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Interaction of Alzheimer's Disease-Associated Genetic Risk with Indicators of Socioeconomic Position on Mild Cognitive Impairment in the Heinz Nixdorf Recall Study

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Abstract.

Background: The apolipoprotein E (*APOE*) ε4 allele is reported to be a strong genetic risk factor for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Additional genetic loci have been detected that influence the risk for late-onset AD. As socioeconomic position (SEP) is also strongly related to cognitive decline, SEP has been suggested to be a possible modifier of the genetic effect on MCI.

Objective: To investigate whether *APOE* ε4 and a genetic sum score of AD-associated risk alleles (GRS_{AD}) interact with SEP indicators to affect MCI in a population-based cohort.

Methods: Using data of 3,834 participants of the Heinz Nixdorf Recall Study, *APOE* ε4 and GRS_{AD} by SEP interactions were assessed using logistic regression models, as well as SEP-stratified genetic association analysis. Interaction on additive scale was calculated using the relative excess risk due to interaction (RERI). All analysis were additionally stratified by sex.

Results: Indication for interaction on the additive scale was found between *APOE* ε4 and low education on MCI (RERI: 0.52 [95% confidence interval (CI): 0.01; 1.03]). The strongest genetic effects of the *APOE* ε4 genotype on MCI were observed in groups of low education (Odds ratio (OR): 1.46 [95% CI: 0.79; 2.63] for $\leq$ 10 years of education versus OR: 1.00 [95% CI: 0.43; 2.14] for $\geq$ 18 years of education). Sex stratified results showed stronger effects in women. No indication for interaction between the GRS_{AD} and SEP indicators on MCI was observed.

Conclusion: Results indicate that low education may have an impact on *APOE* ε4 expression on MCI, especially among women.

Keywords: Apolipoprotein E4, gene environment interaction, mild cognitive impairment, socioeconomic position

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INTRODUCTION

Alzheimer's disease (AD) is a common age-related neurodegenerative disease. Mild cognitive impairment (MCI) represents an intermediate and potentially modifiable stage between normal cognition and dementia, including AD [1–3]. MCI involves minor problems of cognition, such as memory loss, problems with language, reasoning, attention, and visual depth perception [4]. As people with MCI can remain stable for many years or even return to a normal cognitive state over time, MCI is a promising target in the prevention of dementia [5, 6]. Studies have identified the apolipoprotein E (*APOE*) ε4 allele not only to be a strong genetic risk factor for AD [7–11], but also for MCI [1–3, 12–14]. Studies have further indicated that the effect of *APOE* ε4 on developing MCI is sex-dependent, with women being at greater risk than men [15, 16]. However, not all *APOE* ε4 carriers develop dementia, and about one-half of AD is not *APOE* ε4 associated [17], meaning that further genetic or non-genetic factors potentially may modify the expression of *APOE* ε4 risk. In accordance with the involvement of further genetic factors, genome-wide association studies (GWAS) have detected several genetic loci in addition to *APOE* that influence the risk for late-onset AD, together accounting for ∼31% of its genetic variance (25.2% of this variance was reported for *APOE* ε3 and ε4 alleles) [18]. In a population-based study, AD-related genetic variants detected by GWAS were also found to be associated with MCI status, even after excluding *APOE* ε4 from the score [19].

Research has shown that indicators of socioeconomic position (SEP), such as education and occupational status, are also strongly related to cognitive decline, following a social gradient [2, 20]. Compared to people from high socioeconomic groups, people with a lower SEP are more likely to be exposed to unfavorable health behaviors such as low physical activity and poor diet, which are linked to poor mental health, cognitive impairment, and dementia [21]. Studies suggested that interactions between the *APOE* ε4 genotype with such environmental factors (GxE) might modify the effect of *APOE* ε4 on cognitive impairment or dementia [7, 20, 22–25]. However, empirical studies examining gene-by-SEP interactions (GxSEP) on MCI are limited and the impact of sex on the genetic risk of MCI has not been sufficiently examined. The aim of this study therefore was to investigate whether *APOE* ε4 and a genetic sum score of AD-associated risk alleles (GRS_{AD}) detected by GWAS interact with educational attainment and monthly household income as indicators of socioeconomic position (SEP) to affect MCI in a population-based cohort including sex-stratified analysis.

METHODS

Study population

Data of the baseline and the second examination of the prospective population-based Heinz Nixdorf Recall Study (Risk Factors, Evaluation of Coronary Calcium, and Lifestyle) were used. The rationale and the design of the study have been previously described [26]. Briefly, between 2000 and 2003 individuals were randomly selected from mandatory registries of the cities Bochum, Essen, and Mülheim/Ruhr. 4,814 study participants aged 45–75 years were enrolled for the baseline examination in 2001–2003 [27]. The study population derives from a population-based sample of participants without dementia, meaning that the rate of comorbidities represents the rate in the general population (e.g., mean BMI of 27.8 (standard deviation: 4.6), 472 (12.3%) participants had diabetes mellitus and 208 (5.4%) coronary heart disease at study baseline). After five years, 4,157 participants joined the second examination ($n = 430$ were lost to follow-up and $n = 227$ were deceased). The study was approved by the ethics committee of the University Hospital Essen and included extended quality management procedures and certification according to DIN ISO 9001 : 2000. Written informed consent was obtained from all participants.

Mild cognitive impairment

Standardized cognitive assessment procedures were introduced at the second examination. A detailed description of the assessment procedures has been reported earlier [28, 29]. Briefly, cognitive performance was conceptualized as a multidimensional test, using established measures of immediate and delayed verbal memory (eight word list, performance measured as number of words recalled in each trial), verbal fluency (semantic category "animals", number of recalled words within one minute), speed of processing (labyrinth test, time in seconds needed to complete the task), and visuospatial ability (clock-drawing test, performance was rated from 1 (perfect clock) to 6 (poor performance)) [30–32]. The raw data for each subtest were z-transformed (mean = 0,

standard deviation (SD)±1) according to three age groups (50–59 years, 60–69 years, and 70–80 years) and within every age group according to the following education groups (≤ 10 years, 11–13 years, ≥ 14 years). Based on the age and education adjusted z scores, the performance was rated as impaired (> 1 SD below the mean). MCI was defined according to the then current International Working Group on MCI criteria [2]. In short, the MCI diagnosis required a cognitive complaint and therefore participants were asked if their cognitive performance had declined during the past two years. Furthermore, the diagnosis required a cognitive impairment that is insufficient to fulfill criteria for dementia (DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [33]) and reflects generally intact activities of daily living. A cognitive subtest was rated as impaired if the performance was more than 1 SD below the age and education-adjusted mean or a score of ≥ 3 in the clock drawing test. Participants without MCI or dementia were categorized as no-MCI.

Socioeconomic position

Educational attainment and household income were used as indicators for SEP and assessed using a standardized computer-assisted face-to-face interview at study baseline. Education was defined by combining school and vocational training as total years of formal education according to the International Standard Classification of Education [34]. Duration of education was categorized into four groups as ≤ 10 years, 11–13 years, 14–17 years, and ≥ 18 years of education. The lowest educational group is equivalent to a minimum compulsory school attendance and no additional vocational degree, and the highest educational group is comparable to a vocational training including additional qualification or a university degree. Income was measured as the monthly household equivalent income (in Euros) calculated by weighting the participants' total household net income by a factor for each household member [35]. Income was divided into four groups, using sex-specific quartiles.

For SEP stratified analyses, SEP variables categorized in the four groups were used. For all other analyses, income was included as a dichotomized variable with groups of low and high income using the sex-specific median as cut off and education was dichotomized in low education with < 14 years and high education with ≥ 14 years. Education and income were analyzed separately to account for their different mechanisms in causing health inequalities [36, 37].

Genetic data

Lymphocyte DNA was isolated from EDTA anticoagulated venous blood using the Chemagic Magnetic Separation Module I (Chemagen, Baesweiler, Germany). In order to discriminate between *APOE* alleles ε2, ε3, and ε4, the two single-nucleotide polymorphisms (SNPs) rs429358 and rs7412 were used, genotyped on the MetaboChip Illumina BeadArray. Study participants with at least one allele ε4 (2/4, 3/4, 4/4) were defined as *APOE* ε4 status positive, all others as *APOE* ε4 status negative.

Using the meta-analyses of genome-wide association studies by [38], 22 SNPs (Supplementary Table 1) representing independent genetic loci robustly associated with late-onset AD were identified on the global screening array 24v1.0 available for all study participants included in the analysis. Study participants were all of European ancestry. Neither SNPs rs62039712 at *WWOX* and rs3752246 at *ABCA7* nor suitable proxy SNPs were found within genetic data of the study population and had to be excluded from analysis. An unweighted genetic risk score (GRS_{AD}) was calculated by aggregating the total number of disease risk alleles for each individual across the selected 22 SNPs not including the *APOE* locus. In addition, a weighted GRS_{AD} was calculated by summing up and weighting each of the risk alleles, by their previously published effect sizes [38]. The weighted GRS was then rescaled to reflect the number of risk alleles. As the main results using the weighted score did not differ to those resulting from the unweighted GRS_{AD}, only the latter were reported.

Quality control was applied separately to each of the 22 SNPs prior to analysis and first performed on subject level including sex-, ethnicity-, and relatedness-checks, using Plink (v. 1.07). No deviation from Hardy-Weinberg equilibrium (HWE) ($p \leq 0.001$) was detected, and none of the SNPs had to be excluded with a missing genotype frequency > 5%. One individual was removed due to a low genotyping rate of > 5% missing genotypes.

Statistical analyses

Overall, 3,834 non-demented participants with complete information on the GRS, *APOE* ε4 status, and MCI were included in the analysis (Supplementary Figure 1). Participants with a

physician's diagnosis of dementia or AD, with intake of cholinesterase inhibitors (ATC, anatomic-therapeutic-chemical classification issued by the World Health Organization, code: N06DA) or other antidementia drugs (N06DX), or fulfilling the DSM-IV dementia diagnosis, were excluded from the analyses population ($n = 22$). Some participants had missing information on education ($n = 5$) or income ($n = 225$) and therefore populations differed in respective analyses.

Separate logistic regression models were fitted to estimate sex- and age-adjusted odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) for the association of education, income, *APOE* ε4 status (carrier versus noncarrier), and the GRS_{AD} with MCI (versus non-MCI). To assess interaction of *APOE* ε4 genotype/GRS_{AD} by indicators of SEP on MCI and to give sufficient information on the magnitude of interaction, analyses were based on recommendations by Knol and van der Weele [39]. First, the genetic effects of *APOE* ε4 genotype/GRS_{AD} on MCI were stratified by educational groups and income quartiles to see whether the genetic effect differs between SEP groups. Second, single reference joint effects of *APOE* ε4 genotype/GRS_{AD} tertiles and SEP groups on MCI were calculated in separate logistic regression models for income quartiles and education categories, with the group of a negative *APOE* ε4 status/low GRS_{AD} and a high socioeconomic position as reference category to check whether the genetic effect on MCI was modified by SEP. To assess *APOE*xSEP and GRS_{AD}xSEP interaction on the multiplicative scale, *APOE* ε4 status, and GRS_{AD} main effects and the corresponding interaction terms were included into age- and sex-adjusted regression models. To consider interaction on the additive scale, the relative excess risk due to interaction (RERI) was calculated. For this, the GRS_{AD} was dichotomized using a median split. For interaction analyses, the SEP-variables income and education were dichotomized. Interaction analysis was also repeated for each AD-associated SNP and SEP indicator. Analyses were additionally stratified by sex.

Sensitivity analysis was performed using a more rigorously defined non-MCI group by including only those participants who did not report a cognitive complaint and did not show any impairment in the applied cognitive tests ($n = 1380$). In addition, sensitivity analysis including only participants with amnestic MCI (i.e., participants presenting with an objective impairment in memory (immediate and/or delayed verbal memory subtest) with or without impairment in any other cognitive tests applied; $n = 293$) was also performed to examine the robustness of study results.

The statistical computing software R v3.6.0 [40] was used for all analyses. For the calculation of the genetic risk score and for single SNP analyses Plink v1.07 software package for Windows was used [41].

RESULTS

In the study population, 560 participants were defined as having MCI (prevalence: 14.6%) (Table 1). Women had lower formal education and a lower median income than men. One fourth of the study population was positive for the *APOE* ε4 genotype. The number of genetic risk alleles ranged from 13 to 34 risk alleles with a mean of 24.1 ± 2.9 in the whole study population. The mean number of AD associated risk alleles showed no differences between men (24.1 ± 2.8) and women (24.2 ± 2.8).

Table 1
Characteristics of study population stratified by sex

	All ($n = 3,834$)	Men ($n = 1,905$)	Women ($n = 1,929$)
Age (y) [0] mean ± SD	59.1 ± 7.6	59.2 ± 7.6	59.1 ± 7.7
MCI [0] *n* (%)	560 (14.6%)	275 (14.4%)	285 (14.8%)
Amnestic MCI *n* (%)	293 (7.6%)	161 (8.5%)	132 (6.8%)
APOE ε4 positive [0] *n* (%)	981 (25.6%)	479 (25.1%)	502 (26.0%)
AD risk alleles (GRS_{AD}) [0] mean ± SD	24.1 ± 2.8	24.1 ± 2.8	24.2 ± 2.8
Income (€/mo) [225] median (IQR)	2,833 (2,167–3,750)	3,167 (2,250–4,074)	2,750 (2,027–3,667)
Education (y) [5] *n* (%)			
≤ 10	378 (9.9%)	76 (4.0%)	302 (15.7%)
11–13	2142 (55.9%)	898 (47.2%)	1244 (64.5%)
14–17	871 (22.8%)	653 (34.3%)	218 (11.3%)
≥ 18	438 (11.4%)	274 (14.5%)	164 (8.5%)

[number of participants with missing values]; MCI, mild cognitive impairment; *APOE*, apolipoprotein E; AD, Alzheimer's disease; SD, standard deviation; IQR, interquartile range (first quartile-third quartile).

Table 2
Sex- and age- adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association of income, education, *APOE* ε4 genotype, and the Alzheimer's disease-associated genetic risk score (GRS_{AD}) with mild cognitive impairment calculated using separate logistic regression models

	n	OR (95% CI)	*p*
Intercept	3,609	0.02 (0.01; 0.04)	$<2*10^{-16}$
Low income		1.38 (1.14; 1.68)	0.001
Sex		1.04 (0.86; 1.25)	0.68
Age		1.03 (1.02; 1.05)	$4.0*10^{-8}$
Intercept	3,829	0.02 (0.01; 0.04)	$<2*10^{-16}$
Low education		1.37 (1.11; 1.69)	0.004
Sex		0.94 (0.78; 1.14)	0.52
Age		1.04 (1.02; 1.05)	$7.4*10^{-9}$
Intercept	3,834	0.01 (0.008; 0.03)	$<2*10^{-16}$
APOE ε4		1.27 (1.04; 1.55)	0.02
Sex		1.03 (0.86; 1.23)	0.79
Age		1.04 (1.03; 1.05)	$7.1*10^{-10}$
Intercept	3,834	0.02 (0.01; 0.05)	$1.5*10^{-13}$
GRS_{AD}		0.99 (0.96; 1.03)	0.94
Sex		1.03 (0.86; 1.23)	0.77
Age		1.04 (1.03; 1.05)	$5.8*10^{-10}$

A higher chance of having MCI was observed for participants with low income (OR: 1.38 [95% CI: 1.14; 1.68]) or < 14 years of formal education (OR: 1.37 [95% CI: 1.11, 1.69]) (Table 2). A positive *APOE* ε4 status was associated with a higher chance of MCI (OR: 1.27 [95% CI: 1.04; 1.55]), while no effect of the genetic risk score on MCI was observed. Sex-stratified analyses showed that low income had a greater effect on MCI in men (OR: 1.52 [95% CI: 1.15; 2.01]), while low education (OR: 1.58 [95% CI: 1.10; 2.33]) and a positive *APOE* ε4 status (OR: 1.40 [95% CI: 1.06; 1.84]) had a greater effect on MCI in women (Supplementary Table 2). The GRS_{AD} showed no effect in both sexes.

Overall, SEP-stratified analysis showed a stronger genetic effect of *APOE* ε4 in groups with low education (Fig. 2). This trend was not evident across income quartiles, where similar effect size estimates were observed in the lowest and the highest quartile. Results for the genetic effect on MCI across the two lower education groups revealed that participants with < 14 years of formal education showed a considerably higher genetic effect of *APOE* ε4 on MCI, while no effect was present in the two highest education groups ≥ 14 years (Fig. 1). Results of the SEP-stratified analysis for the GRS_{AD} showed no trend of genetic effects on MCI across income quartiles or educational group (Fig. 2).

In the analysis of joint effects with a single reference group, ORs showed a trend within and between groups: with decreasing income and years of education and a positive *APOE* ε4 status compared to a negative *APOE* ε4 status, the joint effects were observed to be stronger. Compared to the reference group with the lowest SEP and a negative *APOE* ε4 status, the strongest joint effects were seen in groups with *APOE* ε4 genotype and lowest SEP (OR: 2.29 [95% CI: 1.53; 3.43] for income and OR: 2.29 [95% CI: 1.18; 4.33] for education) (Supplementary Figure 2). Less clear patterns were seen for the joint effects of SEP indicators and tertiles of the GRS_{AD} on MCI (Supplementary Figure 3).

Some indication for positive interaction on the multiplicative scale was observed between *APOE* ε4 status and education ($OR_{APOE*Education\_low}$: 1.42 [0.91; 2.24]). No indication for interaction on the multiplicative scale was found between *APOE* ε4 status and income, nor between the GRS_{AD} with indicators of SEP (Table 3). Sex-stratified analyses revealed also some indication for *APOE* ε4 by education interaction in women ($OR_{APOE*Education\_low}$: 2.17 [95% CI: 0.94; 5.48]), indicating that the observed *APOE* ε4 by education interaction was mainly present in women (Supplementary Table 3).

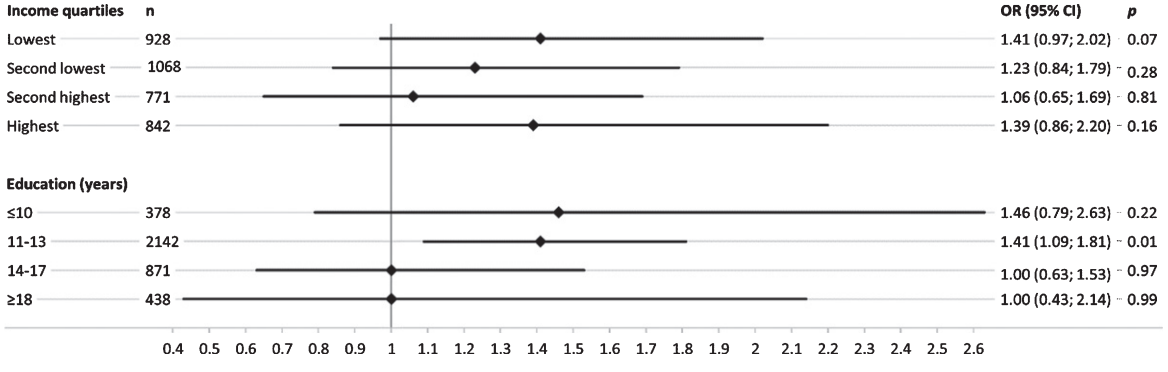

Fig. 1. Sex- and age-adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association of *APOE* ε4 genotype with mild cognitive impairment, stratified by income quartiles and education groups (years) in separate logistic regression models.

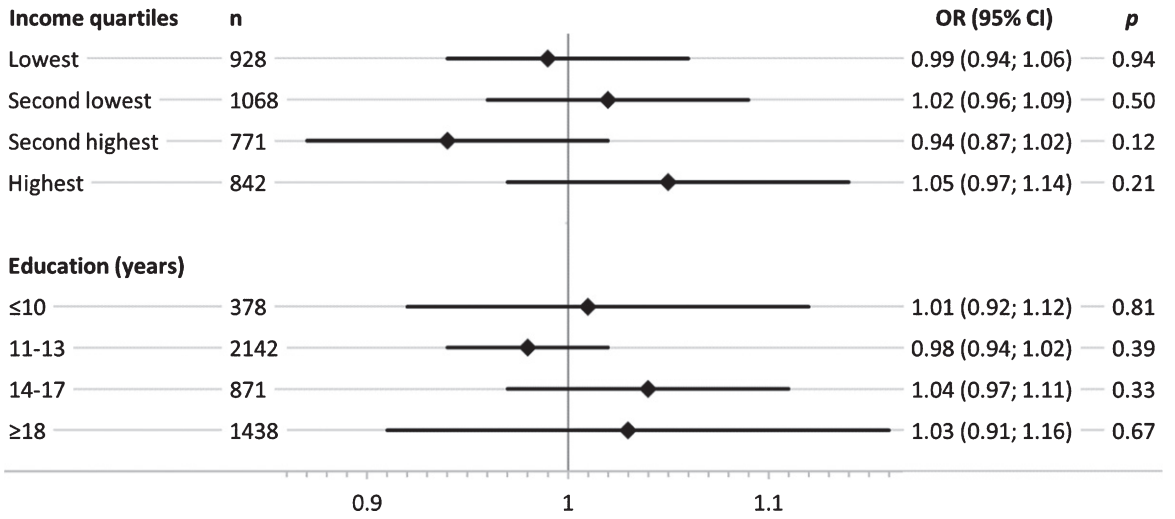

Fig. 2. Sex- and age-adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association of the AD-associated genetic risk score (GRS_{AD}) with mild cognitive impairment, stratified by income quartiles and education groups (years) in separate logistic regression models.

Table 3
Sex- and age- adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) in logistic regression models including main effects and interaction terms for the interaction of *APOE* ε4 status and AD-associated genetic risk score (GRS_{AD}) with education and income on mild cognitive impairment

	n	OR (95% CI)	*p*
Intercept	3,609	0.02 (0.01; 0.04)	$<2.0^{*}10^{-16}$
Income low		1.35 (1.08; 1.71)	0.01
APOE ε4		1.21 (0.87; 1.68)	0.25
Sex		1.04 (0.86; 1.25)	0.70
Age		1.04 (1.02; 1.05)	$6.0^{*}10^{-8}$
APOE ε4* Income low		1.09 (0.71; 1.67)	0.70
Intercept	3,829	0.02 (0.01; 0.04)	$<2.0^{*}10^{-16}$
Education low		1.24 (0.98; 1.59)	0.08
APOE ε4		1.00 (0.67; 1.45)	0.99
Sex		0.94 (0.77; 1.13)	0.50
Age		1.03 (1.02; 1.05)	$1.0^{*}10^{-8}$
APOE ε4* Education low		1.42 (0.91; 2.24)	0.13
Intercept	3,609	0.02 (0.004; 0.09)	$4.3^{*}10^{-7}$
Income low		0.97 (0.19; 5.05)	0.97
GRS_{AD}		0.99 (0.94; 1.05)	0.81
Sex		1.04 (0.86; 1.25)	0.68
Age		1.04 (1.02; 1.05)	$4.1^{*}10^{-8}$
GRS_{AD}* Income low		1.01 (0.95; 1.09)	0.68
Intercept	3,829	0.01 (0.002; 0.04)	$5.8^{*}10^{-9}$
Education low		3.86 (0.70; 21.46)	0.12
GRS_{AD}		1.03 (0.97; 1.10)	0.32
Sex		0.94 (0.77; 1.14)	0.54
Age		1.04 (1.02; 1.05)	$8.2^{*}10^{-9}$
GRS_{AD}* Education low		0.96 (0.89; 1.03)	0.23

Table 4
Age- and sex-adjusted relative excess risk due to interaction (RERI) and corresponding 95% confidence intervals (95% CI) as a measure of interaction between *APOE* ε4xSEP and the GRS_{AD}xSEP on the additive scale

	n	RERI (95% CI)	*p*
APOE ε4*Income	3,609	0.22 (–0.35; 0.79)	>0.05
APOE ε4*Education	3,829	0.52 (0.01; 1.03)	0.02
GRS_{AD}*Income	3,609	–0.19 (–0.73; 0.35)	>0.05
GRS_{AD}*Education	3,829	–0.35 (–0.94; 0.24)	>0.05

On the additive scale, an indication for a positive interaction between *APOE* ε4 status and education was observed (RERI: 0.52 [95% CI: 0.01; 1.03]) (Table 4). Within sex-stratified analyses, an indication for a positive interaction between *APOE* ε4 status and education was only present among women (RERI: 1.00 [95% CI: 0.26; 1.75]) (Supplementary Table 4).

The single SNP analysis of each of the 22 AD-associated SNPs revealed that only ∼50% of the AD risk alleles reported by [38] showed directionally consistent effect size estimates for the association with MCI within the study population (Supplementary Table 1). Overall, no strong indication was found for SNP by SEP interaction, except an indication for additive interaction at locus *SPI1* with education (Supplementary Tables 5 and 6). Interaction effect size estimates of the single SNP interaction analysis differed strongly for both SEP indicators in the range of ORs of 0.82 to 1.53 and RERIs of –0.30 to 0.62 for interaction with income and in the range of ORs

of 0.73 to 1.31 and RERIs of –0.40 to 0.27 for interaction with education. Results of sensitivity analysis revealed no substantial differences to the main study results (Supplementary Tables 7–12). While there was no indication for an association of the GRS_{AD} with MCI, the GRS_{AD} effect size estimate was at least directionally consistent when using the amnestic MCI phenotype (OR: 1.02 [95% CI: 0.97; 1.06]) (Supplementary Table 10).

DISCUSSION

The aim of the present study was to investigate whether *APOE* ε4 and a genetic sum score of AD-associated risk alleles interact with educational attainment and household income to affect MCI in a population-based cohort. Study results gave indication for positive interaction on the additive scale between *APOE* ε4 and low education, as the combination of the genetic effect and low education was more than the sum of their marginal effects. This was supported by results of stratified genetic association analysis, in which the strongest effects of the *APOE* ε4 genotype on MCI were seen in groups of low education. Also, single reference joint effects of all possible combinations of the *APOE* ε4 status and SEP groups showed the strongest effect on MCI in participants with a positive *APOE* ε4 status and low SEP. Sex stratified results showed stronger interaction effects in women. No indication for interaction was observed for the genetic sum score of AD-associated risk alleles with indicators of SEP.

To our knowledge, this is the first study to examine possible interactions between *APOE* ε4, an AD-associated genetic risk allele score and indicators of SEP on MCI within a population-based cohort including also sex-stratified analyses. The main finding that *APOE* ε4 and education interact on the additive scale to affect MCI is in line with results of a study by Arenaza-Urquijo et al. (2015), who have reported an interaction between *APOE* ε4 and education on frontal and temporal metabolism in a French study sample [25]. Likewise, another study has found an interaction between education and *APOE* ε4 on dementia in pooled data of three major population-based studies from Northern Europe [22]. Cook and Fletscher (2015) have reported an interaction between *APOE* ε4 genotype and years of schooling and also found that a higher educational attainment is adequate to cancel out the increased risk of the *APOE* ε4 genotype on late-life cognitive decline, using data of the Wisconsin Longitudinal Study [42]. Similar results were observed in the study presented here, which showed that no effect of *APOE* ε4 on MCI was detected in groups with ≥ 14 years of formal education.

Sex-stratified analyses revealed that women had a much higher risk of MCI when carrying the *APOE* ε4 genotype compared to men. An indication for the *APOE* ε4 by education interaction was observed to be substantially stronger in women on both, multiplicative and additive scales. The direction of effects in men was consistent to those in women. A large number of epidemiological studies has supported sex differences in the association between a positive *APOE* ε4 genotype and cognitive deficits, with women being at higher risk of AD or cognitive decline [43–46]. A previous study in a longitudinal sample of 11,654 subjects recruited through the National Alzheimer's Coordinating Center in the United States has demonstrated that the risk of clinical conversion conferred by the *APOE* ε4 allele and the transformation from healthy aging to MCI/AD and from MCI to AD is much greater in women than in men [15]. The authors have hypothesized that tau pathology could be a possible explanation for the observed sex differences. Female *APOE* ε4 carriers were found to show increased cerebrospinal fluid tau concentrations and tau/Aβ ratios, compared with male carriers.

A study by Müller-Gerards et al. (2019) have observed an indication for a positive interaction between subjective cognitive decline and *APOE* ε4 genotype on incident MCI during 5 years of follow-up in women. The authors have mentioned the role of sex hormones, such as the loss of estrogen through menopause, as a possible explanation for the observed sex differences [47]. Several studies have found that estrogen use in elderly women has a favorable effect on cognition and prevention of dementia, independent of age, education, ethnicity, and *APOE* genotype [48–50], while other studies have not found an association [51]. Beyond that, another study has found an interaction between estrogen use and the presence of the *APOE* ε4 genotype, whereas current estrogen use reduced the risk of cognitive impairment compared with never users in *APOE* ε4 negative women and not in *APOE* ε4 positive women [52].

The present study did not find an association between a sum score of 22 AD-associated risk alleles on MCI, which contrasts results of previous studies that found associations between genetic sum scores of AD-associated risk alleles and MCI in the population-based Rotterdam Study [19, 53]. This may be in part

explained by differences in the SNPs used for calculating the genetic sum scores, because compared to previous studies, the GRS used here was based on a more recent genome-wide meta-analysis including more individuals [38]. However, in the sensitive analysis including only cases of amnestic MCI, the GRS_{AD} effect size estimate was at least directionally consistent. This seems plausible, as amnestic MCI usually shows a higher progression to AD compared to non-amnestic MCI.

The effect of the *APOE ε4* genotype on non-amnesic MCIs that are not prodromal to AD may be explained by the effect of *APOE* on the lipid and lipoprotein metabolism which affects brain function in various ways [54]. The fact that no indication for interaction between the AD-associated risk alleles and SEP was observed in the present study is in line with a study using data of the UK Biobank where an increased dementia risk was reported within groups of high genetic risk for AD, while no interaction was reported with SEP-related lifestyle risk score including smoking, physical activity, diet, and alcohol consumption [55].

The present study adds further knowledge to the results of previous studies with the investigation of interactions between SEP and the *APOE ε4* genotype and additional AD-associated variants on MCI in sex-stratified analyses. Strengths of the present study include a population-based study sample and the use of two different individual SEP indicators in the analyses. Further, evidence for interaction was not only based on testing *APOE*xSEP and GRS-$_{AD}$xSEP interaction terms in regression models, but also on stratified analyses, single references joint effects and calculating the RERI. Despite these strengths, the following limitations need to be acknowledged: The power of the study was not sufficient for detection of small interaction effect size estimates. Especially for robustly analyzing single SNP by SEP interactions, larger samples are required. Further, the neuropsychological tests used in this study were rather limited. Nevertheless, the cognitive assessment was validated in 656 participants against an MCI diagnosis that was based on a detailed neuropsychological examination conducted by a neuropsychologist and a neurological examination by a senior neurologist and found a good accuracy in identifying participants with MCI (Area under the curve (AUC) = 0.82 (0.78–0.85)) [28].

In conclusion, the results of the present study provide an indication of an interaction of *APOE* ε4 with education on MCI in a population-based study sample, showing stronger genetic effects in groups of low education, especially among women. This gives support to the hypothesis that SEP influences the expression of genetic risk related to MCI. Higher educated groups seem to be better equipped to reduce their genetic susceptibility for MCI. However, it has to be assumed that SEP does not directly affect MCI and SEP-related factors not considered in the present analysis may be responsible for the observed differences in the genetic risk for MCI. Literature suggests that cognitive leisure activities and diet as modifiable SEP-related risk factors play a role in the development of MCI [21, 56]. However, further studies are needed to investigate the risk factors involved.

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SUPPLEMENTARY MATERIAL

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