0.032	0.037	3.90E-01	42.3	1.77E-04
rs1889571	1:32195819	G/T	0.13	0.022	0.004	4.19E-09	23	14387	0.12	0.010	0.040	8.13E-01	0	1.12E-04
rs10914684	1:33795572	G/A	0.68	0.016	0.003	6.32E-09	23	14387	0.66	-0.027	0.027	3.16E-01	9.1	1.09E-04
rs951740	1:44011737	A/G	0.62	0.030	0.003	3.82E-29	23	14387	0.61	-0.041	0.026	1.24E-01	5.5	4.09E-04
rs12022778	1:50603995	C/A	0.20	0.027	0.003	3.18E-17	23	14387	0.18	0.060	0.033	6.97E-02	5	2.32E-04
rs4912332	1:58815243	T/C	0.49	0.014	0.003	2.94E-08	23	14387	0.47	0.028	0.026	2.82E-01	0	9.97E-05
rs80054503	1:72900406	T/C	0.88	0.024	0.004	3.10E-09	NA in COURAGE-PD							
rs10789369	1:73824909	A/G	0.38	0.023	0.003	3.39E-19	23	14387	0.43	-0.041	0.026	1.21E-01	12.5	2.60E-04
rs1514176	1:74991596	G/A	0.42	0.019	0.003	7.67E-14	23	14387	0.42	0.007	0.026	8.02E-01	16.3	1.81E-04
rs11162019	1:87913176	C/T	0.64	0.015	0.003	5.06E-09	23	14387	0.65	-0.026	0.027	3.35E-01	10.5	1.11E-04
rs1008078	1:91189731	T/C	0.40	0.023	0.003	1.63E-18	23	14387	0.40	-0.025	0.040	5.27E-01	48.6	2.50E-04
rs12027999	1:154206358	T/C	0.88	0.024	0.004	5.33E-10	23	14387	0.89	0.001	0.042	9.77E-01	0	1.25E-04
rs45444697	1:155034632	G/C	0.21	0.020	0.003	2.72E-10	23	14387	0.20	-0.019	0.033	5.69E-01	21.8	1.30E-04
rs2901785	1:174104743	G/A	0.55	0.017	0.003	1.47E-11	23	14387	0.54	-0.008	0.026	7.60E-01	10.4	1.48E-04
rs147052174	1:179783167	T/G	0.02	0.062	0.010	2.30E-10	13	7882	Excluded for MR					
rs35656245	1:190957480	A/G	0.28	0.016	0.003	2.23E-08	23	14387	0.29	-0.003	0.028	9.14E-01	0	1.02E-04
rs12739243	1:210302043	T/C	0.78	0.021	0.003	4.45E-12	23	14387	0.78	0.017	0.031	5.70E-01	0	1.56E-04
rs876793	1:237852083	T/C	0.65	0.018	0.003	5.69E-11	23	14387	0.66	0.051	0.028	6.89E-02	17	1.46E-04
rs6731872	2:624205	G/T	0.83	0.032	0.003	5.35E-21	23	14387	0.80	0.016	0.033	6.34E-01	0	2.87E-04
rs1022376	2:22067213	T/C	0.48	0.015	0.003	1.66E-08	23	14387	0.51	0.002	0.026	9.33E-01	0	1.09E-04
rs61533748	2:22582968	C/T	0.38	0.017	0.003	2.82E-11	23	14387	0.37	-0.012	0.027	6.58E-01	8	1.44E-04

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²
rs2710634	2:32808804	T/C	0.48	0.018	0.003	3.36E-12	23	14387	0.51	-0.039	0.026	1.31E-01	0	1.57E-04
rs7598402	2:50735943	C/G	0.51	0.015	0.003	7.38E-09	23	14387	0.50			Excluded for MR		
rs10490159	2:51341259	T/C	0.39	0.017	0.003	3.86E-11	23	14387	0.39	-0.027	0.026	3.04E-01	0	1.42E-04
rs359247	2:60477052	T/A	0.64	0.022	0.003	9.89E-17	23	14387	0.61	-0.017	0.027	5.36E-01	24.7	2.24E-04
rs12714017	2:80999398	C/T	0.51	0.015	0.003	3.65E-09	23	14387	0.52	0.011	0.026	6.71E-01	0	1.18E-04
rs13392222	2:100672408	A/C	0.86	0.023	0.004	1.93E-10	23	14387	0.87	0.012	0.039	7.53E-01	0	1.31E-04
rs1901477	2:104126983	G/A	0.51	0.030	0.003	2.07E-31	23	14387	0.52	0.024	0.038	5.33E-01	45.5	4.63E-04
rs3811038	2:113240183	C/T	0.28	0.019	0.003	1.58E-11	23	14387	0.28	-0.004	0.029	8.90E-01	9.1	1.47E-04
rs34399632	2:137571174	G/A	0.23	0.019	0.003	1.46E-10	23	14387	0.17	-0.035	0.044	4.30E-01	26.8	1.33E-04
rs6756212	2:146140132	C/T	0.47	0.034	0.003	3.49E-40	23	14387	0.46	-0.023	0.026	3.72E-01	3.4	5.71E-04
rs16826827	2:147825689	T/C	0.88	0.022	0.004	9.17E-09	23	14387	0.89	-0.041	0.040	3.08E-01	0	1.07E-04
rs1445649	2:155682556	C/T	0.54	0.021	0.003	8.48E-16	23	14387	0.54	-0.023	0.026	3.58E-01	0	2.10E-04
rs12474587	2:162802993	T/G	0.43	0.024	0.003	4.83E-21	23	14387	0.40	0.043	0.027	1.08E-01	5	2.88E-04
rs13007361	2:166250244	A/G	0.21	0.018	0.003	2.29E-08	23	14387	0.21	0.014	0.031	6.52E-01	9.7	1.01E-04
rs6750529	2:182027603	T/C	0.74	0.020	0.003	9.26E-12	23	14387	0.75	-0.025	0.030	3.96E-01	10.5	1.51E-04
rs17229285	2:199523122	C/T	0.50	0.015	0.003	1.27E-09	23	14387	0.52	0.013	0.026	6.11E-01	0	1.20E-04
rs62193862	2:202843875	A/G	0.10	0.024	0.004	1.99E-08	12	6492				Excluded for MR		
rs4674993	2:226332033	A/G	0.80	0.024	0.003	4.85E-14	23	14387	0.80	-0.006	0.044	8.84E-01	33.7	1.84E-04
rs11713899	3:2365026	C/A	0.17	0.019	0.003	3.15E-08	23	14387	0.17	-0.032	0.034	3.49E-01	0	9.93E-05
rs748832	3:16851202	G/A	0.37	0.017	0.003	6.60E-11	23	14387	0.34	0.051	0.027	5.61E-02	0	1.38E-04
rs2526390	3:50192760	T/C	0.33	0.020	0.003	3.62E-14	23	14387	0.33	-0.007	0.027	7.88E-01	0	1.86E-04
rs221988	3:64234307	A/C	0.62	0.015	0.003	1.43E-08	23	14387	0.62	0.024	0.027	3.90E-01	0	1.05E-04
rs11128203	3:71064431	A/T	0.53	0.020	0.003	1.29E-15	10	4792				Excluded for MR		
rs62246017	3:71483084	G/A	0.68	0.016	0.003	3.03E-09	23	14387	0.67	-0.045	0.029	1.18E-01	7.9	1.14E-04
rs12633090	3:83241365	G/C	0.82	0.023	0.003	3.16E-12	23	14387	0.80	0.065	0.043	1.31E-01	31.5	1.58E-04
rs1549979	3:85460131	C/T	0.38	0.025	0.003	8.80E-21	23	14387	0.39	0.019	0.026	4.69E-01	0	2.85E-04
rs6437769	3:107997514	T/C	0.58	0.014	0.003	3.74E-08	23	14387	0.59	0.024	0.026	3.54E-01	12.9	9.84E-05
rs9288999	3:114147927	A/G	0.74	0.017	0.003	1.50E-09	23	14387	0.73	-0.043	0.029	1.47E-01	0	1.18E-04
rs6438436	3:117822149	T/C	0.82	0.025	0.003	5.33E-14	23	14387	0.82	0.058	0.035	9.38E-02	16.4	1.84E-04
rs9826984	3:131945722	G/A	0.46	0.014	0.003	3.87E-08	23	14387	0.44	0.017	0.026	5.24E-01	0.3	9.80E-05
rs2279829	3:147106319	C/T	0.78	0.017	0.003	2.05E-08	23	14387	0.80	0.024	0.033	4.57E-01	0	1.02E-04
rs2319545	3:147719648	A/C	0.15	0.023	0.004	8.30E-11	23	14387	0.13	0.017	0.052	7.45E-01	34.6	1.37E-04
rs1714521	3:158284861	A/C	0.59	0.016	0.003	3.07E-10	23	14387	0.61	-0.007	0.026	8.01E-01	22.4	1.29E-04
rs1449012	3:159048333	C/T	0.54	0.015	0.003	1.77E-09	23	14387	0.53	-0.010	0.036	7.82E-01	37.8	1.18E-04
rs1187820	3:173072584	C/T	0.56	0.014	0.003	2.69E-08	23	14387	0.57	0.015	0.038	6.84E-01	34.4	1.00E-04
rs7631379	3:181409057	C/T	0.21	0.021	0.003	3.94E-11	23	14387	0.19	-0.059	0.047	2.12E-01	36.2	1.42E-04
rs4140932	4:15458598	T/A	0.57	0.014	0.003	4.89E-08	23	14387	0.57			Excluded for MR		
rs59537158	4:28246049	T/C	0.21	0.022	0.003	4.62E-13	23	14387	0.20	-0.001	0.033	9.73E-01	12.1	1.70E-04
rs58400863	4:31184484	G/A	0.65	0.020	0.003	4.89E-14	23	14387	0.63	0.018	0.027	5.09E-01	3.3	1.84E-04
rs112725451	4:68017710	T/C	0.17	0.026	0.003	1.65E-14	23	14387	0.18	0.010	0.033	7.69E-01	0	1.91E-04
rs1160685	4:94052854	G/C	0.45	0.015	0.003	2.31E-09	23	14387	0.49			Excluded for MR		
rs3934797	4:112467612	G/A	0.82	0.021	0.003	1.12E-10	23	14387	0.83	0.015	0.035	6.77E-01	18.4	1.35E-04
rs71602617	4:136406155	C/T	0.78	0.018	0.003	2.10E-08	23	14387	0.80	-0.010	0.032	7.58E-01	0	1.07E-04
rs7696257	4:137474783	A/G	0.37	0.015	0.003	6.78E-09	23	14387	0.35	-0.006	0.027	8.13E-01	7	1.09E-04
rs1116690	4:143510148	G/A	0.74	0.016	0.003	2.16E-08	21	13928	0.71	-0.020	0.030	5.05E-01	0	1.02E-04
rs13110073	4:147797913	T/C	0.60	0.025	0.003	3.24E-21	23	14387	0.62	-0.055	0.026	3.61E-02	0	2.90E-04
rs62340589	4:176875795	C/G	0.20	0.017	0.003	4.31E-08	23	14387	0.19	-0.002	0.033	9.48E-01	0	9.74E-05
rs12517438	5:30842054	G/T	0.54	0.015	0.003	1.89E-09	23	14387	0.52	0.005	0.026	8.46E-01	0	1.17E-04

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD								
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²	
rs35375873	5:43190647	G/C	0.89	0.027	0.004	3.29E-11	15	8384				Excluded for MR			
rs71592686	5:60121271	C/T	0.27	0.021	0.003	3.85E-13	23	14387	0.26	0.055	0.029	5.69E-02	19.2	1.71E-04	
rs6874731	5:80263865	G/T	0.48	0.015	0.003	1.83E-09	23	14387	0.47	-0.002	0.026	9.45E-01	0	1.17E-04	
rs6452785	5:87685500	C/T	0.53	0.027	0.003	4.69E-26	23	14387	0.51	-0.044	0.026	8.56E-02	0	3.60E-04	
rs42417	5:94198290	T/C	0.69	0.017	0.003	8.27E-10	23	14387	0.70	-0.079	0.037	3.33E-02	29	1.22E-04	
rs72780746	5:103929588	T/C	0.83	0.026	0.003	2.05E-14	23	14387	0.81	-0.071	0.033	2.97E-02	6.7	1.90E-04	
rs329124	5:133865452	A/G	0.57	0.016	0.003	1.96E-10	23	14387	0.57	-0.042	0.026	1.01E-01	0	1.31E-04	
rs1385108	5:154839646	T/C	0.24	0.019	0.003	3.84E-10	23	14387	0.22	-0.017	0.031	5.71E-01	0	1.27E-04	
rs6890961	5:166778503	C/T	0.38	0.019	0.003	2.13E-13	23	14387	0.40	-0.038	0.028	1.68E-01	0	1.75E-04	
rs4044321	5:166989513	A/G	0.36	0.023	0.003	1.75E-17	23	14387	0.37	-0.016	0.028	5.63E-01	0	2.35E-04	
rs2173019	5:167614971	A/T	0.18	0.028	0.003	2.98E-17	23	14387	0.17	0.051	0.034	1.37E-01	0	2.32E-04	
rs1150668	6:28129789	T/G	0.58	0.019	0.003	8.54E-13	23	14387	0.59	0.020	0.027	4.68E-01	0	1.67E-04	
rs3218116	6:41901763	C/T	0.74	0.020	0.003	1.05E-11	23	14387	0.77	-0.010	0.030	7.49E-01	0	1.50E-04	
rs160631	6:52895230	T/G	0.27	0.017	0.003	1.87E-09	23	14387	0.28	0.042	0.029	1.47E-01	0	1.17E-04	
rs7743165	6:67521222	G/T	0.50	0.019	0.003	4.15E-14	23	14387	0.47	-0.060	0.034	8.30E-02	32.5	1.85E-04	
rs10945141	6:69470709	A/G	0.26	0.018	0.003	3.59E-10	23	14387	0.26	0.001	0.029	9.68E-01	0	1.28E-04	
rs17554906	6:92226609	C/G	0.44	0.014	0.003	3.14E-08	23	14387	0.42			Excluded for MR			
rs6568832	6:97702876	A/G	0.75	0.019	0.003	1.74E-10	23	14387	0.74	0.023	0.039	5.47E-01	28.9	1.32E-04	
rs12195240	6:98636905	A/G	0.28	0.025	0.003	1.08E-18	23	14387	0.30	-0.041	0.028	1.39E-01	0	2.53E-04	
rs6936160	6:100347745	T/C	0.70	0.020	0.003	4.20E-13	23	14387	0.69	0.018	0.028	5.17E-01	0	1.70E-04	
rs118202	6:111658371	G/T	0.19	0.037	0.003	1.90E-29	23	14387	0.19	-0.060	0.043	1.63E-01	29.2	4.12E-04	
rs1737329	6:163807748	G/C	0.74	0.017	0.003	5.08E-09	23	14387	0.73	-0.014	0.041	7.41E-01	36.1	1.11E-04	
rs6948707	7:1870794	G/T	0.42	0.024	0.003	4.24E-21	23	14387	0.41	<0.001	0.026	9.93E-01	11	2.89E-04	
rs7809303	7:69484366	G/A	0.68	0.021	0.003	3.48E-15	23	14387	0.70	-0.053	0.027	5.14E-02	0	2.01E-04	
rs1030015 ^a	7:78139581	T/G	0.52	0.014	0.003	2.15E-08	23	14387	0.52	0.009	0.031	7.75E-01	23.1	1.02E-04	
rs4727189	7:88442568	C/T	0.34	0.015	0.003	3.00E-08	23	14387	0.36	0.031	0.027	2.40E-01	0	9.97E-05	
rs11768481	7:96629103	C/A	0.66	0.019	0.003	5.23E-12	5	3107				Excluded for MR			
rs13437771	7:99071478	A/G	0.84	0.027	0.004	1.39E-14	23	14387	0.85	-0.012	0.036	7.27E-01	0	1.93E-04	
rs10233018	7:117523709	G/A	0.52	0.025	0.003	4.77E-22	23	14387	0.50	0.014	0.026	5.76E-01	0	3.03E-04	
rs10953957	7:121954709	A/G	0.39	0.014	0.003	3.66E-08	23	14387	0.39	0.036	0.027	1.77E-01	10.3	9.84E-05	
rs77283305	7:132593831	G/A	0.69	0.015	0.003	3.91E-08	23	14387	0.70	-0.037	0.028	1.78E-01	0	9.80E-05	
rs10279261	7:133589846	G/A	0.38	0.019	0.003	6.05E-13	23	14387	0.39	-0.010	0.027	7.05E-01	0	1.68E-04	
rs4326350	8:10763655	C/G	0.51	0.018	0.003	5.16E-12	23	14387	0.53			Excluded for MR			
rs11783093	8:27425349	C/T	0.84	0.047	0.003	2.07E-41	23	14387	0.84	-0.021	0.035	5.46E-01	21.5	5.91E-04	
rs7836565	8:52569449	C/T	0.28	0.016	0.003	4.36E-08	23	14387	0.29	0.060	0.029	3.85E-02	0	9.74E-05	
rs13261666	8:59814666	G/T	0.48	0.020	0.003	4.36E-15	23	14387	0.48	-0.019	0.026	4.64E-01	0	2.00E-04	
rs3850736	8:64912021	G/C	0.47	0.019	0.003	6.43E-14	23	14387	0.46			Excluded for MR			
rs2063976	8:91096366	C/T	0.34	0.020	0.003	7.45E-14	23	14387	0.34	-0.019	0.027	4.81E-01	0	1.81E-04	
rs6986430	8:93048104	T/C	0.78	0.024	0.003	1.99E-15	23	14387	0.77	0.019	0.030	5.26E-01	0	2.05E-04	
rs290601	8:115374642	T/C	0.27	0.016	0.003	1.14E-08	23	14387	0.27	-0.003	0.029	9.19E-01	0	1.06E-04	
rs3847244	9:3025368	T/C	0.47	0.019	0.003	2.60E-13	23	14387	0.48	-0.026	0.027	3.34E-01	0	1.74E-04	
rs11791671	9:3398679	T/C	0.07	0.028	0.005	4.24E-08	23	14387	0.07	0.019	0.073	8.00E-01	35.7	9.74E-05	
rs7024924	9:8282399	C/T	0.17	0.019	0.003	1.90E-08	23	14387	0.17	-0.004	0.034	9.18E-01	0	1.03E-04	
rs10966092	9:23831658	T/C	0.73	0.020	0.003	1.12E-12	23	14387	0.74	-0.023	0.029	4.35E-01	0	1.64E-04	
rs4877285	9:81354129	G/A	0.33	0.018	0.003	2.10E-11	23	14387	0.36	-0.052	0.028	5.89E-02	0	1.46E-04	
rs2378662	9:86707289	A/G	0.54	0.015	0.003	2.67E-09	23	14387	0.53	-0.010	0.034	7.70E-01	28.6	1.15E-04	
rs4837631	9:122061948	C/T	0.55	0.015	0.003	2.03E-09	23	14387	0.58	0.022	0.027	4.08E-01	0	1.17E-04	
rs34553878	9:134334588	G/A	0.11	0.025	0.004	1.17E-09	15	9465				Excluded for MR			

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²
rs10858334	9:137989785	G/C	0.14	0.023	0.004	1.18E-09	23	14387	0.14	-0.045	0.054	4.05E-01	37.9	1.26E-04
rs7920501	10:10043159	T/A	0.54	0.016	0.003	1.25E-09	23	14387	0.53			Excluded for MR		
rs1291821	10:11133823	G/A	0.53	0.014	0.003	1.39E-08	23	14387	0.54	-0.015	0.026	5.60E-01	24.1	1.05E-04
rs7072776	10:22032942	A/G	0.29	0.022	0.003	5.66E-15	22	13367	0.33	0.011	0.030	7.11E-01	0	1.98E-04
rs2796793	10:36634124	A/G	0.45	0.014	0.003	1.55E-08	22	13367	0.42	0.059	0.035	8.98E-02	29.8	1.04E-04
rs1733760	10:56698174	C/T	0.51	0.015	0.003	6.70E-09	23	14387	0.50	0.024	0.026	3.68E-01	0	1.09E-04
rs7921378	10:63674885	G/C	0.52	0.023	0.003	6.10E-20	23	14387	0.53			Excluded for MR		
rs11594623	10:103960351	C/T	0.23	0.027	0.003	7.45E-20	23	14387	0.21	-0.067	0.031	3.24E-02	0	2.70E-04
rs12244388	10:104640052	A/G	0.35	0.026	0.003	4.31E-22	23	14387	0.37	-0.055	0.026	3.57E-02	0	3.03E-04
rs10885480	10:115378364	T/C	0.72	0.019	0.003	3.83E-11	23	14387	0.73	-0.014	0.029	6.46E-01	18.9	1.42E-04
rs4752018	10:118678712	A/C	0.23	0.019	0.003	4.42E-10	23	14387	0.24	-0.023	0.030	4.46E-01	21.6	1.26E-04
rs9423279	10:125680419	C/G	0.36	0.019	0.003	3.06E-12	1	950				Excluded for MR		
rs6265 ^a	11:27679916	C/T	0.81	0.029	0.003	2.81E-19	23	14387	0.79	0.038	0.032	2.44E-01	0	2.62E-04
rs2939756	11:41436297	G/A	0.52	0.016	0.003	7.45E-10	23	14387	0.56	-0.007	0.026	7.96E-01	5.7	1.23E-04
rs1381775	11:42442826	T/C	0.29	0.016	0.003	2.79E-08	23	14387	0.29	-0.038	0.029	1.87E-01	0	1.00E-04
rs61886926	11:64133552	C/T	0.62	0.018	0.003	7.30E-12	23	14387	0.64	-0.004	0.035	9.05E-01	34.3	1.52E-04
rs644740	11:65561468	C/T	0.54	0.014	0.003	3.67E-08	23	14387	0.54	-0.007	0.026	7.95E-01	0	9.84E-05
rs7943721	11:73309393	G/A	0.17	0.021	0.003	3.58E-10	NA in COURAGE-PD							
rs7929518	11:85980958	G/A	0.77	0.019	0.003	2.55E-10	23	14387	0.77	-0.062	0.038	1.10E-01	27.6	1.30E-04
rs2155646	11:112912811	C/T	0.40	0.038	0.003	9.44E-48	23	14387	0.39	-0.012	0.026	6.61E-01	0	6.85E-04
rs1713676 ^a	11:113660576	A/G	0.48	0.017	0.003	5.38E-11	23	14387	0.46	0.034	0.026	1.96E-01	0	1.40E-04
rs540860	11:121530888	G/A	0.54	0.018	0.003	5.75E-12	23	14387	0.52	0.038	0.026	1.40E-01	0	1.54E-04
rs1106363	11:131966264	T/C	0.34	0.017	0.003	9.20E-11	23	14387	0.37	0.013	0.026	6.14E-01	0	1.36E-04
rs2010921	11:132098205	A/G	0.31	0.017	0.003	2.47E-10	23	14387	0.30	0.034	0.028	2.25E-01	0	1.30E-04
rs11057005	12:16748721	A/G	0.56	0.016	0.003	9.12E-10	23	14387	0.58	-0.034	0.038	3.73E-01	40	1.22E-04
rs13906	12:49952394	C/T	0.89	0.025	0.004	1.98E-09	23	14387	0.89	0.019	0.042	6.56E-01	0	1.17E-04
rs4759229	12:56474480	G/A	0.66	0.016	0.003	6.53E-09	22	14205	0.66	<0.001	0.029	9.98E-01	0	1.09E-04
rs7969559	12:69655167	A/G	0.29	0.017	0.003	1.53E-09	23	14387	0.34	-0.016	0.028	5.67E-01	6.6	1.18E-04
rs7134009	12:75263193	T/C	0.71	0.016	0.003	4.30E-08	23	14387	0.70	-0.015	0.028	5.96E-01	0	1.02E-04
rs77215829	12:112618346	A/C	0.87	0.024	0.004	2.02E-10	18	9799	0.87	0.005	0.051	9.25E-01	16	1.32E-04
rs1109480	12:121083279	G/A	0.62	0.017	0.003	1.84E-10	23	14387	0.62	-0.030	0.027	2.63E-01	0	1.32E-04
rs11611651	12:133380790	A/G	0.09	0.027	0.005	2.05E-09	23	14387	0.08	-0.008	0.048	8.65E-01	0	1.17E-04
rs17197663	13:38172867	G/A	0.88	0.022	0.004	2.06E-08	23	14387	0.87	0.030	0.038	4.30E-01	23	1.02E-04
rs4264267	13:38359676	T/C	0.53	0.015	0.003	6.82E-09	23	14387	0.53	-0.025	0.026	3.46E-01	0	1.09E-04
rs61959481	13:55834929	G/A	0.79	0.020	0.003	7.95E-11	23	14387	0.79	-0.022	0.032	4.94E-01	0	1.37E-04
rs55786907	13:59871584	G/A	0.16	0.019	0.003	1.84E-08	23	14387	0.17	0.021	0.034	5.41E-01	0	1.03E-04
rs9540731 ^a	13:66949370	C/T	0.49	0.018	0.003	3.42E-12	23	14387	0.50	-0.036	0.031	2.46E-01	20.4	1.57E-04
rs9545155	13:80191873	T/C	0.52	0.016	0.003	3.04E-10	23	14387	0.53	-0.004	0.026	8.70E-01	0	1.29E-04
rs1772572	13:81191176	C/A	0.68	0.017	0.003	5.62E-10	23	14387	0.68	-0.045	0.027	9.54E-02	0	1.25E-04
rs1108130	13:100648356	A/T	0.21	0.024	0.003	1.57E-14	23	14387	0.20	-0.022	0.033	5.06E-01	0	1.92E-04
rs12878369	14:28346502	A/C	0.41	0.017	0.003	1.60E-11	23	14387	0.42	-0.035	0.038	3.47E-01	42.9	1.48E-04
rs9323328 ^a	14:58653514	A/G	0.46	0.014	0.003	2.55E-08	23	14387	0.45	0.003	0.026	9.21E-01	0	1.01E-04
rs1811739	14:77529375	A/G	0.25	0.018	0.003	5.97E-10	23	14387	0.25	0.022	0.030	4.67E-01	0	1.25E-04
rs8005334	14:79563654	G/T	0.36	0.017	0.003	3.44E-10	23	14387	0.35	-0.016	0.027	5.55E-01	0	1.28E-04
rs2925128	14:98362355	T/C	0.39	0.017	0.003	3.67E-10	23	14387	0.38	-0.028	0.040	4.90E-01	48.2	1.34E-04
rs1381287	14:98597552	T/C	0.47	0.018	0.003	1.81E-12	23	14387	0.49	0.020	0.026	4.39E-01	14.1	1.62E-04
rs1435672	15:36399479	C/T	0.56	0.014	0.003	3.82E-08	23	14387	0.54	-0.018	0.026	4.95E-01	0	9.80E-05
rs281296	15:47685010	A/G	0.36	0.025	0.003	1.59E-20	23	14387	0.37	-0.046	0.027	9.02E-02	0	2.80E-04

SNP	Chr:Pos (GRCh37)	EA/BA	Exposure				Courage-PD							
			EAF	Beta	SE	P-value	N studies	N samples	EAF	Beta	SE	P-value	I² (%)	R²
rs2289791	15:67476952	G/T	0.75	0.018	0.003	2.01E-09	10	4792				Excluded for MR		
rs62007780	15:78025464	G/T	0.58	0.016	0.003	7.48E-10	23	14387	0.60	-0.002	0.026	9.37E-01	0	1.23E-04
rs4310804	15:96858409	C/G	0.75	0.018	0.003	7.55E-10	20	11001	0.77	0.029	0.038	4.46E-01	24.5	1.23E-04
rs1139897	16:720986	G/A	0.77	0.024	0.003	1.77E-15	22	14161	0.78	0.050	0.032	1.20E-01	10.2	2.06E-04
rs11076962	16:5811367	C/T	0.28	0.018	0.003	1.20E-10	23	14387	0.26	0.010	0.029	7.27E-01	0	1.35E-04
rs9922607	16:17570220	C/T	0.80	0.022	0.003	3.42E-12	23	14387	0.80	-0.014	0.033	6.66E-01	0	1.57E-04
rs9941217	16:18050926	C/G	0.65	0.019	0.003	3.50E-12	23	14387	0.68	0.019	0.028	5.05E-01	20.7	1.57E-04
rs6497840	16:25351633	A/G	0.71	0.023	0.003	2.01E-15	23	14387	0.69	-0.012	0.028	6.61E-01	4.1	2.15E-04
rs12918191	16:50945156	A/G	0.76	0.020	0.003	3.14E-11	23	14387	0.76	-0.004	0.030	8.95E-01	0	1.43E-04
rs9302604	16:69576894	G/A	0.44	0.019	0.003	3.29E-13	23	14387	0.44	-0.016	0.033	6.41E-01	26.3	1.72E-04
rs117657830	16:75766873	A/G	0.96	0.038	0.006	3.18E-09	23	14387	0.96	0.003	0.066	9.64E-01	0	1.14E-04
rs1050847	16:87443734	C/T	0.44	0.015	0.003	7.37E-09	23	14387	0.49	-0.013	0.026	6.21E-01	11.3	1.08E-04
rs11642231	16:89608702	G/A	0.63	0.016	0.003	3.44E-09	23	14387	0.68	<u>0.072</u>	0.028	1.06E-02	0	1.13E-04
rs4790874	17:1995177	T/C	0.53	0.017	0.003	8.43E-12	23	14387	0.54	-0.035	0.026	1.85E-01	0	1.52E-04
rs28441558	17:7803118	T/C	0.94	0.036	0.006	1.24E-10	16	9769				Excluded for MR		
rs67777803	17:27323322	G/T	0.83	0.025	0.003	3.18E-13	23	14387	0.84	-0.014	0.035	6.79E-01	4.8	1.72E-04
rs3764351	17:37824339	G/A	0.34	0.015	0.003	3.89E-08	23	14387	0.37	-0.033	0.028	2.34E-01	13.7	9.80E-05
rs72836318	17:44121579	T/C	0.75	0.017	0.003	7.00E-09	23	14387	0.75	<u>-0.085</u>	0.030	5.21E-03	0	1.09E-04
rs75919030	17:50193197	T/C	0.73	0.021	0.003	3.35E-13	23	14387	0.74	0.003	0.029	9.27E-01	0	1.72E-04
rs2587507 ^a	17:77790135	T/C	0.50	0.015	0.003	8.69E-09	23	14382	0.52	-0.042	0.026	9.96E-02	0	1.07E-04
rs34342129	18:5872472	T/C	0.49	0.014	0.003	2.13E-08	23	14387	0.50	-0.038	0.026	1.45E-01	0	1.02E-04
rs4476253	18:25253297	G/A	0.76	0.018	0.003	5.78E-10	23	14387	0.76	0.014	0.038	7.14E-01	26.8	1.25E-04
rs8096225	18:36921851	C/A	0.70	0.016	0.003	2.63E-08	23	14387	0.70	-0.006	0.028	8.23E-01	1.4	1.01E-04
rs67050670	18:39297254	A/G	0.77	0.020	0.003	2.34E-11	23	14387	0.74	0.051	0.030	8.56E-02	14.6	1.45E-04
rs1373178	18:49967811	T/G	0.41	0.020	0.003	4.16E-15	23	14387	0.42	-0.023	0.026	3.87E-01	0	2.00E-04
rs72938304	18:53661743	G/A	0.89	0.027	0.004	1.36E-11	23	14387	0.88	0.051	0.041	2.12E-01	18.7	1.48E-04
rs71367544	18:77574374	T/C	0.20	0.021	0.003	8.54E-11	23	14387	0.17	0.025	0.034	4.58E-01	0	1.37E-04
rs76608582	19:4474725	C/A	0.95	0.035	0.006	4.88E-09	NA in COURAGE-PD							
rs10853981	19:4965064	A/G	0.33	0.015	0.003	4.88E-08	23	14387	0.31	-0.016	0.028	5.72E-01	1.9	9.67E-05
rs113230003	19:18460956	G/A	0.74	0.019	0.003	1.05E-10	23	14387	0.76	0.055	0.031	7.61E-02	0	1.35E-04
rs117734003	19:51129745	C/G	0.07	0.030	0.005	2.57E-09	15	8384				Excluded for MR		
rs1126757 ^a	19:55879872	T/C	0.47	0.014	0.003	2.92E-08	23	14369	0.47	-0.001	0.029	9.68E-01	12.9	1.00E-04
rs6050446 ^d	20:25195509	G/A	0.97	0.054	0.008	8.80E-13	18	12644	0.98	-0.070	0.091	4.42E-01	0	2.81E-04
rs6073075	20:42015801	T/A	0.18	0.019	0.003	2.44E-08	23	14387	0.20	-0.008	0.033	8.05E-01	4.9	1.01E-04
rs3810496	20:62406886	C/T	0.62	0.016	0.003	1.54E-09	22	14205	0.63	-0.047	0.042	2.61E-01	44.2	1.19E-04
rs4818005	21:40588819	G/A	0.42	0.020	0.003	1.09E-14	23	14387	0.43	-0.036	0.026	1.70E-01	0	2.03E-04
rs4822102	22:42698430	C/T	0.38	0.017	0.003	2.78E-10	23	14387	0.38	0.022	0.036	5.34E-01	33.4	1.29E-04

NA, not available; EA/BA, effect allele/base allele; EAF, effect allele frequency; SE, standard error.

Bold coefficients with their corresponding SE and p-values are significant at $p \leq 0.05$; those underlined with a solid line are negative and those underlined with a dashed line are positive.

R² is the proportion of the variance of the exposure explained by the genetic variant according to the formula: $2 \times \text{Beta}_{\text{exposure}} \times \text{EAF}_{\text{exposure}} \times (1 - \text{EAF}_{\text{exposure}})$.

^a SNPs genotyped.

^b SNPs associated with both alcohol and coffee consumption.

^c Proxy SNP used in Courage-PD: rs61857951.

^d Proxy SNP used in Courage-PD: rs117495226.

Supplementary table 4: SNPs used for Mendelian randomization analyses: individual associations with PD stratified by age and disease duration.

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
Alcohol drinking (per 1-SD increase of ln(drinks per week))													
rs705687	G/A	0.024	0.051	6.36E-01	-0.013	0.052	8.09E-01	0.033	0.040	4.07E-01	0.037	0.042	3.81E-01
rs58107686	A/C	-0.014	0.043	7.42E-01	0.014	0.043	7.40E-01	0.031	0.033	3.60E-01	-0.010	0.036	7.72E-01
rs12088813	C/A	-0.024	0.065	7.11E-01	0.026	0.046	5.80E-01	0.042	0.036	2.36E-01	0.045	0.038	2.41E-01
rs5024204	A/T	0.088	0.045	5.11E-02	0.012	0.046	7.90E-01	0.042	0.035	2.30E-01	0.080	0.037	3.34E-02
rs10753661	A/G	0.026	0.045	5.65E-01	0.080	0.045	7.70E-02	0.032	0.035	3.65E-01	0.026	0.037	4.90E-01
rs28680958	A/G	-0.013	0.049	7.83E-01	0.012	0.049	8.09E-01	-0.007	0.038	8.60E-01	0.019	0.040	6.39E-01
rs823114	G/A	-0.082	0.041	4.63E-02	0.002	0.042	9.71E-01	-0.015	0.033	6.48E-01	-0.064	0.035	6.42E-02
rs77165542	T/C	Excluded for MR											
rs1260326	T/C	-0.103	0.042	1.35E-02	-0.072	0.042	8.51E-02	-0.075	0.032	2.05E-02	-0.070	0.035	4.42E-02
rs13383034	C/T	-0.033	0.044	4.49E-01	-0.088	0.044	4.66E-02	-0.077	0.034	2.46E-02	-0.029	0.036	4.18E-01
rs13032049	A/G	0.049	0.044	2.67E-01	0.069	0.046	1.30E-01	0.037	0.045	4.12E-01	0.055	0.038	1.44E-01
rs828867	G/A	Excluded for MR											
rs11692435	G/A	NA in COURAGE-PD											
rs13024996	A/C	0.064	0.043	1.30E-01	-0.005	0.043	9.10E-01	0.010	0.033	7.54E-01	0.022	0.035	5.37E-01
rs72859280	G/T	Excluded for MR											
rs56337305	C/T	-0.045	0.042	2.84E-01	-0.014	0.042	7.34E-01	0.005	0.033	8.76E-01	-0.039	0.035	2.64E-01
rs13094887	T/A	0.013	0.043	7.72E-01	-0.101	0.044	2.26E-02	-0.033	0.034	3.35E-01	-0.035	0.037	3.34E-01
rs62250685	G/A	-0.036	0.041	3.82E-01	-0.014	0.042	7.39E-01	0.012	0.032	7.06E-01	-0.048	0.034	1.61E-01
rs9838144	C/G	-0.075	0.070	2.86E-01	-0.053	0.070	4.47E-01	-0.029	0.041	4.74E-01	-0.099	0.042	2.04E-02
rs2011092	C/T	-0.037	0.045	4.08E-01	0.036	0.060	5.50E-01	0.026	0.035	4.49E-01	-0.054	0.037	1.40E-01
rs6787172	G/T	0.047	0.040	2.48E-01	0.019	0.041	6.35E-01	0.012	0.031	6.94E-01	0.044	0.034	1.88E-01
rs3748034	T/G	-0.071	0.061	2.44E-01	0.038	0.060	5.24E-01	0.003	0.047	9.51E-01	0.009	0.049	8.53E-01
rs11940694	A/G	-0.016	0.058	7.86E-01	-0.029	0.042	4.92E-01	-0.017	0.039	6.54E-01	-0.020	0.034	5.65E-01
rs4501255	C/G	-0.017	0.072	8.12E-01	-0.024	0.050	6.24E-01	0.005	0.038	8.99E-01	-0.063	0.041	1.29E-01
rs1229984	T/C	-0.092	0.083	2.70E-01	0.023	0.086	7.90E-01	0.022	0.098	8.23E-01	-0.056	0.077	4.66E-01
rs2165670	G/A	0.019	0.075	7.99E-01	0.114	0.118	3.33E-01	Excluded for MR			0.008	0.059	8.92E-01
rs13107325	T/C	-0.221	0.081	6.28E-03	-0.012	0.093	8.95E-01	-0.122	0.062	4.81E-02	-0.040	0.068	5.58E-01
rs4690727	C/G	-0.016	0.045	7.21E-01	-0.016	0.046	7.30E-01	-0.043	0.035	2.22E-01	0.043	0.038	2.52E-01
rs12651313	G/C	Excluded for MR											
rs4916723	C/A	-0.051	0.056	3.56E-01	-0.056	0.044	1.97E-01	-0.023	0.034	4.87E-01	-0.056	0.036	1.13E-01
rs12655091	A/G	-0.013	0.041	7.56E-01	0.005	0.053	9.24E-01	-0.035	0.032	2.76E-01	-0.022	0.034	5.24E-01
rs55872084	G/T	0.085	0.050	9.28E-02	-0.014	0.051	7.87E-01	0.019	0.039	6.35E-01	-0.021	0.041	6.17E-01
rs6460047	T/C	0.019	0.053	7.27E-01	-0.001	0.069	9.93E-01	-0.003	0.041	9.41E-01	-0.034	0.043	4.23E-01
rs10236149	G/A	0.058	0.060	3.29E-01	0.039	0.061	5.15E-01	0.086	0.046	6.46E-02	0.045	0.051	3.77E-01
rs35034355	A/G	0.009	0.040	8.24E-01	-0.015	0.041	7.19E-01	-0.011	0.032	7.22E-01	-0.013	0.034	7.10E-01
rs6951574	T/C	-0.007	0.042	8.71E-01	-0.008	0.042	8.42E-01	-0.030	0.033	3.52E-01	0.030	0.035	3.87E-01
rs13250583	T/C	-0.022	0.052	6.80E-01	-0.009	0.053	8.68E-01	-0.018	0.041	6.55E-01	-0.009	0.043	8.37E-01
rs1217091	T/C	0.049	0.052	3.51E-01	0.090	0.054	9.42E-02	0.090	0.041	2.72E-02	0.063	0.043	1.45E-01
rs28601761	C/G	Excluded for MR											
rs55932213	A/G	-0.051	0.048	2.87E-01	0.002	0.049	9.70E-01	-0.014	0.037	7.17E-01	-0.020	0.040	6.15E-01
rs10978550	C/T	0.017	0.052	7.39E-01	0.004	0.071	9.50E-01	0.008	0.045	8.54E-01	0.028	0.042	5.09E-01
rs7074871	A/G	0.014	0.068	8.41E-01	0.001	0.047	9.81E-01	0.033	0.036	3.65E-01	-0.013	0.039	7.35E-01
rs17665139	T/C	0.033	0.059	5.78E-01	0.002	0.058	9.68E-01	0.061	0.058	2.91E-01	-0.039	0.049	4.30E-01
rs7950166	T/C	-0.039	0.042	3.50E-01	0.011	0.043	7.96E-01	-0.020	0.042	6.35E-01	-0.038	0.035	2.74E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs11030084	T/C	-0.059	0.051	2.48E-01	0.020	0.052	7.04E-01	-0.031	0.040	4.42E-01	-0.024	0.043	5.80E-01
rs56030824	A/G	0.016	0.043	7.06E-01	<0.001	0.044	9.92E-01	<0.001	0.048	9.94E-01	0.050	0.036	1.63E-01
rs10750025	C/T	0.008	0.045	8.67E-01	-0.056	0.044	2.02E-01	-0.025	0.034	4.62E-01	0.004	0.040	9.13E-01
rs4938230	C/A	Excluded for MR											
rs682011	T/C	-0.053	0.041	1.99E-01	-0.012	0.041	7.72E-01	-0.038	0.035	2.73E-01	-0.017	0.034	6.14E-01
rs12795042	C/A	-0.002	0.044	9.60E-01	-0.034	0.044	4.40E-01	0.018	0.034	6.06E-01	-0.043	0.036	2.34E-01
rs3809162	A/G	-0.014	0.043	7.52E-01	-0.034	0.044	4.38E-01	-0.054	0.034	1.10E-01	0.010	0.046	8.30E-01
rs10506274	T/G	0.054	0.041	1.84E-01	-0.013	0.041	7.55E-01	0.036	0.032	2.53E-01	-0.013	0.034	7.10E-01
rs4842786	A/G	-0.020	0.042	6.27E-01	0.012	0.043	7.80E-01	0.002	0.033	9.57E-01	-0.002	0.035	9.52E-01
rs500321	T/A	<0.001	0.046	9.98E-01	0.026	0.048	5.91E-01	0.037	0.036	3.03E-01	-0.045	0.039	2.50E-01
rs1123285	G/C	0.024	0.064	7.06E-01	-0.066	0.044	1.34E-01	-0.059	0.034	8.19E-02	0.002	0.036	9.56E-01
rs28929474	T/C	Excluded for MR											
rs2472297	C/T	-0.022	0.056	6.93E-01	-0.011	0.072	8.75E-01	-0.077	0.046	9.74E-02	-0.021	0.045	6.43E-01
rs12907323	A/G	-0.016	0.041	6.94E-01	0.039	0.042	3.51E-01	0.045	0.032	1.65E-01	-0.010	0.034	7.59E-01
rs17177078	T/C	-0.035	0.074	6.35E-01	-0.001	0.079	9.90E-01	-0.020	0.059	7.30E-01	-0.015	0.064	8.18E-01
rs378421	A/G	-0.036	0.043	4.02E-01	0.006	0.043	8.93E-01	-0.034	0.033	3.07E-01	-0.038	0.035	2.76E-01
rs62044525	G/C	<u>0.119</u>	<u>0.053</u>	<u>2.42E-02</u>	0.071	0.053	1.81E-01	<u>0.098</u>	<u>0.041</u>	<u>1.76E-02</u>	0.053	0.044	2.27E-01
rs1104608	C/G	Excluded for MR											
rs4548913	A/G	-0.019	0.042	6.57E-01	0.024	0.044	5.87E-01	0.005	0.048	9.21E-01	-0.046	0.035	1.98E-01
rs3803800	A/G	0.037	0.053	4.91E-01	-0.004	0.052	9.40E-01	0.018	0.050	7.18E-01	-0.001	0.043	9.75E-01
rs2854334	A/G	Excluded for MR						<u>0.076</u>	<u>0.037</u>	<u>4.14E-02</u>	-0.018	0.039	6.37E-01
rs10438820	C/T	<u>0.088</u>	<u>0.044</u>	<u>4.55E-02</u>	0.019	0.046	6.78E-01	0.027	0.035	4.48E-01	0.061	0.037	1.00E-01
rs9950000	T/C	-0.023	0.041	5.82E-01	-0.011	0.042	7.96E-01	-0.040	0.032	2.18E-01	0.019	0.035	5.89E-01
rs4092465	G/A	NA in COURAGE-PD											
rs281379	G/A	0.052	0.058	3.67E-01	0.038	0.042	3.57E-01	0.054	0.032	9.22E-02	-0.013	0.034	6.96E-01
rs4815364	G/A	0.042	0.043	3.27E-01	0.063	0.043	1.48E-01	0.050	0.033	1.33E-01	0.011	0.036	7.65E-01
rs9607814	A/C	<u>-0.162</u>	<u>0.051</u>	<u>1.56E-03</u>	<u>-0.116</u>	<u>0.051</u>	<u>2.41E-02</u>	<u>-0.118</u>	<u>0.040</u>	<u>3.19E-03</u>	<u>-0.144</u>	<u>0.058</u>	<u>1.34E-02</u>
Coffee drinking (per ln(cups per day))													
rs574367	T/G	-0.105	0.077	1.73E-01	-0.094	0.055	8.85E-02	<u>-0.148</u>	<u>0.061</u>	<u>1.43E-02</u>	-0.103	0.061	9.03E-02
rs10865548	G/A	-0.037	0.052	4.76E-01	0.083	0.072	2.48E-01	-0.005	0.040	9.10E-01	0.032	0.044	4.66E-01
rs1260326	C/T	<u>0.103</u>	<u>0.042</u>	<u>1.35E-02</u>	0.072	0.042	8.51E-02	<u>0.075</u>	<u>0.032</u>	<u>2.05E-02</u>	<u>0.070</u>	<u>0.035</u>	<u>4.42E-02</u>
rs4410790	C/T	-0.027	0.042	5.17E-01	0.008	0.043	8.48E-01	-0.030	0.044	4.94E-01	-0.008	0.035	8.24E-01
rs34060476	G/A	0.067	0.066	3.07E-01	0.002	0.066	9.76E-01	0.020	0.052	6.95E-01	0.082	0.053	1.18E-01
rs1057868	T/C	0.005	0.061	9.28E-01	0.031	0.045	4.86E-01	0.019	0.035	5.93E-01	0.031	0.037	4.02E-01
rs597045	A/T	0.011	0.044	7.99E-01	-0.015	0.045	7.39E-01	-0.039	0.050	4.40E-01	0.006	0.037	8.64E-01
rs1956218	G/A	-0.048	0.041	2.45E-01	0.002	0.041	9.61E-01	-0.036	0.032	2.59E-01	-0.026	0.034	4.51E-01
rs2472297	T/C	0.022	0.056	6.93E-01	0.011	0.072	8.75E-01	0.077	0.046	9.74E-02	0.021	0.045	6.43E-01
rs66723169	A/C	-0.004	0.049	9.38E-01	-0.057	0.050	2.53E-01	0.005	0.038	8.91E-01	-0.057	0.041	1.64E-01
rs2330783	G/T	Excluded for MR											
Lifetime smoking index													
rs1193237	C/G	Excluded for MR											
rs4949465	C/T	-0.007	0.064	9.13E-01	0.004	0.064	9.54E-01	0.016	0.049	7.50E-01	0.010	0.052	8.48E-01
rs549845	G/A	-0.102	0.066	1.19E-01	0.030	0.045	5.05E-01	-0.060	0.046	1.93E-01	-0.046	0.047	3.27E-01
rs1933270	T/G	0.044	0.042	3.00E-01	0.020	0.042	6.34E-01	0.038	0.033	2.49E-01	<u>0.075</u>	<u>0.035</u>	<u>3.33E-02</u>
rs7528604	G/A	0.018	0.040	6.57E-01	-0.005	0.041	9.01E-01	0.007	0.032	8.13E-01	0.014	0.042	7.39E-01
rs11210229	A/G	-0.041	0.042	3.19E-01	-0.005	0.042	9.08E-01	-0.015	0.032	6.43E-01	-0.008	0.035	8.21E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs7553348	G/A	0.003	0.042	9.41E-01	-0.018	0.043	6.65E-01	0.008	0.033	8.07E-01	0.008	0.035	8.29E-01
rs10922907	A/T	Excluded for MR											
rs1931263	T/G	0.010	0.041	8.15E-01	-0.048	0.041	2.47E-01	-0.027	0.032	3.91E-01	-0.041	0.034	2.28E-01
rs7519626	C/T	0.007	0.044	8.68E-01	0.001	0.044	9.84E-01	-0.015	0.044	7.30E-01	0.035	0.036	3.32E-01
rs9435340	T/A	NA			-0.010	0.044	8.16E-01	0.002	0.034	9.44E-01	0.019	0.036	5.96E-01
rs10918701	G/A	0.004	0.042	9.15E-01	-0.077	0.042	6.64E-02	0.002	0.043	9.54E-01	-0.018	0.035	6.11E-01
rs2867112	T/G	-0.044	0.054	4.11E-01	0.095	0.074	1.99E-01	-0.002	0.042	9.67E-01	0.028	0.045	5.42E-01
rs6741228	T/C	-0.021	0.057	7.13E-01	0.035	0.042	4.02E-01	-0.025	0.032	4.38E-01	0.009	0.034	7.82E-01
rs62135536	C/T	Excluded for MR											
rs7569203	C/A	0.025	0.044	5.65E-01	0.093	0.044	3.61E-02	0.073	0.034	3.18E-02	0.029	0.036	4.31E-01
rs13016665	A/C	0.006	0.042	8.87E-01	0.103	0.043	1.58E-02	0.046	0.033	1.61E-01	0.042	0.035	2.34E-01
rs4671357	C/T	0.002	0.042	9.70E-01	0.001	0.041	9.74E-01	0.018	0.032	5.84E-01	-0.030	0.036	3.99E-01
rs359243	C/T	-0.031	0.042	4.70E-01	0.050	0.043	2.49E-01	0.047	0.042	2.65E-01	-0.031	0.047	5.06E-01
rs2678670	A/T	Excluded for MR											
rs62155874	G/A	0.003	0.062	9.66E-01	-0.069	0.063	2.71E-01	-0.032	0.049	5.15E-01	-0.006	0.052	9.08E-01
rs3811038	C/T	-0.049	0.046	2.84E-01	-0.008	0.061	8.91E-01	0.001	0.036	9.82E-01	-0.011	0.038	7.74E-01
rs2890772	T/G	0.006	0.041	8.91E-01	0.040	0.042	3.38E-01	0.013	0.032	6.87E-01	-0.004	0.034	9.00E-01
rs62175972	T/C	0.075	0.111	5.03E-01	0.016	0.111	8.82E-01	0.093	0.087	2.85E-01	-0.009	0.090	9.19E-01
rs3769949	A/T	Excluded for MR											
rs13009008	A/G	0.057	0.042	1.77E-01	0.046	0.043	2.84E-01	0.008	0.033	8.02E-01	0.079	0.036	2.72E-02
rs4473348	T/A	0.006	0.048	8.95E-01	-0.085	0.049	8.13E-02	-0.071	0.037	5.79E-02	-0.014	0.040	7.24E-01
rs12623702	G/A	-0.035	0.042	4.06E-01	-0.012	0.043	7.74E-01	-0.028	0.033	3.92E-01	-0.054	0.035	1.26E-01
rs6779302	T/G	0.032	0.042	4.51E-01	0.049	0.043	2.55E-01	0.047	0.033	1.59E-01	0.011	0.035	7.45E-01
rs6778080	T/C	-0.014	0.046	7.67E-01	0.005	0.047	9.20E-01	0.005	0.042	8.97E-01	-0.023	0.038	5.52E-01
rs775758	A/T	Excluded for MR											
rs421983	T/C	-0.029	0.040	4.71E-01	0.020	0.041	6.25E-01	0.007	0.031	8.30E-01	-0.004	0.034	9.16E-01
rs326341	G/A	-0.086	0.042	3.86E-02	0.025	0.042	5.50E-01	-0.028	0.032	3.89E-01	-0.005	0.034	8.73E-01
rs73220544	C/A	-0.086	0.060	1.50E-01	-0.050	0.085	5.54E-01	-0.037	0.047	4.26E-01	-0.114	0.050	2.21E-02
rs9842947	T/C	0.026	0.046	5.79E-01	0.020	0.046	6.69E-01	0.020	0.036	5.77E-01	0.045	0.038	2.39E-01
rs624833	T/G	-0.046	0.045	2.97E-01	-0.088	0.063	1.62E-01	-0.113	0.034	1.02E-03	-0.039	0.047	4.06E-01
rs61796681	T/A	0.068	0.078	3.85E-01	0.065	0.080	4.15E-01	0.074	0.061	2.27E-01	-0.007	0.066	9.17E-01
rs317021	A/T	0.007	0.075	9.23E-01	0.049	0.057	3.91E-01	0.093	0.044	3.50E-02	0.012	0.046	7.94E-01
rs72678864	G/A	0.050	0.057	3.86E-01	0.015	0.060	7.96E-01	0.065	0.046	1.54E-01	-0.008	0.048	8.68E-01
rs17576594	G/A	-0.059	0.046	2.01E-01	-0.009	0.047	8.42E-01	-0.026	0.036	4.67E-01	-0.063	0.038	9.77E-02
rs11948770	C/T	-0.026	0.049	6.00E-01	-0.045	0.049	3.57E-01	-0.017	0.038	6.52E-01	-0.091	0.040	2.52E-02
rs71627581	G/A	Excluded for MR											
rs10052591	T/C	0.036	0.041	3.74E-01	-0.008	0.041	8.45E-01	0.005	0.032	8.73E-01	0.059	0.034	8.25E-02
rs2080870	A/T	0.067	0.047	1.50E-01	0.080	0.048	9.20E-02	0.086	0.037	1.91E-02	0.051	0.039	1.95E-01
rs4571506	C/T	-0.072	0.052	1.67E-01	0.004	0.058	9.44E-01	-0.019	0.036	5.95E-01	-0.076	0.034	2.58E-02
rs4957528	C/A	Excluded for MR											
rs329120	C/T	-0.056	0.042	1.78E-01	-0.034	0.042	4.12E-01	-0.070	0.032	2.94E-02	0.009	0.034	7.96E-01
rs986391	G/A	-0.005	0.043	9.07E-01	-0.022	0.044	6.22E-01	-0.019	0.034	5.67E-01	-0.042	0.036	2.46E-01
rs13153393	G/A	0.046	0.102	6.54E-01	0.052	0.065	4.22E-01	0.002	0.071	9.75E-01	0.134	0.054	1.30E-02
rs245774	G/A	-0.060	0.046	1.88E-01	-0.054	0.046	2.40E-01	-0.094	0.035	8.18E-03	0.004	0.039	9.08E-01
rs6935954	A/G	0.021	0.042	6.24E-01	0.012	0.043	7.77E-01	-0.019	0.043	6.52E-01	0.084	0.035	1.57E-02
rs2254710	C/A	0.028	0.073	7.05E-01	0.055	0.051	2.87E-01	0.022	0.039	5.78E-01	0.041	0.041	3.18E-01
rs2894808	A/T	0.034	0.067	6.09E-01	-0.020	0.071	7.74E-01	0.004	0.054	9.36E-01	0.043	0.057	4.55E-01
rs12202536	G/A	-0.043	0.041	2.99E-01	-0.106	0.042	1.11E-02	-0.068	0.032	3.45E-02	-0.067	0.034	4.87E-02

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs7766610	C/A	-0.101	0.074	1.71E-01	-0.044	0.055	4.18E-01	-0.090	0.042	3.33E-02	-0.014	0.067	8.34E-01
rs1922018	C/T	0.010	0.043	8.22E-01	0.001	0.044	9.77E-01	-0.004	0.033	8.98E-01	0.009	0.035	8.06E-01
rs10226228	G/A	-0.050	0.042	2.31E-01	-0.035	0.044	4.32E-01	-0.024	0.033	4.67E-01	-0.033	0.036	3.61E-01
rs11768481	C/A	Excluded for MR											
rs6962772	A/G	-0.059	0.057	2.95E-01	-0.019	0.057	7.36E-01	-0.058	0.044	1.90E-01	-0.026	0.047	5.80E-01
rs10282292	C/T	-0.026	0.043	5.40E-01	0.027	0.050	5.95E-01	0.006	0.033	8.52E-01	0.005	0.038	8.99E-01
rs2401924	G/C	Excluded for MR											
rs7807019	G/A	0.013	0.041	7.56E-01	0.004	0.042	9.21E-01	-0.006	0.032	8.59E-01	0.044	0.034	1.98E-01
rs6957896	T/C	-0.027	0.052	6.07E-01	-0.039	0.052	4.57E-01	-0.040	0.047	3.97E-01	-0.022	0.040	5.86E-01
rs4731925	T/C	-0.014	0.044	7.50E-01	-0.042	0.044	3.42E-01	0.026	0.045	5.54E-01	-0.084	0.036	2.07E-02
rs35169606	T/G	Excluded for MR											
rs11783093	C/T	-0.004	0.080	9.61E-01	0.011	0.055	8.47E-01	0.010	0.043	8.19E-01	-0.048	0.057	4.02E-01
rs2062882	A/G	0.007	0.042	8.71E-01	-0.024	0.041	5.56E-01	-0.007	0.035	8.41E-01	-0.054	0.044	2.21E-01
rs72674867	A/T	0.033	0.045	4.70E-01	0.042	0.047	3.75E-01	0.028	0.036	4.42E-01	-0.017	0.048	7.16E-01
rs4543592	C/T	-0.036	0.041	3.84E-01	-0.071	0.042	9.30E-02	-0.023	0.033	4.74E-01	-0.036	0.034	2.91E-01
rs7039819	G/A	-0.009	0.043	8.27E-01	0.002	0.043	9.58E-01	0.010	0.033	7.74E-01	-0.001	0.036	9.69E-01
rs1246265	C/T	0.061	0.045	1.76E-01	-0.006	0.045	8.95E-01	0.011	0.035	7.42E-01	-0.005	0.037	8.98E-01
rs1221148	C/G	0.056	0.043	1.89E-01	0.030	0.055	5.93E-01	0.050	0.034	1.34E-01	-0.031	0.035	3.86E-01
rs13296519	T/G	-0.016	0.059	7.89E-01	-0.044	0.043	3.01E-01	-0.020	0.033	5.53E-01	-0.010	0.035	7.76E-01
rs113382419	A/C	0.037	0.068	5.87E-01	-0.045	0.070	5.21E-01	0.036	0.054	5.01E-01	-0.073	0.060	2.24E-01
rs11255908	G/T	0.008	0.045	8.66E-01	-0.036	0.048	4.45E-01	-0.014	0.036	6.93E-01	0.027	0.039	4.92E-01
rs2675638	G/A	0.014	0.064	8.32E-01	0.014	0.042	7.48E-01	-0.040	0.033	2.19E-01	-0.010	0.037	7.88E-01
rs10823968	A/T	0.002	0.044	9.55E-01	0.029	0.044	4.98E-01	0.028	0.034	4.09E-01	-0.010	0.036	7.76E-01
rs61857951	C/A	Excluded for MR											
rs7077678	C/T	-0.010	0.041	8.09E-01	-0.020	0.043	6.42E-01	-0.013	0.033	6.97E-01	0.007	0.035	8.40E-01
rs12244388	A/G	-0.098	0.042	2.00E-02	-0.048	0.042	2.57E-01	-0.086	0.033	8.52E-03	-0.036	0.035	2.95E-01
rs3896224	A/G	0.028	0.042	5.08E-01	-0.019	0.042	6.57E-01	-0.006	0.032	8.55E-01	0.004	0.034	9.12E-01
rs34866095	G/A	-0.101	0.044	2.38E-02	-0.051	0.045	2.49E-01	-0.020	0.034	5.70E-01	-0.085	0.037	2.27E-02
rs75742406	G/A	-0.050	0.049	3.10E-01	-0.063	0.051	2.19E-01	-0.033	0.039	4.01E-01	-0.052	0.050	2.97E-01
rs17309874	A/G	-0.059	0.051	2.45E-01	-0.032	0.051	5.30E-01	-0.054	0.039	1.67E-01	0.003	0.041	9.48E-01
rs4391802	A/G	0.003	0.045	9.41E-01	0.113	0.046	1.34E-02	0.051	0.035	1.51E-01	0.050	0.038	1.85E-01
rs112282219	A/G	-0.061	0.108	5.69E-01	Excluded for MR			0.022	0.087	7.97E-01	0.051	0.091	5.75E-01
rs9919670	A/G	-0.019	0.042	6.49E-01	-0.028	0.042	5.09E-01	-0.019	0.033	5.69E-01	-0.013	0.035	7.17E-01
rs74086911	G/A	-0.201	0.079	1.13E-02	0.116	0.083	1.60E-01	0.006	0.063	9.21E-01	-0.134	0.065	3.97E-02
rs7297175	C/T	0.042	0.043	3.25E-01	-0.044	0.044	3.16E-01	0.011	0.034	7.40E-01	0.029	0.036	4.21E-01
rs10879871	G/T	0.045	0.043	2.95E-01	-0.046	0.044	2.99E-01	-0.003	0.034	9.34E-01	-0.005	0.036	8.85E-01
rs12831617	T/C	-0.033	0.045	4.66E-01	0.047	0.047	3.18E-01	0.029	0.036	4.27E-01	0.021	0.039	5.84E-01
rs6562474	C/G	0.001	0.043	9.72E-01	0.041	0.043	3.45E-01	0.024	0.033	4.64E-01	-0.010	0.035	7.73E-01
rs7333559	G/A	-0.064	0.053	2.26E-01	-0.027	0.052	6.06E-01	-0.079	0.041	5.14E-02	0.009	0.055	8.73E-01
rs860326	C/T	0.049	0.063	4.35E-01	-0.023	0.043	5.97E-01	0.011	0.033	7.32E-01	-0.030	0.035	3.95E-01
rs7155595	C/A	0.009	0.045	8.44E-01	0.021	0.045	6.35E-01	-0.008	0.035	8.11E-01	0.004	0.048	9.26E-01
rs3742365	C/T	-0.012	0.043	7.80E-01	0.015	0.043	7.33E-01	0.001	0.033	9.72E-01	0.013	0.035	7.09E-01
rs35175834	A/G	-0.027	0.049	5.78E-01	-0.062	0.050	2.13E-01	-0.036	0.038	3.55E-01	-0.037	0.041	3.68E-01
rs28485305	C/T	0.036	0.042	3.86E-01	0.001	0.042	9.87E-01	0.058	0.033	7.68E-02	-0.040	0.035	2.41E-01
rs8042849	C/T	-0.035	0.043	4.26E-01	0.053	0.043	2.23E-01	0.032	0.034	3.33E-01	-0.041	0.036	2.60E-01
rs8042134	G/T	0.009	0.056	8.79E-01	0.067	0.042	1.11E-01	0.041	0.033	2.07E-01	0.026	0.035	4.49E-01
rs6598539	C/T	<0.001	0.042	9.98E-01	-0.017	0.042	6.94E-01	-0.021	0.033	5.27E-01	-0.013	0.047	7.88E-01
rs11861214	G/T	0.011	0.051	8.31E-01	0.050	0.052	3.35E-01	0.047	0.040	2.42E-01	0.044	0.042	2.91E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs12708665	G/A	<0.001	0.044	9.99E-01	-0.065	0.045	1.51E-01	-0.038	0.035	2.68E-01	0.009	0.037	8.18E-01
rs57611503	G/A	Excluded for MR						-0.111	0.036	2.14E-03	-0.080	0.049	9.86E-02
rs889398	C/T	Excluded for MR						0.019	0.061	7.52E-01	0.019	0.060	7.47E-01
rs60952428	T/C	Excluded for MR											
rs1050847	C/T	0.006	0.042	8.81E-01	-0.014	0.043	7.39E-01	0.019	0.033	5.69E-01	-0.074	0.035	3.51E-02
rs369230	T/G	-0.019	0.048	6.94E-01	-0.057	0.049	2.47E-01	-0.036	0.038	3.44E-01	-0.044	0.050	3.75E-01
rs8614	A/C	0.141	0.059	1.65E-02	0.011	0.061	8.52E-01	0.098	0.046	3.27E-02	0.064	0.048	1.86E-01
rs732083	G/A	-0.041	0.044	3.57E-01	-0.015	0.045	7.45E-01	-0.035	0.035	3.06E-01	-0.031	0.037	4.04E-01
rs9904288	T/C	-0.016	0.045	7.19E-01	-0.038	0.046	4.13E-01	-0.037	0.035	2.92E-01	-0.007	0.038	8.61E-01
rs67596067	A/G	-0.026	0.043	5.42E-01	0.047	0.044	2.86E-01	0.008	0.034	8.12E-01	0.035	0.036	3.31E-01
rs12967855	A/G	-0.102	0.044	2.06E-02	0.010	0.045	8.31E-01	-0.052	0.035	1.33E-01	0.002	0.037	9.47E-01
rs62098013	A/G	0.067	0.044	1.22E-01	0.025	0.044	5.78E-01	0.102	0.034	2.81E-03	-0.014	0.050	7.77E-01
rs71367545	A/G	-0.063	0.054	2.41E-01	0.077	0.055	1.63E-01	-0.014	0.043	7.40E-01	0.062	0.044	1.64E-01
rs76608582	C/A	NA in COURAGE-PD											
rs35343344	C/A	0.030	0.069	6.64E-01	0.068	0.050	1.76E-01	0.037	0.039	3.46E-01	0.040	0.041	3.31E-01
rs4814873	C/T	-0.008	0.048	8.62E-01	-0.043	0.049	3.80E-01	0.013	0.038	7.35E-01	-0.079	0.040	4.76E-02
rs6119897	A/G	0.034	0.053	5.18E-01	-0.061	0.053	2.42E-01	-0.032	0.041	4.40E-01	0.003	0.042	9.52E-01
rs12481282	C/G	-0.010	0.048	8.38E-01	-0.080	0.048	9.98E-02	-0.041	0.038	2.71E-01	-0.013	0.040	7.43E-01
rs348809	G/A	-0.024	0.043	5.77E-01	-0.005	0.043	9.07E-01	-0.037	0.044	4.06E-01	0.009	0.035	8.03E-01
rs6011779	C/T	-0.107	0.072	1.38E-01	0.042	0.051	4.17E-01	-0.056	0.040	1.63E-01	0.036	0.042	3.96E-01
rs147412694	A/G	-0.072	0.060	2.31E-01	0.053	0.060	3.76E-01	-0.024	0.047	6.03E-01	-0.032	0.050	5.20E-01
rs2838834	T/C	0.037	0.044	3.97E-01	-0.013	0.059	8.27E-01	0.003	0.035	9.26E-01	0.038	0.050	4.41E-01
rs136233	G/A	0.034	0.051	5.04E-01	-0.114	0.052	2.98E-02	-0.035	0.040	3.85E-01	-0.025	0.042	5.52E-01
rs202645	G/A	0.172	0.051	7.11E-04	0.100	0.067	1.37E-01	0.121	0.039	2.13E-03	0.138	0.055	1.17E-02
Smoking initiation (per 1-SD increase in the of prevalence of ever smoking)													
rs12130857	G/A	-0.028	0.043	5.16E-01	-0.009	0.045	8.38E-01	-0.038	0.034	2.70E-01	0.003	0.037	9.43E-01
rs3820277	G/T	-0.036	0.041	3.79E-01	-0.041	0.057	4.74E-01	-0.042	0.048	3.83E-01	-0.035	0.034	3.02E-01
rs1889571	G/T	-0.002	0.065	9.81E-01	0.009	0.065	8.91E-01	0.030	0.050	5.48E-01	0.011	0.053	8.27E-01
rs10914684	G/A	0.010	0.043	8.11E-01	-0.023	0.044	5.93E-01	-0.039	0.034	2.45E-01	0.006	0.036	8.72E-01
rs951740	A/G	-0.109	0.059	6.57E-02	0.033	0.043	4.44E-01	-0.039	0.033	2.43E-01	-0.055	0.046	2.28E-01
rs12022778	C/A	0.068	0.052	1.93E-01	-0.012	0.054	8.26E-01	0.042	0.041	3.11E-01	0.078	0.061	2.05E-01
rs4912332	T/C	0.074	0.057	1.95E-01	0.036	0.042	3.91E-01	0.084	0.032	8.77E-03	-0.031	0.034	3.67E-01
rs80054503	T/C	NA in COURAGE-PD											
rs10789369	A/G	-0.046	0.042	2.72E-01	-0.047	0.043	2.74E-01	-0.034	0.033	2.93E-01	-0.018	0.035	5.99E-01
rs1514176	G/A	-0.001	0.042	9.82E-01	0.023	0.055	6.72E-01	0.005	0.033	8.82E-01	0.014	0.035	6.99E-01
rs11162019	C/T	-0.010	0.043	8.17E-01	-0.031	0.044	4.86E-01	-0.016	0.034	6.38E-01	-0.034	0.036	3.45E-01
rs1008078	T/C	-0.052	0.041	2.07E-01	0.047	0.042	2.61E-01	-0.038	0.041	3.54E-01	0.008	0.055	8.86E-01
rs12027999	T/C	-0.007	0.067	9.15E-01	0.096	0.086	2.67E-01	0.028	0.052	5.98E-01	-0.009	0.056	8.70E-01
rs45444697	G/C	-0.013	0.053	8.02E-01	-0.011	0.075	8.78E-01	-0.016	0.042	6.98E-01	0.005	0.043	9.04E-01
rs2901785	G/A	0.041	0.054	4.44E-01	0.004	0.053	9.37E-01	0.052	0.045	2.47E-01	-0.015	0.034	6.67E-01
rs147052174	T/G	Excluded for MR											
rs35656245	A/G	0.006	0.044	8.97E-01	-0.019	0.045	6.79E-01	-0.006	0.046	8.90E-01	-0.007	0.037	8.44E-01
rs12739243	T/C	0.003	0.048	9.44E-01	-0.017	0.050	7.41E-01	0.035	0.038	3.65E-01	0.013	0.040	7.50E-01
rs876793	T/C	0.034	0.045	4.43E-01	0.084	0.045	6.08E-02	0.005	0.051	9.27E-01	0.074	0.037	4.37E-02
rs6731872	G/T	-0.026	0.051	6.20E-01	0.058	0.053	2.71E-01	0.005	0.040	9.04E-01	0.029	0.044	5.08E-01
rs1022376	T/C	0.020	0.041	6.25E-01	0.015	0.042	7.27E-01	-0.005	0.032	8.74E-01	0.023	0.035	5.12E-01
rs61533748	C/T	-0.011	0.057	8.50E-01	0.042	0.043	3.29E-01	-0.020	0.034	5.53E-01	0.021	0.036	5.53E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs2710634	T/C	-0.035	0.041	4.02E-01	-0.031	0.042	4.52E-01	-0.027	0.032	4.00E-01	-0.054	0.034	1.12E-01
rs7598402	C/G	Excluded for MR											
rs10490159	T/C	-0.009	0.041	8.29E-01	-0.124	0.055	2.37E-02	-0.006	0.032	8.42E-01	-0.061	0.034	7.61E-02
rs359247	T/A	-0.009	0.042	8.32E-01	0.022	0.043	6.13E-01	0.020	0.033	5.49E-01	-0.025	0.035	4.88E-01
rs12714017	C/T	0.042	0.041	3.10E-01	-0.018	0.042	6.76E-01	-0.019	0.032	5.63E-01	0.059	0.034	8.36E-02
rs13392222	A/C	0.067	0.065	3.01E-01	0.005	0.088	9.54E-01	0.022	0.050	6.57E-01	-0.032	0.052	5.34E-01
rs1901477	G/A	-0.031	0.041	4.48E-01	0.047	0.041	2.57E-01	<0.001	0.043	9.94E-01	0.034	0.050	5.03E-01
rs3811038	C/T	-0.049	0.046	2.84E-01	-0.008	0.061	8.91E-01	0.001	0.036	9.82E-01	-0.011	0.038	7.74E-01
rs34399632	G/A	0.050	0.059	3.98E-01	-0.026	0.084	7.58E-01	0.001	0.059	9.81E-01	-0.052	0.046	2.50E-01
rs6756212	C/T	-0.022	0.041	5.97E-01	0.027	0.041	5.15E-01	-0.015	0.032	6.33E-01	-0.015	0.034	6.52E-01
rs16826827	T/C	-0.003	0.065	9.68E-01	-0.086	0.064	1.79E-01	-0.054	0.049	2.77E-01	-0.017	0.052	7.41E-01
rs1445649	C/T	0.005	0.041	9.11E-01	-0.059	0.041	1.51E-01	-0.014	0.032	6.50E-01	-0.033	0.034	3.25E-01
rs12474587	T/G	0.081	0.042	5.53E-02	0.019	0.043	6.63E-01	0.062	0.033	6.28E-02	0.021	0.035	5.59E-01
rs13007361	A/G	0.047	0.072	5.12E-01	0.007	0.049	8.93E-01	0.082	0.038	2.98E-02	-0.053	0.042	2.05E-01
rs6750529	T/C	0.004	0.047	9.30E-01	-0.066	0.048	1.66E-01	-0.054	0.037	1.43E-01	-0.006	0.039	8.79E-01
rs17229285	C/T	0.058	0.065	3.73E-01	-0.038	0.042	3.62E-01	-0.016	0.032	6.17E-01	0.040	0.035	2.49E-01
rs62193862	A/G	Excluded for MR											
rs4674993	A/G	0.015	0.052	7.70E-01	0.034	0.075	6.51E-01	0.044	0.057	4.37E-01	-0.048	0.053	3.67E-01
rs11713899	C/A	-0.049	0.053	3.55E-01	-0.006	0.055	9.18E-01	-0.082	0.042	5.29E-02	0.016	0.045	7.20E-01
rs748832	G/A	0.045	0.043	2.91E-01	0.054	0.044	2.15E-01	0.062	0.034	6.52E-02	0.020	0.035	5.64E-01
rs2526390	T/C	-0.061	0.062	3.29E-01	0.049	0.044	2.62E-01	-0.001	0.034	9.69E-01	-0.006	0.036	8.58E-01
rs221988	A/C	0.047	0.066	4.75E-01	-0.017	0.044	7.02E-01	0.049	0.034	1.52E-01	-0.009	0.036	8.02E-01
rs11128203	A/T	Excluded for MR											
rs62246017	G/A	-0.028	0.045	5.31E-01	-0.046	0.046	3.14E-01	-0.038	0.036	2.84E-01	-0.050	0.048	2.92E-01
rs12633090	G/C	0.087	0.052	9.46E-02	0.014	0.052	7.87E-01	0.072	0.057	2.06E-01	0.021	0.059	7.17E-01
rs1549979	C/T	0.037	0.042	3.75E-01	0.017	0.042	6.91E-01	-0.009	0.033	7.83E-01	0.050	0.035	1.51E-01
rs6437769	T/C	-0.028	0.057	6.21E-01	0.086	0.058	1.40E-01	0.032	0.033	3.31E-01	0.013	0.034	7.11E-01
rs9288999	A/G	0.018	0.046	6.98E-01	-0.137	0.048	4.24E-03	-0.044	0.036	2.31E-01	-0.067	0.038	7.91E-02
rs6438436	T/C	0.028	0.084	7.40E-01	0.075	0.057	1.86E-01	0.016	0.043	7.09E-01	0.071	0.046	1.24E-01
rs9826984	G/A	0.017	0.042	6.89E-01	0.029	0.042	4.82E-01	-0.019	0.032	5.65E-01	0.069	0.034	4.42E-02
rs2279829	C/T	0.057	0.053	2.82E-01	0.027	0.053	6.13E-01	0.026	0.041	5.31E-01	-0.004	0.043	9.28E-01
rs2319545	A/C	-0.025	0.063	6.86E-01	-0.020	0.062	7.46E-01	-0.019	0.066	7.70E-01	0.032	0.050	5.31E-01
rs1714521	A/C	-0.034	0.042	4.12E-01	-0.036	0.043	4.06E-01	0.002	0.033	9.41E-01	-0.036	0.044	4.10E-01
rs1449012	C/T	0.034	0.054	5.29E-01	-0.048	0.042	2.57E-01	-0.024	0.044	5.79E-01	0.066	0.034	5.49E-02
rs1187820	C/T	0.031	0.044	4.84E-01	0.069	0.061	2.61E-01	0.002	0.035	9.57E-01	0.037	0.053	4.82E-01
rs7631379	C/T	0.010	0.076	8.92E-01	-0.133	0.074	7.15E-02	0.006	0.043	8.86E-01	-0.093	0.046	4.13E-02
rs4140932	T/A	Excluded for MR											
rs59537158	T/C	-0.109	0.053	4.12E-02	0.070	0.054	1.96E-01	-0.049	0.042	2.43E-01	0.048	0.043	2.69E-01
rs58400863	G/A	0.018	0.043	6.85E-01	0.048	0.044	2.68E-01	-0.003	0.034	9.39E-01	0.029	0.036	4.24E-01
rs112725451	T/C	-0.016	0.052	7.54E-01	0.055	0.054	3.04E-01	-0.013	0.041	7.51E-01	0.030	0.044	4.97E-01
rs1160685	G/C	Excluded for MR											
rs3934797	G/A	0.020	0.055	7.12E-01	0.010	0.058	8.60E-01	0.041	0.044	3.54E-01	0.003	0.068	9.60E-01
rs71602617	C/T	-0.016	0.052	7.64E-01	0.047	0.064	4.60E-01	-0.035	0.040	3.84E-01	0.033	0.042	4.42E-01
rs7696257	A/G	0.020	0.043	6.40E-01	-0.035	0.044	4.17E-01	0.024	0.034	4.68E-01	-0.041	0.036	2.53E-01
rs1116690	G/A	-0.061	0.048	2.03E-01	-0.046	0.050	3.58E-01	-0.049	0.038	1.95E-01	0.001	0.040	9.78E-01
rs13110073	T/C	-0.010	0.042	8.02E-01	-0.074	0.042	7.85E-02	-0.054	0.032	9.92E-02	-0.052	0.035	1.38E-01
rs62340589	C/G	-0.067	0.054	2.14E-01	0.048	0.053	3.65E-01	0.014	0.042	7.40E-01	-0.011	0.044	8.02E-01
rs12517438	G/T	0.040	0.041	3.23E-01	-0.003	0.042	9.36E-01	0.026	0.032	4.05E-01	-0.009	0.034	7.92E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs35375873	G/C	Excluded for MR											
rs71592686	C/T	0.048	0.046	2.94E-01	0.053	0.046	2.50E-01	0.085	0.036	1.71E-02	0.023	0.038	5.57E-01
rs6874731	G/T	0.017	0.041	6.81E-01	-0.020	0.041	6.28E-01	0.008	0.032	7.94E-01	-0.022	0.034	5.22E-01
rs6452785	C/T	-0.066	0.041	1.05E-01	0.013	0.058	8.20E-01	-0.012	0.032	7.16E-01	-0.065	0.034	5.53E-02
rs42417	T/C	-0.070	0.046	1.32E-01	-0.129	0.072	7.50E-02	-0.116	0.052	2.51E-02	-0.055	0.038	1.52E-01
rs72780746	T/C	-0.134	0.051	9.26E-03	0.002	0.052	9.64E-01	-0.063	0.040	1.15E-01	-0.049	0.043	2.53E-01
rs329124	A/G	-0.040	0.041	3.31E-01	-0.045	0.042	2.78E-01	-0.061	0.032	5.71E-02	0.004	0.034	9.07E-01
rs1385108	T/C	-0.011	0.049	8.25E-01	0.033	0.050	5.11E-01	-0.005	0.038	8.96E-01	-0.016	0.040	6.92E-01
rs6890961	C/T	-0.109	0.066	1.00E-01	0.007	0.044	8.74E-01	-0.018	0.034	5.91E-01	-0.064	0.036	7.78E-02
rs4044321	A/G	-0.003	0.043	9.46E-01	-0.016	0.044	7.20E-01	-0.010	0.034	7.62E-01	-0.045	0.036	2.18E-01
rs2173019	A/T	0.050	0.080	5.29E-01	0.021	0.055	7.03E-01	0.018	0.043	6.71E-01	0.091	0.045	4.15E-02
rs1150668	T/G	-0.027	0.042	5.20E-01	0.034	0.044	4.34E-01	0.021	0.033	5.31E-01	-0.006	0.035	8.69E-01
rs3218116	C/T	-0.045	0.079	5.65E-01	0.013	0.049	7.85E-01	0.001	0.038	9.78E-01	-0.026	0.040	5.14E-01
rs160631	T/G	0.063	0.046	1.71E-01	0.040	0.047	3.88E-01	0.071	0.036	4.84E-02	0.011	0.038	7.71E-01
rs7743165	G/T	<0.001	0.062	9.94E-01	-0.104	0.042	1.26E-02	-0.065	0.032	4.49E-02	-0.059	0.044	1.85E-01
rs10945141	A/G	-0.002	0.046	9.72E-01	0.017	0.047	7.21E-01	-0.011	0.036	7.59E-01	0.040	0.038	2.90E-01
rs17554906	C/G	Excluded for MR											
rs6568832	A/G	-0.096	0.048	4.55E-02	0.006	0.049	9.01E-01	-0.022	0.038	5.57E-01	-0.026	0.040	5.11E-01
rs12195240	A/G	0.009	0.045	8.37E-01	-0.096	0.044	3.03E-02	-0.031	0.034	3.68E-01	-0.023	0.037	5.24E-01
rs6936160	T/C	0.080	0.045	7.41E-02	-0.001	0.045	9.80E-01	0.053	0.035	1.26E-01	-0.025	0.037	4.99E-01
rs118202	G/T	-0.098	0.075	1.91E-01	-0.045	0.055	4.08E-01	-0.093	0.042	2.82E-02	-0.016	0.067	8.08E-01
rs1737329	G/C	-0.041	0.047	3.84E-01	0.011	0.067	8.70E-01	-0.024	0.037	5.14E-01	-0.001	0.053	9.85E-01
rs6948707	G/T	-0.003	0.041	9.51E-01	-0.032	0.057	5.73E-01	0.002	0.032	9.45E-01	0.007	0.035	8.48E-01
rs7809303	G/A	-0.104	0.043	1.68E-02	-0.020	0.044	6.52E-01	-0.068	0.034	4.63E-02	-0.063	0.036	8.17E-02
rs1030015	T/G	-0.028	0.049	5.61E-01	0.014	0.051	7.81E-01	0.026	0.048	5.80E-01	-0.011	0.034	7.56E-01
rs4727189	C/T	0.083	0.042	4.58E-02	-0.005	0.043	9.08E-01	-0.004	0.033	8.94E-01	0.068	0.035	5.47E-02
rs11768481	C/A	Excluded for MR											
rs13437771	A/G	-0.060	0.057	2.93E-01	-0.018	0.057	7.46E-01	-0.058	0.044	1.88E-01	-0.025	0.047	5.92E-01
rs10233018	G/A	0.011	0.041	7.88E-01	0.008	0.042	8.42E-01	-0.017	0.032	5.93E-01	0.054	0.034	1.13E-01
rs10953957	A/G	0.071	0.055	1.99E-01	-0.017	0.043	6.83E-01	0.023	0.033	4.76E-01	0.048	0.035	1.75E-01
rs77283305	G/A	-0.018	0.044	6.84E-01	-0.047	0.044	2.92E-01	0.015	0.035	6.60E-01	-0.085	0.036	1.86E-02
rs10279261	G/A	-0.011	0.062	8.58E-01	-0.019	0.044	6.62E-01	0.011	0.034	7.33E-01	-0.037	0.036	3.10E-01
rs4326350	C/G	Excluded for MR											
rs11783093	C/T	-0.004	0.080	9.61E-01	0.011	0.055	8.47E-01	0.010	0.043	8.19E-01	-0.048	0.057	4.02E-01
rs7836565	C/T	0.038	0.046	4.09E-01	0.114	0.046	1.37E-02	0.047	0.036	1.90E-01	0.083	0.038	2.82E-02
rs13261666	G/T	-0.052	0.055	3.41E-01	-0.020	0.041	6.28E-01	-0.014	0.032	6.54E-01	-0.020	0.034	5.59E-01
rs3850736	G/C	Excluded for MR											
rs2063976	C/T	0.021	0.043	6.34E-01	-0.059	0.044	1.79E-01	0.001	0.034	9.71E-01	-0.030	0.036	4.14E-01
rs6986430	T/C	-0.034	0.048	4.73E-01	0.068	0.049	1.63E-01	-0.010	0.037	7.85E-01	0.053	0.040	1.86E-01
rs290601	T/C	0.040	0.046	3.85E-01	0.032	0.047	4.89E-01	0.039	0.035	2.76E-01	-0.027	0.038	4.80E-01
rs3847244	T/C	-0.046	0.042	2.72E-01	-0.058	0.043	1.78E-01	-0.028	0.033	3.99E-01	-0.036	0.035	3.10E-01
rs11791671	T/C	-0.027	0.130	8.34E-01	-0.016	0.088	8.57E-01	-0.012	0.096	9.00E-01	0.078	0.088	3.78E-01
rs7024924	C/T	-0.061	0.054	2.61E-01	-0.014	0.055	7.92E-01	-0.010	0.042	8.15E-01	-0.002	0.045	9.71E-01
rs10966092	T/C	-0.009	0.047	8.53E-01	-0.046	0.046	3.24E-01	-0.048	0.046	2.95E-01	0.018	0.039	6.42E-01
rs4877285	G/A	-0.069	0.074	3.53E-01	-0.046	0.060	4.47E-01	-0.036	0.034	2.92E-01	-0.088	0.037	1.58E-02
rs2378662	A/G	0.019	0.043	6.51E-01	-0.019	0.067	7.81E-01	-0.017	0.044	6.96E-01	0.011	0.035	7.57E-01
rs4837631	C/T	0.049	0.042	2.44E-01	0.028	0.043	5.08E-01	0.045	0.033	1.72E-01	-0.028	0.035	4.29E-01
rs34553878	G/A	Excluded for MR											

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs10858334	G/C	-0.076	0.060	2.11E-01	-0.124	0.079	1.14E-01	-0.068	0.048	1.55E-01	-0.076	0.069	2.72E-01
rs7920501	T/A	Excluded for MR											
rs1291821	G/A	-0.012	0.041	7.65E-01	0.004	0.042	9.20E-01	-0.024	0.032	4.64E-01	-0.009	0.034	7.95E-01
rs7072776	A/G	0.020	0.047	6.77E-01	-0.019	0.048	6.98E-01	-0.014	0.037	6.99E-01	0.040	0.040	3.10E-01
rs2796793	A/G	0.100	0.043	2.11E-02	0.011	0.043	7.88E-01	0.081	0.033	1.55E-02	0.038	0.053	4.73E-01
rs1733760	C/T	-0.005	0.042	8.98E-01	0.008	0.043	8.57E-01	-0.014	0.033	6.73E-01	0.052	0.035	1.38E-01
rs7921378	G/C	Excluded for MR											
rs11594623	C/T	-0.043	0.050	3.89E-01	-0.133	0.051	9.75E-03	-0.076	0.039	5.41E-02	-0.032	0.042	4.36E-01
rs12244388	A/G	-0.098	0.042	2.00E-02	-0.048	0.042	2.57E-01	-0.086	0.033	8.52E-03	-0.036	0.035	2.95E-01
rs10885480	T/C	-0.072	0.047	1.28E-01	0.046	0.047	3.35E-01	0.003	0.037	9.34E-01	-0.044	0.039	2.54E-01
rs4752018	A/C	-0.040	0.048	4.02E-01	0.017	0.049	7.27E-01	-0.049	0.050	3.33E-01	-0.030	0.040	4.63E-01
rs9423279	C/G	Excluded for MR											
rs6265	C/T	0.060	0.052	2.46E-01	-0.012	0.052	8.17E-01	0.039	0.040	3.30E-01	0.023	0.043	5.88E-01
rs2939756	G/A	-0.019	0.041	6.33E-01	-0.010	0.042	8.17E-01	-0.019	0.032	5.52E-01	-0.017	0.034	6.28E-01
rs1381775	T/C	-0.006	0.046	9.02E-01	-0.071	0.047	1.26E-01	-0.034	0.036	3.45E-01	-0.060	0.038	1.14E-01
rs61886926	C/T	-0.056	0.042	1.82E-01	-0.003	0.064	9.63E-01	-0.020	0.033	5.38E-01	-0.001	0.044	9.78E-01
rs644740	C/T	-0.015	0.041	7.21E-01	-0.008	0.041	8.48E-01	-0.015	0.032	6.42E-01	-0.003	0.034	9.33E-01
rs7943721	G/A	NA in COURAGE-PD											
rs7929518	G/A	<0.001	0.048	9.99E-01	-0.027	0.048	5.75E-01	-0.042	0.037	2.55E-01	-0.014	0.040	7.20E-01
rs2155646	C/T	-0.018	0.042	6.63E-01	-0.027	0.042	5.27E-01	-0.018	0.033	5.81E-01	-0.012	0.035	7.24E-01
rs1713676	A/G	0.019	0.042	6.49E-01	0.060	0.045	1.86E-01	0.048	0.032	1.31E-01	0.039	0.034	2.56E-01
rs540860	G/A	0.061	0.040	1.34E-01	0.030	0.042	4.67E-01	0.034	0.032	2.82E-01	0.055	0.034	1.04E-01
rs1106363	T/C	-0.013	0.042	7.62E-01	0.057	0.043	1.83E-01	-0.026	0.033	4.26E-01	0.067	0.035	5.57E-02
rs2010921	A/G	0.017	0.045	6.98E-01	0.034	0.045	4.48E-01	0.037	0.035	2.88E-01	0.037	0.037	3.29E-01
rs11057005	A/G	-0.045	0.061	4.57E-01	-0.082	0.043	6.05E-02	-0.033	0.048	4.92E-01	-0.021	0.036	5.62E-01
rs13906	C/T	-0.139	0.066	3.55E-02	0.122	0.068	7.26E-02	0.058	0.052	2.72E-01	-0.057	0.054	2.95E-01
rs4759229	G/A	0.008	0.060	8.94E-01	-0.005	0.046	9.20E-01	<0.001	0.036	9.94E-01	0.008	0.037	8.29E-01
rs7969559	A/G	-0.018	0.044	6.75E-01	-0.038	0.045	3.88E-01	-0.065	0.035	6.19E-02	0.041	0.037	2.70E-01
rs7134009	T/C	-0.006	0.044	8.96E-01	-0.030	0.044	4.95E-01	-0.030	0.034	3.79E-01	<0.001	0.037	9.92E-01
rs77215829	A/C	Excluded for MR											
rs1109480	G/A	-0.021	0.043	6.22E-01	-0.041	0.043	3.33E-01	0.041	0.084	6.22E-01	-0.030	0.066	6.45E-01
rs1109480	G/A	-0.021	0.043	6.22E-01	-0.041	0.043	3.33E-01	-0.043	0.033	1.99E-01	-0.026	0.035	4.61E-01
rs11611651	A/G	-0.054	0.077	4.82E-01	Excluded for MR			-0.005	0.060	9.28E-01	0.032	0.063	6.13E-01
rs17197663	G/A	0.092	0.059	1.17E-01	0.023	0.060	7.06E-01	0.018	0.072	8.04E-01	-0.021	0.051	6.83E-01
rs4264267	T/C	-0.046	0.042	2.72E-01	-0.008	0.043	8.58E-01	-0.031	0.033	3.44E-01	-0.017	0.035	6.16E-01
rs61959481	G/A	0.046	0.050	3.60E-01	-0.049	0.052	3.40E-01	-0.040	0.039	3.01E-01	0.020	0.042	6.34E-01
rs55786907	G/A	-0.030	0.054	5.75E-01	0.102	0.055	6.43E-02	0.037	0.042	3.82E-01	0.025	0.045	5.74E-01
rs9540731	C/T	-0.027	0.057	6.37E-01	-0.042	0.055	4.44E-01	-0.033	0.035	3.48E-01	-0.031	0.047	5.10E-01
rs9545155	T/C	-0.032	0.041	4.37E-01	0.007	0.042	8.72E-01	0.013	0.043	7.57E-01	0.005	0.034	8.89E-01
rs1772572	C/A	-0.040	0.043	3.51E-01	-0.017	0.044	7.04E-01	-0.047	0.044	2.83E-01	-0.060	0.036	8.98E-02
rs1108130	A/T	0.031	0.053	5.54E-01	-0.037	0.054	4.94E-01	0.024	0.041	5.59E-01	-0.030	0.043	4.84E-01
rs12878369	A/C	-0.005	0.041	9.07E-01	-0.044	0.053	4.10E-01	-0.028	0.045	5.33E-01	-0.029	0.043	5.10E-01
rs9323328	A/G	-0.037	0.042	3.76E-01	0.022	0.041	5.89E-01	-0.026	0.032	4.25E-01	0.016	0.034	6.31E-01
rs1811739	A/G	0.058	0.047	2.18E-01	0.069	0.048	1.52E-01	0.044	0.037	2.33E-01	0.019	0.039	6.20E-01
rs8005334	G/T	0.018	0.064	7.82E-01	-0.041	0.044	3.45E-01	0.004	0.034	9.14E-01	-0.025	0.036	4.84E-01
rs2925128	T/C	-0.067	0.065	3.05E-01	-0.017	0.042	6.92E-01	-0.040	0.033	2.17E-01	0.015	0.045	7.36E-01
rs1381287	T/C	0.004	0.041	9.31E-01	0.024	0.042	5.58E-01	0.026	0.032	4.23E-01	0.033	0.034	3.37E-01
rs1435672	C/T	0.012	0.042	7.65E-01	-0.032	0.042	4.44E-01	-0.022	0.033	5.07E-01	-0.027	0.048	5.75E-01
rs281296	A/G	-0.080	0.043	6.09E-02	-0.038	0.043	3.76E-01	-0.045	0.033	1.73E-01	-0.052	0.036	1.47E-01

SNP	EA/BA	Age ≤ 67y (2,878 cases; 2,944 controls)			Age > 67y (3,208 cases; 2,728 controls)			PD duration ≤ 7y (3,633 cases; 6,836 controls)			PD duration > 7y (3,271 cases; 6,836 controls)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs2289791	G/T	Excluded for MR											
rs62007780	G/T	-0.025	0.042	5.53E-01	0.036	0.042	3.87E-01	-0.007	0.032	8.39E-01	-0.008	0.035	8.07E-01
rs4310804	C/G	Excluded for MR											
rs1139897	G/A	-0.001	0.051	9.90E-01	0.070	0.052	1.83E-01	0.065	0.040	1.05E-01	0.035	0.042	4.13E-01
rs11076962	C/T	0.020	0.047	6.64E-01	-0.011	0.047	8.18E-01	-0.002	0.036	9.61E-01	0.004	0.038	9.17E-01
rs9922607	C/T	0.018	0.051	7.31E-01	-0.027	0.075	7.21E-01	-0.044	0.040	2.66E-01	0.002	0.044	9.71E-01
rs9941217	C/G	0.004	0.044	9.33E-01	0.029	0.046	5.24E-01	-0.004	0.047	9.24E-01	-0.016	0.047	7.28E-01
rs6497840	A/G	-0.082	0.071	2.44E-01	0.055	0.046	2.25E-01	0.022	0.035	5.35E-01	-0.048	0.038	2.00E-01
rs12918191	A/G	-0.009	0.047	8.44E-01	-0.007	0.048	8.85E-01	-0.016	0.037	6.57E-01	0.006	0.040	8.84E-01
rs9302604	G/A	-0.051	0.042	2.26E-01	-0.068	0.055	2.13E-01	-0.017	0.047	7.14E-01	0.021	0.035	5.44E-01
rs117657830	A/G	0.108	0.107	3.16E-01	-0.041	0.104	6.94E-01	-0.050	0.081	5.32E-01	0.037	0.090	6.82E-01
rs1050847	C/T	0.006	0.042	8.81E-01	-0.014	0.043	7.39E-01	0.019	0.033	5.69E-01	-0.074	0.035	3.51E-02
rs11642231	G/A	0.032	0.045	4.86E-01	0.094	0.045	3.95E-02	0.056	0.035	1.12E-01	0.057	0.037	1.29E-01
rs4790874	T/C	-0.050	0.042	2.33E-01	-0.020	0.042	6.43E-01	0.002	0.033	9.46E-01	-0.064	0.035	6.59E-02
rs28441558	T/C	Excluded for MR											
rs67777803	G/T	0.056	0.054	3.08E-01	-0.065	0.057	2.50E-01	-0.049	0.054	3.69E-01	-0.006	0.046	8.91E-01
rs3764351	G/A	-0.043	0.044	3.35E-01	0.001	0.058	9.86E-01	-0.026	0.035	4.62E-01	-0.045	0.037	2.26E-01
rs72836318	T/C	-0.062	0.073	3.94E-01	-0.135	0.049	5.54E-03	-0.068	0.038	7.09E-02	-0.124	0.040	1.85E-03
rs75919030	T/C	-0.019	0.047	6.84E-01	0.003	0.048	9.55E-01	0.014	0.037	7.12E-01	-0.030	0.039	4.33E-01
rs2587507	T/C	-0.029	0.044	5.03E-01	-0.037	0.041	3.61E-01	-0.046	0.034	1.72E-01	-0.022	0.034	5.08E-01
rs34342129	T/C	-0.011	0.042	7.92E-01	-0.079	0.042	6.03E-02	-0.057	0.032	7.66E-02	-0.026	0.034	4.50E-01
rs4476253	G/A	0.042	0.049	3.83E-01	-0.021	0.075	7.81E-01	-0.010	0.038	7.88E-01	0.024	0.056	6.73E-01
rs8096225	C/A	-0.021	0.045	6.34E-01	0.045	0.045	3.18E-01	0.016	0.035	6.47E-01	-0.033	0.037	3.76E-01
rs67050670	A/G	0.036	0.046	4.40E-01	0.057	0.048	2.35E-01	0.038	0.051	4.64E-01	0.051	0.039	1.94E-01
rs1373178	T/G	-0.001	0.042	9.81E-01	-0.057	0.043	1.82E-01	-0.042	0.033	2.01E-01	-0.010	0.035	7.64E-01
rs72938304	G/A	0.034	0.065	6.07E-01	0.113	0.067	9.06E-02	0.104	0.070	1.38E-01	-0.033	0.054	5.47E-01
rs71367544	T/C	-0.059	0.054	2.74E-01	0.078	0.055	1.62E-01	-0.011	0.043	8.03E-01	0.063	0.044	1.59E-01
rs76608582	C/A	NA in COURAGE-PD											
rs10853981	A/G	0.001	0.045	9.90E-01	-0.054	0.045	2.35E-01	0.004	0.044	9.22E-01	-0.020	0.037	5.79E-01
rs113230003	G/A	0.020	0.071	7.78E-01	0.073	0.050	1.41E-01	0.031	0.039	4.22E-01	0.047	0.041	2.59E-01
rs117734003	C/G	Excluded for MR											
rs1126757	T/C	0.030	0.042	4.73E-01	-0.050	0.058	3.87E-01	0.015	0.035	6.75E-01	-0.017	0.039	6.61E-01
rs117495226	G/A	Excluded for MR											
rs6073075	T/A	0.063	0.052	2.26E-01	-0.060	0.053	2.59E-01	0.020	0.041	6.28E-01	-0.010	0.044	8.23E-01
rs3810496	C/T	-0.031	0.065	6.31E-01	-0.026	0.059	6.63E-01	-0.047	0.046	3.07E-01	-0.038	0.053	4.67E-01
rs4818005	G/A	-0.075	0.041	6.81E-02	0.018	0.042	6.68E-01	-0.026	0.032	4.26E-01	-0.056	0.034	1.06E-01
rs4822102	C/T	0.071	0.060	2.36E-01	-0.006	0.043	8.98E-01	0.011	0.050	8.31E-01	0.021	0.035	5.48E-01

NA, not available; EA/BA, effect allele/base allele; SE, standard error.

Bold coefficients with their corresponding SE and p-values are significant at p≤0.05; those underlined with a solid line are negative and those underlined with a dashed line are positive.

Supplementary table 5: Number of SNPs retained for each exposure in Mendelian randomization analyses and distribution of F-statistics.

Exposure	Number of SNPs				F-statistic ^c
	Total ^a	Not available in Courage-PD	Excluded ^b	Retained for MR	
Smoking initiation	203	3	18	182	205.75
Lifetime smoking index	126	1	12	113	20.03
Alcohol	71	2	7	62	73.68
Coffee	11	-	-	11	70.47

^a SNPs selected after clumping ($r^2=0.001$, genomic region=10,000 kb).

^b Ambiguous palindromic SNPs with $MAF \geq 0.42$, SNPs with $MAF < 0.01$, or SNPs available in less than 17 studies.

^c For each instrument, the F-statistic is given by the formula $\left(\frac{n-k-1}{k}\right)\left(\frac{R^2}{1-R^2}\right)$, with R^2 the proportion of variance explained by the genetic variants, n the sample size, and k the number of instruments. (Burgess S et al., Int J Epidemiol 2011;40(3):755-64).

Supplementary table 6: Mendelian randomization analyses stratified by age at study.

Exposure	Age ≤ 67y			Age > 67y		
	(2,878 cases; 2,944 controls)			(3,208 cases; 2,728 controls)		
	OR _{IVW} (95% CI)	P-value	P-het.	OR _{IVW} (95% CI)	P-value	P-het.
Smoking initiation	0.68 (0.48-0.97)	0.031	0.92	0.83 (0.58-1.18)	0.29	0.50
Lifetime smoking	0.46 (0.19-1.09)	0.077	0.66	0.88 (0.37-2.07)	0.76	0.59
Alcohol drinking	0.51 (0.22-1.16)	0.11	0.19	0.85 (0.39-1.83)	0.68	0.93
Alcohol drinking after exclusion of 2 SNPs associated with coffee	0.61 (0.27-1.38)	0.24	0.26	0.97 (0.44-2.13)	0.94	0.94
Coffee drinking	1.15 (0.25-5.33)	0.86	0.24	1.45 (0.34-6.14)	0.62	0.44
Coffee drinking after exclusion of 2 SNPs associated with alcohol	0.53 (0.10-2.88)	0.47	0.69	1.01 (0.19-5.42)	0.99	0.52

OR, odds ratio; IVW, inverse-variance weighted; CI, confidence interval; p-het., p for heterogeneity; IVW, inverse variance weighted.

Supplementary table 7: Mendelian randomization analyses stratified by disease duration in PD cases.

Exposure	PD duration $\leq$ 7y			PD duration > 7y		
	(3,633 cases; 6,836 controls)			(3,271 cases; 6,836 controls)		
	OR _{IVW} (95% CI)	P-value	P-het.	OR _{IVW} (95% CI)	P-value	P-het.
Smoking initiation	0.70 (0.53-0.91)	0.009	0.59	0.74 (0.56-1.00)	0.046	0.46
Lifetime smoking	0.69 (0.32-1.48)	0.34	0.008	0.61 (0.29-1.30)	0.20	0.17
Alcohol drinking	0.81 (0.36-1.83)	0.61	0.032	0.53 (0.27-1.02)	0.057	0.36
Alcohol drinking after exclusion of 2 SNPs associated with coffee	1.03 (0.46-2.31)	0.95	0.075	0.59 (0.30-1.16)	0.13	0.38
Coffee drinking	1.77 (0.37-8.56)	0.48	0.066	1.53 (0.41-5.70)	0.52	0.17
Coffee drinking after exclusion of 2 SNPs associated with alcohol	0.55 (0.11-2.85)	0.48	0.31	1.05 (0.22-4.98)	0.95	0.24

OR, odds ratio; IVW, inverse-variance weighted; CI, confidence interval; p-het., p for heterogeneity; IVW, inverse variance weighted.

Supplementary table 8: SNPs used for reverse Mendelian randomization analyses: individual associations with PD (exposure) and smoking, alcohol, and coffee drinking (outcomes).

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EAF	Beta	SE	P-value	EAF	Beta	SE	P-value	
Outcome: Alcohol drinking											
rs35749011	1:155135036	A/G	0.02	0.607	0.034	1.72E-70	0.01	-0.002	0.008	7.80E-01	1.22E-02
rs6658353	1:161469054	C/G	0.50	0.065	0.009	6.10E-12	Excluded for reverse MR				
rs11578699	1:171719769	C/T	0.81	0.070	0.012	4.47E-09	0.80	0.002	0.002	3.08E-01	1.56E-03
rs823118	1:205723572	T/C	0.57	0.107	0.009	1.11E-29	0.55	0.008	0.002	3.21E-05	5.58E-03
rs4653767	1:226916078	T/C	0.72	0.083	0.010	1.38E-15	0.70	<0.001	0.002	9.60E-01	2.80E-03
rs10797576	1:232664611	T/C	0.14	0.111	0.013	6.84E-17	0.14	0.001	0.003	7.80E-01	2.99E-03
rs76116224	2:18147848	A/T	0.90	0.110	0.019	1.27E-08	0.91	0.003	0.003	4.29E-01	2.11E-03
rs2042477	2:96000943	T/A	0.76	0.066	0.012	1.38E-08	0.75	0.001	0.002	8.15E-01	1.58E-03
rs11683001	2:102396963	A/T	0.34	0.070	0.010	8.04E-13	0.33	0.002	0.002	2.71E-01	2.22E-03
rs57891859	2:135464616	A/G	0.72	0.081	0.011	4.55E-14	0.69	0.001	0.002	7.86E-01	2.63E-03
rs1474055	2:169110394	T/C	0.13	0.180	0.014	2.54E-39	0.13	0.004	0.003	2.29E-01	7.35E-03
rs73038319	3:18361759	C/A	0.04	0.169	0.024	5.94E-13	0.04	0.008	0.005	1.07E-01	2.24E-03
rs6808178	3:28705690	T/C	0.38	0.066	0.010	8.09E-12	0.36	0.002	0.002	3.26E-01	2.04E-03
rs12497850	3:48748989	T/G	0.65	0.064	0.010	1.36E-10	0.64	-0.001	0.002	5.16E-01	1.85E-03
rs55961674	3:122196892	T/C	0.17	0.086	0.013	9.98E-12	0.16	0.003	0.003	2.21E-01	2.11E-03
rs11707416	3:151108965	T/A	0.63	0.063	0.010	1.13E-10	0.64	0.003	0.002	9.36E-02	1.83E-03
rs10513789	3:182760073	T/G	0.81	0.148	0.012	1.22E-34	0.79	0.003	0.002	2.03E-01	6.75E-03
rs34311866	4:951947	C/T	0.19	0.213	0.012	9.98E-70	0.18	-0.004	0.003	1.03E-01	1.41E-02
rs4698412	4:15737348	A/G	0.55	0.104	0.009	2.06E-28	0.54	0.003	0.002	1.84E-01	5.30E-03
rs6854006	4:77198054	C/T	0.64	0.091	0.010	5.82E-21	0.64	-0.006	0.002	1.21E-03	3.85E-03
rs356182	4:90626111	G/A	0.37	0.277	0.011	3.89E-154	0.35	0.002	0.002	4.42E-01	3.60E-02
rs13117519	4:114369065	T/C	0.17	0.088	0.012	9.82E-13	0.16	-0.008	0.003	3.76E-03	2.20E-03
rs62333164	4:170583157	G/A	0.67	0.064	0.010	2.00E-10	0.67	-0.001	0.002	7.06E-01	1.79E-03
rs1867598	5:60137959	G/A	0.10	0.155	0.016	2.52E-23	0.09	-0.002	0.003	4.85E-01	4.27E-03
rs26431	5:102365794	C/G	0.70	0.062	0.010	1.57E-09	0.70	-0.002	0.002	3.76E-01	1.61E-03
rs11950533	5:134199105	C/A	0.90	0.092	0.016	7.16E-09	0.88	-0.003	0.003	3.20E-01	1.54E-03
rs12528068	6:72487762	T/C	0.28	0.066	0.010	1.63E-10	0.28	0.004	0.002	9.82E-02	1.76E-03
rs997368	6:112243291	A/G	0.80	0.071	0.012	1.84E-09	0.79	-0.001	0.003	7.74E-01	1.60E-03
rs75859381	6:133210361	C/T	0.03	0.221	0.034	1.04E-10	0.03	0.005	0.006	3.97E-01	3.08E-03
rs199351	7:23300049	A/C	0.59	0.102	0.010	5.25E-26	0.57	<0.001	0.002	9.38E-01	4.98E-03
rs76949143	7:66009851	T/A	0.95	0.143	0.025	1.43E-08	0.94	0.009	0.004	4.49E-02	1.97E-03
rs1293298	8:11712443	A/C	0.74	0.093	0.011	3.99E-16	0.76	-0.003	0.002	1.75E-01	3.29E-03
rs2280104	8:22525980	T/C	0.36	0.056	0.010	1.16E-08	0.35	-0.004	0.002	5.44E-02	1.43E-03
rs2086641	8:130901909	C/T	0.28	0.060	0.011	1.81E-08	0.26	-0.002	0.002	2.82E-01	1.47E-03
rs13294100	9:17579690	G/T	0.66	0.086	0.010	8.72E-18	0.63	0.001	0.002	6.44E-01	3.32E-03
rs6476434	9:34046391	C/T	0.27	0.062	0.011	6.58E-09	0.26	0.008	0.002	2.06E-04	1.48E-03
rs896435	10:15557406	T/C	0.69	0.074	0.010	3.41E-13	0.67	-0.003	0.002	1.39E-01	2.31E-03
rs10748818	10:104015279	G/A	0.15	0.079	0.013	1.05E-09	0.14	-0.006	0.003	4.30E-02	1.58E-03
rs117896735	10:121536327	A/G	0.02	0.435	0.039	2.36E-28	0.01	0.003	0.007	6.47E-01	6.19E-03
rs7938782	11:10558777	A/G	0.88	0.087	0.015	2.12E-09	0.86	0.001	0.003	7.58E-01	1.63E-03
rs12283611	11:83487277	C/A	0.59	0.064	0.010	2.61E-10	0.57	-0.001	0.002	5.01E-01	2.02E-03
rs3802920	11:133787001	T/G	0.21	0.107	0.012	6.26E-20	0.20	0.004	0.002	1.10E-01	3.76E-03
rs76904798	12:40614434	T/C	0.14	0.144	0.013	1.52E-28	0.13	0.003	0.003	3.17E-01	5.12E-03
rs7134559	12:46419086	C/T	0.60	0.054	0.010	3.96E-08	0.61	0.007	0.002	4.06E-04	1.40E-03

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EA	Beta	SE	P-value	EA	Beta	SE	P-value	
rs10847864	12:123326598	T/G	0.36	0.148	0.012	1.47E-37	0.35	0.004	0.002	8.08E-02	1.01E-02
rs9568188	13:49927732	T/C	0.74	0.062	0.011	1.15E-08	0.72	0.007	0.002	8.55E-04	1.47E-03
rs4771268	13:97865021	T/C	0.23	0.068	0.011	1.45E-09	0.24	0.004	0.002	5.31E-02	1.61E-03
rs12147950	14:37989270	C/T	0.56	0.053	0.010	3.54E-08	0.56	0.003	0.002	1.74E-01	1.38E-03
rs11158026	14:55348869	C/T	0.68	0.084	0.010	1.66E-16	0.66	-0.001	0.002	7.35E-01	3.11E-03
rs3742785	14:75373034	A/C	0.79	0.071	0.012	1.92E-09	0.77	-0.004	0.002	1.27E-01	1.68E-03
rs979812	14:88464264	T/G	0.44	0.061	0.009	6.19E-11	0.44	0.004	0.002	2.31E-02	1.84E-03
rs2251086	15:61997385	C/T	0.86	0.119	0.014	6.08E-18	0.84	0.008	0.003	5.45E-03	3.42E-03
rs6497339	16:19277493	A/T	0.45	0.063	0.010	2.76E-11	Excluded for reverse MR				
rs11150601	16:30977799	A/G	0.64	0.091	0.010	5.12E-20	0.63	0.004	0.002	3.90E-02	3.77E-03
rs3104783	16:52636242	A/C	0.43	0.067	0.009	1.29E-12	0.44	-0.003	0.002	1.95E-01	2.19E-03
rs12600861	17:7355621	C/A	0.35	0.056	0.010	1.01E-08	0.35	-0.003	0.002	1.04E-01	1.46E-03
rs850738	17:42434630	G/A	0.39	0.071	0.011	1.29E-11	0.39	0.003	0.002	1.89E-01	2.41E-03
rs62053943	17:43744203	C/T	0.84	0.270	0.016	3.58E-68	0.86	0.017	0.003	6.83E-10	1.91E-02
rs61169879	17:59917366	T/C	0.16	0.082	0.013	9.28E-10	0.17	0.005	0.003	4.52E-02	1.84E-03
rs666463	17:76425480	A/T	0.83	0.076	0.013	3.20E-09	0.84	<0.001	0.003	9.20E-01	1.61E-03
rs1941685	18:31304318	T/G	0.50	0.053	0.009	1.69E-08	0.52	<0.001	0.002	8.23E-01	1.41E-03
rs12456492	18:40673380	G/A	0.32	0.098	0.010	3.80E-23	0.32	0.007	0.002	9.12E-04	4.19E-03
rs8087969	18:48683589	G/T	0.45	0.058	0.010	1.41E-08	0.44	0.001	0.002	4.92E-01	1.65E-03
rs55818311	19:2341047	C/T	0.31	0.070	0.011	4.18E-10	0.33	0.002	0.002	2.27E-01	2.06E-03
rs77351827	20:6006041	T/C	0.13	0.080	0.014	8.87E-09	0.12	-0.001	0.003	8.50E-01	1.43E-03
rs2248244	21:38852361	A/G	0.28	0.071	0.011	2.74E-11	0.28	-0.003	0.002	1.28E-01	2.07E-03
Outcome: Coffee drinking											
rs35749011	1:155135036	A/G	0.02	0.607	0.034	1.72E-70	0.01	<0.001	0.007	9.60E-01	1.22E-02
rs6658353	1:161469054	C/G	0.50	0.065	0.009	6.10E-12	Excluded for reverse MR				
rs11578699	1:171719769	C/T	0.81	0.070	0.012	4.47E-09	0.80	0.002	0.002	4.16E-01	1.56E-03
rs823118	1:205723572	T/C	0.57	0.107	0.009	1.11E-29	0.55	-0.001	0.002	3.79E-01	5.58E-03
rs4653767	1:226916078	T/C	0.72	0.083	0.010	1.38E-15	0.72	<0.001	0.002	8.75E-01	2.80E-03
rs10797576	1:232664611	T/C	0.14	0.111	0.013	6.84E-17	0.12	-0.002	0.002	3.16E-01	2.99E-03
rs76116224	2:18147848	A/T	0.90	0.110	0.019	1.27E-08	0.90	-0.002	0.003	3.66E-01	2.11E-03
rs2042477	2:96000943	T/A	0.76	0.066	0.012	1.38E-08	0.74	0.002	0.002	1.90E-01	1.58E-03
rs11683001	2:102396963	A/T	0.34	0.070	0.010	8.04E-13	0.34	<0.001	0.002	7.90E-01	2.22E-03
rs57891859	2:135464616	A/G	0.72	0.081	0.011	4.55E-14	0.75	0.002	0.002	3.94E-01	2.63E-03
rs1474055	2:169110394	T/C	0.13	0.180	0.014	2.54E-39	0.12	0.003	0.002	2.51E-01	7.35E-03
rs73038319	3:18361759	C/A	0.04	0.169	0.024	5.94E-13	0.04	<0.001	0.004	9.15E-01	2.24E-03
rs6808178	3:28705690	T/C	0.38	0.066	0.010	8.09E-12	0.38	0.001	0.002	4.74E-01	2.04E-03
rs12497850	3:48748989	T/G	0.65	0.064	0.010	1.36E-10	0.65	0.004	0.002	6.44E-03	1.85E-03
rs55961674	3:122196892	T/C	0.17	0.086	0.013	9.98E-12	0.15	0.002	0.002	3.26E-01	2.11E-03
rs11707416	3:151108965	T/A	0.63	0.063	0.010	1.13E-10	0.63	-0.001	0.002	5.21E-01	1.83E-03
rs10513789	3:182760073	T/G	0.81	0.148	0.012	1.22E-34	0.81	<0.001	0.002	9.52E-01	6.75E-03
rs34311866	4:951947	C/T	0.19	0.213	0.012	9.98E-70	0.18	0.001	0.002	6.12E-01	1.41E-02
rs4698412	4:15737348	A/G	0.55	0.104	0.009	2.06E-28	0.55	<0.001	0.002	8.79E-01	5.30E-03
rs6854006	4:77198054	C/T	0.64	0.091	0.010	5.82E-21	0.62	-0.001	0.002	7.34E-01	3.85E-03
rs356182	4:90626111	G/A	0.37	0.277	0.011	3.89E-154	0.34	<0.001	0.002	8.71E-01	3.60E-02
rs13117519	4:114369065	T/C	0.17	0.088	0.012	9.82E-13	0.17	-0.001	0.002	6.43E-01	2.20E-03
rs62333164	4:170583157	G/A	0.67	0.064	0.010	2.00E-10	0.67	0.002	0.002	2.01E-01	1.79E-03
rs1867598	5:60137959	G/A	0.10	0.155	0.016	2.52E-23	0.08	0.007	0.003	2.38E-02	4.27E-03

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EA/BA	Beta	SE	P-value	EA/BA	Beta	SE	P-value	
rs26431	5:102365794	C/G	0.70	0.062	0.010	1.57E-09	0.69	-0.001	0.002	3.83E-01	1.61E-03
rs11950533	5:134199105	C/A	0.90	0.092	0.016	7.16E-09	0.90	0.003	0.003	2.36E-01	1.54E-03
rs112485576	6:32578772	C/A	0.84	0.168	0.015	6.96E-28	0.81	0.005	0.002	1.63E-02	7.66E-03
rs12528068	6:72487762	T/C	0.28	0.066	0.010	1.63E-10	0.28	0.003	0.002	1.28E-01	1.76E-03
rs997368	6:112243291	A/G	0.80	0.071	0.012	1.84E-09	0.82	0.003	0.002	1.87E-01	1.60E-03
rs75859381	6:133210361	C/T	0.03	0.221	0.034	1.04E-10	0.03	0.001	0.005	8.48E-01	3.08E-03
rs199351	7:23300049	A/C	0.59	0.102	0.010	5.25E-26	0.59	-0.001	0.002	5.75E-01	4.98E-03
rs76949143	7:66009851	T/A	0.95	0.143	0.025	1.43E-08	0.95	-0.004	0.004	2.38E-01	1.97E-03
rs1293298	8:11712443	A/C	0.74	0.093	0.011	3.99E-16	0.74	0.004	0.002	3.34E-02	3.29E-03
rs2280104	8:22525980	T/C	0.36	0.056	0.010	1.16E-08	0.35	-0.001	0.002	4.61E-01	1.43E-03
rs2086641	8:130901909	C/T	0.28	0.060	0.011	1.81E-08	0.26	<0.001	0.002	8.43E-01	1.47E-03
rs13294100	9:17579690	G/T	0.66	0.086	0.010	8.72E-18	0.65	0.001	0.002	6.77E-01	3.32E-03
rs6476434	9:34046391	C/T	0.27	0.062	0.011	6.58E-09	0.27	-0.001	0.002	4.28E-01	1.48E-03
rs896435	10:15557406	T/C	0.69	0.074	0.010	3.41E-13	0.68	0.002	0.002	3.35E-01	2.31E-03
rs10748818	10:104015279	G/A	0.15	0.079	0.013	1.05E-09	0.15	-0.001	0.002	8.14E-01	1.58E-03
rs117896735	10:121536327	A/G	0.02	0.435	0.039	2.36E-28	0.02	-0.002	0.006	7.05E-01	6.19E-03
rs7938782	11:10558777	A/G	0.88	0.087	0.015	2.12E-09	0.88	0.007	0.002	3.36E-03	1.63E-03
rs12283611	11:83487277	C/A	0.59	0.064	0.010	2.61E-10	0.59	0.001	0.002	6.20E-01	2.02E-03
rs3802920	11:133787001	T/G	0.21	0.107	0.012	6.26E-20	0.20	-0.002	0.002	2.51E-01	3.76E-03
rs76904798	12:40614434	T/C	0.14	0.144	0.013	1.52E-28	0.14	-0.003	0.002	2.09E-01	5.12E-03
rs7134559	12:46419086	C/T	0.60	0.054	0.010	3.96E-08	0.60	0.001	0.002	4.01E-01	1.40E-03
rs10847864	12:123326598	T/G	0.36	0.148	0.012	1.47E-37	0.35	-0.001	0.002	3.89E-01	1.01E-02
rs9568188	13:49927732	T/C	0.74	0.062	0.011	1.15E-08	0.73	<0.001	0.002	7.92E-01	1.47E-03
rs4771268	13:97865021	T/C	0.23	0.068	0.011	1.45E-09	0.22	<0.001	0.002	8.36E-01	1.61E-03
rs12147950	14:37989270	C/T	0.56	0.053	0.010	3.54E-08	0.57	0.001	0.002	4.10E-01	1.38E-03
rs11158026	14:55348869	C/T	0.68	0.084	0.010	1.66E-16	0.66	0.002	0.002	2.33E-01	3.11E-03
rs3742785	14:75373034	A/C	0.79	0.071	0.012	1.92E-09	0.78	-0.005	0.002	1.13E-02	1.68E-03
rs979812	14:88464264	T/G	0.44	0.061	0.009	6.19E-11	0.42	-0.001	0.002	4.81E-01	1.84E-03
rs2251086	15:61997385	C/T	0.86	0.119	0.014	6.08E-18	0.86	0.004	0.002	7.31E-02	3.42E-03
rs6497339	16:19277493	A/T	0.45	0.063	0.010	2.76E-11	Excluded for reverse MR				
rs11150601	16:30977799	A/G	0.64	0.091	0.010	5.12E-20	0.63	-0.001	0.002	6.47E-01	3.77E-03
rs3104783	16:52636242	A/C	0.43	0.067	0.009	1.29E-12	0.41	<0.001	0.002	9.08E-01	2.19E-03
rs12600861	17:7355621	C/A	0.35	0.056	0.010	1.01E-08	0.36	<0.001	0.002	7.89E-01	1.46E-03
rs850738	17:42434630	G/A	0.39	0.071	0.011	1.29E-11	0.39	0.002	0.002	1.81E-01	2.41E-03
rs62053943	17:43744203	C/T	0.84	0.270	0.016	3.58E-68	0.84	-0.001	0.002	6.85E-01	1.91E-02
rs61169879	17:59917366	T/C	0.16	0.082	0.013	9.28E-10	0.16	0.012	0.002	4.00E-08	1.84E-03
rs666463	17:76425480	A/T	0.83	0.076	0.013	3.20E-09	0.83	0.001	0.002	6.75E-01	1.61E-03
rs1941685	18:31304318	T/G	0.50	0.053	0.009	1.69E-08	0.50	<0.001	0.002	9.46E-01	1.41E-03
rs12456492	18:40673380	G/A	0.32	0.098	0.010	3.80E-23	0.31	-0.005	0.002	1.98E-03	4.19E-03
rs8087969	18:48683589	G/T	0.45	0.058	0.010	1.41E-08	0.46	<0.001	0.002	9.20E-01	1.65E-03
rs55818311	19:2341047	C/T	0.31	0.070	0.011	4.18E-10	0.32	0.001	0.002	4.97E-01	2.06E-03
rs77351827	20:6006041	T/C	0.13	0.080	0.014	8.87E-09	0.12	0.001	0.002	7.28E-01	1.43E-03
rs2248244	21:38852361	A/G	0.28	0.071	0.011	2.74E-11	0.28	0.006	0.002	3.86E-04	2.07E-03
Outcome: Lifetime smoking index											
rs35749011	1:155135036	A/G	0.02	0.607	0.034	1.72E-70	0.01	-0.005	0.006	4.10E-01	1.22E-02
rs6658353	1:161469054	C/G	0.50	0.065	0.009	6.10E-12	Excluded for reverse MR				

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EAF	Beta	SE	P-value	EAF	Beta	SE	P-value	
rs11578699	1:171719769	C/T	0.81	0.070	0.012	4.47E-09	0.80	-0.001	0.002	6.90E-01	1.56E-03
rs823118	1:205723572	T/C	0.57	0.107	0.009	1.11E-29	0.55	0.004	0.001	6.50E-03	5.58E-03
rs4653767	1:226916078	T/C	0.72	0.083	0.010	1.38E-15	0.72	-0.001	0.002	3.60E-01	2.80E-03
rs10797576	1:232664611	T/C	0.14	0.111	0.013	6.84E-17	0.12	0.006	0.002	8.50E-03	2.99E-03
rs76116224	2:18147848	A/T	0.90	0.110	0.019	1.27E-08	0.90	<0.001	0.002	8.60E-01	2.11E-03
rs2042477	2:96000943	T/A	0.76	0.066	0.012	1.38E-08	0.74	-0.001	0.002	7.10E-01	1.58E-03
rs11683001	2:102396963	A/T	0.34	0.070	0.010	8.04E-13	0.34	0.004	0.001	5.00E-03	2.22E-03
rs57891859	2:135464616	A/G	0.72	0.081	0.011	4.55E-14	0.75	<0.001	0.002	7.80E-01	2.63E-03
rs1474055	2:169110394	T/C	0.13	0.180	0.014	2.54E-39	0.12	0.004	0.002	6.00E-02	7.35E-03
rs73038319	3:18361759	C/A	0.04	0.169	0.024	5.94E-13	0.04	0.005	0.004	1.90E-01	2.24E-03
rs6808178	3:28705690	T/C	0.38	0.066	0.010	8.09E-12	0.38	0.001	0.001	6.30E-01	2.04E-03
rs12497850	3:48748989	T/G	0.65	0.064	0.010	1.36E-10	0.65	-0.006	0.001	1.50E-05	1.85E-03
rs55961674	3:122196892	T/C	0.17	0.086	0.013	9.98E-12	0.15	0.002	0.002	2.40E-01	2.11E-03
rs11707416	3:151108965	T/A	0.63	0.063	0.010	1.13E-10	0.63	0.003	0.001	2.20E-02	1.83E-03
rs10513789	3:182760073	T/G	0.81	0.148	0.012	1.22E-34	0.81	0.003	0.002	4.80E-02	6.75E-03
rs34311866	4:951947	C/T	0.19	0.213	0.012	9.98E-70	0.18	<0.001	0.002	8.90E-01	1.41E-02
rs4698412	4:15737348	A/G	0.55	0.104	0.009	2.06E-28	0.55	-0.001	0.001	3.10E-01	5.30E-03
rs6854006	4:77198054	C/T	0.64	0.091	0.010	5.82E-21	0.62	-0.004	0.001	6.00E-03	3.85E-03
rs356182	4:90626111	G/A	0.37	0.277	0.011	3.89E-154	0.34	-0.001	0.001	6.20E-01	3.60E-02
rs13117519	4:114369065	T/C	0.17	0.088	0.012	9.82E-13	0.17	0.001	0.002	5.40E-01	2.20E-03
rs62333164	4:170583157	G/A	0.67	0.064	0.010	2.00E-10	0.67	-0.001	0.001	4.00E-01	1.79E-03
rs1867598	5:60137959	G/A	0.10	0.155	0.016	2.52E-23	0.08	0.002	0.003	5.60E-01	4.27E-03
rs26431	5:102365794	C/G	0.70	0.062	0.010	1.57E-09	0.69	-0.002	0.002	2.60E-01	1.61E-03
rs11950533	5:134199105	C/A	0.90	0.092	0.016	7.16E-09	0.90	-0.003	0.002	1.50E-01	1.54E-03
rs112485576	6:32578772	C/A	0.84	0.168	0.015	6.96E-28	0.81	-0.002	0.002	3.00E-01	7.66E-03
rs12528068	6:72487762	T/C	0.28	0.066	0.010	1.63E-10	0.28	-0.001	0.002	6.20E-01	1.76E-03
rs997368	6:112243291	A/G	0.80	0.071	0.012	1.84E-09	0.82	0.002	0.002	2.30E-01	1.60E-03
rs75859381	6:133210361	C/T	0.03	0.221	0.034	1.04E-10	0.03	-0.002	0.004	6.90E-01	3.08E-03
rs199351	7:23300049	A/C	0.59	0.102	0.010	5.25E-26	0.59	-0.001	0.001	3.70E-01	4.98E-03
rs76949143	7:66009851	T/A	0.95	0.143	0.025	1.43E-08	0.95	0.005	0.003	1.30E-01	1.97E-03
rs1293298	8:11712443	A/C	0.74	0.093	0.011	3.99E-16	0.74	0.005	0.002	2.20E-03	3.29E-03
rs2280104	8:22525980	T/C	0.36	0.056	0.010	1.16E-08	0.35	-0.004	0.001	1.10E-02	1.43E-03
rs2086641	8:130901909	C/T	0.28	0.060	0.011	1.81E-08	0.26	-0.002	0.002	1.70E-01	1.47E-03
rs13294100	9:17579690	G/T	0.66	0.086	0.010	8.72E-18	0.65	0.005	0.001	2.00E-03	3.32E-03
rs6476434	9:34046391	C/T	0.27	0.062	0.011	6.58E-09	0.27	0.001	0.002	6.50E-01	1.48E-03
rs896435	10:15557406	T/C	0.69	0.074	0.010	3.41E-13	0.68	<0.001	0.001	8.30E-01	2.31E-03
rs10748818	10:104015279	G/A	0.15	0.079	0.013	1.05E-09	0.15	-0.006	0.002	3.40E-03	1.58E-03
rs117896735	10:121536327	A/G	0.02	0.435	0.039	2.36E-28	0.02	-0.007	0.005	2.20E-01	6.19E-03
rs7938782	11:10558777	A/G	0.88	0.087	0.015	2.12E-09	0.88	<0.001	0.002	8.50E-01	1.63E-03
rs12283611	11:83487277	C/A	0.59	0.064	0.010	2.61E-10	0.59	-0.001	0.001	4.40E-01	2.02E-03
rs3802920	11:133787001	T/G	0.21	0.107	0.012	6.26E-20	0.20	-0.002	0.002	2.90E-01	3.76E-03
rs76904798	12:40614434	T/C	0.14	0.144	0.013	1.52E-28	0.14	-0.002	0.002	2.70E-01	5.12E-03
rs7134559	12:46419086	C/T	0.60	0.054	0.010	3.96E-08	0.60	<0.001	0.001	8.10E-01	1.40E-03
rs10847864	12:123326598	T/G	0.36	0.148	0.012	1.47E-37	0.35	-0.002	0.001	2.10E-01	1.01E-02
rs9568188	13:49927732	T/C	0.74	0.062	0.011	1.15E-08	0.73	-0.001	0.002	5.80E-01	1.47E-03
rs4771268	13:97865021	T/C	0.23	0.068	0.011	1.45E-09	0.22	0.001	0.002	5.90E-01	1.61E-03
rs12147950	14:37989270	C/T	0.56	0.053	0.010	3.54E-08	0.57	0.002	0.001	1.90E-01	1.38E-03

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EA	Beta	SE	P-value	EA	Beta	SE	P-value	
rs11158026	14:55348869	C/T	0.68	0.084	0.010	1.66E-16	0.66	-0.002	0.001	2.50E-01	3.11E-03
rs3742785	14:75373034	A/C	0.79	0.071	0.012	1.92E-09	0.78	-0.002	0.002	1.60E-01	1.68E-03
rs979812	14:88464264	T/G	0.44	0.061	0.009	6.19E-11	0.42	<0.001	0.001	8.90E-01	1.84E-03
rs2251086	15:61997385	C/T	0.86	0.119	0.014	6.08E-18	0.86	-0.003	0.002	7.80E-02	3.42E-03
rs6497339	16:19277493	A/T	0.45	0.063	0.010	2.76E-11	Excluded for reverse MR				
rs11150601	16:30977799	A/G	0.64	0.091	0.010	5.12E-20	0.63	-0.004	0.001	1.30E-02	3.77E-03
rs3104783	16:52636242	A/C	0.43	0.067	0.009	1.29E-12	0.42	0.001	0.001	3.10E-01	2.19E-03
rs12600861	17:7355621	C/A	0.35	0.056	0.010	1.01E-08	0.36	-0.005	0.001	1.40E-03	1.46E-03
rs850738	17:42434630	G/A	0.39	0.071	0.011	1.29E-11	0.39	0.002	0.001	2.00E-01	2.41E-03
rs62053943	17:43744203	C/T	0.84	0.270	0.016	3.58E-68	0.85	0.006	0.002	8.50E-04	1.91E-02
rs61169879	17:59917366	T/C	0.16	0.082	0.013	9.28E-10	0.16	-0.001	0.002	7.00E-01	1.84E-03
rs666463	17:76425480	A/T	0.83	0.076	0.013	3.20E-09	0.83	0.002	0.002	2.10E-01	1.61E-03
rs1941685	18:31304318	T/G	0.50	0.053	0.009	1.69E-08	0.50	-0.002	0.001	1.90E-01	1.41E-03
rs12456492	18:40673380	G/A	0.32	0.098	0.010	3.80E-23	0.31	-0.003	0.001	2.80E-02	4.19E-03
rs8087969	18:48683589	G/T	0.45	0.058	0.010	1.41E-08	0.46	-0.001	0.001	4.40E-01	1.65E-03
rs55818311	19:2341047	C/T	0.31	0.070	0.011	4.18E-10	0.32	-0.001	0.002	4.00E-01	2.06E-03
rs77351827	20:6006041	T/C	0.13	0.080	0.014	8.87E-09	0.12	0.005	0.002	2.50E-02	1.43E-03
rs2248244	21:38852361	A/G	0.28	0.071	0.011	2.74E-11	0.28	-0.001	0.002	3.60E-01	2.07E-03
Outcome: Smoking initiation											
rs35749011	1:155135036	A/G	0.02	0.607	0.034	1.72E-70	0.01	0.011	0.015	4.50E-01	1.22E-02
rs6658353	1:161469054	C/G	0.50	0.065	0.009	6.10E-12	Excluded for reverse MR				
rs11578699	1:171719769	C/T	0.81	0.070	0.012	4.47E-09	0.80	0.006	0.005	1.70E-01	1.56E-03
rs823118	1:205723572	T/C	0.57	0.107	0.009	1.11E-29	0.55	0.011	0.004	2.75E-03	5.58E-03
rs4653767	1:226916078	T/C	0.72	0.083	0.010	1.38E-15	0.70	0.002	0.004	5.68E-01	2.80E-03
rs10797576	1:232664611	T/C	0.14	0.111	0.013	6.84E-17	0.14	0.009	0.005	9.08E-02	2.99E-03
rs76116224	2:18147848	A/T	0.90	0.110	0.019	1.27E-08	0.91	0.006	0.006	3.06E-01	2.11E-03
rs2042477	2:96000943	T/A	0.76	0.066	0.012	1.38E-08	0.75	0.002	0.004	5.47E-01	1.58E-03
rs11683001	2:102396963	A/T	0.34	0.070	0.010	8.04E-13	0.33	0.007	0.004	5.86E-02	2.22E-03
rs57891859	2:135464616	A/G	0.72	0.081	0.011	4.55E-14	0.69	-0.003	0.004	5.19E-01	2.63E-03
rs1474055	2:169110394	T/C	0.13	0.180	0.014	2.54E-39	0.13	0.013	0.006	1.86E-02	7.35E-03
rs73038319	3:18361759	C/A	0.04	0.169	0.024	5.94E-13	0.04	0.014	0.009	1.15E-01	2.24E-03
rs6808178	3:28705690	T/C	0.38	0.066	0.010	8.09E-12	0.36	-0.004	0.004	2.59E-01	2.04E-03
rs12497850	3:48748989	T/G	0.65	0.064	0.010	1.36E-10	0.64	-0.012	0.004	1.76E-03	1.85E-03
rs55961674	3:122196892	T/C	0.17	0.086	0.013	9.98E-12	0.16	0.003	0.005	5.79E-01	2.11E-03
rs11707416	3:151108965	T/A	0.63	0.063	0.010	1.13E-10	0.64	<0.001	0.004	9.17E-01	1.83E-03
rs10513789	3:182760073	T/G	0.81	0.148	0.012	1.22E-34	0.79	0.003	0.004	5.13E-01	6.75E-03
rs34311866	4:951947	C/T	0.19	0.213	0.012	9.98E-70	0.18	0.002	0.005	6.04E-01	1.41E-02
rs4698412	4:15737348	A/G	0.55	0.104	0.009	2.06E-28	0.54	0.002	0.004	6.16E-01	5.30E-03
rs6854006	4:77198054	C/T	0.64	0.091	0.010	5.82E-21	0.64	-0.007	0.004	6.93E-02	3.85E-03
rs356182	4:90626111	G/A	0.37	0.277	0.011	3.89E-154	0.35	<0.001	0.004	9.27E-01	3.60E-02
rs13117519	4:114369065	T/C	0.17	0.088	0.012	9.82E-13	0.16	-0.002	0.005	6.68E-01	2.20E-03
rs62333164	4:170583157	G/A	0.67	0.064	0.010	2.00E-10	0.67	0.006	0.004	1.22E-01	1.79E-03
rs1867598	5:60137959	G/A	0.10	0.155	0.016	2.52E-23	0.09	-0.005	0.006	4.08E-01	4.27E-03
rs26431	5:102365794	C/G	0.70	0.062	0.010	1.57E-09	0.70	-0.006	0.004	1.36E-01	1.61E-03
rs11950533	5:134199105	C/A	0.90	0.092	0.016	7.16E-09	0.88	-0.002	0.006	7.02E-01	1.54E-03
rs12528068	6:72487762	T/C	0.28	0.066	0.010	1.63E-10	0.28	0.003	0.004	4.49E-01	1.76E-03
rs997368	6:112243291	A/G	0.80	0.071	0.012	1.84E-09	0.79	0.003	0.005	4.65E-01	1.60E-03

SNP	Chr:Pos (GRCh37)	EA/BA	PD (Nalls et al., 2019)				Outcome				R ²
			EAF	Beta	SE	P-value	EAF	Beta	SE	P-value	
rs75859381	6:133210361	C/T	0.03	0.221	0.034	1.04E-10	0.03	0.008	0.011	4.57E-01	3.08E-03
rs199351	7:23300049	A/C	0.59	0.102	0.010	5.25E-26	0.57	-0.003	0.004	4.13E-01	4.98E-03
rs76949143	7:66009851	T/A	0.95	0.143	0.025	1.43E-08	0.94	0.009	0.008	2.58E-01	1.97E-03
rs1293298	8:11712443	A/C	0.74	0.093	0.011	3.99E-16	0.76	0.004	0.004	3.41E-01	3.29E-03
rs2280104	8:22525980	T/C	0.36	0.056	0.010	1.16E-08	0.35	-0.006	0.004	1.04E-01	1.43E-03
rs2086641	8:130901909	C/T	0.28	0.060	0.011	1.81E-08	0.26	-0.005	0.004	2.01E-01	1.47E-03
rs13294100	9:17579690	G/T	0.66	0.086	0.010	8.72E-18	0.63	0.009	0.004	1.65E-02	3.32E-03
rs6476434	9:34046391	C/T	0.27	0.062	0.011	6.58E-09	0.26	-0.005	0.004	1.95E-01	1.48E-03
rs896435	10:15557406	T/C	0.69	0.074	0.010	3.41E-13	0.67	0.006	0.004	1.41E-01	2.31E-03
rs10748818	10:104015279	G/A	0.15	0.079	0.013	1.05E-09	0.14	-0.011	0.005	2.47E-02	1.58E-03
rs117896735	10:121536327	A/G	0.02	0.435	0.039	2.36E-28	0.01	0.007	0.013	5.92E-01	6.19E-03
rs7938782	11:10558777	A/G	0.88	0.087	0.015	2.12E-09	0.86	0.015	0.006	8.85E-03	1.63E-03
rs12283611	11:83487277	C/A	0.59	0.064	0.010	2.61E-10	0.57	-0.001	0.004	7.58E-01	2.02E-03
rs3802920	11:133787001	T/G	0.21	0.107	0.012	6.26E-20	0.20	-0.008	0.005	6.51E-02	3.76E-03
rs76904798	12:40614434	T/C	0.14	0.144	0.013	1.52E-28	0.13	-0.003	0.005	5.94E-01	5.12E-03
rs7134559	12:46419086	C/T	0.60	0.054	0.010	3.96E-08	0.61	0.009	0.004	9.77E-03	1.40E-03
rs10847864	12:123326598	T/G	0.36	0.148	0.012	1.47E-37	0.35	<0.001	0.004	9.56E-01	1.01E-02
rs9568188	13:49927732	T/C	0.74	0.062	0.011	1.15E-08	0.72	-0.003	0.004	4.18E-01	1.47E-03
rs4771268	13:97865021	T/C	0.23	0.068	0.011	1.45E-09	0.24	-0.003	0.004	5.51E-01	1.61E-03
rs12147950	14:37989270	C/T	0.56	0.053	0.010	3.54E-08	0.56	0.007	0.004	5.86E-02	1.38E-03
rs11158026	14:55348869	C/T	0.68	0.084	0.010	1.66E-16	0.66	-0.001	0.004	8.68E-01	3.11E-03
rs3742785	14:75373034	A/C	0.79	0.071	0.012	1.92E-09	0.77	-0.001	0.004	9.01E-01	1.68E-03
rs979812	14:88464264	T/G	0.44	0.061	0.009	6.19E-11	0.44	0.008	0.004	2.96E-02	1.84E-03
rs2251086	15:61997385	C/T	0.86	0.119	0.014	6.08E-18	0.84	<0.001	0.005	9.53E-01	3.42E-03
rs6497339	16:19277493	A/T	0.45	0.063	0.010	2.76E-11	Excluded for reverse MR				
rs11150601	16:30977799	A/G	0.64	0.091	0.010	5.12E-20	0.63	-0.005	0.004	1.72E-01	3.77E-03
rs3104783	16:52636242	A/C	0.43	0.067	0.009	1.29E-12	0.44	-0.008	0.004	3.35E-02	2.19E-03
rs12600861	17:7355621	C/A	0.35	0.056	0.010	1.01E-08	0.35	-0.009	0.004	1.37E-02	1.46E-03
rs850738	17:42434630	G/A	0.39	0.071	0.011	1.29E-11	0.39	0.006	0.004	9.01E-02	2.41E-03
rs62053943	17:43744203	C/T	0.84	0.270	0.016	3.58E-68	0.86	0.008	0.005	1.23E-01	1.91E-02
rs61169879	17:59917366	T/C	0.16	0.082	0.013	9.28E-10	0.17	0.001	0.005	7.83E-01	1.84E-03
rs666463	17:76425480	A/T	0.83	0.076	0.013	3.20E-09	0.84	-0.001	0.005	8.93E-01	1.61E-03
rs1941685	18:31304318	T/G	0.50	0.053	0.009	1.69E-08	0.52	-0.002	0.004	6.01E-01	1.41E-03
rs12456492	18:40673380	G/A	0.32	0.098	0.010	3.80E-23	0.32	-0.006	0.004	1.16E-01	4.19E-03
rs8087969	18:48683589	G/T	0.45	0.058	0.010	1.41E-08	0.44	0.002	0.004	5.22E-01	1.65E-03
rs55818311	19:2341047	C/T	0.31	0.070	0.011	4.18E-10	0.33	-0.004	0.004	2.87E-01	2.06E-03
rs77351827	20:6006041	T/C	0.13	0.080	0.014	8.87E-09	0.12	0.006	0.005	3.05E-01	1.43E-03
rs2248244	21:38852361	A/G	0.28	0.071	0.011	2.74E-11	0.28	0.004	0.004	2.79E-01	2.07E-03

NA, not available; EA/BA, effect allele/base allele; EAF, effect allele frequency; SE, standard error.

SNPs associated with PD and corresponding betas come from Nalls et al., Lancet Neurol 2019;18,1091-1102. Associations with smoking, alcohol, and coffee come from Liu et al., Nat Genet 2019;51, 237-244; Zhong et al., Hum Mol Genet 2019;28, 2449-2457; and Wootton et al., Psychol Med 2019;50, 2435-2443.

Bold coefficients and corresponding SE and p-values are significant at $p \leq 0.05$; those underlined with a solid line are negative and those underlined with a dashed line are positive.

R² is the proportion of the variance of the exposure explained by the genetic variant according to the formula: $2 \times \text{Beta}_{\text{exposure}} \times \text{EAF}_{\text{exposure}} \times (1 - \text{EAF}_{\text{exposure}})$.

Supplementary figure 1: Survival bias in Mendelian randomization studies of diseases in elderly populations.

If both the exposure of interest (E) and an unmeasured exposure (U) influence survival (S), conditioning on survival up to the age at inclusion into the study creates an association between U and G (and E) (red dashed double arrow) because S is a collider. If U is not taken into account in the analysis, the association of G (and E) with PD is biased due to the association between U and G. The bias is more important for exposures that have an important effect on survival, and if there is an interaction between U and E in determining survival.

The importance and direction of the bias depends on the direction of the U-S and E-S associations (discordant or concordant) and of the $U \times E$ interaction for S. Depending on these parameters, the bias can go in any direction: it can distort associations towards the null (e.g., true associations that weaken as age increases), or it can create a false association between G and PD in situations where there is no true association (e.g., no association in younger subjects while there is one in older subjects) or make a true association seem stronger; in some extreme situations, it can even revert the direction of a true association (e.g., true positive association becomes negative as age increases).

MR estimates of the association between E and PD are based on the association between G and E, and the association between G and PD. In one-sample MR, both associations are estimated in the same sample and are likely to be similarly biased; therefore, taking the ratio of these associations cancels out much of the bias. Alternatively, in two-sample MR, only the association between G and PD is estimated in the study sample, and the bias of MR estimates equals the bias seen for the G and PD association (Smit RA et al., *Epidemiology* 2019;30(6):813-816).

Supplementary figure 2: MR analyses of the relation of smoking, alcohol, and coffee drinking with PD: (A) Plots relating the effects sizes of the SNP-exposure (x -axis) and SNP-PD (y -axis, log OR) associations with standard error bars: the slope of the lines corresponds to causal estimates using different methods; (B) funnel plots of individual variant effects plotted against the inverse of their standard error.

Supplementary figure 3: Reverse MR analyses of the relation of PD with smoking initiation, lifetime smoking index, and alcohol and coffee drinking: (A) Plots relating the effects sizes of the SNP-PD (x-axis) and SNP-outcomes (smoking, coffee, alcohol; y-axis, log OR) associations with standard error bars: the slope of the lines corresponds to causal estimates using different methods; (B) funnel plots of individual variant effects plotted against the inverse of their standard error.