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Associations of circulating C-reactive proteins, *APOE* ε4, and brain markers for Alzheimer's disease in healthy samples across the lifespan

Yunpeng Wang [a,*], Håkon Grydeland [a], James M. Roe [a], Mengyu Pan [a], Fredrik Magnussen [a], Inge K. Amlien [a], Leiv Otto Watne [b], Ane-Victoria Idland [a,b], Lars Bertram [c], Thomas E. Gundersen [d], Alvaro Pascual-Leone [e,f,g], Maria Cabello-Toscano [h], Jose M. Tormos [e,i], David Bartres-Faz [e,h], Christian A. Drevon [d,j], Anders M. Fjell [a,k], Kristine W. Walhovd [a,k]

[a] *Lifespan Changes in Brain and Cognition (LCBC), Department of Psychology, University of Oslo, 0317 Oslo, Norway*
[b] *Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, 0424 Oslo, Norway*
[c] *University of Lübeck, Lübeck Interdisciplinary Platform for Genome Analytics, Maria-Goeppert-Str. 1 (MFC1), 23562 Lübeck, Germany*
[d] *Vitas AS, Science Park, Gaustadalléen 21, 0349 Oslo, Norway*
[e] *Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona 08916, Spain*
[f] *Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife, Boston, MA 02131, USA*
[g] *Department of Neurology, Harvard Medical School, Boston, MA 02115, USA*
[h] *Department of Medicine, Faculty of Medicine and Health Sciences, and Institute of Neurosciences, University of Barcelona, Barcelona 08036, Spain*
[i] *Department of Medicine, Universitat Aut.noma de Barcelona, Bellaterra 08035, Spain*
[j] *Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, PO Box 1046, 0317 Oslo, Norway*
[k] *Division of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet, POB 4950 Nydalen, 0424 Oslo, Norway*

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ABSTRACT

The apolipoprotein E gene ε4 allele (*APOE* ε4) and higher circulating level of C-reactive protein (CRP) have been extensively investigated as risk factors for Alzheimer's disease (AD). Paradoxically, *APOE* ε4 has been associated with lower levels of blood CRP in middle-aged and older populations. However, few studies have investigated this intriguing relation and its impact on neurological markers for AD in younger ages, nor across the whole lifespan. Here, we examine associations of blood CRP levels, *APOE* ε4, and biomarkers for AD in a cognitively healthy lifespan cohort (N up to 749; 20–81 years of age) and replicate the findings in UK Biobank (N = 304 322; 37–72 years of age), the developmental ABCD study (N = 10 283; 9–11 years of age), and a middle-aged sample (N = 339; 40–65 years of age). Hippocampal volume, brain amyloid-β (Aβ) plaque levels, cerebrospinal fluid (CSF) levels of Aβ and tau species, and neurofilament protein light protein (NFL) were used as AD biomarkers in subsamples. In addition, we examined the genetic contribution to the variation of CRP levels over different CRP ranges using polygenic scores for CRP (PGS-CRP). Our results show *APOE* ε4 consistently associates with low blood CRP levels across all age groups ($p < 0.05$). Strikingly, both ε4 and PGS-CRP associated mainly with blood CRP levels within the low range (<5mg/L). We then show both *APOE* ε4 and high CRP levels associate with smaller hippocampus volumes across the lifespan ($p < 0.025$). *APOE* ε4 was associated with high Aβ plaque levels in the brain (FDR-corrected $p = 8.69x10^{-4}$), low levels of CSF Aβ42 (FDR-corrected $p = 6.9x10^{-2}$), and lower ratios of Aβ42 to Aβ40 (FDR-corrected $p = 5.08x10^{-5}$). Blood CRP levels were weakly correlated with higher ratio of CSF Aβ42 to Aβ40 ($p = 0.03$, FDR-corrected $p = 0.4$). *APOE* ε4 did not correlate with blood concentrations of another 9 inflammatory cytokines, and none of these cytokines correlated with AD biomarkers.

Conclusion: The inverse correlation between *APOE* ε 4 and blood CRP levels existed before any pathological AD biomarker was observed, and only in the low CRP level range. Thus, we suggest to investigate whether *APOE* ε 4 can confer risk by being associated with a lower inflammatory response to daily exposures, possibly leading to greater accumulation of low-grade inflammatory stress throughout life. A lifespan perspective is needed to understand this relationship concerning risk of developing AD.

* Corresponding author at: Lifespan Changes in Brain and Cognition (LCBC), Department of Psychology, University of Oslo, Forskningsveien 3A, 0317 Oslo, Norway.
E-mail address: yunpeng.wang@psykologi.uio.no (Y. Wang).

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1. Introduction

Late onset Alzheimer's disease (AD) is the major cause of dementia, but our understanding of its aetiology is incomplete (Scheltens et al., 2021). Clinical manifestation of AD typically occurs after 60–65 years of age, and includes declined cognitive performance and brain atrophy (Burns and Iliffe, 2009), whereas the pre-symptomatic phase of AD could start 15–20 years before the clinical diagnosis. The most popular hypothesis for the development of AD – the amyloid beta (Aβ) cascade hypothesis (Beyreuther and Masters, 1991; Selkoe and Hardy, 2016) – suggests the disease is initiated by extracellular aggregation of Aβ42 plaques, which in turn causes accumulation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins, and subsequently induces neuroinflammation in the brain. Ultimately, the cascade leads to widespread neuronal and synaptic dysfunction, brain atrophy, and cognitive impairment. Whereas the Aβ-cascade hypothesis explains early-onset AD to a certain extent, it appears to play a smaller role in the more common late-onset form of AD. Recent genome-wide association studies (GWAS) for late-onset AD have reported up to 30 genomic risk loci (Jansen et al., 2019; Kunkle et al., 2019) that implicate involvement of Aβ processing, immune response and lipid metabolism in AD development. However, most of these variants show very weak associations with AD (Scheltens et al., 2021).

The apolipoprotein E gene (*APOE*) ε4 allele is the strongest genetic risk factor established for late onset AD (Corder et al., 1993; Strittmatter and Roses, 1995). *APOE* has three major variants: ε2, ε3, and ε4. Carriers of one *APOE* ε4 copy have 3–4-fold increased risk of developing AD compared to non-carriers, whereas the risk associated with carrying two ε4 copies has been estimated to be up to 15-fold (Farrer et al., 1997; Neu et al., 2017). APOE ε4 carriers have a younger age of onset for AD (Bonham et al., 2016; Sando et al., 2008), and several studies have shown that *APOE* ε4 affects AD in an age-dependent manner, with highest risk for 60–70 years old persons, but smaller effect for those above 75 years (Bonham et al., 2016; Corbin et al., 2018). Nevertheless, the molecular mechanisms for how *APOE* ε4 increases AD risk are unclear (Belloy et al., 2019). Proposed mechanisms of *APOE* ε4 are largely linked to the Aβ-cascade hypothesis, including increased production and decreased clearance of Aβ in the brain, increased formation of intracellular tau tangles, perturbed synaptic function and altered microglial response (Yamazaki et al., 2019). However, *APOE* ε4 has also been associated with reduced cognitive performance and smaller hippocampi in younger ages well before brain Aβ plaques are detectable (Filippini et al., 2009; Luiza K. Axelrud et al., 2018; O'Dwyer et al., 2012). Thus, other physiological pathways linking *APOE* ε4 to AD risk remain to be explored.

Among several postulated mechanisms by which *APOE* ε4 could impact AD risk, immune-related pathways have gained increased attention (Yamazaki et al., 2019). In particular, *APOE* ε4 has been associated with low concentration of CRP (Eiriksdottir et al., 2006; Haan et al., 2008; Martiskainen et al., 2018; März et al., 2004). CRP is an acute-phase serum protein, produced mainly by the liver but also other organs, including the brain (Du Clos, 2000; Dumitrescu et al., 2020). High CRP levels typically indicate a recent infection and sustained medium concentration may suggest chronic inflammation (Dumitrescu et al., 2020). For AD, although the general trend is that high CRP levels correlate with high risk of developing AD, such a trend may not be causal (Prins et al., 2016). Furthermore, a recent study suggested the effect of blood CRP levels on AD may depend on the age of the sample (Gabin et al., 2018). Despite that both *APOE* ε4 and CRP derived from blood measures (Desikan et al., 2015; Fernandes et al., 2020; Morgan et al., 2019; Silverman et al., 2012) have been extensively studied in terms of their association with AD, less efforts have been made to understand the intriguing relation between the three. Although the association between *APOE* ε4 and CRP levels and AD development may depend on age, previous studies were rarely performed on samples younger than the currently accepted age of pre-symptomatic AD (Eiriksdottir et al., 2006; Haan et al., 2008; Martiskainen et al., 2018; März et al., 2004). Thus, interpretations of the *APOE* ε4 vs. CRP relation in terms of AD risk are incomplete.

Here, we investigate associations of *APOE* ε4, blood CRP levels and established biomarkers for AD in a cognitively healthy adult lifespan cohort (N up to 749; 20–81 years of age), and in three replication datasets comprising different age-ranges: a UK Biobank subsample (N = 304,322; 37–72 years of age), the developmental ABCD study (N = 10,283; 9–11 years of age), and a middle-aged sample (N = 399; 40–65 years of age). Total hippocampal volume (HippV), brain amyloid-β (Aβ) plaque levels measured by PET-imaging, and CSF levels of Aβ, tau and NFL were examined as AD biomarkers. We also studied genetic contributions to the variation in CRP levels in different ranges using a polygenic score for CRP (PGS-CRP). We hypothesized that the previously observed negative *APOE* ε4-CRP relations could also exist in young people well before the accepted AD pathological biomarkers are detectable. If so, that may indicate that any effects of lower inflammatory response in *APOE* ε4 carriers could accumulate throughout the lifespan.

2. Methods

Fig. 1 shows our analysis steps, datasets and sample age distributions, and analytical models used in the present study. In brief, we used our local LCBC sample for discovery and three independent external datasets (UKBB, UB-BBHI and ABCD) for replications.

2.1. Participants

The study was approved by the Regional Committee for Ethic in Medical Research in Norway. All participants provided written informed consent.

LCBC sample. Subsets of the Lifespan Changes in Brain and Cognition (LCBC) cohort (Walhovd et al., 2019) were studied. They were cognitively healthy, and well-screened for psychiatric, neurological, and health conditions known to affect the brain, but participants with common health conditions, such as moderately elevated blood pressure and those receiving hypertensive treatment were not excluded. Participants were selected based on availability of measures of cytokines, HippV, brain Aβ or DNA genotype information. Besides high sensitivity C-reactive protein levels (CRP), nine additional cytokines were also investigated as supplementary analyses: interleukin-6 (IL6), interleukin-1 beta (IL1b), interleukin-8 (IL8), interleukin-1 alpha antagonist (IL1RA), interleukin-10 (IL10), interleukin-17A (IL17A), interferon-gamma (IFNg), tumor necrosis factor-alpha (TNFa), and monocyte chemoattractant protein-1 (MCP1, also known as CCL2). The number of unique participants varies with variables available (Fig. 1**A and C**, **Fig. S10 and S11**), ranging from N = 507 (both CRP and HippV available; age range: 20.1–81.9 years; 329 women) to N = 749 (both *APOE* and >=1 HippV available; age range: 20–81.9 years; women: 516; Fig. 1**B, Fig. S1, S2, S4 and S5**). The number of unique participants and total scan observations (*i.e.*, including longitudinal scans) for each analysis is clearly shown in Fig. 1**A**. Body mass index (BMI) was also collected for all LCBC participants.

COGNORM sample. Participants with CSF biomarkers, cytokine levels, and DNA genotypes from the COGNORM-study (Idland et al., 2017) 2012 to 2013, Oslo University Hospital and Diakonhjemmet Hospital, Oslo) were included. The COGNORM-study included 172 patients of at least 65 years of age undergoing elective gynecological, urological and orthopedic surgeries in spinal anesthesia in the two hospitals. Patients with dementia, previous stroke with sequelae, Parkinson's disease and other conditions that probably affect cognition, were excluded. In the present study, 99 participants were included (64–93.0 years of age; 49 women; see **Figs. S8 and S9 for CSF and blood marker distributions**). Body mass index (BMI) was also collected for these participants.

UK biobank population (UKBB). Participants in the UK Biobank (UKBB) (Sugden et al., 2019) with HippV, CRP levels and DNA genotype information, were included. Ethical approval was obtained from the National Health Service National Research Ethics Service (Ref. 11/NW/0382) and all participants provided written informed consent. The dataset released February 2020 was used, including 502,507 participants, of whom 40,682 had undergone MRI scanning, 487,409 have DNA genotypes, and 468,569 had CRP measured. Participants with diagnosis of any neurodegenerative disease (N = 2,030; ICD10, G30-32), any injury to the head (N = 12,722; ICD10 S00-09), were excluded from our study. Participants with ambiguous *APOE* genotypes (N = 12,252), and that were genetically related with at least one other participant, were also excluded. In total, 304,322 participants (37–72 years of age; 164,303 women; 12,123 having CRP > 10 mg/L) were included to study the association of *APOE* ε4 with CRP levels; and 26,573 participants (45–82 years of age; 13,894 women; 1,581 having 2 MRI scans) were used to study the association of CRP and *APOE* ε4 with HippV.

ABCD population. The ABCD study aims to discover factors affecting human brain development from childhood to adolescence (Casey et al., 2018), and has included > 10,000 children 9–10 years old. In the present study, we analyzed the full release 3.0, which also included brain scans for the second timepoint for a subset. There was no blood CRP measure available. In total, 10,283 unique participants (4,865 girls; 9–11 years of age), among which 3,519 have two MRI scans, were included here.

UB-BBHI population. Samples were obtained from participants in the Barcelona Brain Health Initiative (BBHI) (Cattaneo et al., 2018). BBHI is a population based prospective study including cognitively preserved individuals without a diagnosis of a medical neuropsychiatric condition. Inclusion in our study was based on the availability of blood CRP measures, genotypes, and MRI scans. In total, 339 individuals were included (179 women; 41–67 years of age).

2.2. Genotyping and imputation

LCBC, COGNORM and UB-BBHI Sample. Genotyping and imputation for participants of these three samples were performed previously using identical protocols (Walhovd et al., 2020). Briefly, buccal swabs were collected and genotyped using the Global Screening Array (GSA; Illumina, Inc.) with shared custom content. Pre-imputation quality check were performed using the GenomeStudio and PLINK (Chang et al., 2015) software. Samples with low call-rate (<0.95), with genetically determined non-European ancestry, genetically related to other participants, or with abnormal heterozygosity rates, were excluded. Single nucleotide polymorphisms (SNP) with low frequencies (minor allele frequency (MAF) < 0.01), or with violation of the Hardy-Weinberg equilibrium (HWE, $p < 5x10^{-6}$), were excluded. Sample imputation to the HRC data (McCarthy et al., 2016) were performed using Minimac3 (Das et al., 2016) with pre-phased haplotypes estimated by SHAPEIT2 (Delaneau et al., 2011). After imputation, SNPs with MAF < 0.01, imputation $R^2 < 0.6$, or HWE $p < 10^{-6}$, were excluded from subsequent analysis.

UK biobank population (UKBB). Imputed genotypes for the 487,409 participants were obtained from UKBB (Category 100314). The UKBB Axiom Array from Affymetrix (about 90% of participants) and the UK BiLEVE Axiom Array (5% participants) were used for genotyping. Samples with autosome missing call-rate > 0.02, or mismatched

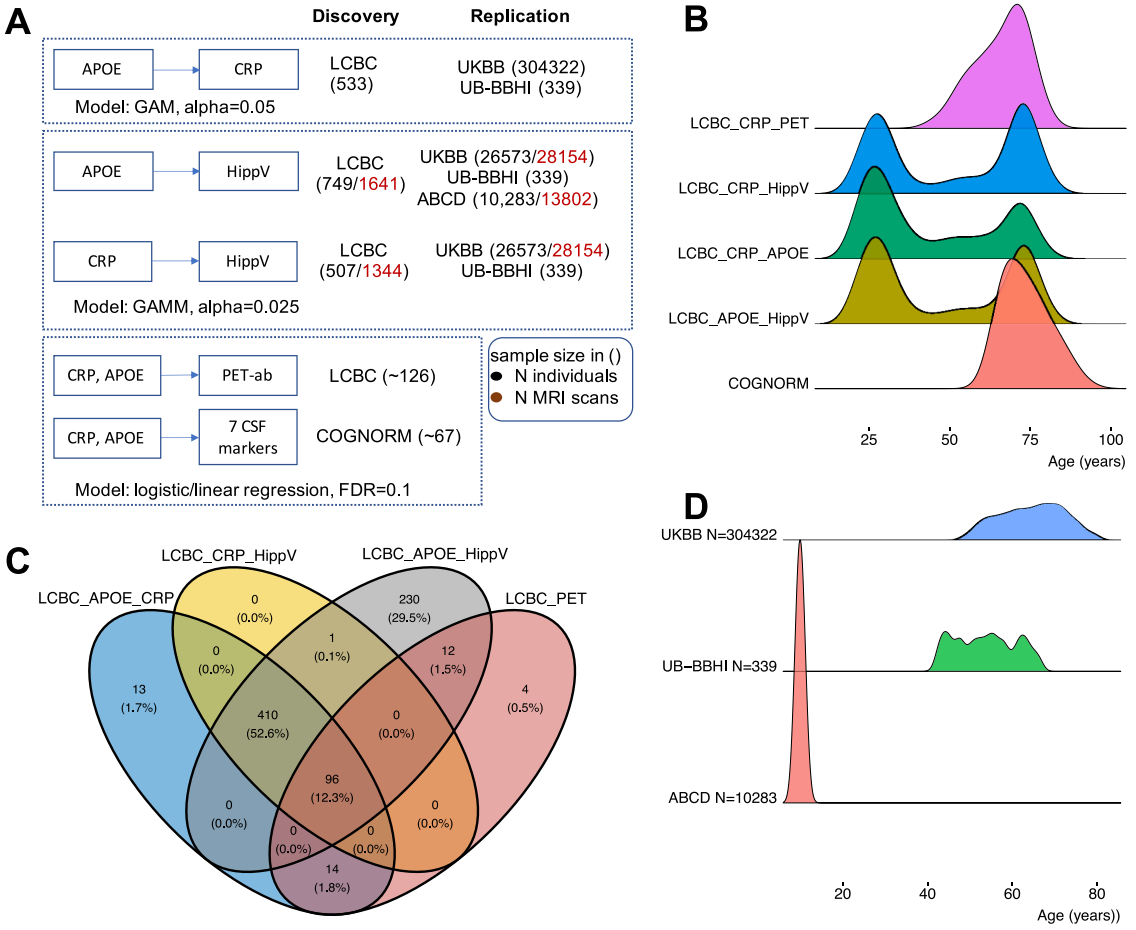

Fig. 1. Analysis procedures and samples. A) Analysis flowchart; B) Age distributions for discovery samples; C) sample overlaps among different discovery analyses; D) Age distributions for replication samples.

genetically inferred and self-reported sex, were removed. Genotype imputation was performed by the UKBB center based on haplotypes from the HRC (McCarthy et al., 2016) and UK10K (Walter et al., 2015) data (further details see (Sugden et al., 2019)).

ABCD population. Imputed genotypes from the ABCD release 3.0 were obtained (https://abcdstudy.org/). Briefly, the Affymetrix NIDA SmokeScreen Array was used for genotyping, which resulted in 733,293 SNPs. After quality control of these genotyped SNPs, the TOPMED reference data was used for imputation. Detailed information can be obtained from https://nda.nih.gov/study.html?id = 901. In the present study, we filtered out rare variants (MAF < 0.05), and variants showing strong deviation from Hardy-Weinberg equilibrium ($p < 10^{-6}$).

2.3. APOE genotype determination

APOE genotypes in the four datasets were determined by the two SNPs, rs429358 and rs7412. Four haplotypes (https://www.snpedia.com/index.php/APOE), TCCT, CTCT, TCTC and CTTC, of the two SNPs could not be resolved to a unique *APOE* haplotype, and such cases were excluded from subsequent analysis. Our present study focused on the effect of the *APOE* ε4 allele on CRP levels and HippV. *APOE* ε4 was coded as binary, *i.e.* carrier vs. non-carrier (low proportions of ε4 homozygotes were observed in all four samples; see Table S1 for ε4 frequencies).

2.4. Population structure

To correct for subtle population structure effects in statistical analyses, the first 10 principal components (PC) were computed using PLINK (Chang et al., 2015) for the LCBC, UB-BBHI and ABCD sample. Imputed genotypes were first quality checked by removing SNPs that have MAF < 0.05, HWE $p < 10^{-6}$, missing-rate > 0.05. Then, correlated SNPs were removed by the PLINK command –indep-pairwise 100 50 0.1. The top 10 PCs were obtained by the –pca command from PLINK. This procedure was independently performed for the LCBC, UB-BBHI and ABCD population. PCs for the UKBB population were computed by the UK biobank team.

2.5. Polygenic scores for CRP levels (PGS-CRP)

Effect sizes of genome-wide significant SNPs for CRP levels reported by Dehghan *et al* (Dehghan et al., 2011) and Ligthart *et al* (MacBean et al., 2020) were extracted from their published papers. Among 60 reported SNPs, 56 also existed in our sample. The SNP rs4420638 close to the *APOE* gene showed the largest effect on CRP levels and thus, was excluded in PGS computation. PGS for all participants were computed using the weighted sums methods implemented by the –score function from PLINK.

2.6. CRP determination

LCBC, COGNORM and UB-BBHI sample Circulating levels of CRP were measured by the AM-438 Quantification of CRP in Dried Blood Spots (DBS) using MSD Mesoscale ECL platform. One 3.1 mm punch from dried human whole blood samples (DBS) was eluted in 60 μL kit diluent and left standing at 4 °C overnight. After bringing the eluate to room temperature, 10 μL of the eluate were diluted in 500 μL kit diluent and analyses were performed on a MESO® QuickPlex SQ 120 Multiplex Imager using the V-PLEX Human CRP kit (K151STD-2; MSD, Rockville, Maryland, USA) as described in the manual. The lower limit of detection (LLD) was 0.08 mg/L. Samples with levels below this value were set to half of this value, 0.04 mg/L. Among the 533 samples used to discover the APOE-CRP relation, 42 had a CRP level below LLD. The number of samples with a below LLD CRP levels analyzed for the CRP-HippV relation is 83.

UK biobank population (UKBB) The serum CRP level for all participants were measured by the UK Biobank biomarker panel (http://www.ukbiobank.ac.uk/uk-biobank-biomarker-panel/). Levels of CRP were determined by the Beckman Coulter AU5800 platform (Beckman Coulter (UK), Ltd) using immune-turbidimetry. The manufacture's detection limits were 0.08–80 mg/L. No sample had a level $<$ 0.08 mg/L.

2.7. Hippocampal volume

LCBC, COGNORM and UB-BBHI population Participants from the LCBC and COGNORM sample were scanned at a total of four Siemens scanners at two sites; 1) Oslo University Hospital; 2) Curato, currently Aleris, Oslo: A 1.5 T Avanto equipped with a 12 channels head coil (site 1 and 2), a 3 T Skyra equipped with a 24 channels Siemens head coil (Site 1) or a 3 T Prisma equipped with a 32 channels head coil (site 1) (all Siemens Medical Systems, Erlangen, Germany). The pulse sequence used for morphometric analyses were one to two 3D sagittal T1-weighted MPRAGE sequences (**Supplementary Information**). All scans were reviewed for quality and automatically corrected for spatial distortion due to gradient nonlinearity (Jovicich et al., 2006) and B1 field inhomogeneity (Sled et al., 1998). Images were first automatically processed cross-sectionally for each time point with the FreeSurfer software package (version 6.0; http://surfer.nmr.mgh.harvard.edu/). The segmentation procedure automatically labels each voxel as one of 40 structures (Fischl et al., 2002), using a probabilistic brain atlas specific for the current image acquisition protocol (Han et al., 2006). Detailed description for image processing is presented in **Supplementary Information.** Brain scans for the UB-BBHI participants were acquired using a 3 Tesla Siemens PRISMA scanner with a 32-channel head coil and detailed protocols have been reported previously (Cattaneo et al., 2018).

UK Biobank population (UKBB). MRIs were collected and processed by the UK Biobank (https://www.ukbiobank.ac.uk) (Alfaro-Almagro et al., 2018). Imaging data were collected using 3.0 T Siemens Skyra scaners (32 channels head coil). Anatomical T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were obtained in the sagittal plane at 1 mm isotropic resolution, and T2 weighted FLAIR images were acquired at 1.05x1x1 mm resolution in the sagittal plane. Images were processed by the UK Biobank using the FreeSurfer 6.0 software package.

2.8. PET-Aβ status

A total of 126 participants (44.4–80.8 years of age) from the LCBC sample underwent a 18F-flutemetamol-PET scan, sensitive to Aβ accumulation (Wolk et al., 2011). Images were acquired on a General Electric Discovery PET/CT 690 scanner at Aleris Hospital and Radiology, Oslo, Norway. The PET-amyloid beta status, *i.e.* positive or negative, was estimated by applying principal component analysis on the standardized uptake value ratios (SUVR) from a set of 68 FreeSurfer-derived cortical regions (Mormino et al., 2014). The cut-off between groups was determined using Gaussian mixture modeling (R package mclust v5.2) for the first two principal components. We fitted 18 models, ranging from 1 to 9 mixtures, allowing for either equal or unequal variance, and selected the model with the lowest Bayesian information criterion value. As previously reported in healthy older participants (Mormino et al., 2014), the optimal model consisted of a two-distribution model with unequal variance. Participants with a > 0.5 probability of belonging to the high Aβ distribution were classified as Aβ positive, and the remaining as Aβ negative. Detailed description for PET image processing is presented in **Supplementary Information**.

2.9. CSF AD biomarkers for the COGNORM sample

CSF specimens were collected in polypropylene tubes at the onset of anesthesia prior to administration of the anesthetic agent. The

specimens were centrifuged, aliquoted and stored at −80 °C (Idland et al., 2017). CSF AD biomarkers, Aβ-42 and Aβ40, were measured using the Meso Scale Discovery Aβ Triplex Assay (Meso Scale Discovery, Rockville, Maryland), and the ratio of Aβ-42 to Aβ40 was computed. Levels of total tau (CSF-t-tau) and phosphorylated 181 total (CSF-p-tau) levels were determined using INNOTEST enzyme-linked immunosorbent assay (ELISA; Fujirebio) at the Sahlgrenska University Hospital, Sweden. CSF levels of neurofilament light protein (NFL) were determined by using a commercial ELISA (UmanDiagnostics, Umea, Sweden). Identical protocols for measuring cytokine levels as in LCBC were applied to the COGNORM sample. No data for PET-Aβ was available for this sample.

2.10. Statistical analysis

2.10.1. Effect of APOE ε4 on CRP levels

The association of *APOE* ε4 with CRP levels was evaluated by generalized additive models (GAM, R package 'mgcv'). CRP levels were first log10-transformed and taken as dependent variables in the models, and a smooth age function was determined by regression splines. *APOE* ε4 status (binary coded; carrier [1] vs. non-carrier [0]) was set as the main predictor, and sex, BMI (to account for possible effect of BMI on CRP levels) and the top 10 PCs (to correct for subtle population stratification) were set as covariates.

2.10.2. Effects of APOE ε4 and CRP levels on HippV

To take advantage of the longitudinal brain scans available for subsets of participants, generalized additive mixed models (GAMM; R package 'mgcv') were used to model the nonlinear relation between HippV and age, taking into account intraindividual correlations. *APOE* ε4 status, estimated intracranial volume (ICV), sex, and the top 10 PCs were coded as fixed effects, and participant unique identifiers were set as the random effect. In addition, we allowed different smooth age functions for the two *APOE* ε4 groups. Standardized HippV (mean zero and standard deviation one) was set as the dependent variable. To estimate the effect of CRP levels on HippV, instead of *APOE* ε4 status, the log10-transformed CRP levels were set as the main predictor. Moreover, both CRP levels and *APOE* ε4 status and the interaction term between the two were used as main predictors to test whether the two variables contribute to HippV variation independently. All statistics reported are on the log10 scale of CRP levels. Bonferroni correction was applied to account for multiple testing.

2.10.3. Effects of APOE ε4 and CRP levels on PET-Aβ status and CSF marker levels

Logistic regression analyses were performed to estimate the effect of *APOE* ε4 and CRP levels on PET-Aβ status. PET-Aβ status was used as dependent variable; *APOE* ε4 status and CRP levels were set as the main predictor, separately. Age at measurement, sex, BMI, and the top 10 PCs were used as covariates. Linear regression models were then used to estimate the effect of *APOE* ε4 and CRP levels on CSF marker levels. Each marker was analyzed separately. In each model, the CSF marker level was inverse-normal transformed to have zero mean and one standard deviation and was used as dependent variables. *APOE* ε4 and CRP levels were used as the main predictor, separately. Age at measurement, sex, BMI were used as covariates. Here, False Discovery Rate (FDR) was used for multiple testing correction (Benjamini and Hochberg, 1995).

2.11. Replication analysis

Corresponding models for the relation between *APOE* ε4 and HippV were applied in the UKBB and ABCD replication samples. For the UB-BBHI sample, which had no longitudinal brain scans, corresponding GAM models were used.

3. Results

The LCBC sample had a wider age-range than the other samples (Fig. 1**B**), but had fewer participants aged 35 to 65 years. The UKBB sample had higher CRP levels than those of the LCBC and UB-BBHI samples (**Fig. S1,** two-sided *t* test, $p < 2x10^{-16}$). ABCD participants had smaller HippV than those in the other three samples, and the UB-BBHI participants had the largest HippV among the four (pairwise two-sided t tests, Bonferroni-corrected $p < 0.05$; **Fig. S2**). The LCBC sample has a higher frequency of *APOE* ε4 than the other three samples; but, the ε4 frequencies in all four samples are consistent with a recent report of geographical frequency differences (Table S1) (Kern et al., 2015).

3.1. Stronger genetic control over lower CRP levels

To investigate if the genetic contributions to CRP levels vary with blood CRP levels, we stratified CRP levels into 5 bins and regressed log10 transformed CRP levels in each bin on *APOE* ε4 status, including age and sex as covariates in the models. The false discovery rate procedure was used for multiple testing correction (along test with the full CRP range in each dataset, 18 tests performed). We found that whereas ε4 was associated with CRP levels overall (bin: All, FDR-corrected $p < 0.05$), only in the bin with lowest CRP level ranges (<1mg/L) was ε4 nominally associated with lower CRP level in the LCBC and the UB-BBHI samples (FDR-corrected $p = 0.09$ and 0.02, respectively; Fig. 2**A** and Table S2). To test whether this was due to too few participants having high CRP levels in the two healthy samples, we performed the same analysis for the UKBB dataset (N = 304,322). The results clearly showed that the higher the CRP levels, the less significant was the association between *APOE* ε4 and CRP levels(Fig. 2**A-B**).

We next regressed the log10 transformed CRP levels in each bin on the PGS-CRP (constructed without APOE-region SNPs). The same covariates as used above for *APOE* ε4 were also included in these models. PGS-CRP showed a weaker effect on CRP levels than for *APOE* ε4 (Fig. 2**B,** Table S3), and PGS-CRP values were only positively associated with overall CRP levels (bin: [0–100] mg/L) in both the LCBC and UB-BBHI sample (FDR-corrected $p < 0.05$, Table S3). Whereas, due to large samples in each bin, the UKBB showed significant association for the three bins with lower CRP levels (FDR-corrected $p < 0.05$, Fig. 2**B**). Thus, the same trend as observed for ε4 was also apparent for PGS-CRP – the higher the CRP levels, the less their variations were attributable to genetic variation.

3.2. APOE ε4 is associated with lower CRP levels across lifespan

Across the whole lifespan, we observed a strong and consistent negative association between *APOE* ε4 and CRP levels (Fig. 2**C**). Specifically, in the LCBC sample – where 54% of participants were below 40 years of age – *APOE* ε4 carriers were found to have lower CRP levels on average across the lifespan (N = 533; beta = -0.15, $p = 7.94x10^{-4}$) as compared to non-carriers. When the analysis was restricted to those < 40 years of age, similar effect sizes were obtained but not statistically significant (N = 289; beta = -0.10, p = 0.12), possibly due to reduced sample size. In the first replication dataset (UB-BBHI, N = 339), we also found a strong negative effect of ε4 on CRP levels that existed across the whole age-range (41–67 years; beta = -0.21, $p = 2.22x10^{-3}$). The concave curve in Fig. 2**C** for UB-BBHI may be due to too few individuals having the ε4 allele (N = 69). In the very large UKBB dataset, the effect size of ε4 became smaller but more significant (Fig. 2**C**; N = 304,322; *APOE* ε4 carrier vs non-carrier: beta = -0.13, $p < 2x10^{-16}$). Although we always modelled the age function by regression splines, in this large UKBB sample, CRP levels were almost linearly increasing with age (approximated p for age $< 2x10^{-16}$). The positive associations between CRP levels and age were also significant in the LCBC and UB-BBHI sample ($p < 0.05$) (Fig. 2**C**).

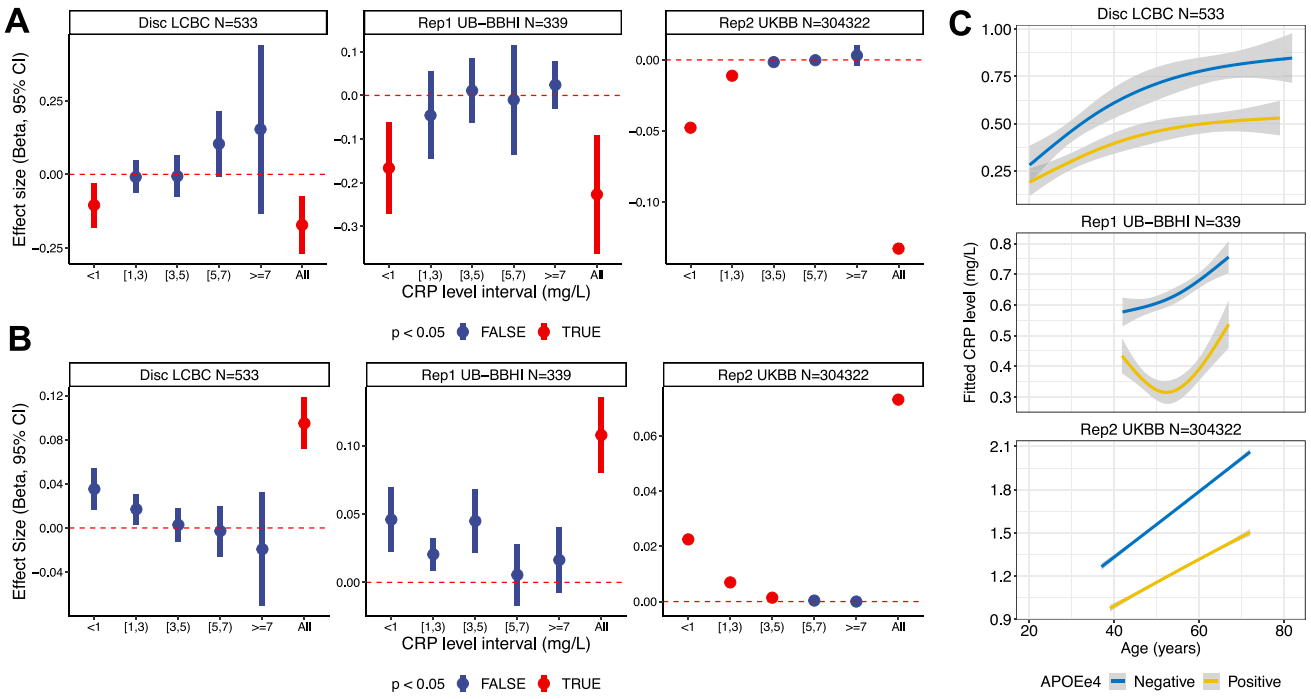

Fig. 2. Associations between *APOE* ε4, PGS-CRP and CRP levels. Associations between APOE e4 (carrier vs non-carrier) (A), PGS-CRP (B) with CRP levels, divided into six bins based on measured CRP levels(mg/L): <1, <1 mg/L; [1–3), equal to or higher than 1 mg/L and lower than 3 mg/L; [3–5), equal to or higher than 3 mg/L and lower than 5 mg/L; >=7, equal to or>7 mg/L. Colors indicate if uncorrected $p < 0.05$; C) Association between APOE e4 and CRP levels across age range and independent samples. Fitted CRP levels were obtained by fitting generalized additive model (GAM), which model age by regression splines, and plot against age at measurement. Colors indicate e4 status. Names of datasets and their sizes are shown on top of each panel.

To corroborate the linear regression results on disjoint bins on CRP levels in Fig. 2**B**, we performed GAM models on inclusive bins on CRP levels (>5mg/L, >7mg/L and > 10 mg/L) using the UKBB sample. While *APOE* ε4 was associated with CRP levels that is below 10 mg/L (N = 29,2199; beta = -0.12; $p < 2x10^{-16}$) it was not associated with CRP levels in any of the three groups (>5mg/L, N = 34,303; beta = -0.0064; p = 0.04; >7mg/L, N = 20,880, beta = -0.002, p = 0.6; >10 mg/L, N = 12,123; beta = 0.004; p = 0.36) after multiple testing correction.

3.3. *APOE ε4 is associated with smaller hippocampal volumes*

We observed a negative association between *APOE* ε4 and HippV (Fig. 3). In the LCBC sample (N = 749, N-MRI scans = 1,641, 20–81 years of age), *APOE* ε4 carriers had a lower hippocampal volume on average across the lifespan as compared to non-carriers (beta = -0.17, $p = 2.97x10^{-3}$). In our first replication sample (UB-BBHI), ε4 showed the same direction of effect on HippV but was not significant (Fig. 2; p = 0.67). However, in the other two replication samples – including the childhood ABCD sample (UKBB, N = 26,573, N-MRI scans = 28,154; ABCD, N = 10,283, N-MRI scans = 13,802) – ε4 was significantly associated with smaller HippV on average across age (UKBB, beta = -0.02, p = 0.025; ABCD, beta = -0.04, p = 0.027). We also tested the *APOE* ε4 by age interactions in the UKBB sample using linear mixed models and detected no significant interacting effects (**Supplementary Information, Fig. S12**).

3.4. *High CRP levels associate with small hippocampal volumes*

CRP levels showed stronger association with smaller HippV than did *APOE* ε4 status (Fig. 4). In the LCBC sample (N = 507, N-MRI scans = 1,344, 20–81 years of age), increased CRP levels associated with small hippocampi (beta = -0.17, $p = 1.21x10^{-2}$). Including *APOE* ε4 status as an additional covariate did not qualitatively change this association. In UKBB, higher CRP levels were also associated with smaller HippV (beta

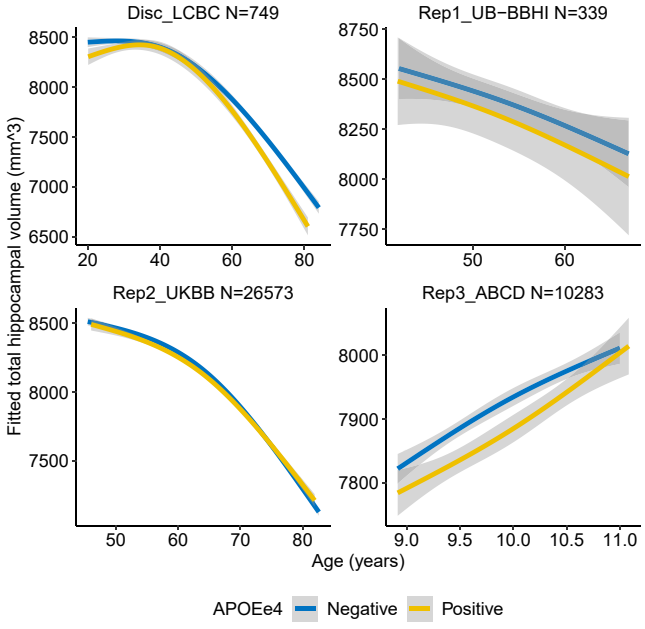

Fig. 3. Associations between *APOE* ε4 and hippocampal volume. Fitted total hippocampal volumes by GAMM (LCBC sample (Disc_ LCBC), UK Biobank subsample (Rep2_UKBB) and the ABCD sample (Rep3_ABCD) and by GAM (Rep1_UB-BBHI) were plotted against baseline age (x axis). Hippocampal volumes were stratified by *APOE* ε4 status (carrier: positive; non-carrier: negative). Model fitting includes sex, age at measurement (smoothing variable in GAM (M), x axis), BMI and the top 10 principal components as covariates. For GAMM, random intercepts were model by taking subject identifiers as random term. Sample sizes were shown on the top of each panel.

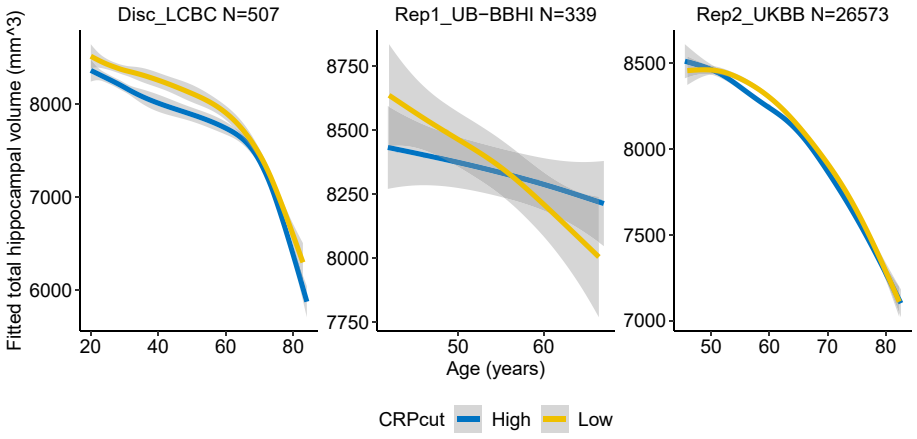

Fig. 4. Associations between *APOE* ε4 and hippocampal volume. Fitted total hippocampal volumes by GAMM (LCBC sample (Disc_LCBC), UK Biobank subsample (Rep2_UKBB)) and by GAM (Rep1_UB-BBHI) were plotted against baseline age (x axis). For demonstration purpose, hippocampal volumes were stratified by high CRP level (above the sample median) and low CRP level (below the sample median). Log10-transformed CRP level were input as continual variable in model fitting including sex, and age at measurement (smoothing variable in GAM(M), x axis), BMI and the top 10 principal components as covariates. For GAMM, random intercepts were modelled by taking subject identifiers as random term. Sample sizes were shown on the top of each panel.

= -0.023, p = 2.74x10^{-2}). When CRP levels as well as *APOE* ε4 status were included in the model, effects of both factors remained similar (CRP: beta = -0.022, p = 6.54.69x10^{-2}; *APOE* ε4: beta = -0.026, p = 1.69x10^{-2}). Moreover, in this big dataset, we did not find significant interactions between CRP levels and *APOE* status on HippV (p = 0.9). Possibly due to the small sample size for the UB-BBHI sample (N = 339), we did not observe significant associations between CRP levels and HippV (p = 0.95). We also investigated CRP by age interactions using the largest UKBB sample (**Supplementary Information**). We found that individuals with high CRP levels had a faster hippocampal atrophy (p = 1.77x10^{-4}, **Fig. S13**).

3.5. *APOE ε4 and CRP levels in relation to PET-Aβ status and CSF biomarker levels*

APOE ε4 carriers exhibited increased levels of amyloid plaque in the brain (N = 126, t = 3.33, FDR-corrected p = 1.30x10^{-2}), decreased levels of CSF-Aβ42 (t = -2.90, FDR-corrected p = 7.438x10^{-2}), and decreased CSF-Aβ42 to CSF-Aβ40 ratio (t = -5.15, FDR-corrected p = 5.81x10^{-5}) (Fig. 5). We did not observe associations between *APOE* ε4 and other AD biomarkers (Table 1), though we did find positive trends between CRP levels and CSF-Aβ42 and CSF-Aβ42 to CSF-Aβ40 ratio at borderline significance (uncorrected p = 0.06 and 0.03, respectively). However, this association was largely accounted for by the effect of the *APOE* ε4 status (after including *APOE* ε4 status as an additional covariate the association disappeared).

3.6. *PGS-CRP was not associated with AD markers*

Because the *APOE* gene has been associated with CRP levels in several previous studies, we tested if genetically predicted CRP levels (excluding APOE-region SNPs) could predict AD biomarkers in the three samples. There were no associations between PGS-CRP and any AD biomarkers studied. In addition, there were no associations between PGS-CRP and APOE ε4 status (**Fig. S3**). Whereas these results may suggest the effect of CRP on AD biomarkers was largely driven by *APOE* ε4, it should be noted that both CRP levels and APOE e4 were significantly associated with HippV in the multivariate model.

4. Discussion

By using four complementary populations comprising an age-span of 9–90 years (total N = 315 753) we showed that *APOE* ε4 was continuously and consistently associated lower circulating CRP levels. This association is mainly for CRP levels in the range of normal physiological conditions (CRP < 3 mg/L). Our findings extend previous knowledge by indicating that the association exists before the typical age at which accepted AD biomarkers can be observed (~40 years) (Selkoe and Hardy, 2016) and continues beyond the typical age of onset for AD (~60 s). Moreover, we demonstrated both *APOE* ε4 and higher CRP levels are associated with smaller hippocampal volumes, a marker that has frequently been linked to low cognitive performance and high risk of AD. Whereas *APOE* ε4 was clearly associated with PET-Aβ and CSF markers for AD, CRP did not show convincing associations with any of

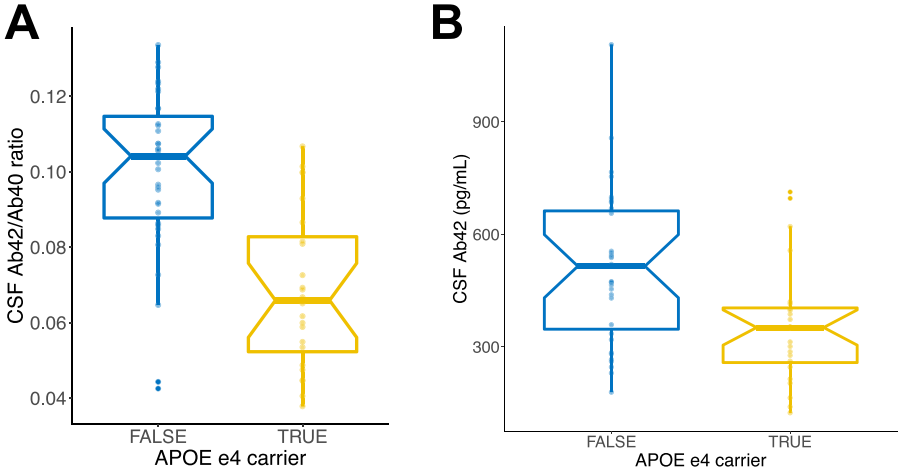

Fig. 5. Associations of *APOE* ε4 with CSF markers. Distributions of CSF Ab42 to Ab40 ratios (A) and level of CSF Ab42 (B) were stratified into APOE e4 carriers and non-carriers (x axis). In total 59 individuals from the COGNORM sample had both CSF marker and APOE data and were analyzed.

Table 1
Effects of *APOE* ε4 and whole blood CRP levels on brain Aβ load and CSF biomarkers.

Marker	*APOE* ε4			CRP		
	N	t-score	p	N	t-score	p
PET-Aβ	126	3.33	**8.69x10^{-4}(1.30x10-2)**	98	−1.52	0.30(1.0)
CSF-Aβ40	59	0.11	0.91(1.0)	66	0.49	0.63(1.0)
CSF-Aβ42	59	−2.90	**5.31x10^{-3} (7.43x10^{-2})**	67	1.91	6.04x10-2 (0.72)
CSF-Aβ42/Aβ40	59	−5.15	**3.63x10^{-6}(5.81x10^{-5})**	66	2.17	3.37x10^{-2}(0.44)
CSF-t-tau	59	1.45	0.15(1.0)	67	−0.45	0.66(1.0)
CSF-p-tau	59	1.05	0.30(1.0)	67	−0.39	0.70(1.0)
CSF-NFL	59	1.26	0.21(1.0)	67	−0.51	0.61(1.0)

The effects of *APOE* ε4 (carriers vs. non-carriers) and CRP levels PET-amyloid beta load in the brain and CSF marker levels were evaluated by general linear models, including age at measurement, BMI, sex and the top 10 genetic principal components as covariates (APOE related analysis only). Logistic regression models were used for PET-Aβ positiveness; and linear regression models were used for other markers, which have been normalized before modelling. Sample size (N), t-score (regression coefficient divided by standard error), and p (FDR corrected p in parentheses) are also shown. The following abbreviations were used: CRP, C-reactive protein; PET-Aβ, total amyloid beta load in the brain; CSF-Aβ40, amyloid beta with 40 amino acids in cerebral spinal fluid; CSF-Aβ42, amyloid beta with 42 amino acids in cerebral spinal fluid; CSF-Aβ42/Aβ40, ratio of CSF-Aβ42 to CSF-Aβ40 in cerebral spinal fluid; CSF-t-tau, level of the total tau proteins in cerebral spinal fluid; CSF-p-tau, level of the phosphorylated tau proteins in cerebral spinal fluid; CSF-NFL, level of the neurofilament light proteins in cerebral spinal fluid.

these AD biomarkers. Our study is to our knowledge the largest examining the CRP-*APOE* ε4 association, and covers the entire adult lifespan as well as relations to other well-established biomarkers for AD also in early adult life.

By taking advantage of big data, the results suggest genetic variants contribute to the variations of CRP levels only within the normal physiological range (Dumitrescu et al., 2020). In the relatively smaller CRP samples (*i.e.* LCBC and UB-BBHI), <30% participants had CRP levels above 1 mg/L (Table S2 and S3), possibly suggesting the null association between genetic markers (both *APOE* ε4 and PGS-CRP) and higher CRP ranges could be due to low statistical power. However, also in the large UKBB subsample – where>20 000 participants had CRP > 7 mg/L and 12 123 had CRP levels > 10 mg/L – the results clearly showed that the effect of genetic variants on CRP levels decreased with increased CRP level. This means the inherited genetic variations, here *APOE* ε4 status and PGS, do not influence CRP's ability to respond to acute infections or other stimuli, where high CRP levels (>10 mg/L) are expected (Dumitrescu et al., 2020). Instead, chronic and low-grade inflammation as indexed by CRP is under strong genetic control.

Martiskainen et al. (2018) have recently reported a similar inverse *APOE* ε4-CRP relation in a large population (N ~ 6,100; 50–75 years of age). Their study showed an association between high CRP levels and low plasma Aβ42, but no association between *APOE* ε4 and plasma Aβ42 levels. In a small postmortem AD sample with neurofibrillary pathology (N = 71), the authors reported null associations between *CRP* expression levels and *APOE* ε4 in brain tissue. Here, we confirmed the *APOE* ε4-CRP relation in three independent samples, with a sample size five times larger and a broader age-range. In our LCBC sample, we also observed significant associations between *APOE* ε4 and PET-Aβ, CSF Aβ42 as well as the ratio of CSF-Aβ42 to Aβ40. It should also be noted that the origins of blood or plasma Aβ arise not only in brain but also the liver, kidney, skeletal muscle, skin, and other organs (Roher et al., 2009; Selkoe et al., 1988), the relations between blood Aβ, CSF-Aβ and PET-Aβ have been inconclusive (Le Bastard et al., 2009; Schindler et al., 2019; Toledo et al., 2011), and thus that differences in physiological measurements likely in part explains some inconsistencies between reports. We observed that whereas high blood CRP level was nominally associated with a low CSF-Aβ42 to Aβ40 ratio in our sample, this association was completely driven by *APOE* ε4 status. Importantly, our sample included participants as young as 20 years where there are hardly any detectable neuropathological antecedents to AD in the brain. Thus, the interpretation by Martiskainen *et al.* that the relation between *APOE* ε4 and CRP may be driven by an anti-inflammatory effect of plasma Aβ, is questionable. Notably, CRP did not show relations to Aβ brain biomarkers in our sample, suggesting another, possibly independent pathway.

Several other explanations for the *APOE* ε4 and CRP relation have been proposed. Because *APOE* ε4 and high circulating CRP levels both have been linked to increased risk of cardiovascular diseases, März et al. have suggested that the reduced CRP levels in *APOE* ε4 carriers might be caused by reduced activity of the hepatic mevalonate pathway, *i.e.* reduced cholesterol synthesis (März et al., 2004). This hypothesis was supported by the clinical observation that inhibiting mevalonate pathway by statin treatment promoted lower CRP levels (Balk et al., 2003). However, a later report from a large Icelandic cohort implicated that the effect of *APOE* ε4 on lowering CRP levels may be independent of statin-related pathways (Eiriksdottir et al., 2006). Moreover, in a population of nonagenarians, Rontu *et al.* interpreted the effect of *APOE* ε4 on extended longevity due to reduced inflammatory response as indicated by low CRP levels (Rontu et al., 2006). At the other end of life, Berrahmoune *et al.* showed that *APOE* ε4 was associated with low CRP levels among children (10–20 years of age). Whereas the association between *APOE* ε4 and low circulating CRP levels has been reported before, most previous studies have been based on clinical case-control samples with a relatively narrower age range, and the interpretations of the associations have been related to the mechanism of the focal diseases in the studies.

Our study fills a gap based on four cognitively healthy populations, with an age span of 9 to 90 years. In the LCBC sample, the levels of both inflammatory (CRP, IL8) and anti-inflammatory (IL1RA) markers monotonically increase with age (**Fig. S14**). This observation cannot simply be explained by the 'inflamm-aging' hypothesis (Franceschi et al., 2000), *i.e.*, increased chronic inflammation with age. Instead, both inflammatory and anti-inflammatory parameters are constantly changing with age across the lifespan (Riveros-Mckay Aguilera et al., 2020). Whereas CRP levels were highly correlated with other cytokine levels (**Fig. S6**), no associations were observed between *APOE* ε4 and these other cytokines, which is in accordance with previous findings (Martiskainen et al., 2018; März et al., 2004; Rontu et al., 2006). Thus, the interpretation of the *APOE* ε4 and CRP association in terms of immune response remains elusive. However, some possible directions for further research may be suggested: Since the inverse correlation between *APOE* ε 4 and blood CRP levels exists before any pathological AD biomarker is observed and exists only in the low CRP level range, one should consider what could be the effects of a lifetime of lowered inflammatory response in terms of increased AD risk. Based on our findings, a novel hypothesis is that *APOE* ε 4 can confer risk by being associated with a lower inflammatory response to daily exposures, possibly leading to greater accumulation of low-grade inflammatory stress though the lifespan. Since the currently measured CRP did not show convincing associations with any of the classical AD biomarkers, nor the currently investigated cytokines, further research should aim to delineate a possible pathway.

Although we found that being an *APOE* ε4 carriers and having higher CRP levels were associated with small hippocampal volumes across the lifespan in the three populations, these effects were relatively weaker than that of *APOE* ε4 on the CRP levels. On the one hand, the association between *APOE* ε4 and hippocampal volume may suggest an offset effect, *i.e.*, *APOE* ε4 carriers start with smaller hippocampi than non-carriers, as shown in our previous work (Walhovd et al., 2020). On the other hand, low CRP levels were associated with large hippocampal volumes. Still, whether there is also an offset effect of CRP levels on hippocampal volume is unclear.

We replicated our findings in three independent datasets with varying age ranges, sizes, and data acquisition platforms, indicating the results are robust. We also accounted for the effect of BMI by including it as a covariate in the models. A limitation is that, due to the high cost of measuring AD biomarkers, only a small number of participants had PET-Aβ and CSF markers in our sample. That we did not find associations between *APOE* ε4 and CSF-Aβ40, CSF-NFL and CSF tau levels might therefore be due to low statistical power, and it remains to be seen whether future larger scale studies may identify such associations. In addition, for a subset of participants (COGNORM study), cytokine levels were measured three years later than the brain scan. However, such a complication does not affect our conclusions.

5. Conclusion and perspectives

By synthesizing four cognitively healthy populations with wide age spans, we observed that *APOE* ε4 was associated with low whole blood/serum CRP levels across the lifespan. While a relationship between acute inflammation and dementia risk has been established (Komaroff, 2020), we think in a lifespan perspective, further investigations of the role of very low-grade inflammatory responses may also be worthwhile. Based on our findings, it may be fruitful in further research to focus on whether *APOE ε* 4 can confer risk by being associated with a lower inflammatory response to daily exposures, possibly leading to greater accumulation of low-grade inflammatory stress though the lifespan. Our study shows previous interpretations of these associations are incomplete, and future mechanistic studies are needed to resolve this intriguing relation.

Author contributions

YW, AMF and KBW conceived and designed the study. JMR, MP, FM, AP, JMT, MC, DB, JMY, IKA, AMF, KBW, LOW and AVI collected sample and performed MRI and cytokine measurements. YW performed statistical analysis. All authors contributed to the interpretation of the results. YW and KBW wrote the draft. All authors edited and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.12.008.

References

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D.C., Zhang, H., Dragonu, I., Matthews, P.M., Miller, K.L., Smith, S.M., 2018. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 166, 400–424.

Balk, E.M., Lau, J., Goudas, L.C., Jordan, H.S., Kupelnick, B., Kim, L.U., Karas, R.H., 2003. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. Ann. Intern. Med. 139, 670–682.

Belloy, M.E., Napolioni, V., Greicius, M.D., 2019. A quarter century of APOE and Alzheimer's disease: Progress to date and the path forward. Neuron 101, 820–838.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B Method. 289–300.

Beyreuther, K., Masters, C.L., 1991. Amyloid Precursor Protein (APP) and BZA4 amyloid in the etiology of Alzheimer's Disease: precursor-product relationships in the derangement of neuronal function. Brain Pathol. 1, 241–251.

Bonham, L.W., Geier, E.G., Fan, C.C., Leong, J.K., Besser, L., Kukull, W.A., Kornak, J., Andreassen, O.A., Schellenberg, G.D., Rosen, H.J., Dillon, W.P., Hess, C.P., Miller, B. L., Dale, A.M., Desikan, R.S., Yokoyama, J.S., 2016. Age-dependent effects of APOE ε4 in preclinical Alzheimer's disease. Ann. Clin. Transl. Neurol. 3, 668–677.

Burns, A., Iliffe, S., 2009. Alzheimer's disease. BMJ (Clinical research ed.) 338, b158.

Casey, B.J., Cannonier, T., Conley, M.I., Cohen, A.O., Barch, D.M., Heitzeg, M.M., Soules, M.E., Teslovich, T., Dellarco, D.V., Garavan, H., Orr, C.A., Wager, T.D., Banich, M.T., Speer, N.K., Sutherland, M.T., Riedel, M.C., Dick, A.S., Bjork, J.M., Thomas, K.M., Chaarani, B., Mejia, M.H., Hagler, D.J., Daniela Cornejo, M., Sicat, C. S., Harms, M.P., Dosenbach, N.U.F., Rosenberg, M., Earl, E., Bartsch, H., Watts, R., Polimeni, J.R., Kuperman, J.M., Fair, D.A., Dale, A.M., 2018. The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. Dev. Cogn. Neurosci. 32, 43–54.

Cattaneo, G., Bartrés-Faz, D., Morris, T.P., Sánchez, J.S., Macià, D., Tarrero, C., Tormos, J.M., Pascual-Leone, A., 2018. The barcelona brain health initiative: A cohort study to define and promote determinants of brain health. Front. Aging Neurosci. 10.

Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M., Lee, J.J., 2015. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience 4, 7.

Corbin, L.J., Tan, V.Y., Hughes, D.A., Wade, K.H., Paul, D.S., Tansey, K.E., Butcher, F., Dudbridge, F., Howson, J.M., Jallow, M.W., John, C., Kingston, N., Lindgren, C.M., O'Donavan, M., O'Rahilly, S., Owen, M.J., Palmer, C.N.A., Pearson, E.R., Scott, R.A., van Heel, D.A., Whittaker, J., Frayling, T., Tobin, M.D., Wain, L.V., Smith, G.D., Evans, D.M., Karpe, F., McCarthy, M.I., Danesh, J., Franks, P.W., Timpson, N.J., 2018. Formalising recall by genotype as an efficient approach to detailed phenotyping and causal inference. Nat. Commun. 9, 711.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G. W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Das, S., Forer, L., Schonherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.R., Iacono, W.G., Swaroop, A., Scott, L.J., Cucca, F., Kronenberg, F., Boehnke, M., Abecasis, G.R., Fuchsberger, C., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48, 1284–1287.

Dehghan, A., Dupuis, J., Barbalic, M., Bis, J.C., Eiriksdottir, G., Lu, C., Pellikka, N., Wallaschofski, H., Kettunen, J., Henneman, P., 2011. Meta-analysis of genome-wide association studies in> 80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation 123, 731–738.

Delaneau, O., Marchini, J., Zagury, J.F., 2011. A linear complexity phasing method for thousands of genomes. Nat. Methods 9, 179–181.

Desikan, R.S., Schork, A.J., Wang, Y., Thompson, W.K., Dehghan, A., Ridker, P.M., Chasman, D.I., McEvoy, L.K., Holland, D., Chen, C.-H., Karow, D.S., Brewer, J.B., Hess, C.P., Williams, J., Sims, R., O'Donovan, M.C., Choi, S.H., Bis, J.C., Ikram, M.A., Gudnason, V., DeStefano, A.L., Lee, S.J.C.D., Psaty, B.M., Duijn, C.M.V., Launer, L., Seshadri, S., Pericak-Vance, M.A., Mayeux, R., Haines, J.L., Farrer, L.A., Hardy, J., Ulstein, I.D., Aarsland, D., Fladby, T., White, L.R., Sando, S.B., Rongve, A.,

Witoelar, A., Djurovic, S., Hyman, B.T., Snaedal, J., Steinberg, S., Stefansson, H., Stefansson, K., Schellenberg, G.D., Andreassen, O.A., Dale, A.M., 2015. Polygenic overlap between C-reactive protein, plasma lipids, and Alzheimer disease. Circulation 131, 2061–2069.

Du Clos, T.W., 2000. Function of C-reactive protein. Ann. Med. 32, 274–278.

Dumitrescu, L., Mahoney, E.R., Mukherjee, S., Lee, M.L., Bush, W.S., Engelman, C.D., Lu, Q., Fardo, D.W., Trittschuh, E.H., Mez, J., Kaczorowski, C., Hernandez Saucedo, H., Widaman, K.F., Buckley, R., Properzi, M., Mormino, E., Yang, H.-S., Harrison, T., Hedden, T., Nho, K., Andrews, S.J., Tommet, D., Hadad, N., Sanders, R. E., Ruderfer, D.M., Gifford, K.A., Moore, A.M., Cambronero, F., Zhong, X., Raghavan, N.S., Vardarajan, B., Initiative, T.A.s.D.N., Alzheimer's Disease Genetics Consortium, A.S.T., Pericak-Vance, M.A., Farrer, L.A., Wang, L.-S., Cruchaga, C., Schellenberg, G., Cox, N.J., Haines, J.L., Dirk Keene, C., Saykin, A.J., Larson, E.B., Sperling, R.A., Mayeux, R., Bennett, D.A., Schneider, J.A., Crane, P.K., Jefferson, A. L., Hohman, T.J., 2020. Genetic variants and functional pathways associated with resilience to Alzheimer's disease. Brain 143, 2561–2575.

Eiriksdottir, G., Aspelund, T., Bjarnadottir, K., Olafsdottir, E., Gudnason, V., Launer, L.J., Harris, T.B., 2006. Apolipoprotein E genotype and statins affect CRP levels through independent and different mechanisms: AGES-Reykjavik Study. Atherosclerosis Ireland 222–224.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R. H., Pericak-Vance, M.A., Risch, N., van Duijn, C.M., 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278, 1349–1356.

Fernandes, A., Tábuas-Pereira, M., Duro, D., Lima, M., Gens, H., Santiago, B., Durães, J., Almeida, M.R., Leitão, M.J., Baldeiras, I., Santana, I., 2020. C-reactive protein as a predictor of mild cognitive impairment conversion into Alzheimer's disease dementia. Exp. Gerontol. 138, 111004.

Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. Proc. Natl. Acad. Sci. 106, 7209–7214.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254.

Gabin, J.M., Saltvedt, I., Tambs, K., Holmen, J., 2018. The association of high sensitivity C-reactive protein and incident Alzheimer disease in patients 60 years and older: The HUNT study. Norway. Immunity & Ageing 15, 4.

Haan, M.N., Aiello, A.E., West, N.A., Jagust, W.J., 2008. C-reactive protein and rate of dementia in carriers and non carriers of Apolipoprotein APOE4 genotype. Neurobiol. Aging 29, 1774–1782.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., Busa, E., Pacheco, J., Albert, M., Killiany, R., Maguire, P., Rosas, D., Makris, N., Dale, A., Dickerson, B., Fischl, B., 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. NeuroImage 32, 180–194.

Idland, A.V., Sala-Llonch, R., Borza, T., Watne, L.O., Wyller, T.B., Braekhus, A., Zetterberg, H., Blennow, K., Walhovd, K.B., Fjell, A.M., 2017. CSF neurofilament light levels predict hippocampal atrophy in cognitively healthy older adults. Neurobiol. Aging 49, 138–144.

Jansen, I.E., Savage, J.E., Watanabe, K., Bryois, J., Williams, D.M., Steinberg, S., Sealock, J., Karlsson, I.K., Hagg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S., Aarsland, D., Almdahl, I.S., Andersen, F., Bergh, S., Bettella, F., Bjornsson, S., Braekhus, A., Brathen, G., de Leeuw, C., Desikan, R.S., Djurovic, S., Dumitrescu, L., Fladby, T., Hohman, T.J., Jonsson, P.V., Kiddle, S.J., Rongve, A., Saltvedt, I., Sando, S.B., Selbaek, G., Shoai, M., Skene, N.G., Snaedal, J., Stordal, E., Ulstein, I.D., Wang, Y., White, L.R., Hardy, J., Hjerling-Leffler, J., Sullivan, P.F., van der Flier, W.M., Dobson, R., Davis, L.K., Stefansson, H., Stefansson, K., Pedersen, N. L., Ripke, S., Andreassen, O.A., Posthuma, D., 2019. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat. Genet. 51, 404–413.

Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., Kennedy, D., Schmitt, F., Brown, G., MacFall, J., Fischl, B., Dale, A., 2006. Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. NeuroImage 30, 436–443.

Kern, S., Mehlig, K., Kern, J., Zetterberg, H., Thelle, D., Skoog, I., Lissner, L., Blennow, K., Börjesson-Hanson, A., 2015. The distribution of apolipoprotein E genotype over the adult lifespan and in relation to country of birth. Am. J. Epidemiol. 181, 214–217.

Komaroff, A.L., 2020. Can Infections Cause Alzheimer Disease? JAMA 324, 239–240.

Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., Boland, A., Vronskaya, M., van der Lee, S.J., Amlie-Wolf, A., Bellenguez, C., Frizatti, A., Chouraki, V., Martin, E.R., Sleegers, K., Badarinarayan, N., Jakobsdottir, J., Hamilton-Nelson, K.L., Moreno-Grau, S., Olaso, R., Raybould, R., Chen, Y., Kuzma, A.B., Hiltunen, M., Morgan, T., Ahmad, S., Vardarajan, B.N., Epelbaum, J., Hoffmann, P., Boada, M., Beecham, G.W., Garnier, J.G., Harold, D., Fitzpatrick, A.L., Valladares, O., Moutet, M.L., Gerrish, A., Smith, A.V., Qu, L., Bacq, D., Denning, N., Jian, X., Zhao, Y., Del Zompo, M., Fox, N.C., Choi, S.H., Mateo, I., Hughes, J.T., Adams, H.H., Malamon, J., Sanchez-Garcia, F., Patel, Y., Brody, J.A., Dombroski, B. A., Naranjo, M.C.D., Daniilidou, M., Eiriksdottir, G., Mukherjee, S., Wallon, D., Uphill, J., Aspelund, T., Cantwell, L.B., Garzia, F., Galimberti, D., Hofer, E., Butkiewicz, M., Fin, B., Scarpini, E., Sarnowski, C., Bush, W.S., Meslage, S., Kornhuber, J., White, C.C., Song, Y., Barber, R.C., Engelborghs, S., Sordon, S., Voijnovic, D., Adams, P.M., Vandenberghe, R., Mayhaus, M., Cupples, L.A., Albert, M.S., De Deyn, P.P., Gu, W., Himali, J.J., Beekly, D., Squassina, A., Hartmann, A.M., Orellana, A., Blacker, D., Rodriguez-Rodriguez, E., Lovestone, S., Garcia, M.E., Doody, R.S., Munoz-Fernadez, C., Sussams, R., Lin, H., Fairchild, T.J., Benito, Y.A., Holmes, C., Karamujic-Comic, H., Frosch, M.P., Thonberg, H., Maier, W., Roschupkin, G., Ghetti, B., Giedraitis, V., Kawalia, A., Li, S., Huebinger, R. M., Kilander, L., Moebus, S., Hernandez, I., Kamboh, M.I., Brundin, R., Turton, J., Yang, Q., Katz, M.J., Concari, L., Lord, J., Beiser, A.S., Keene, C.D., Helisalmi, S., Kloszewska, I., Kukull, W.A., Koivisto, A.M., Lynch, A., Tarraga, L., Larson, E.B., Haapasalo, A., Lawlor, B., Mosley, T.H., Lipton, R.B., Solfrizzi, V., Gill, M., Longstreth Jr., W.T., Montine, T.J., Frisardi, V., Diez-Fairen, M., Rivadeneira, F., Petersen, R.C., Deramecourt, V., Alvarez, I., Salani, F., Ciaramella, A., Boerwinkle, E., Reiman, E.M., Fievet, N., Rotter, J.I., Reisch, J.S., Hanon, O., Cupidi, C., Andre Uitterlinden, A.G., Royall, D.R., Dufouil, C., Maletta, R.G., de Rojas, I., Sano, M., Brice, A., Cecchetti, R., George-Hyslop, P.S., Ritchie, K., Tsolaki, M., Tsuang, D.W., Dubois, B., Craig, D., Wu, C.K., Soininen, H., Avramidou, D., Albin, R.L., Fratiglioni, L., Germanou, A., Apostolova, L.G., Keller, L., Koutroumani, M., Arnold, S.E., Panza, F., Gkatzima, O., Asthana, S., Hannequin, D., Whitehead, P., Atwood, C.S., Caffarra, P., Hampel, H., Quintela, I., Carracedo, A., Lannfelt, L., Rubinsztein, D.C., Barnes, L.L., Pasquier, F., Frolich, L., Barral, S., McGuinness, B., Beach, T.G., Johnston, J.A., Becker, J.T., Passmore, P., Bigio, E.H., Schott, J.M., Bird, T.D., Warren, J.D., Boeve, B.F., Lupton, M.K., Bowen, J.D., Proitsi, P., Boxer, A., Powell, J.F., Burke, J.R., Kauwe, J.S.K., Burns, J.M., Mancuso, M., Buxbaum, J.D., Bonuccelli, U., Cairns, N.J., McQuillin, A., Cao, C., Livingston, G., Carlson, C.S., Bass, N.J., Carlsson, C.M., Hardy, J., Carney, R.M., Bras, J., Carrasquillo, M.M., Guerreiro, R., Allen, M., Chui, H.C., Fisher, E., Masullo, C., Crocco, E.A., DeCarli, C., Bisceglio, G., Dick, M., Ma, L., Duara, R., Graff-Radford, N.R., Evans, D.A., Hodges, A., Faber, K.M., Scherer, M., Fallon, K.B., Riemenschneider, M., Fardo, D.W., Heun, R., Farlow, M.R., Kolsch, H., Ferris, S., Leber, M., Foroud, T.M., Heuser, I., Galasko, D.R., Giegling, I., Gearing, M., Hull, M., Geschwind, D.H., Gilbert, J.R., Morris, J., Green, R.C., Mayo, K., Growdon, J.H., Feulner, T., Hamilton, R.L., Harrell, L.E., Drichel, D., Honig, L.S., Cushion, T.D., Huentelman, M.J., Hollingworth, P., Hulette, C.M., Hyman, B.T., Marshall, R., Jarvik, G.P., Meggy, A., Abner, E., Menzies, G.E., Jin, L.W., Leonenko, G., Real, L.M., Jun, G.R., Baldwin, C.T., Grozeva, D., Karydas, A., Russo, G., Kaye, J.A., Kim, R., Jessen, F., Kowall, N.W., Vellas, B., Kramer, J.H., Vardy, E., LaFerla, F.M., Jockel, K. H., Lah, J.J., Dichgans, M., Leverenz, J.B., Mann, D., Levey, A.I., Pickering-Brown, S., Lieberman, A.P., Klopp, N., Lunetta, K.L., Wichmann, H.E., Lyketsos, C.G., Morgan, K., Marson, D.C., Brown, K., Martiniuk, F., Medway, C., Mash, D.C., Nothen, M.M., Masliah, E., Hooper, N.M., McCormick, W.C., Daniele, A., McCurry, S. M., Bayer, A., McDavid, A.N., Gallacher, J., McKee, A.C., van den Bussche, H., Mesulam, M., Brayne, C., Miller, B.L., Riedel-Heller, S., Miller, C.A., Miller, J.W., Al-Chalabi, A., Morris, J.C., Shaw, C.E., Myers, A.J., Wiltfang, J., O'Bryant, S., Olichney, J.M., Alvarez, V., Parisi, J.E., Singleton, A.B., Paulson, H.L., Collinge, J., Perry, W.R., Mead, S., Peskind, E., Cribbs, D.H., Rossor, M., Pierce, A., Ryan, N.S., Poon, W.W., Nacmias, B., Potter, H., Sorbi, S., Quinn, J.F., Sacchinelli, E., Raj, A., Spalletta, G., Raskind, M., Caltagirone, C., Bossu, P., Orfei, M.D., Reisberg, B., Clarke, R., Reitz, C., Smith, A.D., Ringman, J.M., Warden, D., Roberson, E.D., Wilcock, G., Rogaeva, E., Bruni, A.C., Rosen, H.J., Gallo, M., Rosenberg, R.N., Ben-Shlomo, Y., Sager, M.A., Mecocci, P., Saykin, A.J., Pastor, P., Cuccaro, M.L., Vance, J.M., Schneider, J.A., Schneider, L.S., Slifer, S., Seeley, W.W., Smith, A.G., Sonnen, J.A., Spina, S., Stern, R.A., Swerdlow, R.H., Tang, M., Tanzi, R.E., Trojanowski, J.Q., Troncoso, J.C., Van Deerlin, V.M., Van Eldik, L.J., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Wilhelmsen, K.C., Williamson, J., Wingo, T.S., Woltjer, R.L., Wright, C.B., Yu, C.E., Yu, L., Saba, Y., Pilotto, A., Bullido, M.J., Peters, O., Crane, P.K., Bennett, D., Bosco, P., Coto, E., Boccardi, V., De Jager, P.L., Lleo, A., Warner, N., Lopez, O.L., Ingelsson, M., Deloukas, P., Cruchaga, C., Graff, C., Gwilliam, R., Fornage, M., Goate, A.M., Sanchez-Juan, P., Kehoe, P.G., Amin, N., Ertekin-Taner, N., Berr, C., Debette, S., Love, S., Launer, L.J., Younkin, S.G., Dartigues, J.F., Corcoran, C., Ikram, M.A., Dickson, D.W., Nicolas, G., Campion, D., Tschanz, J., Schmidt, H., Hakonarson, H., Clarimon, J., Munger, R., Schmidt, R., Farrer, L.A., Van Broeckhoven, C.M., C.O.D., DeStefano, A.L., Jones, L., Haines, J.L., Deleuze, J.F., Owen, M.J., Gudnason, V., Mayeux, R., Escott-Price, V., Psaty, B.M., Ramirez, A., Wang, L.S., Ruiz, A., van Duijn, C.M., Holmans, P.A., Seshadri, S., Williams, J., Amouyel, P., Schellenberg, G. D., Lambert, J.C., Pericak-Vance, M.A., 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. Nat. Genet. 51, 414–430.

Le Bastard, N., Aerts, L., Leurs, J., Blomme, W., De Deyn, P.P., Engelborghs, S., 2009. No correlation between time-linked plasma and CSF Aβ levels. Neurochem. Int. 55, 820–825.

Axelrud, L.K., Santoro, M.L., Ph, D., Pine, D.S., Talarico, Fernanda, Gadelha, Ary, Manfro, Gisele G., Pan, Pedro M., Jackowski, Andrea, Felipe Picon, M., Brietzke, Elisa, Grassi-Oliveira, Rodrigo, Bressan, Rodrigo A., Miguel, Eurípedes C., Rohde, Luis A., Hakonarson, Hakon, Pausova, Zdenka, Sintia Belangero, PhD., Paus, Tomas, Salum, Giovanni A., 2018. Polygenic risk score for alzheimer's disease: implications for memory performance and hippocampal volumes in early life. Am. J. Psychiatry 175, 555–563.

MacBean, L.F., Smith, A.R., Lunnon, K., 2020. Exploring beyond the DNA sequence: A review of epigenomic studies of DNA and histone modifications in dementia. Curr. Genet. Med. Rep. 8, 79–92.

Martiskainen, H., Takalo, M., Solomon, A., Stančáková, A., Marttinen, M., Natunen, T., Haapasalo, A., Herukka, S., Kuusisto, J., Soininen, H., Kivipelto, M., Laakso, M., Hiltunen, M., 2018. Decreased plasma C-reactive protein levels in APOE ε4 allele carriers. Ann. Clin. Transl. Neurol. 1229–1240.

März, W., Scharnagl, H., Hoffmann, M.M., Boehm, B.O., Winkelmann, B.R., 2004. The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen risk and cardiovascular health study). Eur. Heart J. 25, 2109–2119.

McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A.R., Teumer, A., Kang, H. M., Fuchsberger, C., Danecek, P., Sharp, K., Luo, Y., Sidore, C., Kwong, A., Timpson, N., Koskinen, S., Vrieze, S., Scott, L.J., Zhang, H., Mahajan, A., Veldink, J., Peters, U., Pato, C., van Duijn, C.M., Gillies, C.E., Gandin, I., Mezzavilla, M., Gilly, A., Cocca, M., Traglia, M., Angius, A., Barrett, J.C., Boomsma, D., Branham, K., Breen, G., Brummett, C.M., Busonero, F., Campbell, H., Chan, A., Chen, S., Chew, E., Collins, F.S., Corbin, L.J., Smith, G.D., Dedoussis, G., Dorr, M., Farmaki, A.-E., Ferrucci, L., Forer, L., Fraser, R.M., Gabriel, S., Levy, S., Groop, L., Harrison, T., Hattersley, A., Holmen, O.L., Hveem, K., Kretzler, M., Lee, J.C., McGue, M., Meitinger, T., Melzer, D., Min, J.L., Mohlke, K.L., Vincent, J.B., Nauck, M., Nickerson, D., Palotie, A., Pato, M., Pirastu, N., McInnis, M., Richards, J.B., Sala, C., Salomaa, V., Schlessinger, D., Schoenherr, S., Slagboom, P.E., Small, K., Spector, T., Stambolian, D., Tuke, M., Tuomilehto, J., Van den Berg, L.H., Van Rheenen, W., Volker, U., Wijmenga, C., Toniolo, D., Zeggini, E., Gasparini, P., Sampson, M.G., Wilson, J.F., Frayling, T., de Bakker, P.I.W., Swertz, M.A., McCarroll, S., Kooperberg, C., Dekker, A., Altshuler, D., Willer, C., Iacono, W., Ripatti, S., Soranzo, N., Walter, K., Swaroop, A., Cucca, F., Anderson, C.A., Myers, R.M., Boehnke, M., McCarthy, M.I., Durbin, R., Abecasis, G., Marchini, J., the Haplotype Reference, C., 2016. A reference panel of 64,976 haplotypes for genotype imputation. Nat. Genet. 48, 1279–1283.

Morgan, A.R., Touchard, S., Leckey, C., O'Hagan, C., Nevado-Holgado, A.J., Barkhof, F., Bertram, L., Blin, O., Bos, I., Dobricic, V., Engelborghs, S., Frisoni, G., Frolich, L., Gabel, S., Johannsen, P., Kettunen, P., Kloszewska, I., Legido-Quigley, C., Lleo, A., Martinez-Lage, P., Mecocci, P., Meersmans, K., Molinuevo, J.L., Peyratout, G., Popp, J., Richardson, J., Sala, I., Scheltens, P., Streffer, J., Soininen, H., Tainta-Cuezva, M., Teunissen, C., Tsolaki, M., Vandenberghe, R., Visser, P.J., Vos, S., Wahlund, L.O., Wallin, A., Westwood, S., Zetterberg, H., Lovestone, S., Morgan, B.P., 2019. Inflammatory biomarkers in Alzheimer's disease plasma. Alzheimer's & Dementia 15, 776–787.

Mormino, E.C., Betensky, R.A., Hedden, T., Schultz, A.P., Ward, A., Huijbers, W., Rentz, D.M., Johnson, K.A., Sperling, R.A., 2014. Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology 82, 1760–1767.

Neu, S.C., Pa, J., Kukull, W., Beekly, D., Kuzma, A., Gangadharan, P., Wang, L.-S., Romero, K., Arneric, S.P., Redolfi, A., Orlandi, D., Frisoni, G.B., Au, R., Devine, S., Auerbach, S., Espinosa, A., Boada, M., Ruiz, A., Johnson, S.C., Koscik, R., Wang, J.-J., Hsu, W.-C., Chen, Y.-L., Toga, A.W., 2017. Apolipoprotein E genotype and sex risk factors for Alzheimer Disease: A meta-analysis. JAMA Neurol. 74, 1178–1189.

O'Dwyer, L., Lamberton, F., Matura, S., Tanner, C., Scheibe, M., Miller, J., Rujescu, D., Prvulovic, D., Hampel, H., 2012. Reduced hippocampal volume in healthy young ApoE4 carriers: an MRI study. PLoS ONE 7, e48895.

Prins, B.P., Abbasi, A., Wong, A., Vaez, A., Nolte, I., Franceschini, N., Stuart, P.E., Guterriez Achury, J., Mistry, V., Bradfield, J.P., Valdes, A.M., Bras, J., Shatunov, A., Lu, C., Han, B., Raychaudhuri, S., Bevan, S., Mayes, M.D., Tsoi, L.C., Evangelou, E., Nair, R.P., Grant, S.F., Polychronakos, C., Radstake, T.R., van Heel, D.A., Dunstan, M.L., Wood, N.W., Al-Chalabi, A., Dehghan, A., Hakonarson, H., Markus, H. S., Elder, J.T., Knight, J., Arking, D.E., Spector, T.D., Koeleman, B.P., van Duijn, C. M., Martin, J., Morris, A.P., Weersma, R.K., Wijmenga, C., Munroe, P.B., Perry, J.R., Pouget, J.G., Jamshidi, Y., Snieder, H., Alizadeh, B.Z., 2016. Investigating the Causal Relationship of C-Reactive Protein with 32 Complex Somatic and Psychiatric Outcomes: A Large-Scale Cross-Consortium Mendelian Randomization Study. PLoS Med. 13, e1001976.

Riveros-Mckay Aguilera, F., Weale, M.E., Moore, R., Selzam, S., Krapohl, E., Sivley, R.M., Tarran, W.A., Sørensen, P., Lachapelle, A.S., Griffiths, J.A., Saffari, A., Deanfield, J., Spencer, C.C.A., Hippisley-Cox, J., Hunter, D.J., O'Sullivan, J.W., Ashley, E.A., Plagnol, V., Donnelly, P., 2020. An integrated polygenic and clinical risk tool enhances coronary artery disease prediction. medRxiv, 2020.2006.2001.20119297.

Roher, A.E., Esh, C.L., Kokjohn, T.A., Castaño, E.M., Van Vickle, G.D., Kalback, W.M., Patton, R.L., Luehrs, D.C., Daugs, I.D., Kuo, Y.M., Emmerling, M.R., Soares, H., Quinn, J.F., Kaye, J., Connor, D.J., Silverberg, N.B., Adler, C.H., Seward, J.D., Beach, T.G., Sabbagh, M.N., 2009. Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer's disease. Alzheimer's & Dementia 5, 18–29.

Rontu, R., Ojala, P., Hervonen, A., Goebeler, S., Karhunen, P.J., Nikkilä, M., Kunnas, T., Jylhä, M., Eklund, C., Hurme, M., Lehtimäki, T., 2006. Apolipoprotein E genotype is related to plasma levels of C-reactive protein and lipids and to longevity in nonagenarians. Clin. Endocrinol. 64, 265–270.

Sando, S.B., Melquist, S., Cannon, A., Hutton, M.L., Sletvold, O., Saltvedt, I., White, L.R., Lydersen, S., Aasly, J.O., 2008. APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. BMC neurology 8, 9.

Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., Cummings, J., van der Flier, W.M., 2021. Alzheimer's disease. The Lancet 397, 1577–1590.

Schindler, S.E., Bollinger, J.G., Ovod, V., Mawuenyega, K.G., Li, Y., Gordon, B.A., Holtzman, D.M., Morris, J.C., Benzinger, T.L.S., Xiong, C., Fagan, A.M., Bateman, R. J., 2019. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology 93, e1647–e1659.

Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med. 8, 595–608.

Selkoe, D.J., Podlisny, M.B., Joachim, C.L., Vickers, E.A., Lee, G., Fritz, L.C., Oltersdorf, T., 1988. β-Amyloid precursor protein of Alzheimer disease occurs as 110- to 135-kilodalton membrane-associated proteins in neural and nonneural tissues. PNAS 85, 7341–7345.

Silverman, J.M., Schmeidler, J., Beeri, M.S., Rosendorff, C., Sano, M., Grossman, H.T., Carrión-Baralt, J.R., Bespalova, I.N., West, R., Haroutunian, V., 2012. C-reactive protein and familial risk for dementia: A phenotype for successful cognitive aging. Neurology 79, 1116–1123.

Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. Ieee T Med Imaging 17, 87–97.

Strittmatter, W.J., Roses, A.D., 1995. Apolipoprotein E and Alzheimer disease. Proc. Natl. Acad. Sci. 92, 4725–4727.

Sugden, K., Hannon, E.J., Arseneault, L., Belsky, D.W., Broadbent, J.M., Corcoran, D.L., Hancox, R.J., Houts, R.M., Moffitt, T.E., Poulton, R., Prinz, J.A., Thomson, W.M., Williams, B.S., Wong, C.C.Y., Mill, J., Caspi, A., 2019. Establishing a generalized polyepigenetic biomarker for tobacco smoking. Transl. Psychiatry 9, 92.

Toledo, J.B., Vanderstichele, H., Figurski, M., Aisen, P.S., Petersen, R.C., Weiner, M.W., Jack, C.R., Jagust, W., Decarli, C., Toga, A.W., Toledo, E., Xie, S.X., Lee, V.M.Y., Trojanowski, J.Q., Shaw, L.M., 2011. Factors affecting Aβ plasma levels and their utility as biomarkers in ADNI. Acta Neuropathol. 122, 401.

Walhovd, K.B., Fjell, A.M., Sørensen, Ø., Mowinckel, A.M., Reinbold, C.S., Idland, A.-V., Watne, L.O., Franke, A., Dobricic, V., Kilpert, F., Bertram, L., Wang, Y., 2019. Genetic risk for Alzheimer's disease predicts hippocampal volume through the lifespan. bioRxiv.

Walhovd, K.B., Fjell, A.M., Sørensen, Ø., Mowinckel, A.M., Reinbold, C.S., Idland, A.-V., Watne, L.O., Franke, A., Dobricic, V., Kilpert, F., Bertram, L., Wang, Y., 2020. Genetic risk for Alzheimer disease predicts hippocampal volume through the human lifespan. Neurol. Genet. 6, e506.

Walter, K., Min, J.L., Huang, J., Crooks, L., Memari, Y., McCarthy, S., Perry, J.R.B., Xu, C., Futema, M., Lawson, D., Iotchkova, V., Schiffels, S., Hendricks, A.E., Danecek, P., Li, R., Floyd, J., Wain, L.V., Barroso, I., Humphries, S.E., Hurles, M.E., Zeggini, E., Barrett, J.C., Plagnol, V., Brent Richards, J., Greenwood, C.M.T., Timpson, N.J., Durbin, R., Soranzo, N., Bala, S., Clapham, P., Coates, G., Cox, T., Daly, A., Danecek, P., Du, Y., Durbin, R., Edkins, S., Ellis, P., Flicek, P., Guo, X., Guo, X., Huang, L., Jackson, D.K., Joyce, C., Keane, T., Kolb-Kokocinski, A., Langford, C., Li, Y., Liang, J., Lin, H., Liu, R., Maslen, J., McCarthy, S., Muddyman, D., Quail, M.A., Stalker, J., Sun, J., Tian, J., Wang, G., Wang, J., Wang, Y., Wong, K., Zhang, P., Barroso, I., Birney, E., Boustred, C., Chen, L., Clement, G., Cocca, M., Danecek, P., Davey Smith, G., Day, I.N.M., Day-Williams, A., Down, T., Dunham, I., Durbin, R., Evans, D.M., Gaunt, T.R., Geihs, M., Greenwood, C.M.T., Hart, D., Hendricks, A.E., Howie, B., Huang, J., Hubbard, T., Hysi, P., Iotchkova, V., Jamshidi, Y., Karczewski, K.J., Kemp, J.P., Lachance, G., Lawson, D., Lek, M., Lopes, M., MacArthur, D.G., Marchini, J., Mangino, M., Mathieson, I., McCarthy, S., Memari, Y., Metrustry, S., Min, J.L., Moayyeri, A., Muddyman, D., Northstone, K., Panoutsopoulou, K., Paternoster, L., Perry, J.R.B., Quaye, L., Brent Richards, J., Ring, S., Ritchie, G.R.S., Schiffels, S., Shihab, H.A., Shin, S.-Y., Small, K.S., Soler Artigas, M., Soranzo, N., Southam, L., Spector, T.D., St Pourcain, B., Surdulescu, G., Tachmazidou, I., Timpson, N.J., Tobin, M.D., Valdes, A.M., Visscher, P.M., Wain, L.V., Walter, K., Ward, K., Wilson, S.G., Wong, K., Yang, J., Zeggini, E., Zhang, F., Zheng, H.-F., Anney, R., Ayub, M., Barrett, J.C., Blackwood, D., Bolton, P.F., Breen, G., Collier, D.A., Craddock, N., Crooks, L., Curran, S., Curtis, D., Durbin, R., Gallagher, L., Geschwind, D., Gurling, H., Holmans, P., Lee, I., Lönnqvist, J., McCarthy, S., McGuffin, P., McIntosh, A.M., McKechanie, A. G., McQuillin, A., Morris, J., Muddyman, D., O'Donovan, M.C., Owen, M.J., Palotie, A., Parr, J.R., Paunio, T., Pietilainen, O., Rehnström, K., Sharp, S.I., Skuse, D., St Clair, D., Suvisaari, J., Walters, J.T.R., Williams, H.J., Barroso, I., Bochukova, E., Bounds, R., Dominiczak, A., Durbin, R., Farooqi, I.S., Hendricks, A.E., Keogh, J., Marenne, G., McCarthy, S., Morris, A., Muddyman, D., O'Rahilly, S., Porteous, D.J., Smith, B.H., Tachmazidou, I., Wheeler, E., Zeggini, E., Al Turki, S., Anderson, C.A., Antony, D., Barroso, I., Beales, P., Bentham, J., Bhattacharya, S., Calissano, M., Carss, K., Chatterjee, K., Cirak, S., Cosgrove, C., Durbin, R., Fitzpatrick, D.R., Floyd, J., Reghan Foley, A., Franklin, C.S., Futema, M., Grozeva, D., Humphries, S.E., Hurles, M.E., McCarthy, S., Mitchison, H.M., Muddyman, D., Muntoni, F., O'Rahilly, S., Onoufriadis, A., Parker, V., Payne, F., Plagnol, V., Lucy Raymond, F., Roberts, N., Savage, D.B., Scambler, P., Schmidts, M., Schoenmakers, N., Semple, R.K., Serra, E., Spasic-Boskovic, O., Stevens, E., van Kogelenberg, M., Vijayarangakannan, P., Walter, K., Williamson, K.A., Wilson, C., Whyte, T., Ciampi, A., Greenwood, C.M.T., Hendricks, A.E., Li, R., Metrustry, S., Oualkacha, K., Tachmazidou, I., Xu, C., Zeggini, E., Bobrow, M., Bolton, P.F., Durbin, R., Fitzpatrick, D.R., Griffin, H., Hurles, M.E., Kaye, J., Kennedy, K., Kent, A., Muddyman, D., Muntoni, F., Lucy Raymond, F., Semple, R.K., Smee, C., Spector, T.D., Timpson, N.J., Charlton, R., Ekong, R., Futema, M., Humphries, S.E., Khawaja, F., Lopes, L.R., Migone, N., Payne, S.J., Plagnol, V., Pollitt, R.C., Povey, S., Ridout, C.K., Robinson, R.L., Scott, R.H., Shaw, A., Syrris, P., Taylor, R., Vandersteen, A.M., Barrett, J.C., Barroso, I., Davey Smith, G., Durbin, R., Farooqi, I.S., Fitzpatrick, D.R., Hurles, M.E., Kaye, J., The, U.K.K.C., Writing, g., Production, g., Cohorts, g., Neurodevelopmental disorders, g., Obesity, g., Rare disease, g., Statistics, g., Ethics, g., Incidental findings, g., Management, c., 2015. The UK10K project identifies rare variants in health and disease. Nature 526, 82-90.

Wolk, D.A., Grachev, I.D., Buckley, C., Kazi, H., Grady, M.S., Trojanowski, J.Q., Hamilton, R.H., Sherwin, P., McLain, R., Arnold, S.E., 2011. Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. Arch. Neurol. 68, 1398–1403.

Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.-C., Bu, G., 2019. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat.Rev. Neurol. 15, 501–518.