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Lower activity of cholesteryl ester transfer protein (CETP) and the risk of dementia: a Mendelian randomization analysis

Amand F. Schmidt^{1,2,3,4*}, Michael H. Davidson^{5,6}, Marc Ditmarsch⁶, John J. Kastelein^{6,7} and Chris Finan^{1,2,4}

Abstract

Background Elevated concentrations of low-density lipoprotein cholesterol (LDL-C) are linked to dementia risk, and conversely, increased plasma concentrations of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A1 (Apo-A1) associate with decreased dementia risk. Inhibition of cholesteryl ester transfer protein (CETP) meaningfully affects the concentrations of these blood lipids and may therefore provide an opportunity to treat dementia.

Methods Drug target Mendelian randomization (MR) was employed to anticipate the on-target effects of lower CETP concentration ($\mu\text{g/mL}$) on plasma lipids, cardiovascular disease outcomes, autopsy confirmed Lewy body dementia (LBD), as well as Parkinson's dementia.

Results MR analysis of lower CETP concentration recapitulated the blood lipid effects observed in clinical trials of CETP-inhibitors, as well as protective effects on coronary heart disease (odds ratio (OR) 0.92, 95% confidence interval (CI) 0.89; 0.96), heart failure, abdominal aortic aneurysm, any stroke, ischemic stroke, and small vessel stroke (0.90, 95%CI 0.85; 0.96). Consideration of dementia related traits indicated that lower CETP concentrations were associated higher total brain volume (0.04 per standard deviation, 95%CI 0.02; 0.06), lower risk of LBD (OR 0.81, 95%CI 0.74; 0.89) and Parkinson's dementia risk (OR 0.26, 95%CI 0.14; 0.48). *APOE4* stratified analyses suggested the LBD effect was most pronounced in *APOE-ε4* + participants (OR 0.61 95%CI 0.51; 0.73), compared to *APOE-ε4*- (OR 0.89 95%CI 0.79; 1.01); interaction *p*-value 5.81×10^{-4} .

Conclusions These results suggest that inhibition of CETP may be a viable strategy to treat dementia, with a more pronounced effect expected in *APOE-ε4* carriers.

Keywords Cholesteryl ester transfer protein, Dementia, *APOE4*, Lewy body dementia, Dementia in Parkinson, Mendelian randomisation, Human genetics

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Background

Cholesteryl ester transfer protein (CETP) facilitates the exchange of triglycerides (TG) and cholesterol ester between high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-B (Apo-B) rich particles such as low-density lipoprotein cholesterol (LDL-C). CETP-inhibition has shown to elicit a plethora of beneficial effects on lipid metabolism, robustly decreasing the plasma concentration of canonical atherosclerosis particles such as total and small LDL, and lipoprotein (a) (Lp[a]), while increasing plasma concentrations of mature HDL, as well as pre-beta HDL and apolipoprotein-A1 (Apo-A1) [1–4].

The four CETP-inhibitors (CETPi) evaluated in phase 3 clinical trials (anacetrapib, evacetrapib, dalcetrapib, torcetrapib) showed heterogenous effects on the magnitude of lipid perturbation, with an HDL-C percentage increase between 29% for dalcetrapib and ~130% for anacetrapib/evacetrapib, and an LDL-C decrease between 1% for dalcetrapib and 20% for anacetrapib/evacetrapib [5]. This resulted in an equally mixed clinical effects profile [5], with only the REVEAL trial for anacetrapib showing a non-HDL-C proportional protective effect of CETPi on CVD onset (rate ratio 0.91; 95% confidence interval (95%CI) 0.85; 0.97) [6]. The presence of meaningful differences in clinical effects profile strongly suggests that previous CETPi failures are likely attributable to the specific compound rather than to CETP inhibitors as a class [7].

We have previously determined the viability of a reduction in CETP concentration using Mendelian randomization (MR), leveraging genetic instruments strongly associating with plasma CETP concentration, finding that lower plasma CETP concentration decreased the risk of CHD, heart failure (HF) and chronic kidney disease [5, 8]. Because genetic variants are protected against confounding bias and reverse causation, MR provides a robust indication of the likely on-target effects of sufficiently potent drug target perturbation using data from human subjects [9–11]. A further benefit of MR is that it can utilize aggregated genetic data (e.g., variant-specific point estimates and standard errors) from independent studies to maximize the available sample size and hence precision.

Given the robust LDL-C lowering effects of CETP-inhibition, research has understandably focussed on its potential implications for cardiovascular disease (CVD) prevention. However, all CETP inhibitors, including the novel CETP-inhibitor obicetrapib, lowers plasma concentrations of apolipoprotein-E (Apo-E) [4] which is a known risk factor for dementia, in particular for Alzheimer's disease (AD). Furthermore, the 2024 Lancet Commissions report determined that LDL-C is a potentially modifiable risk factor for dementia [12]. Multiple lines of evidence support involvement of lipid metabolism with

bioenergetic decline and chronic neuro-inflammation in the brain, which contributes to neurodegenerative disorders [13]. This interrelationship between metabolism and neurodegeneration is for example illustrated by the connection between amyloid- β , Apo-E isoforms and lipid trafficking associating with the onset dementias such as AD, Lewy body dementia (LBD), and dementia associated with Parkinson's Disease (PD) [14–17]. Noting that LBD and dementia in PD are closely related diseases, both caused by underlying Lewy body disorders, which predominantly differ in temporal sequence of symptoms and clinical features [18].

The Apo-E isoform Apo-E4 is a major determinant of AD risk, with homozygote carriers (*APOE- ϵ 4 ϵ 4*) conveying an up to 15 fold increased risk [19, 20]. Through effects on neuroinflammation and blood brain barrier integrity *APOE- ϵ 4* carriership is an important risk factor for AD and non-AD related dementias [21, 22]. AD in *APOE- ϵ 4* carriers [13] is characterized by higher levels of circulating tau, as well as accumulation of phosphorylated tau in brain, which has been associated with insufficient lipidation of Apo-E HDL particles [23]. Lack of particle lipidation dysregulates the fine balance between cholesterol availability to neurons and cholesterol accumulation in astrocytes, which has cytotoxic and pro-inflammatory consequences [24]. The lack of lipidation of Apo-E/HDL additionally affects astrocyte membrane composition, stimulating the formation of β -amyloid containing plaques, which is a major characteristic of AD brains. *APOE- ϵ 4* carriership and cholesterol metabolism has additionally been implicated in the development amyotrophic lateral sclerosis (ALS) as well as multiple sclerosis (MS) [25–27].

Given the central role of CETP in lipid metabolism and the fact that CETP inhibition influences HDL composition of Apo-E [28] as well as brain cholesterol concentration [29], the CETP inhibitor obicetrapib is now being considered for treatment of dementia which is tested in a large phase II clinical trial (BROADWAY). Using multivariable MR, conditioning on LDL-C concentration, we previously revealed an HDL-C mediated protective effect of lower CETP on AD: odds ratio (OR) 0.94 per SD increase in HDL-C (95%CI 0.89; 0.99) [5]. While the observed HDL-C mediated effect of CETP on AD closely follows the aforementioned relationship of Apo-E HDL particles and their role in AD, likely due to the absence of *APOE4* stratification and robust AD case ascertainment, the main univariable MR analysis of CETP concentration and AD did not reach similar statistical significance (OR 0.99, 95%CI 0.91; 1.07).

In the current study we therefore sought to elucidate the potential causal relationship between lower plasma CETP concentration and the risk of dementia and neurodegenerative diseases. Specifically, we considered

independent GWAS on any LBD, LBD stratified by *APOE-ε4* status, PD, dementia in PD – representing a disease clustering with a strong *APOE-ε4* contribution. Furthermore, to rule out potential disease miss-classification, which is common in dementia, we uniquely included autopsy confirmed LBD cases and controls [30, 31]. As a positive control we first sought to confirm our previously reported effects on CHD, expanding this to additional CVD outcomes including small vessel stroke, and abdominal aortic aneurysm (AAA). Finally, we sought to replicate associations with biomarker levels and disease onset by performing additional MR analyses weighting the *cis*-acting CETP variants by their association with Apo-A1, and Apo-B (downstream proxies of CETP activity). Importantly, as shown by Schmidt et al. [9, 11] a *cis*-MR analysis weighted by downstream effects of the protein does not require, or imply, that the weighting factor itself causes disease. Instead, the weights merely function as a proxy for protein value and activity. Hence inference in these Apo-A1 and Apo-B weighted analyses remains on the effect of lower CETP and does not address questions on potential lipoprotein mediation.

Methods

Selection of genetic instruments to model CETP effects

Genetic instruments associating with CETP concentration ($\mu\text{g}/\text{mL}$) were identified from a GWAS conducted by Blauw et al. [32] ($n=4,248$). To limit the potential for bias-inducing pre-translational horizontal pleiotropy [9, 11] we applied a *cis* window of ± 25 kilobase pair (kbp) around *CETP* (ENSG00000087237, GRCh37), noting that this includes the entire GWAS signal observed in the source GWAS. Variants were selected to have an F-statistic of 24 or larger, and a minor allele frequency (MAF) of 0.01 or larger. The F-statistic threshold was used to limit the potential influence of weak-instrument bias [33]. Through our two-sample design any potential remaining weak-instrument bias is expected to act towards a neutral effect direction, guarding against an increased false positive rate. The MAF threshold was chosen to ensure we could robustly model genetic linkage disequilibrium (LD) [9] based on a random sample of 5,000 UK biobank participants as a reference. Using these reference data, the genetic variants were clumped to an R-squared of 0.30, using the same reference data to model the residual LD (see below).

As described in Schmidt et al. 2020 [9] genetic associations with downstream consequences of protein expression can be used as an additional source of instrument selection and modelling using Mendelian randomization (MR). This provides opportunities to replicate the results observed in *cis*-MR using genetic associations with protein concentration. MR analyses using downstream proxies of protein expression reflect effects of protein activity,

complementing analyses of protein concentration. Here we used GWAS on plasma concentration of Apo-A1 and Apo-B (gwas.mrcieu.ac.uk, study ID: met-d, n: 111,078) from which we extracted genetic variants, applying the same variant selection criteria centred on the *cis*-CETP region. We differentiate between the three analysis by referring to MR analyses weighted by “CETP”, “Apo-A1”, or “Apo-B”. Similarly, when utilising CETP variants from the Blauw et al. GWAS on CETP plasma concentration, we refer to these MR effects as the effect of lower CETP concentration, reflecting that under the core instrumental variable assumptions [34] the effects of genetically predicted CETP concentration is equivalent to the effects of CETP concentration itself.

Genetic sources of outcome data

Using MR, the identified CETP instruments were related to GWAS data on the following traits: plasma concentrations of Apo-A1, Apo-B, intermediate-density lipoprotein cholesterol (IDL-C), very-low-density lipoprotein cholesterol (VLDL-C), remnant-C from (<https://gwas.mrcieu.ac.uk/datasets>, dataset: met-d, n: 111,078), LDL-C, HDL-C, and TG from [35] (n: 1,320,016), Lp[a] from (n: 361,194, <http://www.nealelab.is/uk-biobank>), systolic/diastolic blood pressure (SBP/DBP) from [36] (n: 757,601), brain volume from [37] (n: 47,316), white matter hyperintensity volume from [38] (WHM vol., n: 42,310, <https://www.ebi.ac.uk/gwas/publications/32358547>), circulation total tau from [39] (Circ. total tau, n: 14,721), CHD from [40] (cases: 181,522, total n: 1,165,690), any stroke, ischemic stroke, small vessel stroke from [41] (any stroke cases: 110,182, total n: 1,614,080; any ischemic stroke cases: 86,668, total n: 1,590,566; small vessel stroke cases: 9,219, total n: 1,517,518), atrial fibrillation from [42] (AF, cases: 60,620, total n: 1,030,836), HF from [43] (cases: 115,150, total n: 1,665,481), AAA (cases: 8,163, total n: 1,164,713, <https://www.globalbiobankmeta.org/>), LBD from [30] (cases: 2,981, total n: 6,618), LBD stratified on *APOE-ε4* status from [31] (positive cases: 1,180, positive total n: 1,837, negative cases: 1,286, negative total cases: 3,557), PD from [44] (cases: 56,306, total n: 14,056,306), dementia in PD from [45] (cases: 263, total n: 3,923), multiple sclerosis from [46] (cases: 14,498, total n: 38,589), amyotrophic lateral sclerosis from [47] (cases: 15,156, total n: 41,398).

Mendelian randomization analysis

Cis-MR was employed to ascertain the possible causal effects of low CETP concentration on neurodegenerative disease and cardiovascular outcomes. MR estimates were calculated using generalized least squares (GLS) implementations of the inverse-variance weighted (IVW) estimator and the MR-Egger estimator, the latter being unbiased in the presence of horizontal pleiotropy

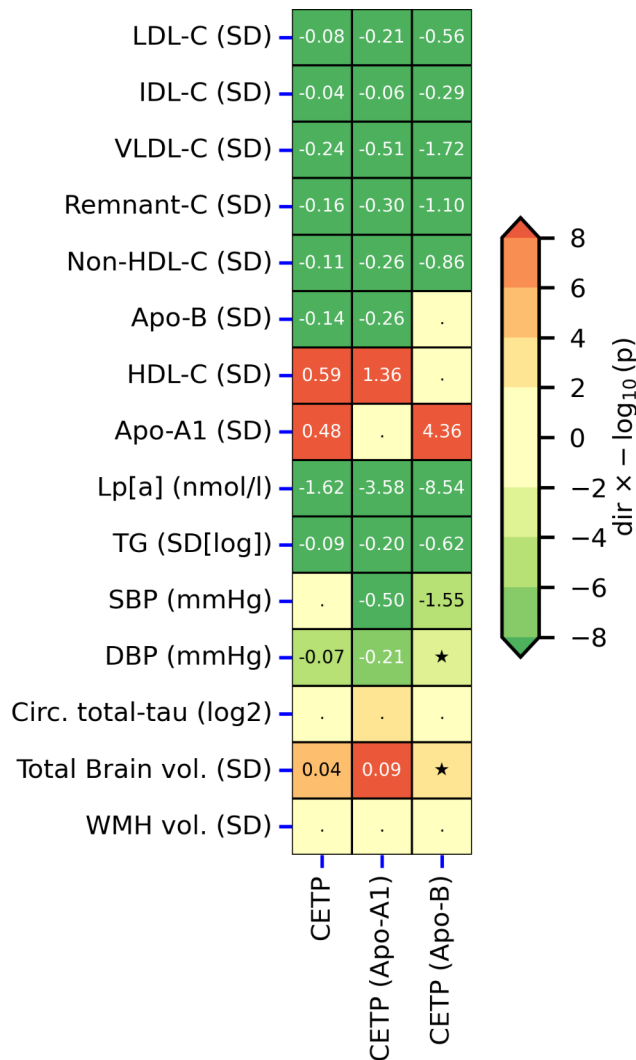


Fig. 1 Biomarker effects of lower CETP level/activity estimated through *cis* Mendelian randomization using three distinct weighting strategies

The MR effects were estimated by alternately selecting instruments based on the genetic association with lower CETP concentration ($\mu\text{g/mL}$), higher Apolipoprotein-A1 (Apo-A1 in g/L), and lower Apolipoprotein-B (Apo-B in g/L). Results are presented as effect direction multiplied by the $-\log_{10}(p\text{-value})$, truncated to a maximum of 8. Results with a p -value smaller than $0.05/29$ are annotated by the point estimates rounded to two decimal places, nominal significance with a p -value between 0.05 and $0.05/29$ is indicated by a star symbol, with results above 0.05 indicated by a dot. For the Apo-A1 weighted analyses, the Apo-A1 association was removed (reflecting identical data), with similar masking for the Apo-B weighted analysis. The outcome traits are listed on the y-axis with their units in brackets. Abbreviations: LDL-C, low-density lipoprotein cholesterol; IDL-C, intermediate-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; Remnant-C, remnant cholesterol, non-HDL-C, non-high-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol; Lp[a], lipoprotein a; TG, total triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMH, white matter hyperintensity; vol., volume, Circ. circulating. Please see Supplementary Table S1 for the full results, and Table S2 for the source data and sample size

at the cost of lower precision. We used GLS to directly model the LD reference structure, after clumping to an R-squared of 0.30, optimizing power while preventing potential multicollinearity-based numerical instability. To minimize the potential influence of horizontal pleiotropy, variants beyond 3 times the mean leverage or with an outlier (Chi-square) statistic larger than 10.83, were pruned [48]. Finally, a model selection framework was applied to select the most appropriate estimator, IVW or MR-Egger [48, 49]. This model selection framework [50] utilizes the difference in heterogeneity between the IVW Q-statistic and the Egger Q-statistic to decide which method provides the best model to describe the available data and hence optimizes the bias-variance trade-off.

Effect estimates and multiple testing

Effect estimates are presented in the CETP lowering direction, for the CETP and Apo-B weighted MR analyses this implies the results are presented towards the decreasing direction, while the Apo-A1 weighted analyses are presented in the increasing direction. Results are provided with 95% confidence intervals (CI) and p -values. Statistical significance was determined by comparing the p -values against a multiplicity corrected threshold of $0.05/29 \approx 1.7 \times 10^{-3}$ for the main analysis focussing on associations with biomarkers and disease. Furthermore, results of the main analysis were replicated by identifying significant and directionally concordant results using the *cis*-MR analysis of CETP activity weighted by Apo-A1 concentration and Apo-B concentration.

Results

Cis-MR was employed to evaluate the potential causal effects lower CETP had on biomarker and disease traits. Specifically, we sourced instruments from a ± 25 kbp window within and around *CETP* (ENSG00000087237), selecting variants based on GWAS' of CETP concentration (no. participants: 4,248), Apo-A1 concentration (no. participants: 355,729), or Apo-B concentration (no. participants: 355,729).

Effects of lower CETP concentration on biomarker traits

Lower CETP concentration (Fig. 1, Table S1-S2) was associated with a decrease in plasma concentration of LDL-C (-0.082 standard deviation (SD), 95%CI -0.086; -0.079), IDL-C (-0.04 SD, 95%CI -0.05; -0.03), VLDL-C (-0.24 SD, 95%CI -0.27; -0.21), remnant-cholesterol (-0.16 SD, 95%CI -0.17; -0.15), non-HDL-C (-0.113 SD, 95%CI -0.119; -0.107), TG (-0.085 SD, 95%CI -0.090; -0.081), Apo-B (-0.144 SD, 95%CI -0.153; -0.135), and Lp[a] (-1.62 nmol/L, 95%CI -1.91; -1.32). Following the canonical CETPi effects, genetically instrumented lower CETP increased the concentration of HDL-C (0.59 SD, 95%CI

0.57; 0.60), and Apo-A1 (0.48 SD, 95%CI 0.45; 0.52), respectively.

CETP additionally affected non-lipid traits, where lower CETP concentration decreased DBP -0.07 mmHg (95%CI -0.11 ; -0.03), and increased total brain volume 0.04 SD (95%CI 0.02 ; 0.06), respectively. The presented results were replicated in MR analyses selecting and weighting *CETP* genetic instruments by Apo-A1 and/or Apo-B concentration as a proxy for reduced CETP activity; Fig. 1.

Effects of lower CETP concentration on cardiovascular outcomes

We confirmed that lower plasma CETP concentration decreased the risk of CHD (OR 0.92, 95%CI 0.89; 0.96, p -value 2.47×10^{-5}), any stroke (OR 0.90, 95%CI 0.85; 0.95), any ischemic stroke (OR 0.96, 95%CI 0.94; 0.98), as well as small vessel stroke (OR 0.90, 95%CI 0.85; 0.96); Fig. 2, Table S1. We additionally observed that lower plasma concentration of CETP decreased the risk of AAA (OR 0.76, 95%CI 0.73; 0.80) and HF (OR 0.97, 95%CI 0.93; 1.00, p -value 4.39×10^{-2}), although the latter only reached nominal significance. Aside from the any stroke and ischemic stroke signals, which were partially replicated by Apo-A1 weighted MRs, the associations with CHD, small vessel stroke, HF and AAA were fully replicated by *cis*-MR analyses selecting and weighting *CETP* variants by their associations on Apo-A1 or Apo-B concentration; Fig. 2.

Effects of lower CETP concentration on neurodegenerative outcomes

Noting that lower plasma concentration of CETP associated with higher brain volume, we next explored associations with neurodegenerative traits. We found that lower CETP concentration was associated with a decrease in LBD (OR 0.81, 95%CI 0.74; 0.89, p -value 2.95×10^{-5}), where *APOE4-ε4* status modified this association: LBD in *APOE-ε4* carriers (OR 0.61, 95%CI 0.51; 0.73, p -value 4.91×10^{-8}), and non *APOE-ε4* carriers (OR 0.89, 95%CI 0.79; 1.01, p -value 8.06×10^{-2}); interaction p -value 5.81×10^{-4} . We further observed that lower CETP concentration protected against dementia in Parkinson's disease (OR 0.26, 95%CI 0.14; 0.48, p -value 1.29×10^{-5}), which partially overlaps with known LBD pathophysiology; Fig. 3, Table S1. Additionally, we observed a nominal risk decreasing effect of lower CETP on ALS (OR 0.85, 95%CI 0.75; 0.97, p -value 1.64×10^{-2}). The apolipoprotein (both Apo-A1 and Apo-B) weighted analyses replicated the effect on LBD in *APOE-ε4* carriers, with the Apo-A1 weighted analysis also replicating the associations for dementia in PD, as well as the ALS association; Fig. 3.

Discussion

In the current analysis we employed *cis*-MR to determine biological consequences of lower CETP activity. We recapitulated and extended known beneficial effects of lower CETP levels on blood lipids, as well as protective effects on cardiovascular diseases such as CHD, AAA,

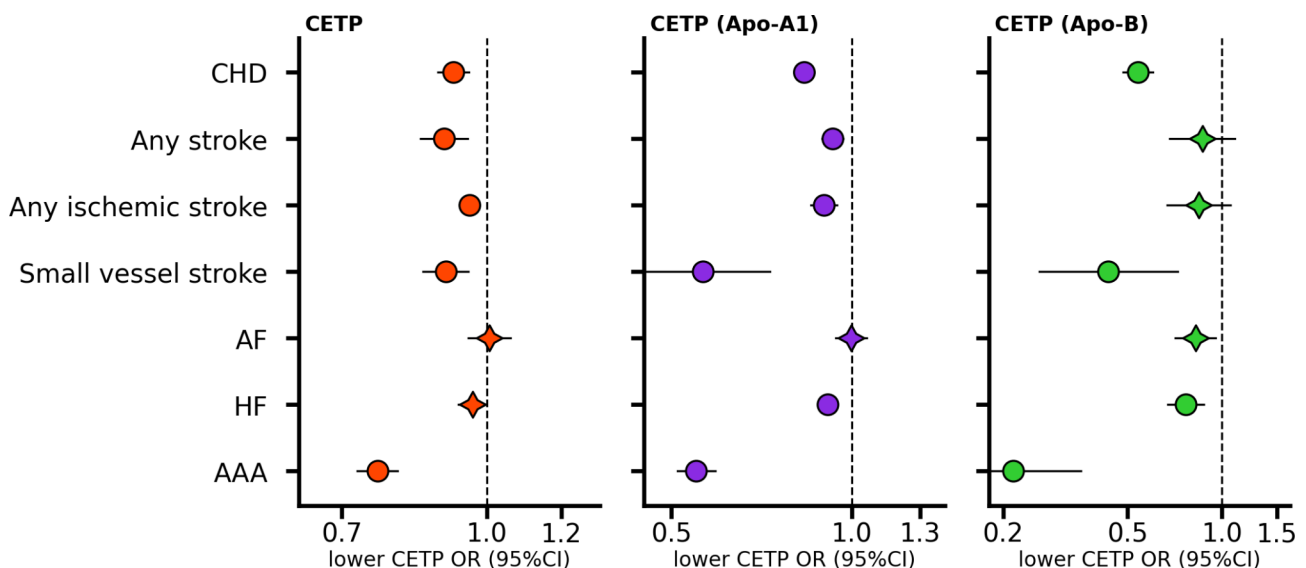


Fig. 2 Cardiovascular effects of lower CETP level/activity on cardiovascular disease estimated through *cis* Mendelian randomization using three distinct weighting strategies

The MR effects are estimated by alternately selecting instruments based on the genetic association with lower CETP concentration ($\mu\text{g/mL}$), higher Apolipoprotein-A1 (Apo-A1 in g/L), and lower Apolipoprotein-B (Apo-B in g/L). The estimated odds ratio (OR) is indicated by a circle if the p -value was smaller than 0.05/29, or by a star otherwise, with the horizontal bars representing 95% confidence intervals (95%CI), a neutral effect of 1 is indicated by the dashed vertical line. Abbreviations: CHD, coronary heart disease; AF, atrial fibrillation; HF, heart failure; AAA, abdominal aortic aneurysm. Please see Supplementary Table S1 for the full results, and Table S2 for the source data and sample size

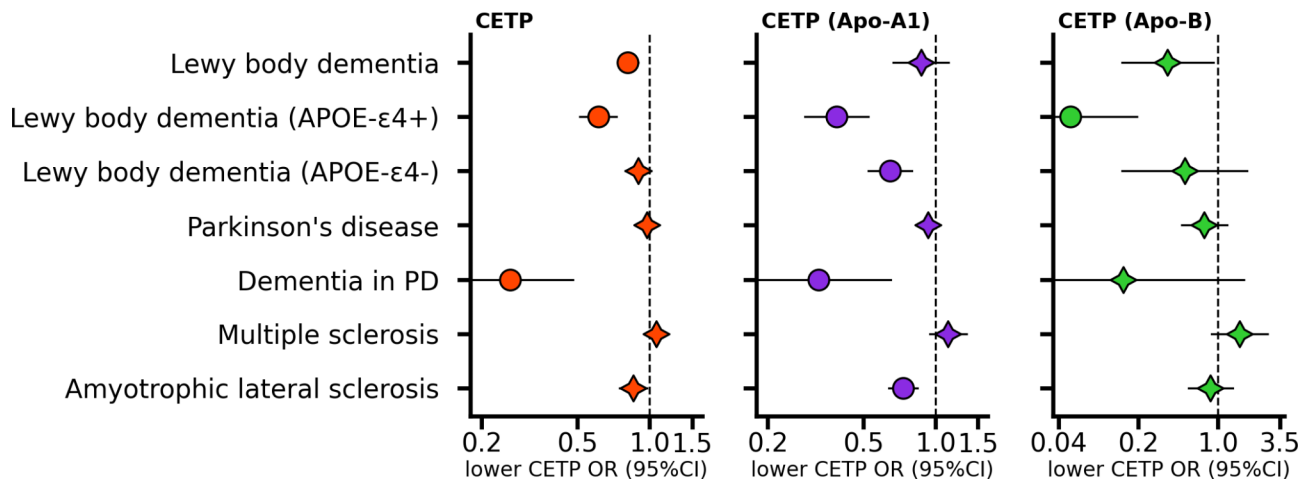


Fig. 3 Effects of lower CETP level/activity on neurological traits estimated through *cis* Mendelian randomization using three distinct weighting strategies. The MR effects are estimated by alternately selecting instruments based on the genetic association with lower CETP concentration ($\mu\text{g}/\text{mL}$), higher Apolipoprotein-A1 (Apo-A1 in g/L), and lower Apolipoprotein-B (Apo-B in g/L). The estimated odds ratio (OR) is indicated by a circle if the p -value was smaller than 0.05/29, or by a star otherwise, with the horizontal bars representing 95% confidence intervals (95%CI), a neutral effect of 1 is indicated by the dashed vertical line. Abbreviations: PD, Parkinson's disease; *APOE*- $\epsilon 4$ + refers to carriers, *APOE*- $\epsilon 4$ - refers to non-carriers. Please see Supplementary Table S1 for the full results, and Table S2 for the source data and sample size

HF, and small vessel stroke. Subsequently we explored potential associations with dementia related traits, noting protective effects of lower CETP concentrations with autopsy confirmed LBD, which was most pronounced in *APOE*- $\epsilon 4$ carriers – compatible with the previously observed protective effect of loss-of-function CETP variants in *APOE*- $\epsilon 4$ carriers [51]. The effects of lower CETP concentration were replicated by performing *cis*-MR weighting CETP variants by their association on Apo-A1 and Apo-B concentration.

The observed association between low activity of CETP and LBD is in-line with our previous observations that CETP has an HDL-C mediated effect on AD. These findings are also supported by our current understanding about the role of lipid metabolism in dementia, where increased concentrations of HDL particles and Apo-A1, may offer an *APOE*- $\epsilon 4$ dependent effect on cholesterol transport, and clearance of oxysterol and β -amyloid. It is worth emphasizing that the LBD GWAS [30, 31] we used, uniquely included autopsy-confirmed case-ascertainment, hence the observed associations reflect true LBD rather than a diagnosis based on clinical manifestation. Importantly, we did observe a protective, albeit relatively attenuated, effect of lower CETP concentration decreasing the risk of LBD in non *APOE*- $\epsilon 4$ carriers when weighting by Apo-A1: OR 0.65 95%CI 0.52; 0.80 (p -value 4.11×10^{-5}). This association did not reach statistical significance in the Apo-B or CETP concentration weighted analyses and therefore requires further confirmation. While we did not have access to genetic data on vascular dementia (VD), we were able to show that decreased plasma concentrations of CETP protect against small vessel stroke, which is the primary risk

factor for VD. Providing further guidance to the current efforts expanding the CETP inhibitor obicetrapib for treatment of dementia. While we did observe replicated effects of lower CETP concentration on larger brain volume, we did not observe a similarly concordant effect of lower CETP on white matter hyperintensity volume or circulation total tau. Potentially, this reflects a lack of *APOE4* stratification [52], lack of data on regional volumes [53], or simply distinct pathways with brain volume more closely relating to plaque forming. Additionally, we observed a protective effect of lower CETP against dementia in PD, which provides further evidence for CETP involvement in *APOE4* driven phenotypes.

The MR analyses performed in this study are protected against bias due to pre-translational horizontal pleiotropy by combining a model selection framework (providing a data-driven choice between IVW and MR-Egger MR methods) with removal of potential pleiotropic variants based on contributions to the leverage or heterogeneity statistics. Furthermore, our analysis of the effect of lower CETP concentration on blood lipids and CVD outcomes are in-line with findings from CETP inhibitor trials [5, 6], strongly suggesting the presented MR findings are protected against pre-translational pleiotropy. Given that the effects of CETP on dementia are anticipated to follow from its effect on lipid metabolism, the positive control CVD effects suggest that the associations with dementia traits may be similarly robust to pre-translational horizontal pleiotropy bias. Furthermore, our analysis was protected against bias due to potential weak-instruments and winner's curse by selecting genetic variants strongly related with CETP concentration, using a F-statistic threshold of 24 or larger. Second, the GWAS

on CETP concentration was sourced from a single study conducted by Blauw et al. [32], which has no sample overlap with the outcome GWAS ensuring that, on average, any potential for weak instrument bias acts towards a neutral effect direction [54].

As described previously [9, 11] a *cis*-MR analysis weighted by a downstream biomarker which is affected by the protein provides inference on the protein effect direction conditional on firm understanding on whether the protein increases or decreases biomarker concentration and/or activity. Such a biomarker weighted MR analysis does not provide evidence of potential downstream mediation effects. As such the presented Apo-A1 and Apo-B weighted *cis*-MR analysis represents directional tests of the effect of CETP activity, not of potential mediation by either apolipoprotein. Given the distinction between protein concentration and activity, the Apo-A1 and Apo-B weighted analyses – representing a combination of CETP concentration and activity rather than concentration alone, not only serve as partial replication, but also complements the *cis*-MR analysis based on CETP concentration. While the current analyses suggest that inhibition of CETP might protect against dementia, it does not provide information on the required dosage, timing and duration of CETP inhibition [8]. As such the reported effect estimates, while robust indicators of effect direction, are unlikely to reflect anticipated effect magnitudes of pharmacological inhibition of CETP. Our findings therefore call for careful re-analysis of existing (pre) clinical data on CETP inhibition, followed by potential *de novo* studies evaluating potential effects of CETP inhibition on dementia. In fact, our analyses are supported by recent studies in mice transgenic for both the human amyloid precursor protein (*APP*) gene, as well as *CETP*, showing accelerated AD progression concomitant with a 22% increase of cholesterol content in brain [28]. Moreover, administration of the CETPi evacetrapib rescued memory deficit in these *AAP/CETP*tg mice [28]. This beneficial change in cognition in evacetrapib treated mice correlated with both decreased LDL-C as well as increased HDL-C concentrations conferred by the CETPi.

In conclusion, our *cis*-MR recapitulated the beneficial on-target effects of lower CETP activity on blood lipids and CVD outcomes, mimicking the effect of pharmacologic CETP-inhibition. Consistent with known pathophysiology we expanded these analyses to show that lower CETP activity may elicit an *APOE4* dependent protective effect on Lewy body dementia and dementia associated with Parkinson's disease. In conjunction with human data of loss-of-function alleles of CETP that protect against dementia in *APOE-ε4*+ carriers and preclinical data in a humanized rodent model of dementia that show rescue of cognition loss by a CETP-inhibition, these

results suggest that CETP-inhibition might be repurposed for treatment of dementia in *APOE-ε4*+ carriers.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-024-01594-6>.

Supplementary Material 1

Supplementary Material 2

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Author contributions

AFS, CF, JJK designed the study. AFS performed the analyses and drafted the manuscript. MHD, MD, JJK, and CF provided critical input on the analysis, as well as the drafted manuscript.

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Data availability

The genetic data used for this analyses are available as Data 1 based on genomic build GRCh37. The individual GWAS data leveraged in this study can be accessed as followed: CETP concentration was available from Blauw et al. (n: 4,248 <https://www.ahajournals.org/doi/full/10.1161/CIRCGEN.117.002034>), Apo-A1, Apo-B, IDL-C, VLDL-C, remnant-C, from (n: 115,078, <https://gwas.mrcieu.ac.uk/datasets>, dataset: met-d), LDL-C, HDL-C, and TG from (n: 1,320,016, <http://csg.sph.umich.edu/willer/public/glgc-lipids2021>), lp[a] from (n: 361,194, <http://www.nealelab.is/uk-biobank>), systolic/diastolic blood pressure (n: 757,601, <https://www.ebi.ac.uk/gwas/publications/30224653>), brain volume, (n: 47,316, https://ctg.cncr.nl/software/summary_statistics), white matter hyperintensity volume (n: 42,310, <https://www.ebi.ac.uk/gwas/publications/32358547>), circulation total tau (n: 14,721, <https://www.ebi.ac.uk/gwas/publications/35396452>), coronary heart disease (cases: 181,522, total n: 1,165,690, <https://www.ebi.ac.uk/gwas/publications/36474045>), any stroke, ischemic stroke, small vessel stroke (any stroke cases: 110,182, total n: 1,614,080; any ischemic stroke cases: 86,668, total n: 1,590,566; small vessel stroke cases: 9,219, total n: 1,517,518, <https://www.nature.com/articles/s41586-022-05165-3>), atrial fibrillation (cases: 60,620, total n: 1,030,836, <https://www.ebi.ac.uk/gwas/publications/30061737>), heart failure (cases: 115,150, total n: 1,665,481, <https://www.ebi.ac.uk/gwas/publications/36376295>), abdominal aortic aneurysm (cases: 8,163, total n: 1,164,713, <https://www.globalbiobankmeta.org/>), Lewy body dementia (cases: 2,981, total n: 6,618, <https://www.ebi.ac.uk/gwas/publications/33589841>), Lewy body stratified on APOE-ε4 status (positive cases: 1,180, positive total n: 1,837, negative cases: 1,286, negative total cases: 3,557, <https://www.ebi.ac.uk/gwas/publications/35381062>), Parkinson's disease (cases: 56,306, total n: 14,056,306, [https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422\(19\)30320-5.pdf](https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(19)30320-5.pdf)), dementia in Parkinson's disease (cases: 263, total n: 3,923, <https://pdgenetics.org/resources>), multiple sclerosis (cases: 14,498, total n: 38,589, <https://imsgc.net/>), amyotrophic lateral sclerosis (cases: 15,156, total n: 41,398, <https://www.nature.com/articles/ng.3622>).

Code availability

Analyses were conducted using Python v3.7.13 (for GNU Linux), Pandas v1.3.5, Numpy v1.21.6, bio-misc v0.1.4, and matplotlib v3.4.3. The code underpinning the presented results can be accessed here: https://gitlab.com/SchmidtAF/cetp_dementia.

Declarations

Ethics approval and consent to participate

The presented analyses exclusively sourced aggregated genetic data and did not analyse individual participants data. The underlying GWAS received appropriate ethical approval, please consult the individual publications. This research received approval by UCL Research Ethics Committee (UCL REC) under application number 27095/001, and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

AFS and CF have received funding from New Amsterdam Pharma for this project. New Amsterdam Pharma is developing the CETP inhibitor Obicetrapib. MHD, MD, JK are employed by New Amsterdam Pharma, as chief executive officer, chief development officer, and chief scientific officer, respectively.

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References

- Kastelein JJ, Kereiakes DJ, Cannon CP, Bays HE, Minini P, Lee LV et al. Additional LDL-C reduction achieved with alirocumab dose increase on background statin. *Circulation*. 2015;132. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01199072/full>
- Nicholls SJ, Ditmarsch M, Kastelein JJ, Rigby SP, Kling D, Curcio DL, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. *Nat Med*. 2022;28(8):1672–8.
- Ballantyne CM, Ditmarsch M, Kastelein JJ, Nelson AJ, Kling D, Hsieh A, et al. Obicetrapib plus Ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. *J Clin Lipidol*. 2023;S1933–2874(23):00186–1.
- Hovingh GK, Kastelein JJP, van Deventer SJH, Round P, Ford J, Saleheen D, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2015;386(9992):452–60.
- Schmidt AF, Hunt NB, Gordillo-Marañón M, Charoen P, Drenos F, Kivimaki M, et al. Cholesteryl Ester transfer protein (CETP) as a drug target for cardiovascular disease. *Nat Commun*. 2021;12(11):5640.
- The HPS3/TIMI55–REVEAL Collaborative Group. Effects of Anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377(13):1217–27.
- Nicholls SJ, Ray KK, Nelson AJ, Kastelein JJP. Can we revive CETP-inhibitors for the prevention of cardiovascular disease? *Curr Opin Lipidol*. 2022;33(6):319–25.
- Cupido AJ, Reeskamp LF, Hingorani AD, Finan C, Asselbergs FW, Hovingh GK, et al. Joint genetic inhibition of PCSK9 and CETP and the association with coronary artery disease: a factorial Mendelian randomization study. *JAMA Cardiol*. 2022;7(9):955–64.
- Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, et al. Genetic drug target validation using Mendelian randomisation. *Nat Commun*. 2020;11(1):3255.
- Hingorani A, Humphries S. Nature's randomised trials. *Lancet*. 2005;366(9501):1906–8.
- Schmidt AF, Hingorani AD, Finan C. Human genomics and drug development. *Cold Spring Harb Perspect Med*. 2021;a039230.
- Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572–628.
- Marsillach J, Adorni MP, Zimetti F, Papotti B, Zuliani G, Cervellati C. HDL proteome and Alzheimer's disease: evidence of a link. *Antioxid (Basel)*. 2020;9(12):1224.
- Suidan GL, Ramaswamy G. Targeting apolipoprotein E for Alzheimer's disease: an industry perspective. *Int J Mol Sci*. 2019;20(9):2161.
- Borràs C, Mercer A, Sirisi S, Alcolea D, Escolà-Gil JC, Blanco-Vaca F, et al. HDL-like-mediated cell cholesterol trafficking in the central nervous system and Alzheimer's disease pathogenesis. *Int J Mol Sci*. 2022;23(16):9356.
- Yin F. Lipid metabolism and Alzheimer's disease: clinical evidence, mechanistic link and therapeutic promise. *FEBS J*. 2023;290(6):1420–53.
- Schmidt AF, Joshi R, Gordillo-Marañón M, Drenos F, Charoen P, Giambartolomei C et al. Biomedical consequences of elevated cholesterol-containing lipoproteins and apolipoproteins. *medRxiv*. 2022 [cited 2022 May 6];2022.03.11.22272251. <https://www.medrxiv.org/content/https://doi.org/10.1101/2022.03.11.22272251v1>
- Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology*. 2007;68(11):812–9.
- Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. *Mol Neurodegener*. 2022;17(1):72.
- Strittmatter WJ, Saunders AM, Schmechel P, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90(5):1977–81.
- Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71–6.
- Snellman A, Ekblad LL, Tuisku J, Koivumäki M, Ashton NJ, Lantero-Rodriguez J, et al. APOE ε4 gene dose effect on imaging and blood biomarkers of neuroinflammation and beta-amyloid in cognitively unimpaired elderly. *Alzheimers Res Ther*. 2023;15(1):71.
- Majewski J, Jones EM, Vander Zanden CM, Biernat J, Mandelkow E, Chi EY. Lipid membrane templated misfolding and self-assembly of intrinsically disordered tau protein. *Sci Rep*. 2020;10(1):13324.
- Lanfranco MF, Ng CA, Rebeck GW. ApoE lipidation as a therapeutic target in Alzheimer's disease. *Int J Mol Sci*. 2020;21(17):6336.
- Fernández-Calle R, Konings SC, Frontiñán-Rubio J, García-Revilla J, Campubí-Ferrer L, Svensson M, et al. APOE in the bullseye of neurodegenerative diseases: impact of the APOE genotype in Alzheimer's disease pathology and brain diseases. *Mol Neurodegener*. 2022;17(1):62.
- Bedlack RS, Strittmatter WJ, Morgenlander JC. Apolipoprotein E and neuromuscular disease: a critical review of the literature. *Arch Neurol*. 2000;57(11):1561–5.
- Berghoff SA, Gerndt N, Winchenbach J, Stumpf SK, Hosang L, Odoardi F, et al. Dietary cholesterol promotes repair of demyelinated lesions in the adult brain. *Nat Commun*. 2017;8:14241.
- Oestereich F, Yousefpour N, Yang E, Phénix J, Nezhad ZS, Nitu A, et al. The cholesteryl ester transfer protein (CETP) raises cholesterol levels in the brain. *J Lipid Res*. 2022;63(9):100260.
- Zak Z, Lagrost L, Gautier T, Masson D, Deckert V, Duverneuil L, et al. Expression of simian CETP in normolipidemic Fisher rats has a profound effect on large sized apoe-containing HDL. *J Lipid Res*. 2002;43(12):2164–71.
- Chia R, Sabir MS, Bandres-Ciga S, Saez-Atienzar S, Reynolds RH, Gustavsson E, et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nat Genet*. 2021;53(3):294–303.
- Kaivola K, Shah Z, Chia R, Scholz SW. Genetic evaluation of dementia with Lewy bodies implicates distinct disease subgroups. *Brain*. 2021;145(5):1757–62.
- Blauw LL, Li-Gao R, Noordam R, de Mutsert R, Trompet S, Berbee JFP, et al. CETP (Cholesteryl Ester Transfer Protein) concentration: a genome-wide association study followed by Mendelian randomization on coronary artery disease. *Circ Genom Precis Med*. 2018;11(5):e002034.
- Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755–64.
- Schmidt AF, Hingorani AD, Jefferis BJ, White J, Groenwold RHH, Dudbridge F. Comparison of variance estimators for meta-analysis of instrumental variable estimates. *Int J Epidemiol*. 2016; 45(6): 1975–86.
- Graham SE, Clarke SL, Wu KHH, Kanoni S, Zajac GJM, Ramdas S, et al. The power of genetic diversity in genome-wide association studies of lipids. *Nature*. 2021;600(7890):675–9.
- Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50(10):1412–25.
- Jansen PR, Nagel M, Watanabe K, Wei Y, Savage JE, de Leeuw CA, et al. Genome-wide meta-analysis of brain volume identifies genomic loci and genes shared with intelligence. *Nat Commun*. 2020;11(1):5606.

38. Persyn E, Hanscombe KB, Howson JMM, Lewis CM, Traylor M, Markus HS. Genome-wide association study of MRI markers of cerebral small vessel disease in 42,310 participants. *Nat Commun*. 2020;11(1):2175.
39. Sarnowski C, Ghanbari M, Bis JC, Logue M, Fornage M, Mishra A, et al. Meta-analysis of genome-wide association studies identifies ancestry-specific associations underlying circulating total tau levels. *Commun Biol*. 2022;5(1):1–11.
40. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, et al. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nat Genet*. 2022;54(12):1803–15.
41. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, et al. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611(7934):115–23.
42. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE, et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet*. 2018;50(9):1234–9.
43. Levin MG, Tsao NL, Singhal P, Liu C, Vy HMT, Paranjpe I, et al. Genome-wide association and multi-trait analyses characterize the common genetic architecture of heart failure. *Nat Commun*. 2022;13(1):6914.
44. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol*. 2019;18(12):1091–102.
45. Real R, Martinez-Carrasco A, Reynolds RH, Lawton MA, Tan MMX, Shoai M, et al. Association between the LRP1B and APOE loci and the development of Parkinson's disease dementia. *Brain*. 2023;146(5):1873–87.
46. International Multiple Sclerosis Genetics Consortium (IMSGC), Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kempainen A, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*. 2013;45(11):1353–60.
47. van Rheenen W, Shatunov A, Dekker AM, McLaughlin RL, Diekstra FP, Pulit SL, et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat Genet*. 2016;48(9):1043–8.
48. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J, et al. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36(11):1783–802.
49. Bowden J, Spiller W, Del Greco MF, Sheehan N, Thompson J, Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the radial plot and radial regression. *Int J Epidemiol*. 2018;47(4):1264–78.
50. Rücker G, Schwarzer G, Carpenter JR, Binder H, Schumacher M. Treatment-effect estimates adjusted for small-study effects via a limit meta-analysis. *Biostatistics*. 2011;12(1):122–42.
51. Chemparathy A, Guen YL, Chen S, Lee EG, Leong L, Gorzynski J et al. APOE loss-of-function variants: compatible with longevity and associated with resistance to Alzheimer's disease pathology. *medRxiv*. 2023;2023.07.20.23292771.
52. Mirza SS, Saeed U, Knight J, Ramirez J, Stuss DT, Keith J, et al. APOE ϵ 4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. *Neurology*. 2019;93(19):e1807–19.
53. Lorenzini L, Ansems LT, Lopes Alves I, Ingala S, Vázquez García D, Tomassen J, et al. Regional associations of white matter hyperintensities and early cortical amyloid pathology. *Brain Commun*. 2022;4(3):fca150.
54. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genetic Epidemiology*. 2016;40(7):597–608.

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