

RESEARCH ARTICLE

Risk of dementia in *APOE* ϵ 4 carriers is mitigated by a polygenic risk score

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Abstract

Introduction: We investigated relationships among genetic determinants of Alzheimer's disease (AD), amyloid/tau/neurodegeneration (ATN) biomarkers, and risk of dementia.

Methods: We studied cognitively normal individuals with subjective cognitive decline (SCD) from the Amsterdam Dementia Cohort and SCIENCe project. We examined associations between genetic variants and ATN biomarkers, and evaluated their predictive value for incident dementia. A polygenic risk score (PRS) was calculated based on 39 genetic variants. The *APOE* gene was not included in the PRS and was analyzed separately.

Results: The PRS and *APOE* ϵ 4 were associated with amyloid-positive ATN profiles, and *APOE* ϵ 4 additionally with isolated increased tau (A-T+N-). A high PRS and *APOE* ϵ 4 separately predicted AD dementia. Combined, a high PRS increased while a low PRS attenuated the risk associated with ϵ 4 carriers.

Discussion: Genetic variants beyond *APOE* are clinically relevant and contribute to the pathophysiology of AD. In the future, a PRS might be used in individualized risk profiling.

KEYWORDS

Alzheimer's disease, *APOE*, ATN classification, biomarkers, dementia, polygenic risk score, subjective cognitive decline

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1 | BACKGROUND

Neuropathologically, Alzheimer's disease (AD) is defined by the presence of amyloid beta ($A\beta$) plaques and neurofibrillary tau tangles.¹ In vivo, a research framework for AD proposed that individuals can be categorized based on biomarker evidence of pathology. According to the ATN system, each individual is rated for the presence of $A\beta$ (A), hyperphosphorylated tau (T), and neurodegeneration (N), resulting in eight possible biomarker combinations.² This categorization is independent of the cognitive stage of the individual, and therefore, cognitively normal individuals can be identified who already harbor the first pathophysiological changes associated with AD, which is referred to as preclinical AD or stage 2 AD.³

It is important to identify which cognitively normal individuals, with or without subjective cognitive decline (SCD), are at risk of future cognitive deterioration. Research interest of secondary prevention trials is shifting increasingly to these early stages, because these individuals could potentially benefit most from disease-modifying therapy. The ATN biomarkers—particularly biomarkers for amyloid pathology—predict cognitive decline and clinical progression.^{4–6} Genetics also have potential for risk estimation of clinical progression. The *APOE* $\epsilon 4$ allele is a strong genetic risk factor for AD, and it has been consistently linked to a higher amyloid burden.⁷ Besides *APOE*, many other genetic variants have been identified in recent years that are also associated with AD.^{8–10} Each of these genetic variants has a small individual effect, but combined in a polygenic risk score (PRS) they are able to differentiate individuals with AD dementia from healthy controls in population-based studies.^{11–13} The extent to which a PRS is associated with biomarkers is less clear, as previous studies have provided contradictory results.^{14–19}

- Genetic variants were associated with amyloid-positive amyloid/tau/neurodegeneration (ATN) profiles.
- A polygenic risk score (PRS) and *APOE* predicted Alzheimer's disease (AD) dementia.
- A low PRS attenuated the risk of incident dementia associated with *APOE* $\epsilon 4$.
- Genetic variants beyond *APOE* contribute to the pathophysiology of AD.

Our aim was to investigate the relationship between genetic risk factors for AD and the ATN classification in cognitively normal individuals presenting with worries about their memory at a memory clinic. Furthermore, we aimed to explore the relationship between genetic risk factors and clinical progression to dementia.

2 | METHODS

2.1 | Population

We retrospectively studied 829 cognitively normal individuals with SCD from the Amsterdam Dementia Cohort and SCIENCE project

RESEARCH IN CONTEXT

1 Systematic Review: We reviewed the literature using traditional sources. While it is well established that *APOE* is related to amyloid status and risk of dementia, literature provided contradictory results regarding the relationship between a polygenic risk score (PRS) and biomarkers or risk of progression to dementia.

2 Interpretation: Our results show that not only *APOE*, but also an independently constructed PRS was associated with amyloid-positive ATN profiles, and that *APOE* was associated with an isolated abnormal tau status (A-T+N-). The PRS added predictive value to *APOE* for risk of Alzheimer's disease (AD) dementia, in such a way that a high PRS increased the effect of *APOE* $\epsilon 4$, while a low PRS attenuated the *APOE* $\epsilon 4$ effect.

3 Future Directions: Genetic variants beyond *APOE* directly contribute to the pathophysiology of AD and affect the risk associated with *APOE*. Future studies are needed to explore how these variants can be used for individualized risk profiling.

(Subjective Cognitive Impairment Cohort).²⁰ We selected all individuals with a baseline SCD diagnosis with available array genotyping, and availability of either ATN biomarkers, and/or follow-up information. In the selection process, we excluded 113 individuals due to non-European ancestry (population outliers) or due to close family relations, which led to a total sample size of 829 individuals (Figure 1). All individuals received a standardized diagnostic workup, which included a medical and neurological investigation, neuropsychological assessment, cerebrospinal fluid (CSF) analysis, and brain magnetic resonance imaging (MRI).^{20,21} The Dutch Verhage system is used for the rating of education.²² In a multidisciplinary consensus meeting, individuals received the label of SCD when they were cognitively normal; that is, there were no formal deficits in cognition according to neuropsychological test scores and criteria for mild cognitive impairment (MCI) or dementia were not met, and when there was no other neurological or psychiatric condition that could cause their cognitive complaints.

Eight hundred and seven individuals (97%) had any biomarker available within 1 year of baseline diagnosis (MRI, CSF, and/or positron emission tomography [PET]). For 491 individuals (59%), follow-up assessments were available (4 ± 3 years). At follow-up, clinical diagnoses were re-assessed as SCD, MCI, AD dementia, or other types of dementia (including frontotemporal dementia [FTD], primary progressive aphasia [PPA], vascular dementia, dementia with Lewy bodies [DLB], progressive supranuclear palsy [PSP], and Huntington's disease).^{23–29} For 469 individuals (57%), both follow-up diagnoses and baseline biomarkers were available. All patients gave written informed consent. The study was approved by the medical ethical committee

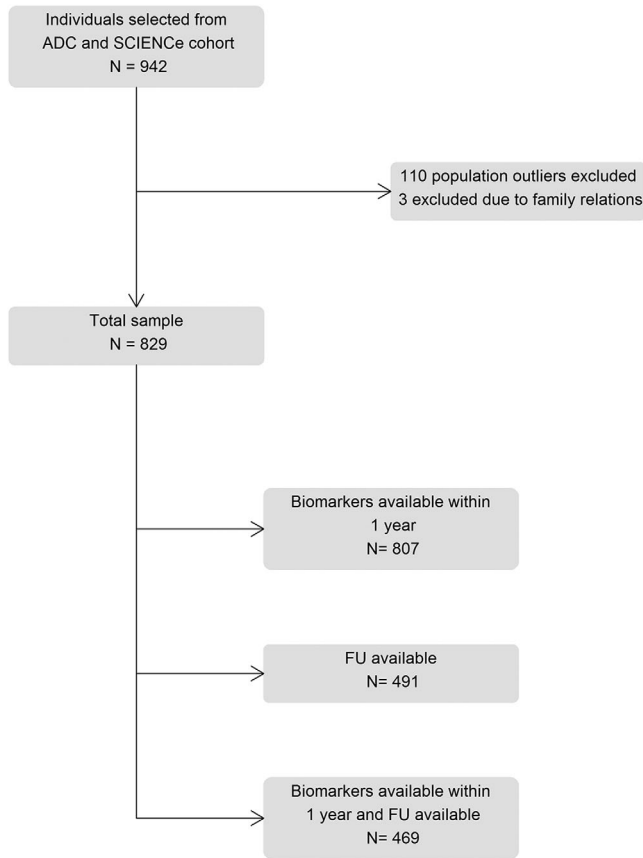


FIGURE 1 Flowchart of participant selection. ADC, Amsterdam Dementia Cohort; FU, follow-up; SCD, subjective cognitive decline; SCIENCE, subjective cognitive impairment cohort

of the VU University and was in accordance with the Declaration of Helsinki.

2.2 | ATN classification

PET, CSF, and MRI procedures were similar to our previous study using the ATN classification in SCD.⁴ The following sections describe the procedures for the ATN classification in brief.

We used amyloid PET or CSF A β to define A, CSF hyperphosphorylated tau (p-tau) to define T, and the medial temporal atrophy score (MTA) on MRI to define N. When both amyloid PET and CSF A β were available, the PET result was used to define A. We additionally clustered the eight biomarker profiles into three categories. The “normal AD biomarker” category consisted of the biomarker profile with all normal biomarkers (A–T–N–). “Non-AD pathologic change” consisted of the remaining A– profiles (A–T–N+, A–T+N–, and A–T+N+). The “Alzheimer’s continuum” consisted of all A+ profiles (A+T–N–, A+T–N+, A+T+N–, A+T+N+).¹

Amyloid PET was available for 72 individuals within 1 year of baseline diagnosis ([¹⁸F]Florbetapir n = 13, [¹⁸F]Florbetaben n = 43, [¹⁸F]Flutemetamol n = 10 and [¹¹C]-PIB [Pittsburgh compound-B]; n = 6). The following systems were used to acquire PET scans:

Gemini TF PET-CT, Ingenuity TF PET-CT, and Ingenuity PET/MRI (Philips Healthcare). For [¹⁸F]Florbetapir³⁰ and [¹¹C]PIB imaging,³¹ a dynamic scanning protocol was used, for [¹⁸F]Florbetaben³² and [¹⁸F]Flutemetamol³³ imaging, a static scanning protocol. A trained nuclear medicine physician (BvB) visually rated scans as “positive” or “negative.”

CSF was available in 644 individuals. A lumbar puncture was performed using a 25-gauge needle and syringe. Concentrations of A β _{1–42} were measured using an Innostest enzyme-linked immunosorbent assay (ELISA; n = 636) or Elecsys assay (n = 8). The Innostest A β levels were corrected for the upward drift in CSF biomarker analyses that occurred over the years.³⁴ We transformed the A β values obtained by Elecsys to the Innostest equivalent values using the following formula: Elecsys A β (pg/mL) = –365 + 1.87 × Innostest A β (pg/mL).³⁵ Adjusted concentrations <813 pg/mL were considered abnormal. Tau phosphorylated threonine 181 (p-tau) was measured using Innostest ELISAs (hTAU-Ag and PhosphoTAU-_{181p}); concentrations >52 pg/mL were considered abnormal.

An MRI scan of the brain was available for 703 individuals (Siemens Avanto, n = 6; GE Discovery MR750, n = 14; Impact, n = 97; 3T Philips Ingenuity TF PET/MR system, n = 141; 1.5T GE Signa HDxt, n = 22; 3.0T GE Signa HDxt, n = 264; 1.5T Siemens Sonata, n = 25; 3T Toshiba Vantage Titan, n = 134). All scans were reviewed by an experienced neuroradiologist. Coronal T1-weighted images were used for visual assessment of MTA (range 0 to 4). The left and right MTA scores were averaged, and age-dependent cut-off values were used. For individuals <65 years of age, an MTA score ≥ 1 was considered abnormal; for individuals ≥ 65 years, an MTA score ≥ 1.5 was considered abnormal.³⁶

2.3 | Genotyping and imputation procedures

We selected 39 genetic variants for which there was evidence of a significant association with AD from previous genome-wide association studies (GWAS) and candidate-gene studies (Table S1 in supporting information).^{8–10} All genetic variants in our cohort were determined by standard genotyping or imputation methods and we applied established quality control methods.³⁷ All individuals were genotyped using Illumina Global Screening Array (GSArray_CUSTOM_20018389_A2). We used high-quality genotyping in all individuals (individual call rate >98%, variant call rate >98%). All individuals’ reported sex matched with their genetic sex. Variants that departed from Hardy–Weinberg equilibrium were excluded at $P < 1 \times 10^{-6}$. Genotypes were prepared for imputation using provided scripts (HRC-1000G-check-bim.pl, <https://www.well.ox.ac.uk/~wrayner/tools/>) to compare variant ID, strand, and allele frequencies to the Haplotype Reference Panel (HRC v1.1, April 2016).³⁸ Finally, all autosomal variants were submitted to the Sanger imputation server (<https://imputation.sanger.ac.uk/>). The server uses MACH3 to phase data and imputation to the reference panel was performed with Positional Burrows-Wheeler Transform (PBWT).³⁹ APOE was determined based on imputation.

We calculated a weighted individual PRS based on the 39 genetic variants that showed genome-wide significant evidence of association

with AD (Table S1). APOE was analyzed separately and was not included in the PRS. The selected variants were directly genotyped (median genotyping rate = 1) or imputed with high quality (median imputation score $R^2 = 0.98$). The PRSs were generated by multiplying the genotype dosage of each risk allele for each variant by its respective weight and then summing across all variants.⁴⁰ We weighted this by the effect size from previous International Genomics of Alzheimer's Project (IGAP) studies (Table S1).^{8,9} The PRS was normalized (mean = 0, standard deviation = 1).

2.4 | Statistics

We performed logistic regression analysis to investigate the relationship between APOE $\epsilon 4$ or the PRS and biomarkers in the ATN classification. The first set of models included APOE $\epsilon 4$ (per allele) or PRS (z-score) as predictor, and A status, T status, or N status as outcome (separate models). In addition, we performed multinomial logistic regression analyses with first the eight-profile ATN classification as outcome, and second the three clustered ATN categories as outcome (A-T-N- reference for both analyses). We created a second set of logistic regression models that included both APOE $\epsilon 4$ and PRS as predictors in the same model. Next, we performed Cox proportional hazards analyses to assess the relationship between APOE $\epsilon 4$ or PRS and the risk of dementia. We studied progression to all-type dementia, AD dementia, and non-AD dementia as outcome separately. In the analyses with AD dementia as outcome, the individuals that progressed to other types of dementia were censored, and vice versa. We created a second set of Cox regression models that included both APOE $\epsilon 4$ and PRS as predictors in the same model.

We additionally investigated the combined predictive value of APOE $\epsilon 4$ and PRS. We first stratified the PRS into low and high (based on the median) and then constructed a four-level variable: APOE $\epsilon 4$ -PRS^{low} (reference), APOE $\epsilon 4$ -PRS^{high}, APOE $\epsilon 4$ +PRS^{low}, APOE $\epsilon 4$ +PRS^{high}. We ran an additional analysis with this four-level variable as predictor.

We corrected all logistic regression analyses for age, sex, and population substructure (principal components 1 to 10). The Cox proportional hazards models were additionally adjusted for baseline score on the Mini-Mental State Examination (MMSE).

All analyses were done using R version 3.6.0. We used the survival package version 2.44.1-1 for Cox proportional hazards analyses.

3 | RESULTS

3.1 | Demographics

At baseline, individuals were on average 60 ± 9 years old, 339 (41%) were female, and MMSE was 28 ± 2 (Table 1). The largest subgroup was that with normal AD biomarkers (57%), followed by non-AD pathologic change (26%) and the Alzheimer's continuum (17%). Among the 491 individuals with available follow-up, 41 (8%) received a diagnosis of dementia (AD dementia $n = 25$, other types of dementia $n = 16$).

TABLE 1 Demographics

		Total N = 829
Demographics	Age, mean (SD)	59.6 (8.8)
	Sex, n (% female)	339 (40.9)
	Education, median (IQR)	6 (5-6)
	MMSE, mean (SD)	28.3 (1.6)
Follow-up	Follow-up time in years, mean (SD)	3.6 (2.8)
	Progression to dementia	
	All-type dementia, n (%)	41 (8.4)
	AD dementia, n (%)	25 (5.1)
	Other dementia, n (%)	16 (3.3)
Follow-up information available $n = 491$		
Biomarkers	Amyloid status, n positive/n total (%)	106/655 (16.2)
	Tau status, n positive/n total (%)	193/644 (30.0)
	Neurodegeneration status, n positive/n total (%)	77/703 (11.0)

Abbreviations: AD, Alzheimer's disease; IQR, interquartile range; SD, standard deviation; MMSE, Mini-Mental State Examination.

Note: Baseline characteristics of the total sample.

3.2 | Associations among the PRS, APOE $\epsilon 4$, and biomarkers

Using logistic regression models, we found that higher PRS was associated with increased likelihood of amyloid positivity (odds ratio [OR] 1.5 [95% confidence interval (CI) 1.2 to 2.0], Figure 2a), but not of tau positivity (OR 1.1 [0.9 to 1.4]) or positivity for neurodegeneration (OR 1.0 [0.8 to 1.3]). APOE $\epsilon 4$ was associated with both amyloid positivity (OR 3.5 [2.5 to 5.1], per allele) and tau positivity (OR 1.6 [1.2 to 2.1]), but not positivity for neurodegeneration (OR 1.4 [1.0 to 2.0]). When performing multinomial logistic regression with the eight-profile ATN classification as outcome, we found that the PRS was associated with an increased likelihood of A+T-N- and A+T+N- compared to A-T-N- (OR 1.9 [1.3 to 2.9] and OR 1.8 [1.2 to 2.6], Figure 2b). APOE $\epsilon 4$ was associated with all A+ profiles, except for A+T+N+ ($n = 6$), as well as with an isolated abnormal tau (A-T+N-, OR 1.5 [1.0-2.3]). Because the eight-profile ATN classification comes with suboptimal power due to small sample sizes in certain profiles, we repeated the analyses with the three-category ATN classification as outcome (Figure 2c). We found that a higher PRS was associated with higher odds of being classified in the Alzheimer's continuum (OR 1.6 [1.2 to 2.2]), but not with higher odds of non-AD pathologic change (OR 1.1 [0.9 to 1.4]). APOE $\epsilon 4$ on the other hand, was associated with both Alzheimer's continuum (OR 4.2 [2.6 to 6.7]) and non-AD pathologic change (1.5 [1.1 to 2.2]). When we repeated the analyses with APOE and PRS both as predictors in the models, results remained comparable (Table S2 in supporting information).

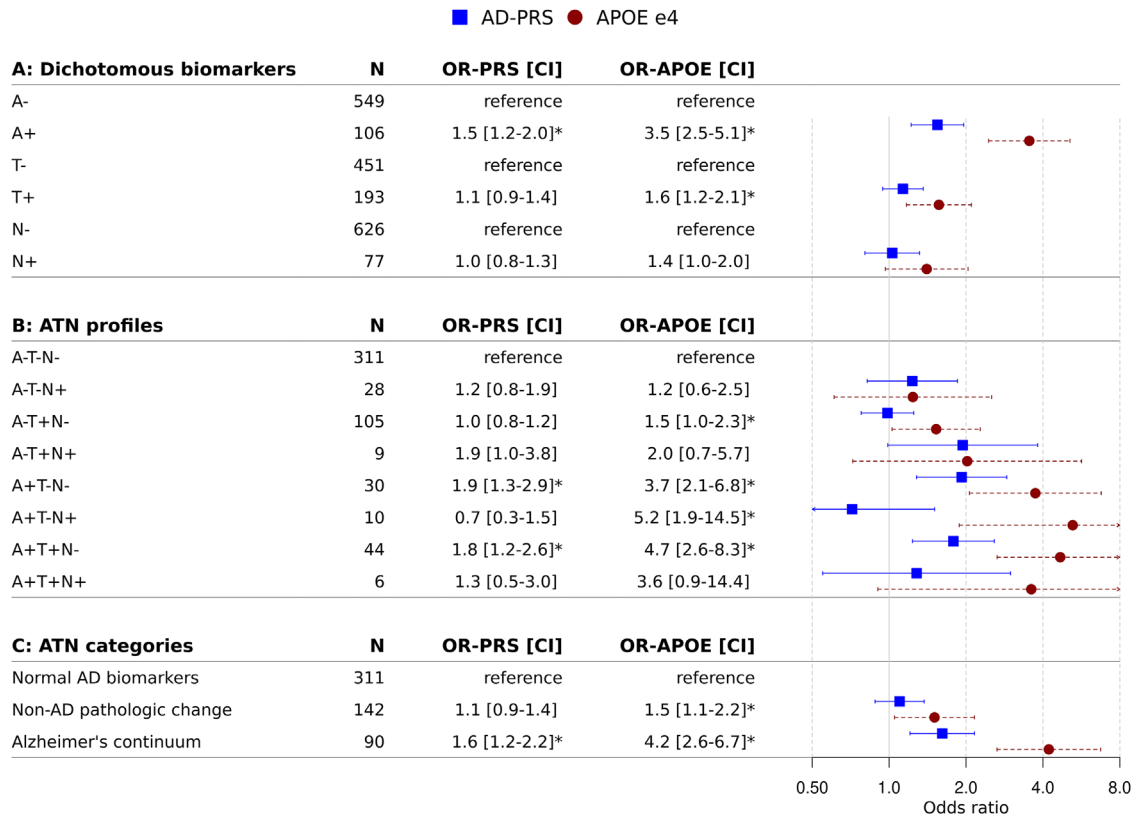


FIGURE 2 Associations between genetic variants and biomarkers. Values given are odds ratio (95% confidence interval) corrected for age, sex, and population substructure, as estimated by logistic regression (predictor: APOE ε4 allele or normalized PRS; outcome: (A) dichotomous biomarker status for A, T, and N separately (reference = negative biomarker status), (B) eight-profile ATN classification (reference = A-T-N-), (C) three-category ATN classification (reference = Normal AD biomarkers). The odds ratio for the PRS reflects the odds of having an abnormal biomarker status or being classified in one of the ATN profiles with abnormal biomarkers, per one standard deviation increase in the PRS. APOE ε4 is per allele. * P-value < .05. APOE, apolipoprotein E; ATN, amyloid/tau/neurodegeneration; OR, odds ratio; PRS, polygenic risk score

TABLE 2 Association between genetic variants and risk of clinical progression

	N	PRS		APOE ε4	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Non-dementia	450				
All-type dementia	41	1.0 (0.7-1.4)	9.6×10^{-1}	2.0 (1.3-3.2)	$3.7 \times 10^{-3*}$
AD dementia	25	1.7 (1.1-2.8)	$2.8 \times 10^{-2*}$	3.3 (1.7-6.3)	$4.6 \times 10^{-4*}$
Other dementia	16	0.5 (0.3-0.9)	$2.2 \times 10^{-2*}$	1.0 (0.4-2.3)	9.8×10^{-1}

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; PRS, polygenic risk score.

Notes: Values are obtained by Cox proportional hazard models, adjusted for age, sex, population substructure, and MMSE (predictor: APOE ε4 allele or normalized PRS, outcome: clinical progression to dementia). The HR associated with the PRS reflects the difference per one standard deviation increase in the PRS. APOE ε4 is per allele.

*P-value < .05.

3.3 | Progression to dementia

Next, we performed Cox proportional hazards analyses to investigate the association between genetic risk factors and the risk of dementia. A higher score on the PRS was not associated with a higher risk of all-type dementia (hazard ratio [HR] 1.0 [95% CI 0.7 to 1.4], Table 2). However, when analyzing AD and non-AD as separate outcomes, we

found that a higher PRS predicted progression to AD dementia specifically (HR 1.7 [1.1 to 2.8], n progression = 25), while individuals with a higher PRS had a lower risk of non-AD dementia (HR 0.5 [0.3 to 0.9], n progression = 16). Additionally, the APOE ε4 allele was associated with a higher risk of progression to all-type dementia (HR 2.0 [1.3 to 3.2]). When AD dementia and other types of dementia were analyzed separately, the APOE ε4 allele was especially associated with a higher risk of

TABLE 3 Combined effect of APOE ϵ 4 and PRS on risk of clinical progression to AD dementia

Category	Total N	Progression to all-type dementia		Progression to AD dementia		Progression to non-AD dementia	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
APOE ϵ 4 non-carrier low PRS	158	Ref	Ref	Ref	Ref	Ref	Ref
APOE ϵ 4 non-carrier high PRS	134	0.5 (0.1–1.8)	2.8×10^{-1}	1.7 (0.3–11.1)	5.9×10^{-1}	0.1 (0.0–1.0)	5.1×10^{-2}
APOE ϵ 4 carrier low PRS	86	0.9 (0.3–2.3)	7.6×10^{-1}	2.4 (0.3–18.0)	3.9×10^{-1}	0.8 (0.2–3.2)	7.5×10^{-1}
APOE ϵ 4 carrier high PRS	109	1.7 (0.7–3.9)	2.5×10^{-1}	4.8 (1.2–18.9)	$2.6 \times 10^{-2*}$	0.4 (0.1–1.8)	2.2×10^{-1}

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; PRS, polygenic risk score.

Notes: Values are obtained by Cox proportional hazard models, adjusted for age, sex, population substructure, and MMSE (predictor: four-level variable [1] APOE ϵ 4 non-carrier and low PRS, [2] APOE ϵ 4 non-carrier and high PRS, [3] APOE ϵ 4 carrier and low PRS, and [4] APOE ϵ 4 carrier and high PRS; outcome: clinical progression to dementia; reference: [1] APOE ϵ 4 non-carrier and low PRS). APOE ϵ 4 status is determined by having one or two ϵ 4 alleles, PRS status is based on median risk.

*P-value < .05.

AD dementia (HR 3.3 [1.7 to 6.3]), but not other types of dementia (HR 1.0 [0.4 to 2.3]). When we repeated the analyses with APOE and PRS both as predictors in the models, the relationship between the PRS and progression to AD dementia was not significant anymore, but results for APOE remained comparable (Table S3 in supporting information).

Next, we investigated the combined effect of APOE ϵ 4 and PRS on risk of dementia. Based on a newly constructed four-level variable (APOE ϵ 4-PRS^{low} as reference), we found that APOE ϵ 4+PRS^{high} had a higher risk of progression to AD dementia (Table 3, Figure 3). By contrast, in APOE ϵ 4+PRS^{low} the risk of progression was attenuated and became comparable to APOE ϵ 4-PRS^{high}. There were no associations with progression to all-type dementia or non-AD dementia.

4 | DISCUSSIONS

The main finding of this study is that an AD PRS predicts biomarker pathology when distributed according to the ATN biomarker classification, independently of APOE. Furthermore, both APOE ϵ 4 and the PRS are associated with risk of AD dementia. When combined we found that only carriers of the APOE ϵ 4 allele who also had a high PRS specifically progressed to AD dementia, implying that the increased risk of APOE ϵ 4 carriers can be “undone” by having a low PRS.

We found that a high AD PRS was associated with abnormal amyloid status and a higher risk of AD dementia. Former studies provided contradictory results about the relationship between the PRS and amyloid status. Discrepancies could be related to differences in disease stage, because amyloid positivity rates differ regarding diagnostic status. Furthermore, some studies found an association between a PRS without APOE and amyloid burden,^{15,41–43} but in others the association was lost when APOE was not included in the PRS.^{14,16,44,45} Similarly, literature is inconsistent about the relationship between the PRS and risk of AD dementia.^{11–13,46–49} Differences could be explained by the use of different populations, as studies that reported no increased risk of clinical progression used an MCI population,⁴⁶ and others reported lower hazard ratios for MCI individuals compared to cognitively normal

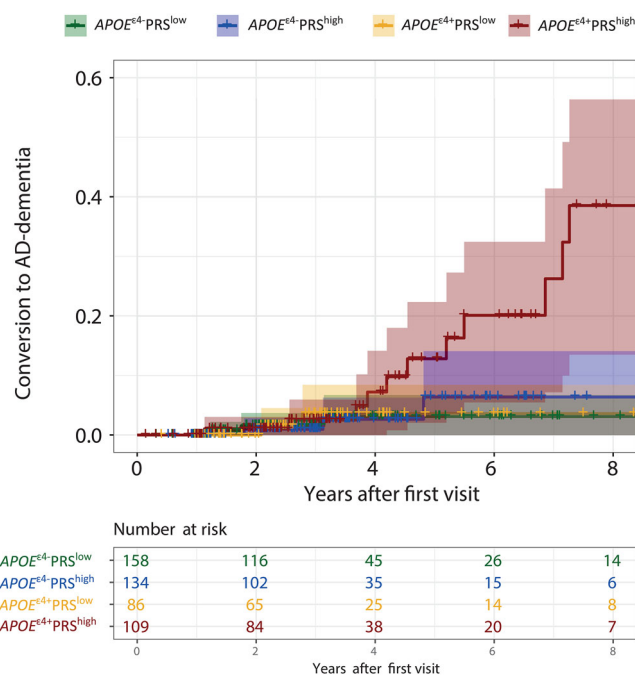


FIGURE 3 Combined effect of APOE ϵ 4 and PRS on risk of clinical progression to AD dementia. Kaplan Meier curve showing the combined effects of APOE ϵ 4 and the PRS on risk of progression to AD dementia, comparing (1) APOE ϵ 4 non-carrier and low PRS, (2) APOE ϵ 4 non-carrier and high PRS, (3) APOE ϵ 4 carrier and low PRS, and (4) APOE ϵ 4 carrier and high PRS. APOE ϵ 4 status is determined by having one or two ϵ 4 alleles, PRS status is based on median risk. AD, Alzheimer's disease; APOE, apolipoprotein E; PRS, polygenic risk score

individuals.^{13,49} Furthermore, the PRSs are not directly comparable, because a different number of single nucleotide polymorphisms (SNPs) is included in the different PRSs. The relationship between APOE and amyloid status has been firmly established.^{7,14,50} We extend those findings by showing not only an association between APOE and amyloid status, but also between APOE and tau status. As amyloid burden and p-tau are closely related, the relationship between APOE and p-tau

could either be mediated through amyloid burden, or be amyloid independent. We found that APOE $\epsilon 4$ carriers have higher odds of being A-T+N- compared to A-T-N-. In line with literature, this suggests the additional involvement of amyloid-independent pathways.⁵¹⁻⁵³ Overall, our results provide evidence for the concept that genetic variants beyond APOE are associated with amyloid status, which is the crucial pathophysiological process underlying AD.

The risk of dementia associated with APOE and the PRS seemed to be additive, as individuals with both an $\epsilon 4$ allele and a high PRS had the highest risk of progression to AD dementia. In line with literature, carriers of the $\epsilon 4$ allele with a low PRS, or non-carriers with a high PRS, had substantially lower risks. This implies that the genetic risk of AD dementia can be more accurately estimated when in addition to APOE, non-APOE genetic variants are also considered. To date, genetic information, including APOE status, is not used for risk profiling in a clinical setting. Although it has been established that the $\epsilon 4$ allele is associated with a higher risk of dementia on a group level, these data do not easily translate to the individual, as not all $\epsilon 4$ carriers will develop dementia, while conversely also individuals without $\epsilon 4$ can develop dementia. We showed that taking into account all genetic variants associated with AD results in more accurate estimates of future AD dementia. In the future, taking into account one's genetic risk of AD could have clinical relevance, especially for individuals who present with worries about their memory at a memory clinic.

Limitations of our study include that the sample size in some ATN profiles was rather small. However, the three clustered ATN categories provided similar results, which confirms robustness of the findings. Furthermore, we based our PRS on current knowledge, but with increasing numbers of genetic studies, the number of variants in the PRS will also change. Comparing results across studies is complicated by the fact that each study uses a slightly different PRS. Using a more liberal threshold for inclusion of genetic variants in the PRS could lead to a higher disease prediction accuracy; however, an extremely liberal approach could also lead to the inclusion of non-informative SNPs, which limits discrimination ability.⁵⁴⁻⁵⁶ In our PRS, we adopted a conservative approach and included only 39 genetic variants with genome-wide significant evidence of association with AD. Also, the results might not be directly generalizable due to the fact that our population included solely individuals of European descent. Additionally, although the follow-up duration in our study was relatively long, the conversion rates were low, as is expected in a cognitively normal population. It is important to note that the differences in conversion to dementia became apparent only after 3 to 4 years of follow-up. With a longer follow-up duration, the predictive value of genetic variants becomes more evident. Strengths of our study include that we have biomarker data used to define ATN categories in a large population of cognitively normal individuals. Individuals of the current study all presented at our memory clinic worrying about their memory and requesting information on likelihood of dementia in the future, which adds to the clinical relevance of our results. Our results are on a group level, but provide proof of principle that in the future, genetic information may inform individualized risk profiling. Furthermore, we tested the association between genetic variants and biomarkers using the ATN classi-

fication system, which has not been done before. With this approach, we used A-T-N- as a reference in our analyses, which enabled us to detect more specific associations than other studies that used a broader amyloid negative group as a reference, because this group could also include tau pathology or neurodegeneration.

In conclusion, we found that an AD-specific PRS is associated with AD biomarkers, particularly amyloid positivity, independent of APOE $\epsilon 4$ in cognitively normal elderly. In addition, both PRS and APOE $\epsilon 4$ were associated with risk of AD dementia, in such a way that a low PRS attenuated the detrimental effect of APOE $\epsilon 4$. This could have implications for the selection of participants for trials, risk stratification, and personalized medicine. Genetic variants other than APOE should not be ignored, because they have a relevant contribution to the disease.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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