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A multivariate Mendelian randomization study of Parkinson's disease and coronary heart disease on amyotrophic lateral sclerosis

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Abstract

O*bjective*: To investigate the causal relationship between Parkinson's disease (PD) and coronary heart disease (CHD) on amyotrophic lateral sclerosis (ALS) using genetic methods, and to investigate whether PD and CHD are independent factors influencing ALS. M*ethod*: This study is based on the summary statistics of genome-wide association studies in the IEU Open GWAS database, with PD and CHD as exposure and ALS as outcome. Single-factor Mendelian randomization analysis was used to explore the causal relationship between exposure and results, and sensitivity analysis was performed. We also examined whether there is a reverse causal relationship between exposure and outcome. Finally, multivariate Mendelian randomization analysis was used to explore whether exposure independently affected outcomes. R*esult*: Genetically predicted IVW results showed CHD (ID=ieu-a-7; OR=1.018 ; 95%CI=1.004-1.043; P=0.015) and PD (ID=ieu-b-7; OR=1.025; 95%CI=1.012-1.038; P<0.001) had a significant causal relationship with ALS. Multivariate Mendelian randomization analysis showed that CHD and PD were independent risk factors for ALS (P<0.05).
Conclusion: Our Mendelian randomization results show that the increased risk of PD and CHD has a negative impact on ALS and there is a significant causal relationship, which may provide new insights into the pathogenesis and treatment of ALS.

K*eywords*: Parkinson's disease, coronary heart disease, amyotrophic lateral sclerosis, CRP, frontal lobe metabolic level, Mendel randomization method

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive motor neuron damage. However, due to the complexity of ALS, the aetiology and potential pathogenesis of most patients remain unclear. To date, a number of factors have been associated with ALS, including smoking, antioxidant intake, body mass index, physical activity, head trauma, metabolic and inflammatory status, cancer, and occupational or environmental exposure to electromagnetic fields, metals or pesticides.

Parkinson's disease (PD) and ALS are both neurodegenerative diseases caused by a complex interaction between environmental factors and susceptibility genes. Neurodegenerative diseases lead to an increase in the degree of physical disability and a decrease in the standard of living due to specific movement disorders. Currently, there are reports on the mechanism of comorbidity between PD and ALS. The causal relationship between PD and ALS has been demonstrated by univariate Mendelian randomization analysis, but it is not clear whether PD is an independent factor in ALS.

Coronary heart disease (CHD) is one of the major cardiovascular diseases affecting the life expectancy of the world's population. It has been shown to be the leading cause of death in the global population. Lifestyle, environmental and genetic factors are risk factors for the development of cardiovascular disease. At the same time, studies have shown that CHD is no longer simply considered as a simple lipid storage disease, but a systemic inflammatory disease. CHD and ALS share some similarities in aetiology and potential pathogenesis, i.e. they are both related to inflammation. However, it is not clear whether there is a causal relationship

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between CHD and ALS. We are therefore using Mendelian randomization to investigate whether there is a causal relationship between CHD and ALS.

Mendelian randomization is one of the innovative research methods in genetic epidemiology and is similar to randomised controlled trials (RCTs). Because single nucleotide polymorphisms (SNPs) follow the principle of random distribution during meiosis, using SNPs as instrumental variables (IVs) instead of exposure factors can avoid the effect of confounding factors on the investigation of the causal relationship between exposure and outcome.[7] Therefore, under the premise of excluding confounding factors, this study used the univariate randomization method to investigate whether there was a causal relationship between CHD and ALS, and used the multivariate Mendelian randomization method to investigate whether PD and CHD were independent risk factors for ALS.

METHODS

Data sources

The independent instrumental variables (IVs) we choose are derived from the summary statistics of genome-wide association studies in the IEU Open GWAS database. The study subjects include both men and women and are all European populations, which avoids bias in the data results due to different races. We strictly adhere to the three assumptions of Mendelian randomization when selecting IVs: (i) the variable is only associated with the exposure of choice; (ii) the variables are not associated with confounders between exposure and outcome; (iii) the variables only affect outcomes through exposure.[8] We selected SNP that were significantly associated with exposure ($P < 5e^{-8}$), removed SNP that were under linkage disequilibrium (clump = TRUE), and cut the SNP into a 10000kb window ($R^2 < 0.001$) to ensure the independence of the SNP, while retaining SNP with F-statistics > 10 to ensure that the selected IV was a strong instrumental variable.

Mendelian randomization analysis

CHD (ID = ieu-a-7 ; NCASE = 60801) and PD (ID = ieu-b-7; NCASE = 12577) was used as an exposure factor. ALS (ID = ieu-a-1085; NCASE = 33674) as the outcome factor. We conducted univariate Mendelian randomization and multivariate Mendelian randomization studies.[9] We used univariate Mendelian randomization to study whether CHD and PD have a causal relationship with ALS. In addition, we also used reverse Mendelian randomization to study whether ALS has a causal relationship with CHD and PD. Multivariate Mendelian randomization was used to study whether CHD and PD were independent influencing factors of ALS.

Univariance Mendelian randomization analysis

The main method for analyzing causality is inverse variance weighting (IVW).[10] Genetic prediction is used to assess whether PD and CHD are significantly related to the risk of muscle ALS. When $P < 0.05$, it is considered that there is a significant causal relationship between exposure and outcome, otherwise there is no causal relationship. In order to make the stability and directionality of the results more convincing, we use MR-Egger to test the global directional pleiotropicity when detecting the potential pleiotropicity of IV of the selected variable[11], if the intercept term is different from zero, the IVW estimate may be biased. MR-PRESSO was used to test the pleiotropic residuals and outliers of this Univariance Mendelian randomization[12], this method is an extension of the method of summarizing statistics for multi-instrument MR general models, and detects single SNP that lead to horizontal pleiotropic effects. If at least 50% of the SNPs are valid SNPs, they meet the weighted median standard. Therefore, the weighted median method is used to strengthen the rigor of the experiment.[10] Cochran's Q test was used to assess IV heterogeneity. If $Q > 0.05$, the IVW of the fixed effect model was used in the final result, otherwise the IVW of the random effect model was used.[13] Finally, we visualize the univariate Mendelian randomization results as MR _ leave One Out _ plot and MR _ forest _ plot and MR _ scatter _ plot (Figure 1).

Multivariable Mendelian randomization analysis

Multivariate Mendelian randomization is a further analysis of the significant exposures and outcomes in univariate Mendelian randomization. It is based on the theory of Mendelian genetics through the analysis of multiple instrumental variables to explore the degree of their combined or independent effects on disease. In this study, we estimated whether PD and CHD had independent effects on ALS in the regression analysis model by extracting the genetic variation information associated with both PD and CHD as instrumental variables.[14] In order to filter the key IVW and

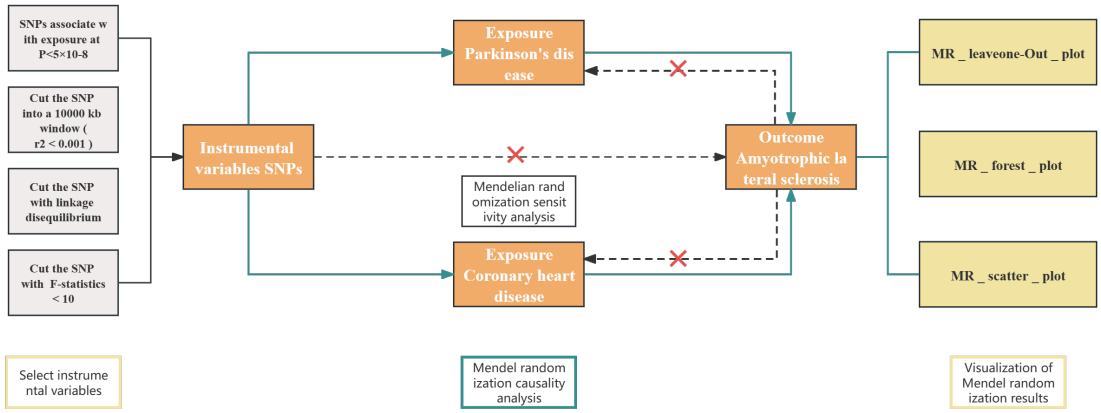

Figure 1. Single variable Mendelian randomization flow chart

improve the accuracy of the results, we used the lasso algorithm in the 'TwoSampleMR' package to filter the collinearity exposure. The IVW was considered a strong independent instrumental variable to assess whether PD or CHD had an independent risk effect on ALS.

Statistical analysis

The univariate Mendelian randomization and reverse Mendelian randomization analyses we used are based on 'TwoSampleMR', 'Mendelian randomization', 'MRPRESSO' in the R package, and the multivariate Mendelian randomization analysis is based on 'MVMR' in the R package. Among them, 'TwoSampleMR' is a package based on GWAS summary data to perform Mendelian randomization. It completes the extraction of instrumental variables in this study by automatically obtaining data from the IEU GWAS database, and completes the main causal analysis method IVW and the weighted median method in sensitivity analysis and Cochran's Q test. Visualisation of Mendelian randomization results such as MR _ leave one out _ plot and MR _ forest _ plot and MR _ scatter _ plot are generated. Mendelian randomization was used as a complement to the TwoSampleMR method to complete the MR-Egger sensitivity analysis. 'MVMR' used genetic variables as a tool to assess the direct effects of multiple exposures on outcomes, to assess the causal effects of exposures to CHD and PD and the outcome ALS in this multivariate Mendelian randomization study, and to use the lasso analysis method to exclude palindromic instrumental variables (such as allele A / T or G / C). The versions of the R package used in the above analysis methods are R (version 4.3.1).

RESULT

In the univariate Mendelian randomization, we found 18 independent instrumental variables for PD (PD independent instrumental variables) and 36 independent instrumental variables for CHD (CHD independent instrumental variables). There was no heterogeneity between PD and CHD in the Cochran's Q test. Therefore, the fixed effect model IVW was selected for evaluation, and CHD (ID = ieu-a-7; OR = 1.018; 95 % CI = 1.004-1.043; P = 0.015); PD (ID = ieu-b-7; OR = 1.025; 95 % CI =1.012-1.038; P < 0.001) indicated that there was a significant causal relationship between CHD and PD and ALS. When CHD increased by one unit, the relative adverse risk of ALS increased. There is no pleiotropic effect in CHD results in MR Egger, but there is a certain pleiotropic effect in PD. In the MRPRESSO analysis, we found that there was no heterogeneity between PD and CHD. On the weighted median there was also pleiotropy in PD (OR = 1.020; 95% CI = 1.002-1.038; P = 0.032), but in CHD (OR = 1.012; 95% CI = 0.990-1.035; P = 0.285) we found no pleiotropy. (Figure 2). In addition, we added MR _ leave One Out _ plot and MR _ forest _ plot and MR _ scatter _ plot (supplementary materials). Among them, the results in MR _ left One Out _ plot did not change significantly due to the elimination of SNP, which confirmed the robustness of the Mendelian randomization analysis method. The overall direction of MR Egger and IVW in MR _ forest _ plot was consistent, and PD and CHD in MR _ scattering _ plot were positively correlated with the increased risk of ALS.

In the visualisation of the results of the reverse causality analysis, the first table represents the Mendelian randomization analysis of ALS and CHD, and the second table represents the

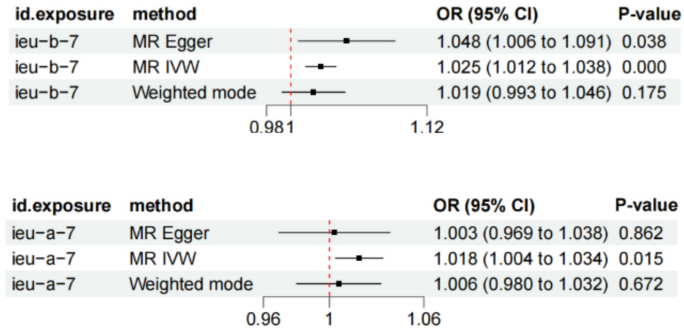

Figure 2. The effect of coronary heart disease and Parkinson 's disease on the risk of amyotrophic lateral sclerosis in univariate Mendelian randomization;Coronary heart disease: ieu-a-7; Parkinson 's disease: ieu-b-7

Mendelian randomization analysis of ALS and PD. According to the P value of the main method IVW, the causal relationship is not significant ($P > 0.05$), so there is no reverse causality between ALS and CHD and PD (Figure 3).

The inverse variance weighting method in multivariate Mendelian randomization analysis extracts significant SNP in PD and CHD. On the basis of deduplication, lasso is used to remove SNP with strong collinearity. Finally, a total of 53 SNP are involved in MRPRESSO and multivariate IVW algorithm (Multivariate Mendelian randomization instrumental variables), including 17 SNP in PD and 36 SNP in CHD. Genetic prediction showed that both PD and CHD were direct causal effects of ALS ($P<0.05$). We found no heterogeneity between PD and CHD in the MRPRESSO method ($P = 0.714$). The genetic variables are all strong independent instrumental variables calculated by F statistics ($F > 10$).

DISCUSSION

We performed univariate and multivariate Mendelian randomization analysis to investigate the causal relationship between PD and CHD on ALS and demonstrated that PD and CHD have a significant positive causal relationship with ALS and are independent risk factors for ALS. We found no evidence of a causal relationship between ALS and PD and CHD in reverse Mendelian.

The common feature of PD and ALS is the progressive loss of nerve cells in the nervous system.[15] Previous studies in the field of neurodegenerative diseases have shown that there is a genetic link between ALS and PD, and the GAK locus has been shown to have a high degree of co-localisation between ALS and PD.[4] Parkinson's disease and amyotrophic lateral sclerosis syndrome, known as Brait-Fahn-Schwartz disease.[16] However, the pathogenesis of ALS involves multiple factors, and there is evidence that there is a complex interaction between genetic and molecular pathways.[17] Although our study provides a possible cause for the comorbidity of PD and ALS from a genetic point of view, the mechanism behind Brait-Fahn-Schwartz disease remains unclear. It is worth noting that although our univariate Mendelian randomization results are consistent with the results of Di *et al*.[18] However, unlike Di *et al*, we performed a multivariate Mendelian randomization analysis of PD to investigate whether PD is an independent risk factor for

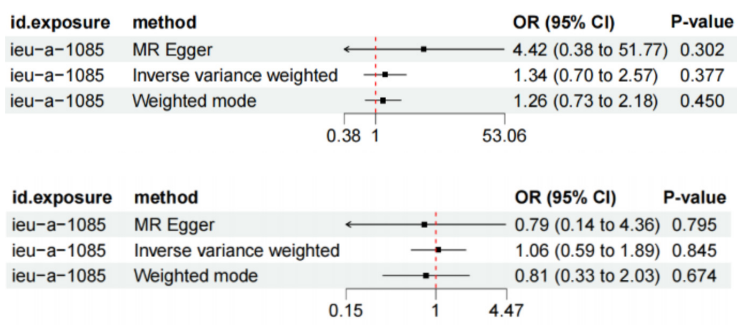

Figure 3. Results of univariate Mendelian random forest plot

ALS. In multivariate Mendelian randomization results, the P value of PD for ALS was statistically significant. This is the evidence that we found that PD has a direct causal effect on ALS, which makes the genetic evidence of PD and ALS risk significantly correlated more convincing. In a prospective multi-population study, 30% of ALS patients were found to have evidence of PD.[19] In addition, cognitive impairment is not only a key factor in the incidence and mortality of PD, but also an important non-motor symptom of ALS, with a wide range of decline from subjective cognitive ability to frontotemporal dementia. A systematic review reported that cognitive dysfunction usually occurs in the late stages of PD, and its cognitive symptoms are related to cholinergic circuit dysfunction and dopaminergic system abnormalities in the prefrontal cortex.[20] A recent observational study found relatively low frontal lobe metabolism in patients with cognitive impairment, resulting in a wider and more significant continuum from ALS with cognitive impairment to ALS with frontotemporal dementia. However, the more severe the cognitive impairment in patients with non-motor disorders compared to patients with simple motor disorders, the more dispersed the metabolic changes were.[21] This suggests that the pathogenesis of ALS is very complex and may be a complex multi-system disease. Our study only found a significant causal relationship between Parkinson's disease and ALS from a genetic perspective, extending previous evidence at a population level.

In our study, we found a significant causal relationship between coronary heart disease and amyotrophic lateral sclerosis. It is worth noting that in MVMR we found the most important evidence that coronary heart disease is an independent factor influencing amyotrophic lateral sclerosis. A retrospective study suggested that cardiovascular disease may be a negative prognostic factor for ALS.[22] And a systematic review showed that coronary heart disease may increase the risk of ALS.[23] Our study supports the view that there is a significant positive causal relationship between CHD and ALS through univariate Mendelian randomization, and the causal relationship is not significant in reverse Mendelian randomization.

Evidence suggests common mechanisms such as systemic inflammation leading to increased risk of cardiovascular disease and central nervous system toxicity.[24] An increasing number of studies have shown that serum C-reactive protein (CRP), as a biomarker of the inflammatory response, has significant prognostic value in many diseases.[6] In addition, an observational study has shown that CRP colocalises with complement in atherosclerotic plaques, which may be due to local generation rather than deposition in its cyclic form.[25] Indeed, Venugopal and his colleagues were able to show that local production of CRP within the arterial wall is derived from coronary smooth muscle cells and that local production of CRP may directly contribute to the initiation of atherosclerosis and the development of cardiovascular complications.[26] Therefore, atherosclerosis can produce CRP through human coronary artery smooth muscle cells. In an observational and genetic study, low baseline CRP was associated with an increased risk of Alzheimer's disease in the general population.[27] As ALS is also a neurodegenerative disease, we wonder whether CRP is associated with the risk of ALS. In a recent prospective cohort study, higher levels of predisease CRP appeared to be associated with an increased risk of ALS.[28] A systematic review has shown that CRP is an activator of microglia. Upregulation of the expression of CRP also alters the permeability of the blood-brain barrier and induces the activation of microglia, where activated microglia can further promote the degeneration of motor neurons.[29] In addition, a multicentre cohort study of Italian ALS patients found that CRP levels were lower before the onset of symptoms, but gradually increased with disease progression, especially in the months before death, suggesting that CRP levels are positively correlated with disease progression.[30] Although there are few clinical examples, the influence of cardiovascular disease on ALS cannot be ignored, and the significant causal relationship provided by univariate and multivariate Mendelian randomization is the main evidence for our belief that CHD has a negative effect on ALS. However, due to the limitations of the IEU Open GWAS, we could not perform further subgroup analyses, so in the future, large sample population studies and further clinical validation are needed to explore the association between CHD and ALS.

Our research has certain advantages. First, to our knowledge, this is the first Mendelian randomization study to evaluate the causal relationship between coronary heart disease and amyotrophic lateral sclerosis, and also the first multivariate Mendelian randomization study to evaluate whether coronary heart disease and Parkinson 's disease are the direct influencing factors of ALS. Secondly, compared with traditional observational research methods and randomized controlled trials. Mendelian

randomization methods avoid the effects of confounding factors and reverse causality. When selecting independent instrumental variables, we strictly follow the three accepted assumptions in Mendel's randomization research, making our research results more convincing. The causal relationship between PD and CHD on ALS was explored by using univariate Mendelian randomization and multivariate Mendelian randomization and reverse Mendelian randomization.

Our research also has some limitations. Our sample selection is from the European population in the IEU Open GWAS database, so this experiment may not be applicable to other races. Secondly, due to the limitations in the IEU Open GWAS database, we cannot stratify the sample by age, height, weight, and past medical history, etc, and stratify the population by different conditions. There is a potential impact of certain pleiotropic mechanisms in MR studies, which may lead to bias in the estimation of causal effects. However, no evidence of pleiotropic effects was found in most of the results in this study. Therefore, there is little possibility of directionality and pleiotropic bias in causality. We found that MR-Egger and weighted median had certain pleiotropy in the detection of PD and ALS, which was consistent with the results of previous studies. However, in the MR-PRESSO method, we did not find evidence of directional level pleiotropy.

The manifestation of the disease is controlled not only by genetic factors, but also by the individual's environment. It is worth noting that the environment may also interact with the individual's genotype to produce different effects in different individuals. In addition, the strength and nature of the effect of heredity itself on disease can also vary with changes in external environmental conditions.[31] Genetic testing can provide more targeted risk information to help individuals understand their genetic risk, improve their quality of life and change their lifestyle. However, human behaviour is complex and not easily predicted.[32] The genetic factors of complex traits in GWAS may not be sufficient to elucidate them all. Human genetics can increase the upper limit of predictive value by focusing on genes and their functions.[33] Future research should combine different omics platforms to conduct in-depth research and analysis of disease pathogenesis from different aspects and angles.

In conclusions, we based on a sample of European populations, by using univariate Mendelian randomization, we found that PD and CHD had a significant positive causal relationship with ALS. In multivariate Mendelian randomization, it was suggested that PD and CHD had a direct causal effect on ALS. This study thus provides new clues for further exploring the relationship between PD and CHD in ALS, and provides some inspiration for further study on the pathogenesis and treatment of ALS.

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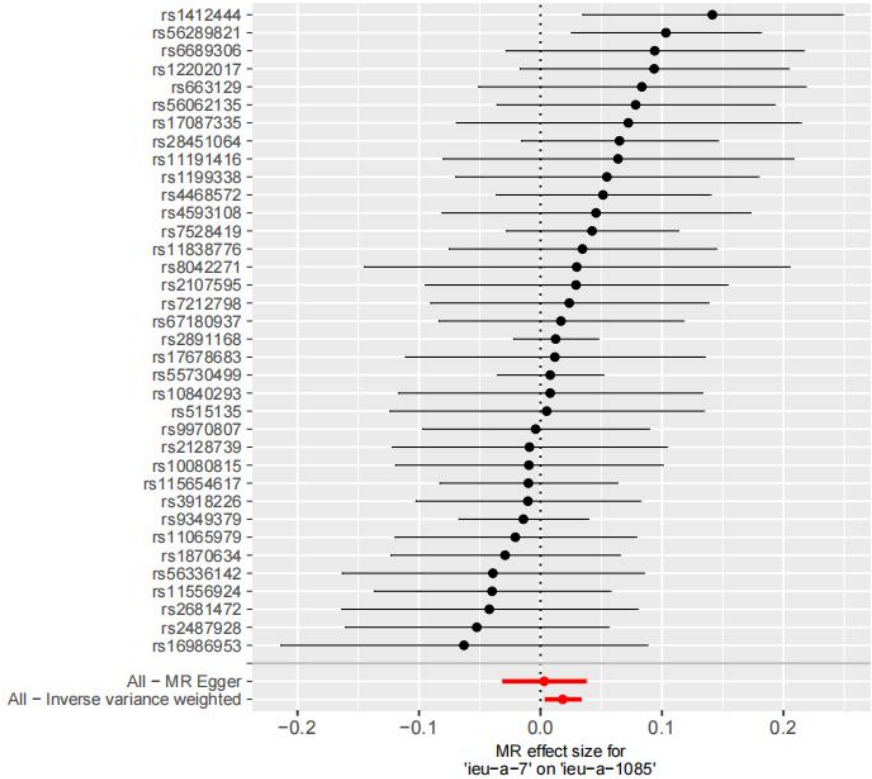
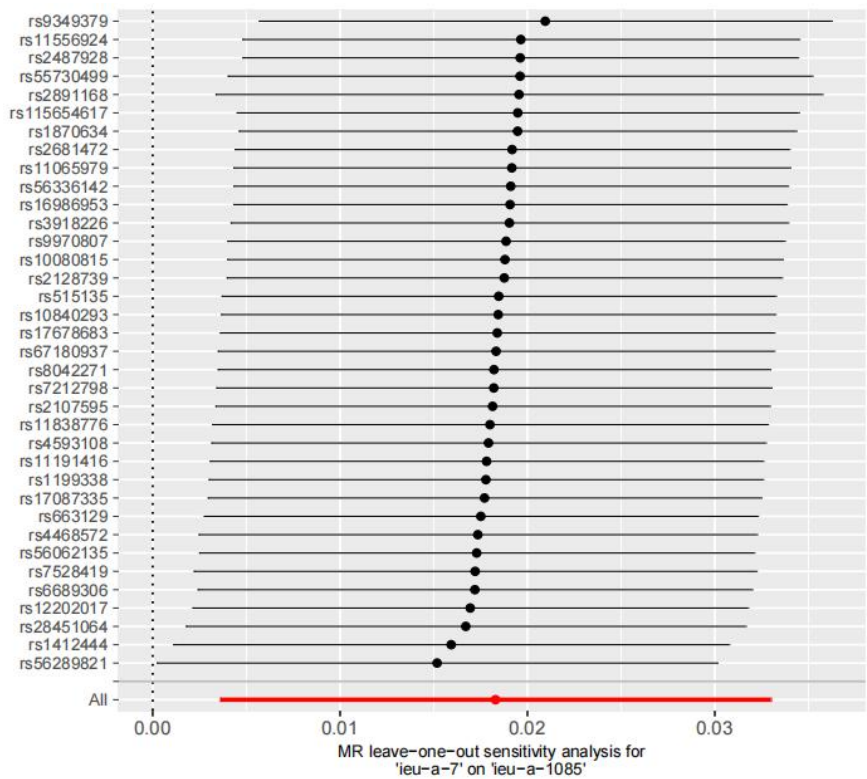
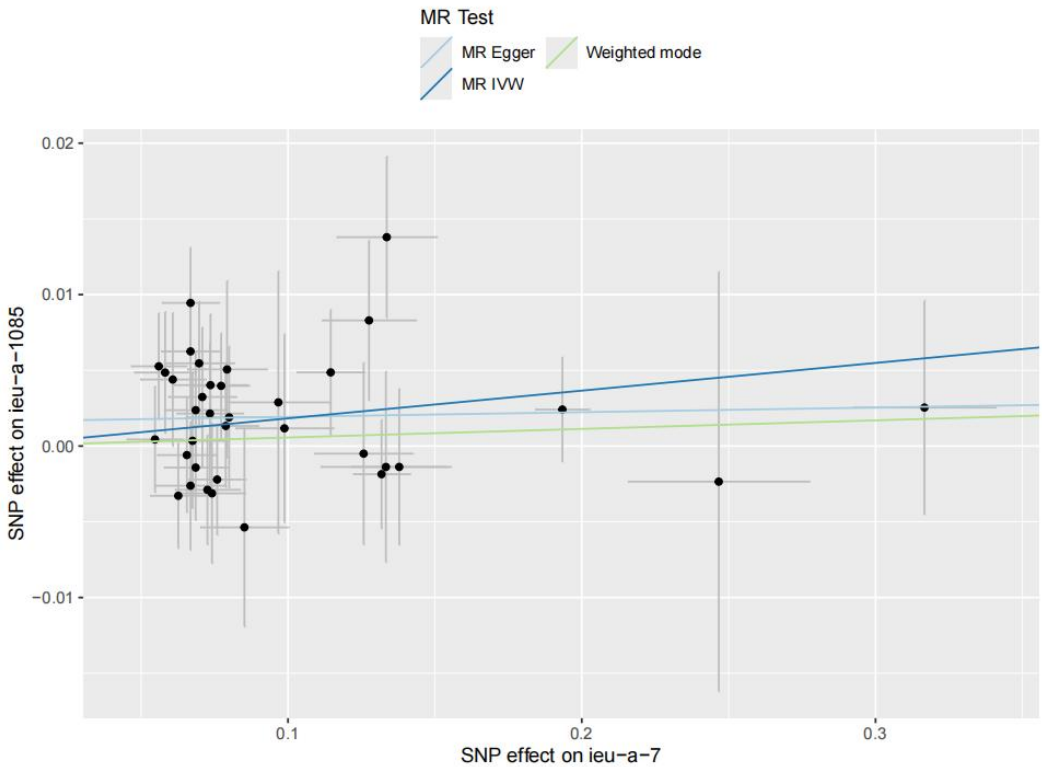
Supplementary figure 1. Coronary heart disease_MR_forest_plot



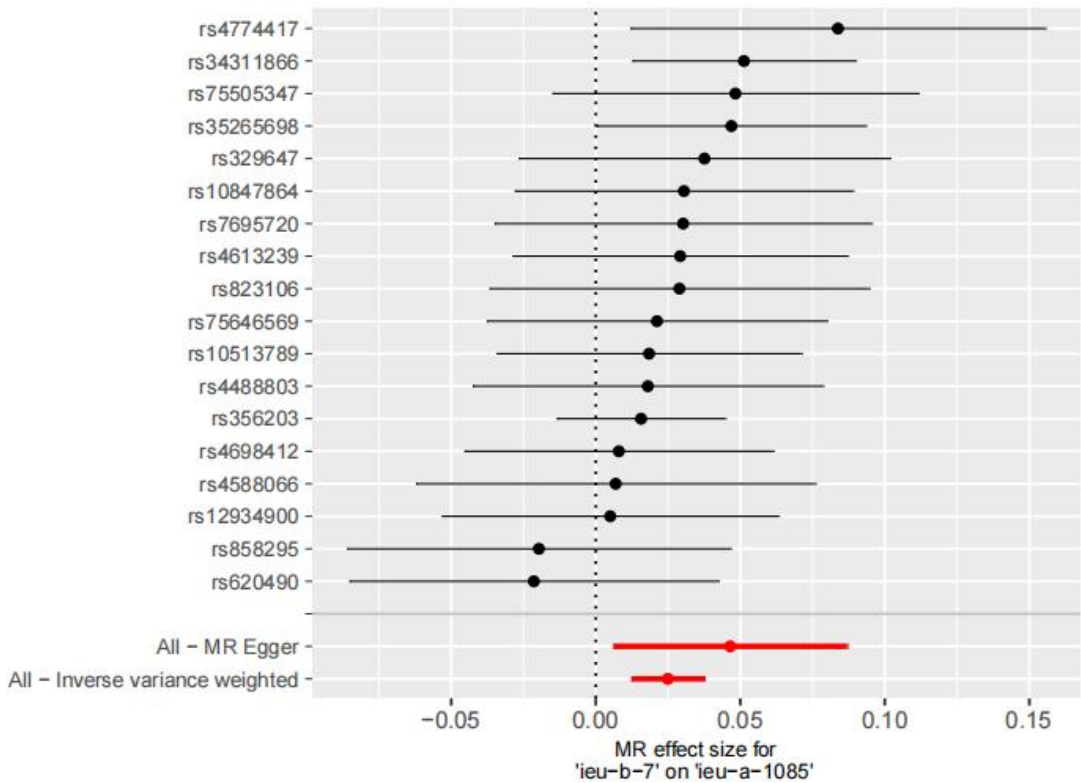
Supplementary figure 2. Coronary heart disease_MR_leaveOneOut_plot



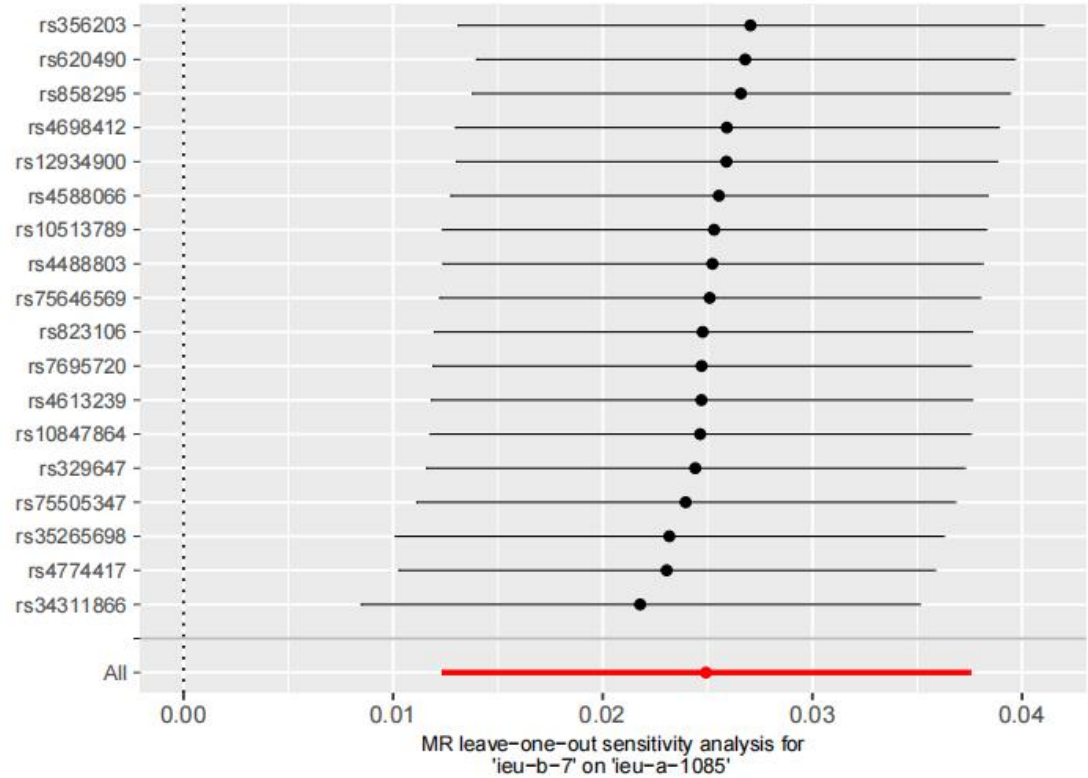
Supplementary figure 3. Coronary heart disease_MR_scatter_plot



Supplementary figure 4. Parkinson 's disease_MR_forest_plot



Supplementary figure 5. Parkinson 's disease_MR_leaveOneOut_plot



Supplementary figure 6. Parkinson 's disease_MR_scatter_plot