Is APOE ε4 associated with cognitive performance in early MS?

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Abstract

Objective
To assess the impact of APOE polymorphisms on cognitive performance in patients newly diagnosed with clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS).

Methods
This multicenter cohort study included 552 untreated patients recently diagnosed with CIS or RRMS according to the 2005 revised McDonald criteria. The single nucleotide polymorphisms rs429358 (APOE ε4) and rs7412 (APOE ε2) of the APOE haplotype were assessed by allelic discrimination assays. Cognitive performance was evaluated using the 3-second paced auditory serial addition test and the Multiple Sclerosis Inventory Cognition (MUSIC). Sum scores were calculated to approximate the overall cognitive performance and memory-centered cognitive functions. The impact of the APOE carrier status on cognitive performance was assessed using multiple linear regression models, also including demographic, clinical, MRI, and lifestyle factors.

Results
APOE ε4 homozygosity was associated with lower overall cognitive performance, whereas no relevant association was observed for APOE ε4 heterozygosity or APOE ε2 carrier status. Furthermore, higher disability levels, MRI lesion load, and depressive symptoms were associated with lower cognitive performance. Patients consuming alcohol had higher test scores than patients not consuming alcohol. Female sex, lower disability, and alcohol consumption were associated with better performance in the memory-centered subtests of MUSIC, whereas no relevant association was observed for APOE carrier status.

Conclusion
Along with parameters of a higher disease burden, APOE ε4 homozygosity was identified as a potential predictor of cognitive performance in this large cohort of patients with CIS and early RRMS.

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German Competence Network of Multiple Sclerosis coinvestigators are listed in the appendix 2 at the end of the article.

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MS is a chronic neuroinflammatory disease, which mostly affects young adults. Apart from physical impairment, decline of cognitive functions is one of its most disabling aspects. A meta-analysis of data acquired by genome-wide association studies identified a total of 234 significant associations and a further 416 variants potentially associated with MS. However, so far, little is known about the contribution of genetic risk factors to the development of cognitive impairment in MS.

The APOE gene locus has been discussed as a possible mediator of cognitive impairment as it is associated with the evolution of dementias like Alzheimer disease (AD). It may encode 3 different isoforms of apolipoprotein E (APOE2, APOE3, and APOE4), which are defined by the haplotype combination of common single nucleotide polymorphisms (SNPs) at 2 nearby loci on the APOE gene. The SNPs are labeled rs429358 (base exchange from cytosine to thymine [C>T] leading to the haplotype APOE e4) and rs7412 (base exchange C>T resulting in the haplotype APOE e2). The APOE e4 haplotype leads to an amino acid exchange from cysteine to arginine at position 112 of the APOE protein resulting in the isoform APOE4, whereas the haplotype APOE e2 leads to an amino acid exchange from arginine to cysteine at position 158 of the APOE protein resulting in the isoform APOE2. APOE e3 is the common variant. APOE e4 is associated with faster memory decline over the adult life course and is a major risk factor for AD, with an 8- to 12-fold increase in APOE e4 homozygotes. Although it was shown in a sufficiently powered study that APOE variants have no effect on MS susceptibility, reports on the influence of APOE variants on cognitive performance in patients with MS have been contradictory. Therefore, this study aims to assess the potential impact of APOE polymorphisms on parameters of cognitive function in a large multicenter, prospectively collected German data set of untreated patients with clinically isolated syndrome (CIS) and early relapsing-remitting MS (RRMS). As a number of demographic, clinical, MRI, and lifestyle risk factors have been shown to enhance cognitive decline in MS and to adversely influence disease progression, these were also included in the analyses.

Methods

Standard protocol approvals, registrations, and patient consents
This multicenter prospective longitudinal observational cohort study (German National MS Cohort) was approved by the ethics committee of Ruhr-University Bochum (registration no. 3714-10) and consecutively all local committees of the participating centers (22 centers in Germany). All patients provided written informed consent.

The German National MS cohort and clinical data
A total of 552 participants from the German National MS cohort, a multicenter, prospective, and observational study, were included. This study was approved by the ethics committee of Ruhr-University Bochum (registration no. 3714-10) as described previously. All participants were aged at least 18 years, untreated regarding disease-modifying therapies, and diagnosed with either CIS with first symptoms within the previous 6 months and fulfilling at least 3 Barkhof criteria or RRMS according to the 2005 revised McDonald criteria with first symptoms not more than 3 years before study enrollment. For inclusion, patients must not have received a steroid pulse due to a relapse in the 4 weeks before study enrollment. All participants provided written informed consent.

Assessments included clinical, demographic, MRI, and lifestyle variables and screening tests for cognitive function and blood sampling. At the point of study enrollment, patients were asked to assess their current drinking and smoking habits via questionnaire. In response to the question “Do you currently drink alcohol?”, patients could select from 3 categories: (0) no, (1) occasionally, and (2) regularly. Based on this, we dichotomized the participants into current no alcohol consumers (category 0) and current alcohol consumers (categories 1 and 2). Similarly, in response to the question “Do you currently smoke?”, patients could select from 6 categories: (0) no, (1) occasionally, but not on a daily basis, (2) up to 5 cigarettes daily, (3) 6–10 cigarettes daily, (4) 11–20 cigarettes daily, and (5) >20 cigarettes daily. We dichotomized the participants into current nonsmokers (category 0) and current smokers (all other categories). Body weight and height were physically measured on site at the time of study enrollment. Body mass index (BMI) was then calculated as BMI = weight (kg)/height (m)^2. School-level education was categorized according to the highest school leaving qualification (level 1: lower-level secondary school [German Hauptschule]; level 2: higher-level secondary school; level 3: higher education entrance qualification [German Abitur]). Depressive symptoms were assessed by the 21-item Beck Depression Inventory II (BDI-II), and severity of fatigue was evaluated by the Fatigue Scale for Motor and Cognitive Functions (FSMC).

Glossary

AD = Alzheimer disease; BDI-II = Beck Depression Inventory II; BMI = body mass index; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; FSMC = Fatigue Scale for Motor and Cognitive Function; HWE = Hardy-Weinberg equilibrium; MCI = mild cognitive impairment; MUSIC = Multiple Sclerosis Inventory Cognition; PASAT 3 = 3-second paced auditory serial addition test; RRMS = relapsing-remitting MS; SNP = single nucleotide polymorphism.
Cognitive assessment

Cognitive assessment included the 3-second paced auditory serial addition test (PASAT 3) and the Multiple Sclerosis Inventory Cognition (MUSIC) cognitive screening tests.

The PASAT 3 is a measure of cognitive function that assesses auditory information processing speed, working memory, divided attention, and calculation ability. PASAT 3 data were extracted from the Multiple Sclerosis Functional Composite. Individual PASAT 3 test scores were z-standardized, stratified for age and education based on normative data from a German sample of n = 241 healthy controls.17,18

MUSIC is a brief multiple-domain cognitive screening test, which is widely used in German-speaking countries and was developed for the rapid assessment of the most frequently impaired cognitive domains in patients with MS. It consists of 5 cognitive subtests. In the subtests (1) and (2), the patient is asked to remember as many words as possible out of 2 consecutive word lists, each consisting of 10 different words to evaluate working memory. In subtest (3), the patient is given 2 alternating word categories, for which they are asked to find as many associated terms as possible within 1 minute. This subtest was designed to test verbal fluency. Subtest (4) is a modified Stroop Task and assesses susceptibility to interference. In subtest (5), the patient is asked to recall the terms of the first given list of words to assess memory consolidation.19 Individual test scores were z-standardized based on normative data from n = 158 German-speaking healthy young adults.17,19 All tests were taken for the first time at study enrollment so that results were not expected to be biased by learning effects.

Biosamples and genotyping

The SNPs rs429358 (e4) and rs7412 (e2) in APOE and the Y chromosome marker rs2032598 (for sampling and handling control) were analyzed using allelic discrimination assays based on TaqMan chemistry according to the manufacturer’s protocol (Applied Biosystems, Inc.). Genotyping was performed on 96-well plates with approximately 5% controls run in duplicates across plates. Genotyping efficiency was ≥99.6% for all SNPs. Deviation of the genotypes from Hardy-Weinberg equilibrium (HWE) as a potential marker for genotyping quality was assessed using the Pearson χ² test. The genotype distribution of rs429358 and rs7412 did not deviate from HWE.

MRI analysis

MRI scans of all patients with CIS and MS included a T1-weighted sequence, a fluid-attenuated inversion recovery sequence, and contrast-enhanced T1-weighted images and were analyzed by a neuroradiologist with regard to lesion number, size, and location and to contrast-enhancing lesions. The neuroradiologist was blinded to clinical data.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 software (IBM Corp.). Continuous variables are described by their median and interquartile range, and categorical variables by numbers and percentages.

A variety of general sociodemographic factors known to influence cognitive status and previously discussed disease-specific risk factors for cognitive impairment in MS20 were assessed. The list of the potential predictors and their baseline characteristics are summarized in table 1. Age and education were not included in the further analyses as cognitive test results had already been corrected for age and education by z-standardization.

To approximate the overall cognitive performance of each patient, we calculated an unweighted mean z-score:

Mean z-score = (z-score of PASAT 3 + z-score of MUSIC total test score)/2.

In addition, the results of the memory-centered MUSIC subtests 1, 2, and 5 were added up to form a memory-centered sum score:

Memory-centered sum score = (z-score of verbal learning list A + z-score of verbal learning list B + z-score of verbal recall)/3.

To extract those factors, which contributed most to cognitive performance in our cohort, variables were preselected by performing univariate linear regression analyses of each potential predictor with the cognitive outcome parameter under investigation. Variables with p values of regression coefficients <0.1 were subsequently selected for inclusion to a multiple linear regression model for the respective outcome. Dichotomous variables were dummy coded.

All our analyses are exploratory. Hence, p values are only given for descriptive reasons. However, we consider an association as statistically relevant in case of p < 0.05.

Data availability

The raw data used in preparation of the figures and tables will be shared in anonymized format on request of a qualified investigator to the corresponding author for purposes of replicating procedures and results.

Results

Characteristics of the 552 patients included in this study are reported in table 1. Of note, 25.2% of the patients were carriers of the APOE e4 allele. Ten of these (1.8%) were homozygotes, which is in line with the reported prevalence in healthy control populations of Caucasians21 and with the prevalence in a larger German cohort of patients with MS.22
Ethnicity of our cohort was homogeneous. Of note, 94.6% of the patients had grandparents of German origin only. The others (5.4%) had 1 grandparent with origin other than German. There were no patients with more than 1 grandparent with origin other than German enrolled in this study.

After preselection as described above, the parameters Expanded Disability Status Scale (EDSS) score, BMI, BDI-II, FSMC, alcohol consumption, smoking, MRI lesion number, and APOE ε4 carrier status were included in a multiple linear regression model for the prediction of the overall cognitive performance evaluated by the mean score of the z-standardized PASAT 3 and MUSIC test scores. It was found that APOE ε4 homozygosity, higher disability level measured by the EDSS, higher MRI lesion number, and higher BDI-II scores were associated with lower performance in cognitive testing, whereas patients who consumed alcohol scored higher compared with patients who did not consume alcohol.

### Table 1 Patient characteristics

| Demographic characteristics | Number (%) | Median (IQR) |
|-----------------------------|------------|--------------|
| **Sex**                     |            |              |
| Female                      | 395 (71.6) |              |
| Male                        | 157 (28.4) |              |
| **Age (y)**                 | 32 (27–42) |              |
| **Education (school leaving level)** | | |
| Level 1                     | 60 (10.9)  |              |
| Level 2                     | 251 (45.5) |              |
| Level 3                     | 241 (43.7) |              |
| **Ethnic origin of grandparents** | | |
| Only German                 | 522 (94.6) |              |
| One other than German       | 30 (5.4)   |              |
| **Clinical characteristics** |           |              |
| **Diagnosis**               |            |              |
| CIS                         | 244 (44.2) |              |
| RRMS                        | 308 (55.8) |              |
| **Disease duration (mo)**   | 4 (2–9)    |              |
| **EDSS score**              | 1.5 (1.0–2.0) |          |
| **Occurrence of relapse within 30 days** | | |
| Relapse                     | 76 (13.8)  |              |
| No relapse                  | 468 (84.8) |              |
| No information              | 8 (1.4)    |              |
| **BMI**                     | 24.1 (21.6–27.7) |        |
| **BDI-II**                  | 5.0 (2.0–9.0) |          |
| **Fatigue score (FSMC)**    | 15.00 (11.00–25.75) |      |
| **Current smoking**         |            |              |
| Smokers                     | 172 (31.2) |              |
| Nonsmokers                  | 380 (68.8) |              |
| **Alcohol consumption**     |            |              |
| Occasional or regular drinking | 426 (77.2) |          |
| No drinking                 | 126 (22.8) |              |
| **MRI characteristics**     |            |              |
| **Lesion number**           | 9 (6–9)    |              |
| **Lesion localization**     |            |              |
| Periventricular (yes/no)    | 528 (95.7)/24 (4.3) |   |
| Juxtacortical (yes/no)      | 416 (75.4)/136 (24.6) |        |

Abbreviations: BDI-II = Beck Depression Inventory II; BMI = Body Mass Index; CEL = contrast-enhancing lesion; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; FSMC = Fatigue Scale for Motor and Cognitive Function; IQR: Interquartile range; RRMS = Relapsing-remitting MS.

The table summarizes the assumed predictors of cognitive performance and their baseline characteristics in our cohort of 552 patients with CIS and early RRMS. Age and education were used for the z-standardization and were therefore not included in the regression models. Continuous variables are described by their median and interquartile range, and categorical variables by numbers and percentages.

**APOE ε4 carriers**

|                | Number (%) | Median (IQR) |
|----------------|------------|--------------|
| Homozygotes    | ε4/ε4      | 10 (1.8)     |
| Heterozygotes  | ε4/ε3 or ε4/ε2 | 129 (23.4) |

**APOE ε4 noncarriers**

|                | Number (%) | Median (IQR) |
|----------------|------------|--------------|
| ε3/ε3 or ε2/ε3 or ε2/ε2 | 413 (74.8) |          |

Ethnicity of our cohort was homogeneous. Of note, 94.6% of the patients had grandparents of German origin only. The others (5.4%) had 1 grandparent with origin other than German. There were no patients with more than 1 grandparent with origin other than German enrolled in this study.

After preselection as described above, the parameters Expanded Disability Status Scale (EDSS) score, BMI, BDI-II, FSMC, alcohol consumption, smoking, MRI lesion number, and APOE ε4 carrier status were included in a multiple linear regression model for the prediction of the overall cognitive performance evaluated by the mean score of the z-standardized PASAT 3 and MUSIC test scores. It was found that APOE ε4 homozygosity, higher disability level measured by the EDSS, higher MRI lesion number, and higher BDI-II scores were associated with lower performance in cognitive testing, whereas patients who consumed alcohol scored higher compared with patients who did not consume alcohol.
To evaluate whether the effect of APOE ε4 carrier status was more pronounced in memory-mediated cognitive domains resembling its effects in AD, a sum score of the memory-centered subparts of the MUSIC test was investigated in a second multiple linear regression model. However, we found no relevant association of APOE ε4 homo- or heterozygosity with the memory-centered sum score in the univariate regression analysis. Therefore, APOE ε4 carrier status was not included in the multiple regression model for the memory-centered sum score. We found that male sex and higher EDSS scores were associated with worse performance in these subtests. In line with the results of the mean score of overall cognitive performance, alcohol consumption was associated with better test results again (table 3). The R² of the overall model was 0.109 (adjusted R² = 0.094).

The findings concerning the effect of alcohol consumption are limited by the fact that they were no longer detectable after variation of dichotomization into nondrinkers and occasional drinkers vs regular drinkers.

We observed no association of the APOE ε2 carrier status with any of the cognitive outcome parameters in the univariate regression analyses. Therefore, APOE ε2 carrier status was not included in any of the multiple linear regression models.

### Discussion

Cognitive impairment is one of the most difficult challenges for young adults faced with a diagnosis of MS because neuropsychological symptoms may already be experienced early on and are among the main reasons for unemployment and reduced quality of life. We here assessed the putative role of APOE polymorphisms on the cognitive outcome parameters PASAT 3 and MUSIC test scores in patients with CIS and early RRMS of a homogenous cohort in terms of origin, short disease duration, and treatment-naive state.

Neither APOE ε2 carrier status nor APOE ε4 heterozygosity showed an influence on the evaluated cognitive outcome parameters. However, we observed a relevant association of APOE ε4 homozygosity with a lower overall cognitive performance.

In AD, APOE ε4 carriers have a higher risk of developing AD and show decreased APOE plasma levels compared with APOE ε2 and APOE ε3 carriers. Among APOE ε4 carriers, lower plasma levels are associated with an even greater risk of developing AD. Therefore, it was suggested that a decrease of

### Table 2: Regression coefficients for mean cognitive test scores

| CI                  | β     | SE     | Standardized β | t Value | 95% lower | 95% upper | p Value |
|---------------------|-------|--------|----------------|---------|-----------|-----------|---------|
| Intercept           | 0.920 | 0.341  |                | 2.698   | 0.250     | 1.590     | 0.007   |
| Genetic characteristics |     |        |                |         |           |           |         |
| APOE ε4 homozygosity| −0.922| 0.394  | −0.095         | −2.340  | −1.697    | −0.148    | 0.020   |
| APOE ε4 heterozygosity| 0.128| 0.124  | 0.043          | 1.035   | −0.115    | 0.372     | 0.301   |
| Clinical characteristics |     |        |                |         |           |           |         |
| Disability (EDSS score) | −0.180| 0.057  | −0.135         | −3.143  | −0.293    | −0.068    | 0.002   |
| BMI                 | −0.010| 0.010  | −0.041         | −0.987  | −0.031    | 0.010     | 0.324   |
| Depressive symptoms (BDI-II) | −0.021| 0.010  | −0.116         | −2.024  | −0.040    | −0.001    | 0.043   |
| Fatigue score (FSMC) | −0.005| 0.004  | −0.065         | −1.121  | −0.013    | 0.003     | 0.263   |
| Alcohol consumption | 0.493 | 0.126  | 0.160          | 3.929   | 0.247     | 0.740     | <0.001  |
| Smoking             | −0.221| 0.115  | −0.079         | −1.932  | −0.446    | 0.004     | 0.054   |
| MRI characteristics  |     |        |                |         |           |           |         |
| Lesion number       | −0.056| 0.022  | −0.103         | −2.514  | −0.099    | −0.012    | 0.012   |

Abbreviations: β = regression coefficient; BDI-II = Beck Depression Inventory II; BMI = body mass index; EDSS = Expanded Disability Status Scale; FSMC = Fatigue Scale for Motor and Cognitive Function; MUSIC = Multiple Sclerosis Inventory Cognition; SE = standard error.
A sum score of the memory-centered subparts of the MUSIC test (Wordlist A and B and verbal recall) was calculated to evaluate the potential effect of relevant predictors (defined by EDSS, and alcohol consumption were associated with better performance in the memory-centered subtests of MUSIC. Parameters, which were found to be duration, EDSS score, BMI, BDI-II, FSMC, alcohol consumption, smoking, and MRI lesion number (n = 538). Female sex, lower disability level measured by the therefor not included in the regression model. The following parameters were selected for inclusion in the multiple linear regression model: sex, disease carrier status on memory function. However, APOE protein function mediates the evolution of AD and that the risk increases dose dependently. As APOE is thought to be involved in repairing neuronal injury, synapse formation, and scavenging of toxins, we hypothesized that impaired repair mechanisms in MS lesions could mediate more pronounced neurodegenerative processes in APOE ε4 carriers compared with noncarriers.

Our current finding that cognitive performance was impaired in homozygous APOE ε4 carriers only might indicate that a dose-dependent decrease of APOE function mediates cognitive decline in MS, as it does in AD, and that a prolonged follow-up would reveal more pronounced effects of APOE later in the course of MS. Supporting this, previous studies in smaller cohorts of patients with MS with mean disease durations of 8.3 and 13 years reported an association of APOE ε4 with dysfunction in some cognitive domains in-cluding verbal fluency and memory.

To evaluate whether the observed negative impact of APOE ε4 homozygosity on cognitive performance was mainly caused by impaired memory functions, resembling the assumed APOE ε4-mediated effects in AD, additional analysis of a memory-centered sum score was performed. However, we found no relevant association of APOE ε4 homo- or heterozygosity with this memory-centered sum score. This might indicate an AD-independent APOE ε4-mediated effect on cognitive performance in patients with MS. This hypothesis is also supported by the young median age of our cohort as APOE ε4-dependent progression of formerly cognitive un-impaired people to mild cognitive impairment (MCI) and AD was found to be most pronounced in older people aged 70–75 years. Furthermore, a recent study using PET imaging biomarkers of AD even suggested that some aspects of MS pathobiology retard the accumulation of β-amyloid, which is one of the main pathologic correlates of AD. Nevertheless, we cannot exclude the possibility that patients with APOE ε4 homozygosity performed worse in the cognitive tests because of an APOE ε4-mediated increased risk of developing MCI or AD.

In an effort to correct for potential confounders, we included a range of parameters known or assumed to influence cognitive performance in patients with MS in our analyses. Apart from the putative impact of APOE ε4 homozygosity, we observed a relevant association of markers of the disease burden with the overall cognitive performance. Patients with a higher disability level as assessed by the EDSS and with a higher number of T2 lesions in MRI performed worse in cognitive testing, which is in line with previous reports. Higher scores of depressive symptoms in BDI-II were also associated with an impaired performance. Depression is known to be

### Table 3 Regression coefficients of the memory-centered MUSIC test subparts

| CI          | B      | SE     | Standardized β | t Value | 95% lower | 95% upper | p Value |
|-------------|--------|--------|----------------|---------|-----------|-----------|---------|
| **Demographic characteristics** |        |        |                |         |           |           |         |
| Sex (female vs male) | 0.370  | 0.088  | 0.176          | 4.178   | 0.196     | 0.543     | <0.001  |
| **Clinical characteristics** |        |        |                |         |           |           |         |
| Disease duration (mo) | −0.006 | 0.005  | −0.052         | −1.249  | −0.016    | 0.004     | 0.212   |
| Disability (EDSS score) | −0.123 | 0.043  | −0.127         | −2.882  | −0.206    | −0.039    | 0.004   |
| BMI | −0.014  | 0.008  | −0.079         | −1.867  | −0.029    | 0.001     | 0.062   |
| Depressive symptoms (BDI-II) | −0.008 | 0.007  | −0.064         | −1.108  | −0.023    | 0.006     | 0.268   |
| Fatigue score (FSMC) | −0.002  | 0.003  | −0.046         | −0.775  | −0.008    | 0.004     | 0.439   |
| Alcohol consumption | 0.236  | 0.093  | 0.106          | 2.536   | 0.053     | 0.418     | 0.012   |
| Smoking | −0.156  | 0.085  | −0.077         | −1.842  | −0.322    | 0.010     | 0.066   |
| **MRI characteristics** |        |        |                |         |           |           |         |
| Lesion number | −0.025 | 0.016  | −0.064         | −1.536  | −0.057    | 0.007     | 0.125   |

Abbreviations: BDI-II = Beck Depression Inventory II; BMI = body mass index; EDSS = Expanded Disability Status Scale; FSMC = Fatigue Scale for Motor and Cognitive Function; SE = standard error.

A sum score of the memory-centered subparts of the MUSIC test (Wordlist A and B and verbal recall) was calculated to evaluate the potential effect of APOE ε4 carrier status on memory function. However, APOE ε4 carrier status did not show any association with this sum score in the preselection process and was therefore not included in the regression model. The following parameters were selected for inclusion in the multiple linear regression model: sex, disease duration, EDSS score, BMI, BDI-II, FSMC, alcohol consumption, smoking, and MRI lesion number (n = 538). Female sex, lower disability level measured by the EDSS, and alcohol consumption were associated with better performance in the memory-centered subtests of MUSIC. Parameters, which were found to be relevant predictors (defined by p < 0.05) of mean cognitive test scores, are written in bold.
associated with reduced attention and processing speed in patients with MS.\textsuperscript{33} As PASAT 3 and MUSIC tests both include an assessment of these cognitive domains, our current finding seems plausible. Surprisingly, we observed a positive influence of alcohol consumption on the cognitive outcome, shedding light on recent reports associating alcohol consumption with lower neurologic disability in MS,\textsuperscript{34} and a reduced risk of developing MS.\textsuperscript{35} However, this finding has to be interpreted with care as it may be attributed to the dichotomization of drinking habits and as the questionnaires used in this study were not laid out for accurate quantification of alcohol consumption (e.g., units/month).

Two additional limitations of this study have to be addressed. First, the observed effect of \textit{APOE} \textit{e4} is based on a very low number of \textit{APOE} \textit{e4} homozygotes, which makes our findings sensitive to potential confounders, not accounted for. As the estimated prevalence of \textit{APOE} \textit{e4} homozygosity in Caucasian MS populations is only 1.8%, an even larger cohort than ours would be needed to improve the statistical power. Second, the tests used to assess cognitive performance in this study pose another potential limitation of our observations. PASAT 3 and MUSIC are both screening tests for cognitive performance, which offer the advantage that they may be incorporated into routine diagnostics comparatively easily. However, they lack the sensitivity and reliability to detect MS-specific cognitive impairment of extended test batteries, like for instance the Symbol Digit Modalities Test.\textsuperscript{36}

Besides markers of disease burden, depression, and lifestyle habits, this study identified \textit{APOE} \textit{e4} homozygosity as a potential predictor of cognitive performance in this cohort of patients with CIS and early RRMS. This indicates a role of \textit{APOE} as a genetic risk factor for cognitive impairment in MS and might even suggest an \textit{APOE} \textit{e4} effect unrelated to concomitant AD. Therefore, future work confirming these findings in young homozygous \textit{APOE} \textit{e4} patients in a larger and independent MS cohort would be valuable.

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| Christian Graetz, MD| University Medical Center of the Johannes Gutenberg University, Mainz, Germany | Design and conceptualization of the study and acquisition of data |
| Anke Salmen, MD     | Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany | Design and conceptualization of the study and revision of the manuscript |
| Muthuraman Muthuraman, PhD | University Medical Center of the Johannes Gutenberg University, Mainz, Germany | Analysis of data |
| Gerrit Toenges, MSc | Institute of Medical Biostatistics, Epidemiology and Informatics (IMBIE), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany | Analysis of data |
| Björn Ambrosius, PhD| Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany | Revision of the manuscript |
| Antonios Bayas, MD  | Department of Neurology, Klinikum Augsburg, Germany | Revision of the manuscript |
| Achim Berthele, MD  | Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany | Revision of the manuscript |
| Name                  | Location                                                                 | Contribution                                                                 |
|-----------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
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| Friedemann Paul, MD   | NeuroCure Clinical Research Center and Experimental and Clinical Research Center, Charité - Universitätsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany | Revision of the manuscript                                                   |
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| Björn Tackenberg, MD  | Department of Neurology, Philipps-University Marburg, Germany              | Revision of the manuscript                                                   |
| Florian Then Bergh, MD| Department of Neurology, University of Leipzig, Germany                    | Revision of the manuscript                                                   |
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| Frank Weber, MD       | Neurology, Max-Planck-Institute of Psychiatry, Munich, Germany Neurological Clinic, Sana Kliniken des Landkreises Cham, Germany | Revision of the manuscript                                                   |
| Brigitte Wildemann, MD| Department of Neurology, University of Heidelberg, Germany                | Revision of the manuscript                                                   |
| Uwe K. Zettl, MD      | Department of Neurology, University of Rostock, Germany                    | Revision of the manuscript                                                   |
| Gisela Antony, Dipl-Psych | Central Information Office (CIO), Philipps-University Marburg, Germany     | Acquisition of data and revision of the manuscript                           |
| Stefan Bittner, MD    | Department of Neurology and Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network (rmn2), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany | Revision of the manuscript                                                   |
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| Ralf Gold, MD         | Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany | Design and conceptualization of the study and revision of the manuscript     |
| Frauke Zipp, MD       | University Medical Center of the Johannes Gutenberg University, Mainz, Germany | Design and conceptualization of the study and revision of the manuscript     |
| Christina Lill, MD    | Department of Neurology and Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network (rmn2), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany | Design and conceptualization of the study; interpretation of data; and revision of the manuscript |
| Felix Luessi, MD      | University Medical Center of the Johannes Gutenberg University, Mainz, Germany | Design and conceptualization of the study; acquisition and analysis of data; and drafting a significant proportion of the manuscript |
References

1. Patsopoulos NA. Genetics of multiple sclerosis: an overview and new directions. Cold Spring Harb Perspect Med 2018;8.
2. Heffernan AL, Chidgey C, Peng P, Masters CL, Roberts BR. The neurobiology and age-related prevalence of the epsilon4 allele of apolipoprotein E in Alzheimer’s disease cohorts. J Mol Neurosci 2016;60:316–324.
3. Bellay ME, Napolioli V, Greicius MD. A quarter century of APOE and Alzheimer’s disease: progress to date and the path forward. Neuron 2019;101:820–838.
4. Rawle MJ, Davis D, Bendayan R, Wong A, Kuh D, Richards M. Apolipoprotein-E (ApoE) epsilon4 and cognitive decline over the adult life course. Transl Psychiatry 2018;8:18.
5. Lill CM, Liu T, Schieple BM, et al. Closing the case of APOE in multiple sclerosis: no association with disease risk in over 29,000 subjects. J Med Genet 2012;49:558–562.
6. Shi J, Zhao CB, Vollner TL, Tyry TM, Kuniyoshi SM. APOE epsilon 4 allele is associated with cognitive impairment in patients with multiple sclerosis. Neurology 2008;70:185–190.
7. van der Walt A, Stankovich J, Bahlo M, et al. Apolipoprotein genotype does not influence MS severity, cognition, or brain atrophy. Neurology 2009;73:1018–1023.
8. Ramanujam R, Hedstrom AK, Manouchehrinia A, et al. Effects of smoking cessation on multiple sclerosis-related fatigue. Mult Scler 2009;15:1509–1517.

Appendix 2 Coinvestigators

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12. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997;120 (pt 11): 2059–2069.
13. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. Ann Neurol 2005;58:840–846.
14. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–597.
15. Pennet IK, Rosell C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 2009;15:1509–1517.
16. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122 (pt 5): 871–882.
17. Johnen A, Burkner PC, Landmeyer NC, et al. Can we predict cognitive decline after initial diagnosis of multiple sclerosis? Results from the German National early MS cohort (KKNMS). J Neurol 2019;266:386–397.
18. Scherer P, Baum K, Bauer H, Gohler H, Miltenburger C. Normalization of the Brief Repeatable Battery of Neuropsychological tests (BRB-N) for German-speaking regions. Application in relapsing-remitting and secondary progressive multiple sclerosis patients [in German]. Nervenarzt 2004;75:984–990.
19. Calabrese P, Kalbe E, Kessler J. Das multiple sklerose inventarium cognition (MUSIC). PsychoNeuro 2004;30:384–388.
20. Benedict RH, Zivadinov R. Risk factors and management of cognitive dysfunction in multiple sclerosis. Nat Rev Neurol 2011;7:332–342.
21. Farrer LA, Capples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278:1349–1356.
22. Lill CM, Liu T, Schieple BM, et al. Closing the case of APOE in multiple sclerosis: no association with disease risk in over 29,000 subjects. J Med Genet 2012;49:558–562.
23. Patti F, Anato MP, Troiano M, et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. Mult Scler 2009;15:779–788.
24. Strober L, Engert J, Munnschauer F, Weinstock-Guttman B, Rao S, Benedict RH. Sensitivity of conventional memory tests in multiple sclerosis: comparing the Rao brief Repeatable neuropsychological battery and the minimal assessment of cognitive function in MS. Mult Scler 2009;15:1077–1084.
25. Campbell J, Rashid W, Cercignani M, Langdon D. Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life. Postgrad Med J 2017;93:143–147.
26. Shi J, Tu JL, Gale SD, et al. APOE epsilon 4 is associated with exacerbation of cognitive decline in patients with multiple sclerosis. Cogn Behav Neurol 2011;24:128–133.
27. Nathan BP, Bellota S, Sanan DA, Weisgerber KH, Mahley RW, Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994;264:850–852.
28. Koutsis G, Panos M, Giogkarakis E, et al. APOE epsilon4 is associated with impaired verbal learning in patients with MS. Neurology 2007;68:546–549.
29. El Haj M, Antoine P, Amouyel P, Lambert JC, Pasquier F, Kapogiannis D. Apolipoprotein E (APOE) epsilon4 and episodic memory decline in Alzheimer’s disease: a review. Ageing Res Rev 2016;27:15–22.
30. Bonham LW, Geier EG, Fan CC, et al. Age-dependent effects of APOE epsilon4 in preclinical Alzheimer’s disease. Ann Clin Transl Neurol 2016;3:668–677.
31. Zeydan B, Lowe VJ, Reichard RR, et al. Imaging biomarkers of Alzheimer disease in multiple sclerosis. Ann Neurol 2020;87:556–567.
32. Ruano L, Portaccio E, Goetzti B, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler 2017;23:1258–1267.
33. Leavitt YM, Brandstatter R, Falsian M, et al. Dissociable cognitive patterns related to depression and anxiety in multiple sclerosis. Mult Scler Epub 2019 Jun 25.
34. Kirby AL, Chua AS, Malik MT, et al. The effect of alcohol and red wine consumption on clinical and MRI outcomes in multiple sclerosis. Mult Scler Relat Disord 2017;17:47–53.
35. Andersen C, Sondbergg HD, Bang Otrust D, et al. Alcohol consumption in adolescence is associated with a lower risk of multiple sclerosis in a Danish cohort. Mult Scler 2019;25:1572–1579.
36. Sonder JM, Burggraaf JK, Knol DL, Polman CH, Utdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Mult Scler 2014;20:481–488.
Is APOE ε4 associated with cognitive performance in early MS?
Sinah Engel, Christiane Graetz, Anke Salmen, et al.
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