A non-*APOE* polygenic risk score for Alzheimer's disease is associated with CSF neurofilament light in a representative sample of cognitively unimpaired 70-year-olds.

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Abstract

The effect of Alzheimer's disease (AD) polygenic risk scores (PRSs) on amyloid and tau pathophysiology and neurodegeneration in cognitively unimpaired older adults is not known in detail. This study aims to investigate non-*APOE* AD-PRS and *APOE* ε4 in relation to AD pathophysiology evaluated by cerebrospinal fluid (CSF) biomarkers in a population-based sample of 70-year-olds. A total of 303 dementia-free individuals from the Gothenburg H70 Birth Cohort Studies were included. Genotyping was performed using the NeuroChip, and AD-PRSs were calculated. CSF levels of amyloid-β (Aβ42), total tau (t-tau), phosphorylated tau (p-tau), neurogranin (Ng), and neurofilament light (NfL) were measured with ELISA. Associations were found between non-*APOE* PRS and both NfL (p=0.001) and Aβ42 (p=0.02), and between *APOE ε4* and Aβ42 ($p=1e^{-10}$), t-tau ($p=5e^{-4}$), and p-tau (p=0.002). Similar results were observed when only including individuals with CDR=0, except for no evidence of an association between non-*APOE* PRS and Aβ42. There was an interaction between non-*APOE* PRS and Aβ42 pathology status in relation to NfL (p=0.005); association was only present in individuals without Aβ42 pathology (p=0.0003). In relation to Aβ42, there was a borderline interaction (p=0.06) between non-*APOE* PRS and *APOE ε4*; association was present in *ε4* carriers only (p=0.03). Similar results were observed in individuals with CDR=0 (n=246). In conclusion, among cognitively healthy 70-year-olds from the general population genetic risk of AD beyond the *APOE* locus was associated with NfL in individuals without Aβ42 pathology, and with Aβ42 in *APOE ε4* carriers, suggesting these associations are driven by different mechanisms.

Key words: CSF biomarkers, amyloid-beta, tau, genetic variants

Introduction

Alzheimer's disease (AD) is characterized by aggregation of amyloid-β (Aβ) protein into plaques, hyperphosphorylation of tau protein with the formation of tangles, and brain atrophy in certain regions of the brain [1]. Studies including neuropathologic series have shown that a large proportion of cognitively normal older individuals exhibit Alzheimer pathology in the brain [2]. Pathological changes (brain amyloidosis, tau pathology, neurodegeneration and synaptic dysfunction) may be reflected by cerebrospinal fluid (CSF) biomarkers [3]. In the Gothenburg H70 Birth Cohort Studies, we recently reported that as much as 45% of cognitively normal 70-year-olds had pathological CSF levels of either Aβ, tau, or both [4]. Such CSF pathology was associated with having at least one *APOE ε4* allele, which is the strongest genetic risk factor for late-onset AD [5].

The contribution of AD-related genetic variants of lower effect than *APOE ε4* is often studied through the use of polygenic risk scores (PRSs), which are based on available summary data from previous large GWASs on AD. Studies using AD-PRSs report associations with disease stage and dementia progression [6, 7]. Previous studies of AD-PRS in relation to AD-biomarkers in CSF have mainly been performed in clinical samples or convenience samples of cognitively healthy individuals (i.e. samples recruited within health care institutions or through advertising), with mixed results [6, 8-15]. Studies involving representative population-based samples of dementia-free individuals are very sparse.

In addition to amyloid-beta and tau, it is now possible to measure other CSF-biomarkers of potential importance for preclinical AD, such as neurogranin (Ng) [16], a marker of early synaptic degeneration, and neurofilament light protein (NfL), a marker of subcortical large-

caliber axonal degeneration [17]. Increased levels of Ng, but not of NfL, have been associated with *APOE ε4* carriership in subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [17]. In the population-based Mayo Clinic Study on Aging (MCSA), presence of the *APOE ε4* allele was associated with increased CSF levels of both biomarkers, but only in individuals with mild cognitive impairment (MCI) or dementia [18]. So far, none of these markers have been studied in relation to AD-PRS.

The aim of the present study was to investigate non-*APOE* AD-PRSs and *APOE ε4* status in relation to CSF biomarkers of AD and neurodegeneration (i.e. Aβ42, total tau (t-tau), phosphorylated tau (p-tau), NfL, and Ng) in a representative sample of 70-year-olds without dementia recruited from the general population. We also aimed to examine possible interactions with Aβ42 pathology status and *APOE ε4* carriership. Further, we wanted to study the same relationship after excluding individuals with mild cognitive impairment (clinical dementia rating (CDR)>0) who do not fulfill all the criteria of a dementia diagnosis.

Methods

Population

The sample used in the present study originates from the 2014 to 2016 examinations of the H70 Gothenburg Birth Cohort Studies in Gothenburg, Sweden [19]. The sample was obtained from the Swedish Population Registry and included persons living in private households and in residential care. Every 70-year-old in Gothenburg, Sweden, born during 1944 on prespecified birthdates, was invited to the examination, and 1203 participated (response rate 72.2%). Of these, 430 (35.8%) consented to a lumbar puncture (LP). Contraindications (anticoagulant therapy, immune-modulated therapy, cancer therapy) were present in 108, leaving 322 (26.8%) with a CSF tap. CSF volume was insufficient for analyses in four

participants, leaving 318 with data on the CSF biomarkers Aβ42, t-tau and p-tau [4]. Due to insufficient CSF volume, one person lacked data on Ng; three were missing NfL. One further person had an outlier value on NfL and was excluded from the analyses involving that biomarker. Ten additional individuals were excluded based on the quality control (QC) of the genetic data (described in detail below), and five had dementia, leaving a final sample of 303 individuals free from dementia with data on Aβ42, t-tau and p-tau, 302 with data on Ng, and 299 with data on NfL. Characteristics of the total sample are presented in Table 1. Analyses were also performed on the subgroup with CDR=0; n=246 (245 for Ng and 242 for NfL).

All participants and/or their close relatives gave written informed consent. The study was approved by the Regional Ethics Review Board in Gothenburg.

Examinations and diagnoses

Neuropsychiatric examinations were performed by experienced psychiatric nurses. The examinations were semi-structured and included comprehensive psychiatric examinations and an extensive battery of neuropsychological tests [20]. Close informant interviews were performed by psychiatric nurses or psychologists. Dementia was diagnosed according to DSM-III-R criteria [21] (which have been used in the Gothenburg studies for over 30 years). A history of stroke/TIA was determined based on self- or close informant report, and on the Swedish Inpatient and Outpatient Registries (ICD codes: I60, I61, I63.0- I63.5, I63.8- I63.9, I64, G45.0, G45.1, G45.3, G45.9, I69.0, I69.1, I69.2, I69.3, I69.4 and I62).

CSF analyses

CSF t-tau and p-tau (tau phosphorylated at threonine 181) concentrations were measured with sandwich enzyme-linked immunosorbent assays (ELISAs) (INNOTEST htau Ag and PHOSPHO_TAU [181P], Fujirebio [formerly Innogenetics], Ghent, Belgium) [22, 23]. CSF Aβ42 was measured with a sandwich ELISA (INNOTEST Aβ1–42) specifically constructed to measure Aβ starting at amino acid 1 and ending at amino acid 42 [24]. For NfL, an in-house sandwich ELISA with capture and detection antibodies that were directed against the central rod domain of the protein (NfL 21 and NfL 23, respectively) was used [25]. An in-house ELISA method [26] was used to measure CSF Ng.

Genotyping

Genotyping was performed with the NeuroChip (Illumina) [27]. QC included the removal of individuals due to any of the following: per-individual call rate <98%, sex mismatch, and excessive heterozygosity (FHET outside +/- 0.2). Further, individuals were defined as non-European ancestral outliers, and removed, if their first two PCs exceeded 6 standard deviations from the mean values of the European samples in the 1000 Genome global reference population. Closely related individuals were removed based on pairwise PI_HAT (i.e. proportion of the genome that is in identity-by-descent; calculated using --genome option in PLINK) >=0.2. Genetic variants were excluded due to: per-SNP call rate <98%, minor allele frequency (MAF) <0.01, and Hardy-Weinberg disequilibrium (P<1e-6). The Sanger imputation service was used to impute post-QC, using the reference panel of Haplotype Reference Consortium data (HRC1.1). The single nucleotide polymorphisms (SNPs) rs7412 and rs429358, defining the *APOE* alleles *ε2*, *ε3* and *ε4*, were also genotyped, using the KASPar PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK).

Construction of polygenic risk scores

Among the AD-PRS constructed in this study was a 39-SNP PRS based on all SNPs (excluding the *APOE* region) that have shown genome-wide significant association with AD after combined meta-analyses in the very recent GWAS by de Rojas and colleagues (2020) [28]. Similar to the study by de Rojas et al., where the PRS was validated for the first time, the 39 SNPs were weighted using published effect sizes from IGAP [29], Sims et al. 2017 [30], and Jun et al. 2016 [31]. All genetic variants included in the PRS represent independent signals [28]. [28][28]In addition, AD-PRSs were generated using summary statistics from stage 1 of the most recently published AD GWAS including clinically-defined AD [29]. SNPs were selected using LD-clumping. In short, the European ancestry samples from the 1000-genomes project were used as reference panel to remove variants in LD; all variants 250kb upstream and downstream of the top signal were removed (R^2< 0.001). All variants in the *APOE* region (chromosome 19, coordinates GRCh37: 44412079 to 46412079) were removed. In the present study, we created PRSs based on four p-value thresholds (p<5e^{-8}, p<1e^{-5}, p<1e^{-3}, p<1e^{-1}), referred to as 5e^{-8} PRS, 1e^{-5} PRS, 1e^{-3} PRS, and 1e^{-1} PRS. All AD-PRSs were calculated as the sum of the β-coefficient multiplied with the number/dosage of effect alleles of each genetic variant, and then standardized.

Statistical analyses

The values of t-tau, p-tau and NfL were logarithmised due to skewed distribution. Linear regressions, adjusted for sex, age at CSF sampling, and 10 principal components (PCs) (computed in PLINK) to correct for population stratification, were used to analyse non-*APOE* PRSs and *APOE ε4* status in relation to levels of CSF biomarkers (Aβ42, t-tau, p-tau, Ng, and NfL), both in the total sample and in the CDR=0 sub-sample. P-values generated during these analyses were further validated against a Bonferroni corrected p-value threshold. This

threshold was based on tests of two different "genetic risk designs" (i.e. *APOE ε4* status and non-*APOE* PRSs) in relation to five different biomarkers (i.e. 2x5 tests=10; corrected p-value level=0.005).

Analyses investigating possible interactions between Aβ42 pathology status (i.e. Aβ42 ≤530 pg/ml yes/no) and the non-*APOE* PRSs, and the *APOE ε4* status, in relation to the other CSF biomarkers were performed using linear regressions including the interaction terms Aβ42 pathology status x non-*APOE* PRS/*APOE ε4* statusscore. Identified interactions were further investigated in analyses stratified on Aβ42 pathology status (linear regressions adjusted for sex, age at CSF sampling, and 10 PCs).

Analyses investigating possible interactions between *APOE ε4* status and non-*APOE* PRSs in relation to the CSF biomarkers were performed using linear regressions including the interaction term *APOE ε4* status x non-*APOE* PRS. Identified interactions were further investigated in analyses stratified on *APOE ε4* status (linear regressions adjusted for sex, age at CSF sampling, and 10 PCs).

The statistical analyses were done in IBM SPSS Statistics v26 and R v4.0.0 using stats and ggplot2 packages.

Results

Associations were found between non-*APOE* PRS and NfL (for the 39-SNP PRS: β=0.07, SE=0.03, p=0.01 and $5e^{-8}$ PRS: β=0.08, SE=0.03, p=0.001) and Aβ42 ($5e^{-8}$ PRS: β=-29.8, SE=13.0, p=0.02) in the total sample. The association with NfL remained after Bonferroni correction for multiple testing, but the association with Aβ42 did not. Associations, surviving correction for multiple testing, were also found between *APOE ε4* status and Aβ42 (β=-171.1, SE=25.5, $p=1e^{-10}$), t-tau (β=0.16, SE=0.05, $p=5e^{-4}$), and p-tau (β=0.13, SE=0.04, p=0.002). Further, a borderline association were found between the *ε4* allele and increased levels of Ng in the total sample (β=15.5, SE=8.6, p=0.07). Apart from an association between the non-*APOE* PRS at level 1e-5 and NfL (β=0.06, SE=0.03, p=0.04), and a lack of evidence of an association between non-*APOE* PRS and Aβ42, similar results were observed in the CDR=0 sub-sample (Table 2). No evidence of associations was found between the non-*APOE* PRSs and t-tau, p-tau, and Ng, or between *APOE ε4* status and NfL (Table 2).

To study if the identified association, at a nominal p-value level, between the $5e^{-8}$ PRS and Aβ42 levels was beyond the effect of *APOE*, we included *APOE ε4* status as a covariate in the linear regression analysis of the relation between the $5e^{-8}$ PRS and Aβ42. The result showed that the $5e^{-8}$ PRS and *APOE* ε4 status were both significantly associated ($p=2e^{-10}$, and p=0.04) with Aβ42 (i.e. both variables had an independent effect in relation to Aβ42). Moreover, the explanatory value (adjusted r2) of a model including *APOE* ε4 status increased slightly, from 0.13 to 0.14, when the non-*APOE* PRS ($5e^{-8}$) was added.

There was an interaction between Aβ42 pathology status (≤530 pg/ml yes/no) and non-*APOE* PRS in relation to NfL levels, both in the total sample (39-SNP PRS: p=0.005, $5e^{-8}$ PRS:

0.04) and in the CDR=0 sub-sample (39-SNP PRS: p=0.005, $5e^{-8}$ PRS: 0.05). Associations between the PRS and CSF NfL were only found among individuals with normal Aβ42 pathology levels, i.e. in those without evidence of brain amyloidosis, (total sample: 39-SNP PRS: β=0.11, SE=0.03, p=0.0003 (Figure 1) and $5e^{-8}$ PRS: β=0.12, SE=0.03, p=0.0002; CDR=0 sub-sample: 39-SNP PRS: β=0.12, SE=0.03, p=0.0003 (Figure 1) and $5e^{-8}$ PRS: β=0.11, SE=0.03, p=0.001). The associations did not change when adjusting for history of stroke (including TIA) (results not shown). There were no interactions between non-*APOE* PRS and CSF Aβ42 (brain amyloidosis) status in relation to any of the other CSF-markers (i.e. t-tau, p-tau, and Ng), either in the total sample, or in the CDR=0 sub-sample (results not shown). Further, there were no interactions between the *APOE ε4* status and CSF Aβ42 status in relation to any of the biomarkers (results not shown).

There was a trend towards an interaction between *APOE ε4* status and the 39-SNP PRS in relation to Aβ42 in the total sample (p=0.06), and an interaction in the CDR=0 sub-sample (p=0.04). An association between the PRSs and CSF Aβ42 was only found among *APOE ε4* carriers in the total sample (β=-62.5, SE=27.7, p=0.03) (Figure 2). In the CDR=0 sub-sample, there was a borderline association in *ε4* carriers (β=-57.9, SE=30.0, p=0.06). The interactions between *APOE ε4* status and the $5e^{-8}$ PRS in relation to Aβ42 only approached significance (total sample: p=0.09, CDR=0 sub-sample p=0.1), but similar to results for the 39-SNP PRS, stratification based on *ε4* status showed an association in *ε4* carriers in the total sample (β=-56.1, SE=22,6 p=0.02), and a borderline association in the CDR=0 sub-sample (β=-48.3, SE=25.1, p=0.06). No interactions were observed between *APOE ε4* status and non-*APOE* PRS in relation to the other CSF-markers in the total sample, and the same was the case for the CDR=0 sub-sample (results not shown).

Discussion

In a representative sample of 70-year-olds free from dementia, non-*APOE* PRS was associated with CSF levels of NfL and Aβ42. The association with NfL remained after correction for multiple testing, while the association with Aβ42 did not. Associations surviving correction were also found between *APOE ε4* status and Aβ42, t-tau, and p-tau, while Ng was associated at a borderline level. Stratified analyses, based on identified interactions, showed associations between the non-*APOE* PRS and CSF levels of NfL only in individuals without CSF biomarker evidence of brain amyloid pathology. In addition, the non-*APOE* PRS was associated with CSF levels of Aβ42 among *APOE ε4* carriers, but not in those without this allele.

Previous studies of AD-PRSs in relation to the CSF-biomarkers Aβ42, t-tau, and p-tau in representative population-based samples of cognitively healthy individuals are lacking. Studies performed among cognitively healthy and MCI individuals from convenience and clinical samples show discrepant results. A possible explanation could be heterogeneity of the samples, regarding both age and diagnostic status. Considering Aβ42, several studies, including ours, show association with either *APOE ε4* status or *APOE* PRS [10, 12, 15], but association with non-*APOE* PRS, or *APOE* PRS adjusted for *APOE ε4* status, is rare [14]. In our study we see an association between a non-*APOE* PRS at the genome-wide significance level, but the finding is not strong enough to survive correction for multiple testing and should therefore be interpreted with caution. A recent study reported that both *APOE* and non-*APOE* PRS predicted MCI and AD, while only *APOE* predicted amyloid deposition based on PET, suggesting that genetic risk for AD can differ from genetic risk for amyloid deposition [32]. Considering tau levels, reports on association with *APOE* in cognitively

healthy individuals are rare [4]. Apart from the AIBL-study, which used a small CSF-biomarker sample, associations between non-*APOE* PRS and tau levels have only been reported in analyses including individuals with MCI [12, 14]. Few studies report results for non-*APOE* PRS in relation to CSF-biomarkers stratified by *APOE ε4* status. We found an association between non-*APOE* PRS and Aβ42 in *ε4* carriers. This type of association could not be seen for the other biomarkers. In contrast to our results, a study on MCI reported an association between non-*APOE* PRS and CSF t-tau and p-tau, which became stronger in *ε4* carriers, while no association was found with Aβ42 in *ε4* carriers [12].

Due to discrepant results, studies in larger samples are needed to sort out the relationship between AD-PRS and CSF-biomarkers in cognitively healthy individuals. Large population-based samples with data on CSF-biomarkers are rare, but combining data from several smaller studies would enable meta-analyses, or even pooled analyses if the data can be homogenised in an appropriate way. Further, discrepant findings among studies could probably to some extent also be explained by differences in the PRS (and PHS) used. Among the PRSs employed in our study, it was apparent that those including SNPs based on a genome wide significance level performed better than the broader versions of PRSs including SNPs based on higher significance levels.

To the best of our knowledge, this is the first study investigating the relation between AD-PRS and novel CSF biomarkers (i.e. Ng and NfL) suggested to be involved in the AD disease process. CSF NfL predicts progression to MCI and dementia among cognitively normal individuals with preclinical AD [33]. Although it is a valuable marker of early neurodegeneration it is not specific for AD pathobiology [17, 33]. However, in patients in the AD spectrum, NfL is more closely linked to concomitant cerebrovascular disease [34-36].

Indeed, we found that NfL was associated with non-*APOE* PRS, but the association was only present among individuals without pathological levels of Aβ42. These results are to some extent in line with the findings by Mattsson et al. [17], showing that although NfL associates with AD, the association was strongest in individuals without Aβ pathology. Moreover, the authors found that the association between NfL and other AD traits, such as cognitive decline, brain atrophy, brain hypometabolism and white matter hyperintensities, often were stronger in individuals without Aβ42 pathology.

We also found an association between the non-*APOE* PRS and Aβ42 in *APOE ε4*-carriers. It may be that the associations we see with the non-*APOE* PRS reflect two different pathways in the process of AD, and that the association with NfL indicates a pre-amyloid phase. The influence of polygenic scores during the prodromal phase of AD has been discussed in previous literature [6, 37]. An association between the non-*APOE* PRS and preclinical, and prodromal, disease independent of amyloid pathology is reasonable, since many of the genetic variants included in the PRS are involved in non-amyloidogenic pathways, such as immune response and inflammation, lipid transport, and endocytosis [28]. Alternative explanations include that the association between AD-PRS and NfL among cognitively unimpaired individuals without amyloid pathology reflects brain processes also involved in accelerated aging or other neurodegenerative diseases (e.g. Lewy Body disease, frontal lobe dementia), in inflammatory diseases, as well as in cerebrovascular disease. A genetic overlap between these types of disorders has been suggested in several previous studies [38-40]. The association between the non-*APOE* PRS and NfL in our sample did not change after adjusting for stroke (including TIA). However, the number of individuals with stroke in our cohort was low. Moreover, a relation between the non-*APOE* PRS and types of pathophysiology other than plaques and tangles characteristic of AD is further supported by the finding that elevated

levels of NfL in our sample were not driven by the *APOE* , the strongest genetic factor modulating risk for AD.

We also found a borderline association between *APOE ε4* carriership and increased CSF levels of Ng in cognitively unimpaired 70-year-olds. This result contrasts the finding in a previous study in one of the other cohorts included in the Gothenburg H70 Birth Cohort Studies, where no association was seen in 129 cognitively healthy individuals with a mean age of 82 years [41]. A similar result was seen in the population-based Mayo Clinic Study on Aging (MCSA), showing no association between *APOE ε4* and Ng in cognitively unimpaired older individuals (n=687) [18]. One reason for the discrepancy may be the high frequency of *APOE ε4* carriers (37%) in our sample. However, as mentioned, the association seen in the present study is relatively weak and has to be further investigated in other samples before any conclusions could be drawn.

Among the strengths of our study are the comprehensive examinations and the homogeneous, and relatively large, CSF biomarker sample of cognitively unimpaired individuals originating from a representative population-based study. All individuals were dementia-free, and analyses including only those with CDR=0 did not change the results, indicating that individuals with CDR above 0 are relatively similar to the rest of the sample. There are also some limitations. Even if the number of individuals with CSF data was relatively large, the overall number is low, at least for a genetic study, which influences the statistical power. Considering the findings for non-*APOE* PRS, only the association with NfL survives Bonferroni correction for multiple testing. Similarly, among the stratified analyses the NfL-related findings seem to be more robust. Further, the cross-sectional design of the study makes it impossible to identify individuals who will stay cognitively healthy over time for

sub-group analyses. Moreover, the study involves a Caucasian 70-year-old population and generalization of the results to other populations should be done with caution.

In conclusion, we found that *APOE* genotype was associated with CSF Aβ42, t-tau, and p-tau among cognitively healthy 70-year-olds recruited from the general population. We also found that genetic risk of AD beyond the *APOE* locus was associated with NfL and Aβ42. However, the association with NfL was only seen in individuals without evidence of Aβ42 pathology, and the association with Aβ42 was only seen in *APOE ε4* carriers, suggesting that associations between the non-*APOE* AD-PRS and these markers of neurodegeneration and brain amyloidosis are driven by different mechanisms.

Conflict of interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

Author Contributions

AZ and IS designed the study; AZ, IS, SK, and JN took part in the acquisition of subjects and data; AZ analyzed the data and AZ, IS, SK, JN, RG, JB, MW, HZ and KB took part in the interpretation of the data; IS and AZ drafted the manuscript and SK, JN, RG, JB, MW, HZ, and KB revised it critically for important intellectual content. AZ, IS, SK, JN, RG, JB, MW, HZ, and KB approved the final version of the manuscript. IS, AZ, MW, HZ, and KB funded the study.

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Tables

Table 1. Sample Characteristics

Total sample[a] (n=303)	
Age at CSF-sampling, mean (SD)	70.9 (0.35)
Sex: women, n (%)	140 (46.2)
APOE e4, n (%)	111 (36.6)
MMSE, mean (SD)	29.0 (1.2)
Years of education, mean (SD)	12.7 (3.9)
Stroke, n (%)	14 (4.6)
Abeta 42 (pg/ml), mean (SD)	718.1 (224.1)
t-tau (pg/ml), mean (SD)	331.7 (135.2)
p-tau (pg/ml), mean (SD)	49.4 (17.4)
Ng (pg/ml),[b] mean (SD)	204.6 (69.7)
NfL (pg/ml),[c] mean (SD)	842.9 (605.6)

[a]Total sample without dementia diagnosis after QC of the genotyping-data.
[b]Mean is based on 302 individuals.
[c]Mean is based on 299 individuals.

Table 2. non-*APOE* PRSs and *APOE* score in relation to CSF-biomarkers.

		Total Sample						**CDR=0 Sample**					
		39-SNP PRS	**5e-8 PRS**	**1e-5 PRS**	**1e-3 PRS**	**1e-1 PRS**	***APOEε4***	**39-SNP PRS**	**5e-8 PRS**	**1e-5 PRS**	**1e-3 PRS**	**1e-1 PRS**	***APOEε4*[a]**
Aβ42	β	16.9	-29.8	-8.2	1.1	6.3	-171.1	17.5	-23.2	-0.7	-3.1-	6.1	-166.8
	S.E.	13.1	13.0	13.3	13.4	13.4	25.5	14.5	14.2	14.7	15.6	14.4	29.5
	p	0.2	**0.02**	0.5	0.9	0.6	**1e-10**	0.2	0.1	0.96	0.8	0.7	**5e-8**
Ln t-tau	β	-0.02	0.03	0.03	0.02	0.007	0.16	-0.02	0.02	0.05	0.002	0.006	0.18
	S.E.	0.02	0.02	0.02	0.02	0.02	0.05	0.03	0.03	0.03	0.03	0.03	0.05
	p	0.4	0.2	0.2	0.5	0.8	**5e-4**	0.4	0.3	0.08	0.9	0.8	**0.001**
Ln p-tau	β	-0.02	0.02	0.02	0.02	0.003	0.13	-0.02	0.02	0.03	0.001	-0.001	0.14
	S.E.	0.02	0.02	0.02	0.02	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.05
	p	0.4	0.2	0.3	0.4	0.9	**0.002**	0.4	0.5	0.2	0.96	0.96	**0.003**
Ng[b]	β	-5.3	0.17	2.4	3.3	-2.6	15.5	-6.0	-0.8	5.2	1.9	-3.3	20.1

	S.E.	4.1	4.2	4.2	4.2	4.2	8.6	4.7	4.7	4.8	5.2	4.7	10.2
	p	0.2	0.97	0.6	0.4	0.5	0.07	0.2	0.99	0.3	0.7	0.5	**0.05**
Ln NfL[c]	β	0.07	0.08	0.05	-0.02	-0.03	0.01	0.07	0.08	0.06	-0.04	-0.03	0.02
	S.E.	0.03	0.03	0.03	0.03	0.03	0.05	0.03	0.03	0.03	0.03	0.03	0.06
	p	**0.01**	**0.001***	0.09	0.4	0.3	0.08	**0.01**	**0.003***	**0.04**	0.2	0.3	0.7

*Surviving Bonferroni correction for multiple testing (based on a corrected p-value level of 0.005).

[a]Similar results for associations between *APOE ε4* and Aβ42, t-tau, and p-tau in the CDR=0 sub-sample have been published previously [4]. Due to removal of samples during the QC of the GWAS data the number of individuals were slightly lower in the present study.

[b]Results for Ng are based on 302 individuals in the total sample, and 245 in the CDR=0 sub-sample.

[c]Results for NfL are based on 299 individuals in the total sample, and 242 individuals in the CDR=0 sub-sample.

Figure legends

Figure 1. Non-*APOE* 39-SNP AD-PRS in relation to CSF NfL in individuals with (A) and without (B) Aβ42 pathology levels, in the total sample without dementia.

Figure 2. Non-*APOE* 39-SNP AD-PRS in relation to CSF Aβ42 in *APOE ε4* carriers (A) and non-carriers (B), in the total sample without dementia.

Figure 1

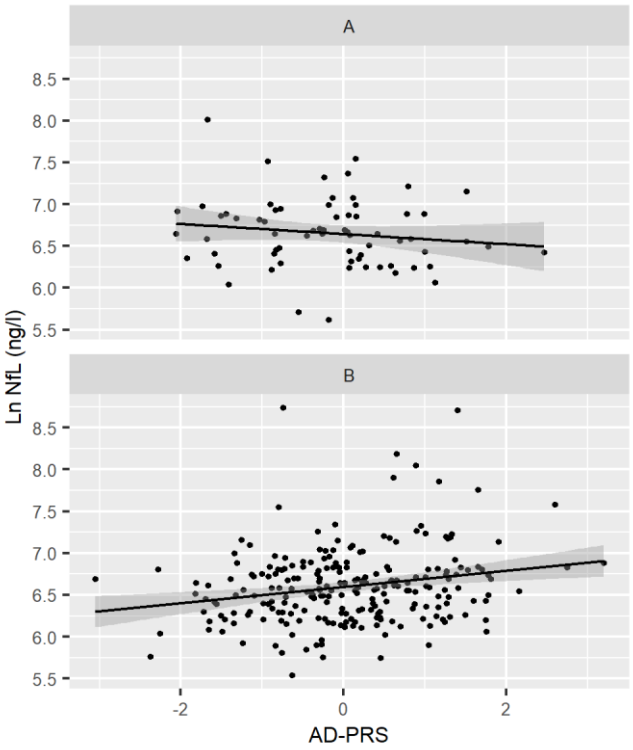

Figure 2