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**Association of Alzheimer's Related Genotypes with Cognitive Decline in Multiple Domains:
Results from the Three-City Dijon Study**

Alexandre Vivot, MD^{1,2}, Maria M. Glymour, ScD^{2,3}, Christophe Tzourio, MD, PhD¹, Philippe Amouyel MD, PhD⁴, Geneviève Chêne, MD, PhD¹ and Carole Dufouil, PhD¹

¹*Bordeaux University, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique & CIC-1401, CHU de Bordeaux, Pole de Sante Publique, Bordeaux, France*

²*Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

³*Department of Epidemiology & Biostatistics, University of California San Francisco, CA, USA*

⁴*Lille University, INSERM U744, Institut Pasteur de Lille, CHU de Lille, Lille, France*

Corresponding Author and offprint requests :

Carole Dufouil, INSERM Unit 897, CIC-1401, ISPED, 146 rue Léo Saignat, 33076 Bordeaux, France. E-mail: carole.dufouil@inserm.fr. Phone : +33 5 57571423. Fax : +33 5 57571129

Running title: Alzheimer's disease genes and cognitive decline

Abstract

Several genetic polymorphisms have been associated with Late Onset Alzheimer's Disease (LOAD), but there has been limited evidence on whether these polymorphisms predict intermediary stage outcomes such as cognitive changes in prospective community-based studies. Our aim was to evaluate whether polymorphisms previously established as predictors of LOAD also predict worse cognitive function and accelerated decline across multiple cognitive domains. We analyzed data from the 3C-Dijon study, in which 4 931 respondents aged 65+ were examined up to 5 times over 10 years with a neuropsychological assessment. We evaluated the associations of polymorphisms in APOE, CR1, BIN1, CLU, PICALM, ABCA7, MS4A6A, CD33, MS4A4E, and CD2AP with level and change in 5 neuropsychological tests, assuming a dominant effect model. To optimize measurement, we used a mixed regression model with a latent process for each cognitive domain: global cognition (MMSE); verbal fluency (Isaac's Set Test); visual memory (Benton Visual Retention Test); information processing (Trail Making Test B); and literacy (NART).

APOE was associated with accelerated decline in global cognition and verbal fluency. Only two non-APOE genetic polymorphisms were associated with cognitive decline: CR1 was associated with rate of change in verbal fluency and BIN1 was associated with rate of change in global cognition. In a large prospective population-based study of dementia-free individuals, only a few cognitive domains were associated with established LOAD risk alleles. The most consistent associations were for global cognition and verbal fluency.

Keywords: Alzheimer's disease, genes, longitudinal cohort study, cognition, genome wide association studies

Introduction

Although genetic factors are thought to influence individual risk of late onset Alzheimer's disease (LOAD), only a few specific polymorphisms have been identified. APOE is the main locus established to have a large effect on LOAD risk. Other single-nucleotide polymorphisms (SNPs) have also been implicated in recent genome wide association studies (GWAS), although these SNPs demonstrated modest effects: CR1, CLU, PICALM, BIN1, MS4A4/MS4A6E, CD2AP, CD33, EPHA1, TREM2, ABCA7.¹⁻⁷ These new susceptibility genes suggested new pathways in the etiology of LOAD: lipid-processing for CLU and ABCA7, cell-membrane trafficking for PICALM, CD2AP and BIN1, and the immune-system for CR1, CD33 and EPHA1.⁸ Nonetheless, except for the APOE genotype,⁹⁻¹¹ evidence for the association between these loci and prospectively assessed cognitive decline has been mixed.¹²⁻¹⁶

Confirming that the genes linked to LOAD also predict accelerated cognitive losses – the hallmark symptom of LOAD – is a critical step for understanding how these genes contribute to the course of LOAD. Without evidence on the association between risk SNPs and cognitive change, we do not understand how the risk loci relate to LOAD. For instance, these polymorphisms may predict LOAD because they are associated with a lower cognitive reserve and thus may be associated with lower cognitive outcomes in a cross-sectional study of old people. Or, these polymorphisms may predict LOAD because they accelerate neurodegeneration and so, may predict a faster cognitive decline in a longitudinal setting.

We tested the hypothesis that genes involved in LOAD were associated with lower average initial cognitive level and with faster cognitive decline in initially non-demented individuals. Therefore, we used a large, prospective community-based cohort of initially non-demented French elderly to

assess whether the 10 top LOAD-associated SNPs also predicted average difference of cognitive level or rate of cognitive decline, measured by five neuropsychological outcomes.

Subjects and Methods

Study sample

We used data from the three-city (3C) study cohort. Between 1999 and 2001, the 3C study enrolled 9 294 non-institutionalized persons aged 65 years and over, sampled from the electoral rolls of three French cities: Bordeaux (South-West), Dijon (North-East) and Montpellier (South-East). Health-related data were collected during face-to-face interviews using standardized questionnaires. The study protocol was approved by the ethical committee of the University Hospital of Kremlin-Bicêtre. Each participant signed an informed consent and was free to refuse any specific part of the examination (such as blood sampling or MRI); partial refusals did not constitute an exclusion criterion. The study was conducted according to the principles expressed in the Declaration of Helsinki. Details about the study design of 3C were previously reported.¹⁷ For the current paper, analyses were restricted to the Dijon center (n=4 931), because this site used the same tests across the study waves.

Outcome Measures

Respondents were assessed up to 5 times over 10 years with a neuropsychological test battery including: Mini Mental State Examination (MMSE) for global cognition;¹⁸ Isaac's Set Test after 30s (IST30) for verbal fluency;¹⁹ National Adult Reading Test (NART), only at baseline and at 4-year follow-ups, for premorbid mental ability;²⁰ Trail Making Test B (TMTB) for visual attention and speed of information processing;²¹ and Benton Visual Retention Test (BVRT) for visual memory.²²

Total MMSE score varies between 0 and 30, a lower score corresponding to worse performances.¹⁸ Until a few years ago, the cut-off of 23 was recommended for screening for dementia, especially in epidemiological studies.^{23,24} There are several reports, mainly from epidemiological studies, showing that lower MMSE scores predict future dementia (including of Alzheimer's type) onset, and also that it predicts rate of cognitive decline.²⁴⁻²⁶ Isaac's set test (IST) consists in naming words during 15s first and then to go on up to 30s in different semantic categories consecutively: colors, animals, fruits, and cities.²⁷ Lower performances in IST have been shown to predict dementia risk and others neuropsychological tests assessing verbal fluency have shown similar predictive values.^{25,28} The BVRT consists in 15 stimulus cards and 15 multiple-choice cards. After the presentation of a stimulus card for 10 seconds, the participants are asked to choose the initial figure among four options.²² The NART is an untimed measure, consisting of 50 words with atypical phonemic pronunciation. Each word is presented individually and subjects are required to read each aloud. It is a marker of premorbid functioning and the maximum score is 50.²⁰ The Trail Making Test B(TMTB) consists of 25 circles including both numbers (1 – 13) and letters (A – L) and the participants has to draws lines to connect the circles in an ascending pattern, but with alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.) as quickly as possible, without lifting the pen or pencil from the paper.²¹ TMTB scores were calculated as the ratio of time to task completion divided by the number of correct connections.

Ascertainment of Genotypes

DNA samples were transferred to the French *Centre National de Génotypage* for genotyping. DNA samples that passed DNA quality control were genotyped with “Illumina Human610-Quad BeadChips” for the following polymorphisms: CR1 (rs3818361), BIN1 (744373), CLU

(rs11136000), PICALM (rs541458), ABCA7 (rs3764650), MS4A6A (rs610932), CD33 (rs3865444), MS4A4E (rs670139) and CD2AP (rs9296559). Genotype data were retained in the study for samples that had been successfully genotyped for >98% of the SNP markers. SNPs with call rates of <98%, with MAF <1% or showing departure from Hardy-Weinberg equilibrium in the control population ($P < 10^{-6}$) were excluded. APOE genotyping was performed using the fluorogenic 5'-nuclease assay with TaqMan chemistry. The sequences of the primers and probe oligonucleotides were designed as previously described.²⁹ Amplification was performed in a final volume of 5 μ L containing 20 ng/L of DNA solution, 900 nM of each primer, 200 nM of each probe, and 2 TaqMan Universal PCR master mix (Applied Biosystems, Foster City, CA).

Statistical Analyses

Due to missing data on genotypes or cognitive assessment, the analytic sample varied slightly across models. Among the 4 931 eligible participants, a maximum of 4 599 (accounting for 17 593 observations) were included for the MMSE–APOE epsilon-4 analysis whereas a minimum of 4 461 (17 039 observations) were included for the IST30–ABCA7 analysis. Cognitive performances outliers were transformed by recoding any values more than 3 standard deviations above or below the mean as a z score of 3 (or –3).

We estimated the relationship between each SNP and cognitive outcomes using nonlinear mixed models with latent process.³⁰ We did this in order to take in account curvilinearity of the link between cognitive tests and underlying cognitive functioning.³¹ These models assume that there is a latent cognitive process (representing the cognition level) evaluated by the neuropsychological tests. The model has two parts: firstly, a standard linear mixed model with the latent cognitive process as dependent variable and secondly, a model for the link between this

latent cognitive process and the neuropsychological test which allows us to consider the metrological properties of the tests (in a standard linear mixed model, this measurement link is linear). These two parts of the models are estimated simultaneously by maximum of likelihood with the function “lcm” of the homonymous R package. We specified a family of transformations to estimate the measurement link between neuropsychological test and the latent cognitive process. For each outcome (except TMTB), we choose a beta cumulative distribution function as recommended previously.³¹ For TMTB, due to convergence problem, we used I-splines with three nodes at tertiles. Analyses were performed with R version 2.15.2.

The estimated effects computed from the models are standardized betas (one SD in the outcome). SNPs were coded as binary indicator variables for the risk allele and presence of epsilon-4 for APOE, assuming a dominant inheritance model (i.e., homozygous for non-risk alleles vs. heterozygous or homozygous for risk alleles). Age was centered so a value of 0 represented age 77 years (the grand mean over all visits). We reversed coding for TMTB by multiplying all regression coefficients by -1 . Models were adjusted for sex and use current age as the time scale. In order to take into account practice effects, an indicator for the first wave of cognitive measures was added into the models.

Effect sizes of individual SNPs on cognition may be small.¹⁴ Risk scores combining information on individual genetic loci may improve statistical power to detect genetic associations. Therefore, in addition to examining individual SNPs, we created a genetic risk score (GRS) combining all SNPs by multiplying the allele count for each polymorphism by the reported beta coefficient from AlzGene² and summing the result for each gene.

Based on previous findings for LOAD, we had strong prior evidence for all of our hypotheses, so

we did not adjust for multiple comparisons; a p-value <0.05 was considered statistically significant. To explore the possible role of selective survival in our findings, we modeled the association between each SNP and mortality in a Cox model, with age as the time scale and delayed entry, adjusted for sex and education level.

Results

Participants' characteristics

Demographics are displayed in Table 1 for each assessment, from baseline (4 931 participants) to the final visit (2 283 participants). Median (Interquartile Range) age at baseline was 74 years (70.0-78.2), a larger fraction of participants were women (62% at baseline) and one third of the sample had 9-12 years of education (i.e., secondary school or more). Frequencies of genotypes of baseline participants are displayed in Table 2. One fifth of participants carried at least one APOE-epsilon-4 allele; for others SNPs, the prevalence of the risk allele ranged from 18% from ABCA7 to more than 90% for CD33.

Association between polymorphisms and rate of change in each cognitive domain

The genetic risk score (Table 3), including all 10 SNPs, was associated with higher rate of decline in global cognition (MMSE: $\beta = -0.21$, 95% CI [-0.35; -0.08]), verbal fluency (IST30: -0.25, 95% CI [-0.43; -0.07]), and visual memory (BVRT: $\beta = -0.13$, 95% CI [-0.25, -0.01]). It was not associated with information processing (TMTB: $\beta = -0.09$, 95% CI [-0.23;0.05]) or NART: $\beta = -0.06$, 95% CI [-0.31;-0.20]). These associations were no longer significant when the genetic risk score was constructed without the APOE allele.

Table 4 shows the association of individual polymorphisms with cognitive level (at age 77) and rate of cognitive change (over ten years) for each tests. Decline in global cognition (measured by

the MMSE) was faster among carriers of APOE epsilon-4 ($\beta = -0.14$, 95% CI [-0.25;-0.02]) and BIN1-G ($\beta = -0.10$, 95% CI [-0.19;-0.01]) alleles. Faster decline in verbal fluency performances (measured by the IST30) were observed in APOE epsilon4 carriers ($\beta = -0.22$, 95% CI [-0.37;-0.07] and CR1-C allele carriers ($\beta = -0.15$, 95% CI [-0.27;-0.02]). None of the loci was associated with cognitive decline in visual memory (BVRT), information processing (TMTB) or premorbid mental abilities (NART).

Association between polymorphisms and survival

Over follow-up, 989 deaths occurred; mortality was higher for APOE epsilon-4 carriers (hazard ratio (HR) =1.16, 95% CI [1.04-1.30], $p=0.01$). None of the other LOAD-associated SNPs predicted survival (CR1: HR=1.11, 95% CI [0.97-1.27], $p=0.13$; CLU: HR=1.07, 95% CI [0.89-1.28], $p=0.46$; BIN1: HR=1.04, 95% CI [0.92-1.18], $p=0.52$); PICALM: HR=1.05, 95% CI [0.93-1.20], $p=0.42$).

Discussion

In this sample of older community dwelling French adults, APOE predicted faster cognitive decline in both global cognition (MMSE) and verbal fluency (IST). CR1 predicted rate of change in verbal fluency and BIN1 predicted rate of change in global cognition. Visual attention and speed of information processing (TMTB) was only associated with APOE for cognitive level at age 77 and was not associated with faster rate of cognitive decline. Visual processing (BVRT) and literacy (NART, a supposed surrogate of cognitive reserve) were not associated with any of the LOAD-associated alleles. Further, polymorphisms in 7 of the 10 loci (in CLU, PICALM, ABCA7, MS4A6A, CD33, MS4A4E and CD2AP) did not predict level or rate of change in any cognitive domain.

Summary of findings of previous published studies is displayed in Table 5 with SNPs as rows and cognitive measures as columns. Associations with APOE haplotype are not displayed since they are widely acknowledged and hence, not always tested. CR1 was associated with cognition in four studies in three cognitive domains: general cognition¹³, attention¹⁶ and episodic memory^{32,33}. In our study, CR1 was also associated with cognition albeit only in one domain, verbal fluency. CLU was associated with cognition in three domains in four studies : general cognition (3MS¹⁶ and a composite score³⁴), episodic memory³⁵ and verbal memory.³⁶ However, in the study reported by Mengel-From et al., CLU was not associated with MMSE,³⁴ as in our study and the association with verbal memory was observed only in the subset of patients subsequently developed LOAD or Mild Cognitive Impairment (MCI).³⁶ This latter result was interpreted as reflecting an association between CLU and pre-symptomatic stage of LOAD but not between CLU and normal ageing.³⁶ PICALM was associated with general cognition (3MS) in the study reported by Sweet et al.,¹⁶ whereas we did not find any association between PICALM and cognitive function. Furthermore, previous studies did not reported any positive associations for BIN1 whereas we found an association between BIN1 and general cognition (MMSE). These discrepancies could be explain by differences in design (e.g., use of case/control design as in Pedraza et al.³⁵), choice of model for cognitive decline (e.g, Sweet et al. use a Bayesian analysis to model cognitive decline trajectory,¹⁶ whereas we use linear mixed model with latent process and others generally use linear mixed model), use of different cognitive instruments or genotyping measures, different populations or by chance.

Several studies reported negative associations and, because of plausible publication bias, it is likely than some negatives studies are not published. By example, a report found no association between any SNPs among CLU, PICALM, EXOC3L2, CR1, and BIN1 and verbal fluency,

logical memory, or general cognitive ability (evaluated by the Moray House Test) in the Lothian Birth Cohort of 1936 (at age 70) and in the Lothian Birth Cohort of 1921 (at age 79).³⁷ Authors did find an interaction between BIN1 and APP in APOE epsilon-4 positive subset of one cohort (the 1936 birth cohort) on verbal declarative memory. However, this discovery was not replicated in the replication cohort, nor in the joint analysis of the two cohorts.³⁷ In two non-demented large prospective cohorts, CR1 was associated with faster decline in both global cognition and episodic memory, but neither CLU nor PICALM predicted either cognitive outcome.¹³

Consistent with our findings, most prior research identifies APOE as the most relevant gene, often fully accounting for associations between any polygenic risk score and cognitive function. For instance, in 5 171 non demented people (age 45–99 years) from the population-based Rotterdam Study, it was found that a genetic AD risk score constructed from APOE, EPHA1, ABCA7, BIN1, CD2AP, CLU, CR1, MS4A4E, MS4A6A, and PICALM genotypes predicted both baseline global cognition and baseline memory function.¹⁴ However, after excluding APOE from the score, these associations were no longer statistically significant.¹⁴ A cross-sectional study across five cohorts find no associations between five polygenic risk scores (created using different thresholds for p-values of SNP–LOAD association) and cognitive ability in later life or age-related cognitive change.³⁸

A major challenge in examining cognitive change is the imperfect correspondence between neuropsychological test score changes and actual cognitive function. In particular for measures such as MMSE, it is known that the tests are not equally sensitive to changes in cognitive function among very high functioning and low functioning individuals.^{24, 39} To address this, we used latent process models, which better describe changes in the true cognitive function accounting for the limitations of the observed neuropsychological test scale.³⁰ In our study, we

chose to study each outcome in order to find domain-specific associations. We anticipated that genes strongly associated with LOAD would have broad cognitive consequences, but this was not the case. In fact, global cognition and verbal fluency showed the clearest associations with LOAD genes, although even these associations were modest. Encouragingly, literacy showed no association with any LOAD-associated allele; this is consistent with prior work using literacy related measures to proxy for premorbid ability.⁴⁰

Our study has several important strengths including the large sample size, the simultaneous study of a large number of the identified LOAD genes, and longitudinal modeling of cognitive outcomes. Indeed, many but not all prior studies of the LOAD genetics have been based on cross-sectional or retrospective study designs. Study designs based on prevalent, rather than incident, cases conflate the predictors of incidence with those of duration/survival, even in genetic research. For example, any allele differentially associated with longer survival among LOAD patients would be more common among LOAD patients than non-patients in an analysis of prevalent cases, even if the allele had no effect on the development of the disease. Therefore, it is important to assess the associations between the LOAD risk alleles and prospectively assessed cognitive change or incidence of cognitive impairment, as in the analyses reported here. The finding that several alleles previously confirmed to predict LOAD do not predict cognitive change in any domain opens the possibility that study design may have contributed to prior findings. This concern is partially allayed by our finding that APOE epsilon-4 was the sole polymorphism associated with mortality, and this association was similar in the whole study sample as in participants with LOAD.

This study has nonetheless some limitations. One of them is that some of the analyses were underpowered. Wide confidence intervals in some of the estimated effect sizes mean that the

study does not provide sufficient evidence to show that some LOAD-associated alleles are related to cognitive outcomes. However, in addition to large confidence intervals, it should be noted that the associated magnitudes of effects estimated were low in most cases and therefore the interpretation of the clinical meaning of such effect sizes is debatable.

Conclusion

APOE, CR1, and BIN1 were associated with rate of change in cognitive function, measured as global cognition or verbal fluency. Seven of the 10 loci we examined, CLU, PICALM, ABCA7, MS4A6A, CD33, MS4A4E and CD2AP—all previously implicated in LOAD—were not associated with average level or rate of change in any cognitive domain. Cognitive domains related to premorbid ability, visual memory and information processing were not associated with any LOAD risk alleles. In most cases, APOE had by far the largest effects dwarfing the importance of other genes.

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Conflict of Interest: The authors have no financial conflict of interest in relation to the reported work to disclose.

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Table 1. Participants' characteristics over the follow-up visits. The three-city study, Dijon, France

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4
N	4931	4352	3889	2961	2283
Follow-up years, Median (IQR)		1.8 (1.7-1.9)	3.6 (3.5-3.7)	6.9 (6.7-7.2)	8.6 (8.4-8.9)
Age (years), Median (IQR)	74.0 (70.0-78.2)	75.5 (71.6-79.7)	77.0 (73.2-81.1)	79.4 (75.9-83.7)	80.6 (77.3-84.8)
Female, n (%)	3043 (62)	2702 (62)	2443 (63)	1894 (64)	1478 (65)
More than 9 years of education, n (%)	1758 (36)	1572 (36)	1417 (36)	1110 (38)	884 (39)
MMSE, Median (IQR)	28 (26-29)	28 (27-29)	28 (26-29)	27 (25-28)	27 (26-28)
IST, Median (IQR)	48 (41-55)	50 (42-57)	49 (42-57)	48 (41-55)	48 (41-56)
TMTB, Median (IQR)	4.8 (3.4-8.3)	Not done	5.0 (3.4-9.2)	5.7 (3.8-11.0)	5.6 (3.8-9.8)
BVRT, Median (IQR)	11 (10-13)	12 (10-13)	11 (10-13)	11 (10-13)	12 (10-13)
NART, Median (IQR)	25 (20-28)	Not done	24 (20-28)	Not done	Not done

Abbreviations: MMSE, Mini-Mental state Examination; IST, Isaac Set Test; TMTB, Trail Making Test B; BVRT, Benton Visual Retention test; NART, National Adult Reading Test; IQR, Inter-Quartiles Range

Table 2. Description of genotypes for top LOAD-associated SNPs. The three-city study, Dijon, France.

SNPs	Risk Allele	Genotypes (n)	N	RAF (%)	OR
APOE	E4	E4+ (3625) E4- (977)	4602	21.2	1.76
CR1 (rs3818361)	A	AA (163) AG (1414) GG (3011)	4588	34.3	1.17
CLU (rs11136000)	C	CC (1690) TC(2153) TT(676)	4519	85.0	1.14
BIN1 (rs744373)	G	AA(2315) GA (1852) GG(350)	4577	48.1	1.16
PICALM (rs541458)	C	TT (2162) CT(1940) CC (483)	4585	52.8	1.14
ABCA7 (rs3764650)	G	TT(3664) GT(753) GG(47)	4464	17.9	1.23
MS4A4E(rs670139)	G	GG(1741) TG(2211) TT(623)	4575	61.9	1.08
CD33 (rs3865444)	C	AA(438) AC(1926) CC(2217)	4581	90.4	1.12
MS4A6A (rs610932)	T	GG (1341) TG (2331) TT(911)	4583	80.1	1.11
CD2AP (rs9296559)	C	CC(330) CT(1813) TT(2352)	4495	47.7	1.12

Abbreviations: OR: odds ratio; RAF: risk allele frequency; SNP: single nucleotide polymorphism.

Table 3. Association between genetic risk scores (GRS), and cognitive outcomes. The three-city study, Dijon, France. Data are standardized betas [95% CI].

Cognitive tests		GRS	GRS without APOE
MMSE	Difference at age 77	-0.27*** [-0.37; -0.17]	-0.22** [-0.36; -0.08]
	Slope for 10 years	-0.21** [-0.35; -0.08]	-0.13 [-0.31; 0.06]
IST	Difference at age 77	-0.22* [-0.39; -0.05]	-0.06 [-0.30; 0.17]
	Slope for 10 years	-0.25** [-0.43; -0.07]	-0.12 [-0.37; 0.12]
Benton	Difference at age 77	-0.06 [-0.14; 0.03]	-0.06 [-0.18; 0.06]
	Slope for 10 years	-0.13* [-0.25; -0.01]	-0.05 [-0.21; 0.11]
TMTB	Difference at age 77	-0.18*** [-0.29; 0.08]	-0.11 [-0.26; 0.03]
	Slope for 10 years	-0.09 [-0.23; 0.05]	-0.04 [-0.23; 0.15]
NART	Difference at age 77	0.05 [-0.15; 0.24]	-0.08 [-0.35; 0.20]
	Slope for 10 years	-0.06 [-0.31; 0.20]	0.00 [-0.25; 0.26]

Table 4. Associations between LOAD-associated SNPs and cognitive outcomes. The three-city study, Dijon, France. Data are standardized betas [95% CI].

Cognitive tests		APOE	CR1	CLU	BIN1	PICALM
MMSE	Difference at age 77	-0.17 ***[-0.26; -0.09]	-0.02[-0.09; 0.06]	-0.02 [-0.12; 0.08]	0.01 [-0.06; 0.08]	0.02 [-0.05; 0.09]
	Slope for 10 years	-0.14 [-0.25; -0.02]	-0.02 [-0.11; 0.08]	-0.09 [-0.21; 0.04]	-0.10* [-0.19; -0.01]	-0.01 [-0.11; 0.09]
IST	Difference at age 77	-0.19 *[-0.33; -0.05]	0.04 [-0.08; 0.16]	-0.13 [-0.29; 0.03]	-0.01 [-0.15; 0.13]	0.09 [-0.02; 0.21]
	Slope for 10 years	-0.22** [-0.37; -0.07]	-0.15 *[-0.27; -0.02]	0.00 [-0.14; 0.15]	-0.08 [-0.19; 0.04]	-0.04 [-0.15; 0.08]
Benton	Difference at age 77	-0.03 [-0.01; 0.04]	-0.00 [-0.03; 0.03]	-0.01 [-0.09; 0.08]	-0.01 [-0.07; 0.05]	0.02 [-0.03; 0.08]
	Slope for 10 years	-0.09 [-0.19; 0.01]	-0.00 [-0.08; 0.08]	-0.04 [-0.15; 0.08]	-0.06 [-0.14; 0.02]	0.02 [-0.07; 0.10]
TMTB	Difference at age 77	-0.15* [-0.23;-0.06]	0.03 [-0.04; 0.11]	-0.02 [-0.12; 0.08]	-0.01 [-0.07; 0.06]	0.02 [-0.05; 0.09]
	Slope for 10 years	-0.07 [-0.19; 0.04]	-0.02 [-0.12; 0.08]	0.09 [-0.04; 0.22]	-0.09 [-0.18; 0.00]	-0.08 [-0.17; 0.01]
NART	Difference at age 77	0.10 [-0.07; 0.26]	-0.01 [-0.13; 0.12]	-0.06 [-0.24; 0.12]	0.10 [-0.03; 0.23]	-0.03 [-0.16; 0.11]
	Slope for 10 years	-0.05 [-0.27; 0.17]	-0.02 [-0.21; 0.17]	0.04 [-0.20; 0.28]	-0.13 [-0.30; 0.05]	-0.12 [-0.30; 0.05]

Table 4 (continued). Associations between LOAD-associated SNPs and cognitive outcomes. The three-city study, Dijon, France. Data are standardized betas [95% CI].

Cognitive tests		ABCA7	MS4A6A	CD33	MS4A4E	CD2AP
MMSE	Difference at age 77	-0.02 [-0.11; 0.07]	-0.05 [-0.14; 0.04]	-0.12 [-0.24; 0.02]	-0.05 [-0.14; 0.04]	-0.04 [-0.11; 0.03]
	Slope for 10 years	-0.04 [-0.17; 0.08]	-0.08 [-0.19; 0.03]	-0.03 [-0.17; 0.11]	-0.08 [-0.19; 0.03]	-0.00 [-0.09; 0.09]
IST	Difference at age 77	-0.13 [-0.28; 0.03]	0.11 [-0.04; 0.03]	-0.11 [-0.31; 0.08]	0.11 [-0.04; 0.25]	-0.01[-0.15; 0.12]

	Slope for 10 years	0.09 [-0.07; 0.24]	0.04 [-0.11; 0.19]	-0.17 [-0.37; 0.03]	0.04 [-0.11; 0.19]	0.05 [-0.07; 0.17]
Benton	Difference at age 77	-0.07 [-0.14; 0.07]	0.04 [-0.03; 0.11]	-0.09 [-0.18; 0.01]	0.04 [-0.03; 0.11]	-0.05 [-0.11; 0.08]
	Slope for 10 years	-0.05 [-0.16; 0.05]	-0.00 [-0.15; 0.15]	0.03 [-0.10; 0.16]	-0.00 [-0.15; 0.15]	-0.01 [-0.09; 0.08]
TMTB	Difference at age 77	-0.06 [-0.16; 0.03]	-0.04 [-0.13; 0.05]	-0.10 [-0.22; 0.02]	-0.04 [-0.13; 0.05]	0.00 [-0.05; 0.06]
	Slope for 10 years	0.06 [-0.06; 0.18]	0.01 [-0.11; 0.12]	-0.04 [-0.19; 0.11]	0.01 [-0.11; 0.12]	0.05 [-0.05; 0.14]
NART	Difference at age 77	-0.02 [-0.19; 0.15]	-0.02 [-0.18; 0.16]	-0.02 [-0.23; 0.19]	-0.02 [-0.18; 0.15]	0.00 [-0.05; 0.05]
	Slope for 10 years	0.08 [-0.15; 0.31]	0.08 [-0.14; 0.30]	0.05 [-0.24; 0.35]	0.08 [-0.14; 0.30]	0.00 [-0.25; 0.26]

Table 5. Published studies reporting positive associations between LOAD-associated SNPs (rows) and cognitive measures (columns).

	General cognition			Attention	Episodic memory	Verbal memory
	MMSE	3MS	Composite score	DSST	Composite score	California Verbal Learning Test
CR1			Chibnik ³²	Sweet ¹⁶	Chibnik ³² , Keenan ³³	
CLU		Sweet ¹⁶	Mengel-From ³⁴		Pedraza ³⁵	Thambisetty ⁴¹
BIN1						
PICALM		Sweet ¹⁶				
ABCA7						
MS4A4E						
CD33						
MS4A6A						
CD2AP						