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RESEARCH ARTICLE

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# Effects of APOE e4-allele and mental work demands on cognitive decline in old age: Results from the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe)

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**Objectives:** Previous studies have observed protective effects of high mental demands at work on cognitive functioning and dementia risk. However, it is unclear what types of demands drive this effect and whether this effect is subject to a person's genetic risk. We investigated to what extent eight different types of mental demands at work together with the APOE e4 allele, a major risk gene for late-onset Alzheimer's disease, affect cognitive functioning in late life.

**Methods/Design:** The population-based German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe, n = 2 154) followed cognitively healthy individuals aged 75 years and older in seven assessment waves. Cognitive functioning was assessed via the mini-mental status examination.

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**Results:** Mixed-effects modeling (adjusted for education, gender, marital status, stroke, depression, and diabetes) indicated that participants who had an occupational history of working in jobs with high compared to low demands in "Language & Knowledge", "Pattern detection", "Information processing", and "Service" had a slower cognitive decline. APOE e4-allele carriers had an accelerated cognitive decline, but this decline was significantly smaller if they had a medium compared to a low level of demands in contrast to non-carriers.

**Conclusions:** Our longitudinal observations suggest that cognitive decline could be slowed by an intellectually enriched lifestyle even in risk gene carriers. Fostering intellectual engagement throughout the life-course could be a key prevention initiative to promote better cognitive health in old age.

**KEYWORDS**

cognitive functioning, cognitive reserve, longitudinal cohort study, mental demands, risk factors, work environment

## 1 | INTRODUCTION

The biological processes of Alzheimer's disease and other dementias can be influenced by lifestyle factors.[1] Mental demands are such a lifestyle factor that can exert a protective effect by influencing the rate of cognitive decline and dementia risk.[2,3] This protective effect is equally explained by the use-it-or-lose-it theory, which postulates that using cognitive abilities at a higher level for a longer lifetime period helps to maintain them,[4] as well as the theory of cognitive reserve, which assumes that exposure to high mental demands provides the capacity to withhold dementia symptoms and delay dementia onset.[5] While the majority of previous studies have focused on the complexity of work tasks, a recent study analyzed the spectrum of mental demands at work and identified two work demands ("Information Processing", "Pattern Detection") that had an exposure-dependent association with dementia risk.[6] We therefore expect that those types of demands have a strong impact on decline of cognitive functioning in old age.

Yet, the effect of mental demands on cognitive health is subject to other risks in a person's life, such as genetic risks. The e4 allele of the apolipoprotein (APOE) gene is the Alzheimer's disease risk gene[7] and persons who carry the APOE e4 allele experience a faster cognitive decline in old age.[8] It is not clear whether APOE e4 allele carriers profit from high mental demands across their lifetime or whether the protective effect of mental demands may offset the genetic risk. Previous studies have shown that low education, a form of lack of mental demands in early lifetime, increased dementia risk in APOE e4 allele carriers.[9] Similarly, APOE e4 allele carriers experience a benefit from a higher number of years of education.[10] If higher mental demands throughout the life-course enhance the protection against cognitive decline, then maybe they weaken the pathway through which an APOE e4 allele increases dementia risk.

To gain a better understanding of how the association between mental at work and cognitive decline in old age differs in APOE e4 carriers and non-carriers, we analyzed longitudinal cohort data of patients aged 75+ years from general practitioners (six German cities, n = 2 154). We hypothesized that people with high mental demands at work might experience a slower cognitive decline and that APOE e4 carriers might benefit from that.

**Key points**

- Results suggest that people who worked in jobs with higher demands throughout their life have a slower cognitive decline later in life
- High levels in demands on "Language & Knowledge", "Pattern detection", "Information processing", and "Service" seem to have the strongest protective affects
- APOE e4-allele carriers had a significantly smaller decline already if they worked in jobs with medium compared to low demands
- Intellectual engagement throughout the occupational history seems to help protect cognitive functioning in old age even in APOE e4 allele carriers

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

In 2003-2004, the Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe), a multi-centered population-based longitudinal cohort study, recruited dementia-free primary care

patients aged 75 years and older in six German cities. The details of the study are described elsewhere.[11] Briefly, 6 619 participants from general practitioners were randomly selected to participate in the study. Exclusion criteria were not being a regular patient to their general practitioner, severe illness deemed fatal within three months, insufficient German language capacities, deafness, blindness, and inability to consent. As 1 775 people refused to participate and 1 517 could not be contacted, 3 327 people participated in the baseline assessment and in up to six follow-up assessments at an average interval of 1.5 years. Standardized personal interviews were conducted with the participant as well as with surrogates. Additional health information were obtained from the participant's general practitioner. All study participants provided written informed consent prior to study participation. The study was approved by the ethics committees of all the participating research centers and was carried out in accordance with *The Code of Ethics of the World Medical Association* (Declaration of Helsinki) for experiments involving humans.

For purpose of analyses, we excluded 70 (2.1%) participants because they had dementia at baseline, 56 (1.7%) with Parkinson's disease, 22 (0.7%) with epilepsy, and 24 (0.7%) with suspected alcohol abuse. We also excluded 884 (26.6%) participants with missing data in their occupational history or who's occupation could not be matched to occupational codes. Further, participants with missing data on diabetes (n = 15, 0.5%), APOE gene (n = 75, 2.3%), and a younger age (n = 27, 0.8%) were excluded (see also supplementary file, Figure S1). Included participants were less likely to have higher education (chi2 = 12.68, $P$ = .002), diabetes (chi2 = 5.42, $P$ = .020), depression (chi2 = 18.73, $P$ < .001), or stroke (chi2 = 9.37, $P$ = .002), and had a lower MMSE score at baseline (M 26.6 points vs M 27.7 points, F = 204.72, $P$ < .001). There were no significant differences regarding gender (chi2 = 0.00, $P$ = .951), marital status (chi2 = 1.047, $P$ = .592), and APOE allele (chi2 = 1.347, $P$ = .246). The final sample comprised 2 154 (64.7%) participants.

## 2.2 | Cognitive functioning

Baseline and subsequent follow-up assessments were performed in participants' homes by trained physicians and psychologists. Cognitive functioning was assessed with the *Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia, and Dementia of other Etiology according to the Diagnostic and Statistical Manual of Mental Disorders, third Edition, Revised (DSM-III-R), Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV), and International Classification of Diseases, 10th Revision (ICD-10)* (SIDAM[12];). The SIDAM includes a section for cognitive testing covering eight cognitive domains (orientation, memory, abstract reasoning, verbal ability, calculation, constructional ability, aphasia, apraxia), a section for clinical diagnostics, and the mini-mental status examination (MMSE). Dementia diagnoses - even though not used in this paper - were made according to DSM-IV criteria in consensus conferences of the interviewer and an experienced geriatrician or geriatric psychiatrist.

## 2.3 | Mental demands at work

The participants provided information on their occupational history (occupational title of the first job, last job, and longest held job) and the length of time each job was held in the second follow-up examination. Being a homemaker or stay-at-home mom was not considered an occupation. Occupational titles of all of the jobs were translated into English and coded according to the *2010 Standard Occupational Classification* (SOC) of the O*NET database (www.onetonline.org/; *US Department of Labor/Employment and Training Administration*) in three phases: Phase 1, the main author and a study assistant matched the occupational codes blind from each other; phase 2, the matchings were compared (discrepancy occurred between similar job types for example, ., “Electricians” vs “Electrical Power-Line Installers”; phase 3, inconsistent matches were discussed in a team meeting according to the criteria (a) entry level requirements, (b) daily tasks, (c) level of responsibility at work, and (d) amount of machinery used. The O*NET codes that corresponded best to the participants' occupational titles were selected. Each O*NET codes comes with a detailed matrix of demands at work from which we extracted eight factors of mental demands at work “Language & Knowledge”, “Information Processing”, “Mathematics”, “Pattern Detection”, “Creativity”, “Perceptual Psychomotor”, “Social Coordinative”, and “Service”, following the approach by Then et al.[6] In their work, these eight factors were derived in a factor analysis of the mental demands at work available in the O*NET database (for details see their publication[13]). The scale of each factor ranged from zero (very low) to six (very high). To obtain exposure-intensity indicators of mental demands at work, we multiplied the scores with the number of years spent in that occupation (as indicated by the participant) and calculated for all occupations of each participant. The correlation between the exposure-intensity indicators of mental demands at work is shown in supplementary file, Table S1. The range of the means of the exposure-intensity adjusted indicators was 0.1-5.0 for “Language & Knowledge”, 0.1-5.6 for “Information Processing”, 0.0-5.8 for “Mathematics”, 0.0-5.8 for “Pattern Detection”, 0.0-5.8 for “Creativity”, 0.0-3.7 for “Perceptual Psychomotor”, 0.1-5.1 “Social Coordinative”, and 0.1-5.1 for “Service”. The occupational history covered was on average 35.2 years (SD 8.1) per participant. Given that the average age of retirement was 60.5 years (SD 6.6), we believe that our study captures most of the occupational history of the participants. For purpose of analysis, the mental demand scores were divided in tertiles (low, medium, high).

## 2.4 | Apolipoprotein (APOE) e4

The APOE genotype was assessed based on leucocyte DNA that was isolated with the Qiagen blood isolation kit according to the manufacturer's instructions (Qiagen, Germany) and by following the approach by Hixson & Vernier.[13] For purpose of analysis, we categorized participants as APOE e4 allele carriers and non-carriers.

## 2.5 | Covariates

A standardized interview at baseline provided information on age, gender, education, marital status, health, and lifestyle. For purpose of analyses, education was categorized into low, medium, and high according to the *Comparative Analysis of the Development and Structure of Educational Systems* (CASMIN, an educational classification system distinguishing general knowledge education from education for practical skills only[14]). Medical diagnoses such as diabetes, depression, and stroke were obtained via a standardized questionnaire that the participants' general practitioner completed.

## 2.6 | Statistical analyses

All statistical analyses employed an alpha level for statistical significance of .05 (two-tailed) and were performed using Stata (version 15). Continuous variables were standardized to z-scores for analysis.

Differences between covariates (age, education, gender, marital status, APOE e4 allele, stroke, depression, and diabetes) and the level of mental demands at work as well as APOE e4 carriers/non-carriers were estimated via Pearson's chi square test if categorical and via analysis of variance (ANOVA) if continuous. Associations between the level of mental demands at work and cognitive functioning at baseline (MMSE scores) were first estimated using pairwise comparison correlation and then using linear regression adjusted for age, education, gender, marital status, APOE e4 allele, stroke, depression, and diabetes, for each mental demand separately.

Associations between the level of mental demands at work and cognitive decline (MMSE) during the follow-up (FU) period were estimated using mixed-effects models, for each mental demand separately. The optimal models were obtained by, first, testing the nature of cognitive change during the FUs. We worked with the cubic model (FU*FU*FU) because it had a slightly better fit than the linear (FU) or the squared model (FU*FU). Further, we added a variable to the model that indicated the number of FU that each participant completed. Reason for doing so was to account for the variance for those who dropped out early compared to those who were followed-up longer. This improved the model. The mixed-effects models on cognitive decline (MMSE scores) over the FUs (time variable) thus contained fixed effects for mental demands at work, FU, cubic term for FU (FU*FU*FU), number of FUs, cubic term for mental demands at work over FU (mental demand*FU*FU), age, random slopes, and the covariates (education, gender, marital status, APOE e4 allele, stroke, depression, diabetes) and their cubic interaction terms with FU (covariate*FU*FU) as well as random effects for age with autoregressive residuals and unstructured covariance. To analyze the interaction with the APOE allele, we repeated exactly these models including additional fixed effects for APOE e4 allele, the interaction between APOE e4 allele and age, the interaction between APOE e4 allele and the mental demand, and the interaction between APOE e4 allele, the mental demand, and FU, for each mental demand separately.

# 3 | RESULTS

At baseline, the participants were on average 79.4 years old (SD [SD] 3.4, range 75-98 years). 34.6% were male (n = 746), 6.5% were single (n = 140), 43.2% married (n = 931), 21.4% had diabetes (n = 461), 7.0% stroke (n = 151), 10.4% depression (n = 223), and

**TABLE 1** Associations between the covariates education, gender, marital status, APOE e4 allele, stroke, depression, and diabetes between APOE e4 carriers and non-carriers and between people with low, medium, or high mental demands at work, as estimated via Pearson's chi square test and Analysis of Variance (N = 2 154)

| Mental demand at work | Education $chi^2$ (*P*) | Gender $chi^2$ (*P*) | Marital status $chi^2$ (*P*) | APOE e4 allele $chi^2$ (*P*) | Stroke $chi^2$ (*P*) | Depression $chi^2$ (*P*) | Diabetes $chi^2$ (*P*) | Age F (*P*) |
|---|---|---|---|---|---|---|---|---|
| Perceptual Psychomotor | 66.57 (<.001) | 378.03 (<.001) | 90.49 (<.001) | 6.42 (.040) | 3.34 (.188) | 8.76 (.013) | 9.14 (.010) | 3.99 (.019) |
| Social Coordinative | 148.76 (<.001) | 429.24 (<.001) | 123.68 (<.001) | 2.89 (.235) | 8.60 (.014) | 11.79 (.003) | 0.25 (.882) | 0.48 (.618) |
| Service | 70.19 (<.001) | 309.39 (<.001) | 79.86 (<.001) | 1.07 (.586) | 5.29 (.071) | 9.87 (.007) | 0.16 (.922) | 0.56 (.571) |
| Language & Knowledge | 140.84 (<.001) | 415.04 (<.001) | 131.75 (<.001) | 1.64 (.441) | 8.81 (.012) | 13.94 (.001) | 3.73 (.155) | 0.92 (.401) |
| Information Processing | 141.75 (<.001) | 487.81 (<.001) | 148.77 (<.001) | 3.35 (.188) | 10.32 (.006) | 15.86 (<.001) | 2.06 (.356) | 1.47 (.231) |
| Mathematics | 121.61 (<.001) | 364.09 (<.001) | 118.96 (<.001) | 0.28 (.868) | 9.09 (.011) | 15.39 (<.001) | 0.88 (.645) | 1.15 (.318) |
| Pattern Detection | 82.63 (<.001) | 443.87 (<.001) | 143.01 (<.001) | 3.79 (.150) | 10.33 (.006) | 13.95 (.001) | 0.47 (.791) | 1.91 (.148) |
| Creativity | 250.23 (<.001) | 526.16 (<.001) | 156.47 (<.001) | 2.03 (.363) | 8.35 (.015) | 19.03 (<.001) | 0.50 (.778) | 3.64 (.027) |
| APOE | 3.86 (.145) | 0.09 (.756) | 0.10 (.952) | / | 4.24 (.039) | 0.27 (.604) | 4.89 (.027) | 1.29 (.256) |

*Notes:* APOE, apolipoprotein genotype; $chi^2$, estimate obtained in Pearson chi square test; p, level of significance.

60.7% low (n = 1 307), 27.4% middle (n = 591), and 11.9% high education (n = 256). The average MMSE score was 27.7 (SD 1.8, range 18-30) at baseline and 26.5 (SD 4.3, range 2-30) at the end of the study. Throughout the follow-up period, 19.4% (n = 417) developed dementia at a mean age of 85.7 (SD 3.8; range 75.7-98.8) and 38.3% (n = 823) died (mean age at death 87.2, SD 4.0). People who had higher scores in mental demands at work were more likely to be men, have higher education, be single or married, have had a stroke, and less likely to have depression (see Table 1).

## 3.1 | Mental demands at work and cognitive functioning

Higher levels of mental demands at work were significantly associated with better cognitive functioning at baseline (pairwise comparison correlation "Language & Knowledge" r = 0.131, $P < .001$, "Information Processing" r = 0.117, $P < .001$, "Mathematics" r = 0.148, $P < .001$, "Pattern Detection" r = 0.106, $P < .001$, "Creativity" r = 0.128, $P < .001$, "Perceptual Psychomotor" r = –0.046, $P = .032$, "Social Coordinative" r = 0.119, $P < .001$, "Service" b = 0.091, $P < .001$). Results from linear regression adjusted for covariates confirmed these associations, except for "Perceptual Psychomotor" demands (see Table 2). Slower cognitive decline was significantly associated with high levels in the work demands "Information processing", 'Service', "Language & Knowledge", and "Pattern detection", as results from mixed-effects models indicate (see Table 3, see Figure 1).

## 3.2 | Interaction with the APOE e4 allele

APOE e4 allele carriers (20.6%, n = 444) were more likely to have had a stroke and less likely to have diabetes or high levels of "Perceptual Psychomotor" demands (see Table 1). APOE e4 carriers did not have a significantly different cognitive functioning at baseline than non-carriers (MMSE 27.7 (SD 1.7) vs 27.6 (SD 1.8), see Table 2).

However, having an APOE e4 allele was associated with an accelerated change in cognitive decline over the FUs (see Table 4). Mixed-effect models indicate that a medium compared to low level of "Language & Knowledge", "Information Processing", "Pattern Detection",

**TABLE 2** Association between mental demands at work and APOE e4 allele on cognitive functioning at baseline (MMSE scores) as estimated via separate linear regression adjusted for age, education, gender, marital status, stroke, depression, and diabetes (N = 2 154)

| | | MMSE at baseline | | |
|---|---|---|---|---|
| **Predictor** | | **b** | **CI** | ***P*** |
| Perceptual Psychomotor (REF: low) | medium | 0.032 | –0.052-0.116 | .454 |
| | high | –0.072 | –0.166-0.022 | .133 |
| APOE (REF non-carrier) | e4 | –0.079 | –0.163-0.004 | .062 |
| Social Coordinative (REF: low) | medium | 0.087 | 0.001-0.173 | .048 |
| | high | 0.172 | 0.077-0.266 | <.001 |
| APOE (REF non) | e4 | –0.076 | –0.159-0.007 | .074 |
| Service (REF: low) | medium | 0.097 | 0.010-0.185 | .028 |
| | high | 0.141 | 0.051-0.231 | .002 |
| APOE (REF non) | e4 | –0.075 | –0.159-0.008 | .076 |
| Language & Knowledge (REF: low) | medium | 0.096 | 0.009-0.182 | .029 |
| | high | 0.187 | 0.092-0.281 | <.001 |
| APOE (REF non) | e4 | –0.074 | –0.157-0.009 | .081 |
| Information Processing (REF: low) | medium | 0.113 | 0.027-0.199 | .010 |
| | high | 0.158 | 0.061-0.524 | .001 |
| APOE (REF non) | e4 | –0.075 | –0.158-0.008 | .078 |
| Mathematics (REF: low) | medium | 0.137 | 0.052-0.222 | .002 |
| | high | 0.231 | 0.139-0.324 | <.001 |
| APOE (REF non) | e4 | –0.077 | –0.159-0.007 | .074 |
| Pattern Detection (REF: low) | medium | 0.120 | 0.034-0.206 | .006 |
| | high | 0.167 | 0.072-0.262 | .001 |
| APOE (REF non) | e4 | –0.074 | –0.157-0.009 | .083 |
| Creativity (REF: low) | medium | 0.022 | –0.064-0.108 | .615 |
| | high | 0.183 | 0.086-0.280 | <.001 |
| APOE (REF non) | e4 | –0.074 | –0.157-0.009 | .082 |

*Notes:* APOE, apolipoprotein genotype; b, regression coefficient; CI, 95% confidence interval; *P*, level of significance; REF, reference group.

**TABLE 3** Mixed-effects estimates of separate estimations of the association between mental demands at work and cognitive decline (MMSE scores) over the follow-up period (with fixed effects for age, number of follow-ups, education, gender, marital status, APOE e4 allele, stroke, depression, diabetes, and their interaction terms with follow-up, and a random effect for age; N = 2 154)

| | | Perceptual Psychomotor b (CI) | *P* | Social Coordinative b (CI) | *P* | Service b (CI) | *P* | Language & Knowledge b (CI) | *P* | Information Processing b (CI) | *P* | Mathematics b (CI) | *P* | Pattern Detection b (CI) | *P* | Creativity b (CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demand (REF: low) | Medium | 0.08 (−0.07-0.24) | .292 | 0.08 (−0.08-0.25) | .303 | 0.11 (0.05-0.27) | .167 | 0.07 (−0.09-0.23) | .409 | 0.11 (0.04-0.27) | .159 | 0.09 (−0.06-0.26) | .225 | 0.12 (−0.04-0.29) | .131 | 0.04 (−0.12-0.19) | .650 |
| | High | −0.03 (−0.21-0.14) | .723 | 0.17 (−0.01-0.35) | .065 | 0.22 (0.06-0.38) | .008 | 0.19 (0.02-0.37) | .031 | 0.22 (0.05-0.39) | .010 | 0.21 (0.03-0.38) | .019 | 0.20 (0.03–0.38) | .024 | 0.13 (−0.05-0.31) | .156 |
| Demand (REF: low) * FU | Medium | −0.06 (−0.15-0.02) | .158 | −0.03 (−0.13-0.06) | .453 | −0.05 (−0.14-0.04) | .244 | −0.01 (−0.10-0.08) | .786 | −0.05 (−0.13-0.04) | .307 | −0.02 (−0.11-0.07) | .666 | −0.06 (−0.15-0.03) | .166 | −0.04 (−0.13-0.05) | .409 |
| | High | −0.04 (−0.14-0.06) | .459 | −0.06 (−0.16-0.04) | .258 | −0.12 (−0.21- -0.03) | .008 | −0.08 (−0.18-0.02) | .125 | −0.12 (−0.20- -0.03) | .010 | −0.06 (−0.15-0.04) | .259 | −0.11 (−0.21- −0.01) | .034 | -0.01 (−0.12-0.09) | .808 |
| Demand (REF: low) * FU * FU | Medium | 0.01 (0.00-0.02) | .033 | 0.01 (−0.01-0.02) | .282 | 0.01 (−0.00-0.02) | .087 | 0.00 (−0.01-0.02) | 0.477 | 0.01 (−0.00-0.02) | .105 | 0.01 (−0.01-0.02) | .396 | 0.01 (−0.00-0.02) | .051 | 0.01 (−0.00-0.02) | .188 |
| | High | 0.01 (−0.00-0.02) | .181 | 0.01 (−0.00-0.02) | .096 | 0.02 (0.01-0.03) | .001 | 0.01 (0.00-0.03) | .025 | 0.02 (0.01-0.03) | <.001 | 0.01 (−0.00-0.02) | .138 | 0.02 (0.01-0.03) | .004 | 0.00 (−0.01-0.02) | .547 |
| AIC | | 27 522 | | 27 521 | | 27 518 | | 27 514 | | 27 508 | | 27 518 | | 27 513 | | 27 521 | |

*Notes*: * FU, rate of change over follow-ups (positive values indicate a flatter rate of decline, negative values indicate a steeper rate of decline); * FU * FU, change in the rate of change over follow-ups (positive values indicate a slowing of the rate of decline throughout the study period, negative values indicate an acceleration of the rate of decline throughout the study period); b, coefficient; CI, 95% confidence interval; p, level of significance; REF, reference group.

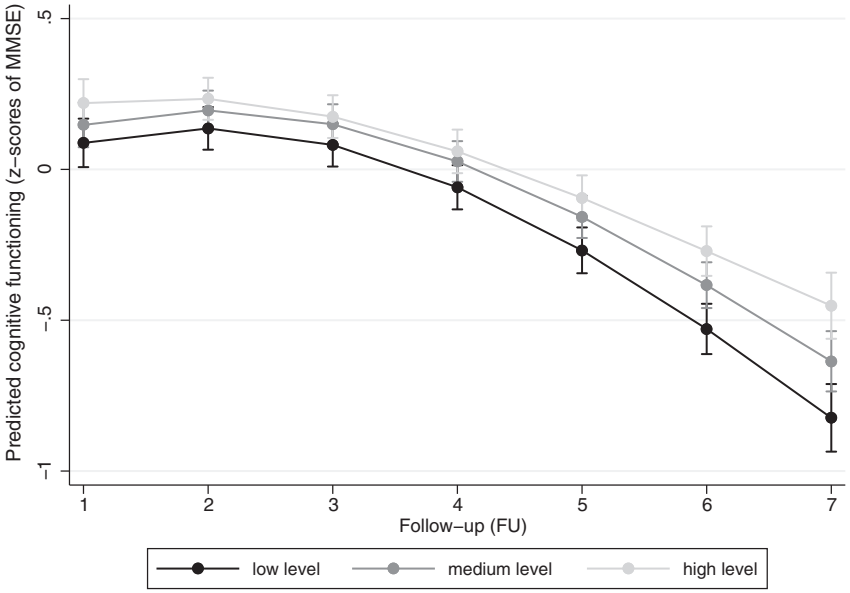


**FIGURE 1** Association between the level in the mental work demand "Language & Knowledge" and cognitive decline in old age as estimated via mixed-effects modeling

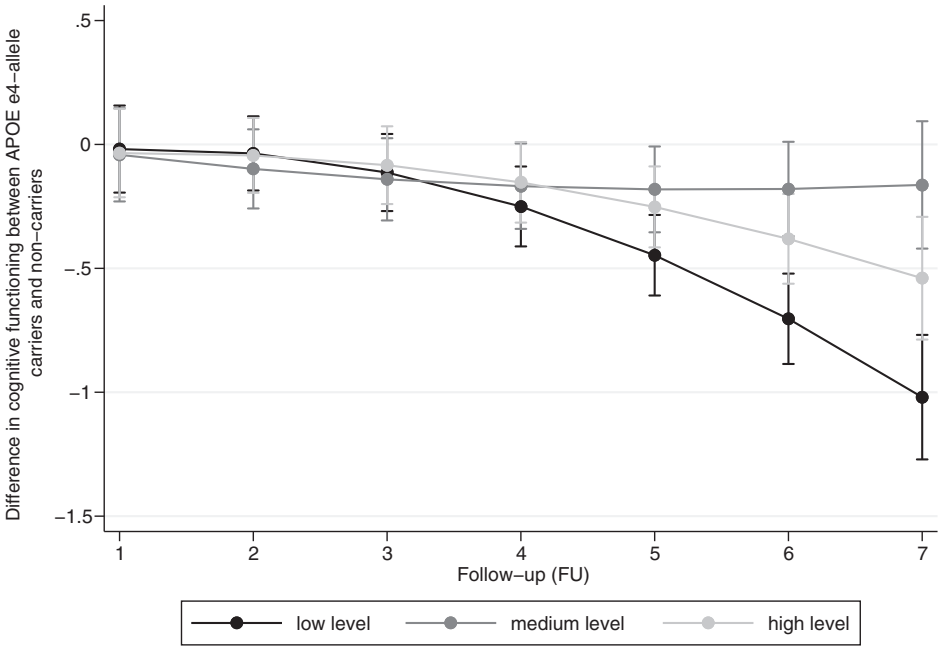


**FIGURE 2** Differences in cognitive functioning between APOE e4 allele carriers and non-carriers by level of the mental work demand "Information Processing" over the follow-up period as estimated via mixed-effects modeling

and "Social Coordinative" demands is associated with a slower change in cognitive decline in APOE e4-allele carriers than in non-carriers (see Table 4); difference shown in Figure 2. Further, a high level in "Perceptual Psychomotor" demands is associated with an acceleration of cognitive decline in the beginning of the study among APOE e4 allele carriers compared to non-carriers (see Table 4).

## 4 | DISCUSSION

Aim of the study was to gain a better understanding of the association between mental demands at work and cognitive decline in old age and how this association differs between APOE e4 carriers and non-carriers. Findings based on a longitudinal cohort study of patients aged 75 years and older indicate that having worked in jobs with higher levels in the mental work demands "Language & Knowledge", "Pattern detection", "Information processing", and "Service" is associated with a slower cognitive decline in old age in APOE e4 allele carriers and non-carriers. While previous studies had demonstrated that higher occupational attainment and occupational complexity protect cognitive health,[2,3] our findings highlight that demands that require the use of language, knowledge, pattern detection abilities, complex information processing, and service-orientation might have the strongest impact. Given that previous studies observed associations between high demands in information processing and pattern detection[6] as well as job complexity with data and people[15,16] and a lower

**TABLE 4** Mixed-effects estimates of interaction effects of the APOE e4 allele and mental demands at work on cognitive decline (MMSE scores) over the follow-up period (with fixed effects for age, number of follow-ups, education, gender, marital status, stroke, depression, diabetes, and their interaction terms with follow-up, and a random effect for age; N = 2 154)

| | | Perceptual Psychomotor b (CI) | *P* | Social Coordinative b (CI) | *P* | Service b (CI) | *P* | Language & Knowledge [a] b (CI) | *P* | Information Processing b (CI) | *P* | Mathematics b (CI) | *P* | Pattern Detection b (CI) | *P* | Creativity b (CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demand (REF: low) | Medium | 0.09 (−0.09-0.27) | .321 | 0.07 (−0.11-0.25) | .468 | 0.05 (−0.13-0.23) | .563 | 0.02 (−0.16-0.20) | .820 | 0.05 (−0.11-0.22) | .416 | 0.15 (−0.03-0.32) | .108 | 0.09 (−0.09-0.27) | .323 | 0.03 (−0.15-0.20) | .785 |
| | High | −0.08 (−0.28-0.11) | .402 | 0.16 (−0.03-0.35) | .104 | 0.18 (−0.01-0.36) | .063 | 0.19 (0.00-0.39) | .048 | 0.16 (−0.04-0.36) | .108 | 0.24 (0.05-0.43) | .015 | 0.21 (0.01-0.40) | .035 | 0.11 (−0.09-0.30) | .291 |
| Demand (REF: low) * FU | Medium | −0.05 (−0.15-0.05) | .300 | −0.01 (−0.11-0.09) | .889 | 0.01 (−0.09-0.11) | .868 | 0.02 (−0.08-0.12) | .651 | 0.00 (−0.09-0.10) | .973 | −0.04 (−0.13-0.06 | .488 | −0.03 (−0.13-0.07) | .617 | −0.02 (−0.12-0.08) | .671 |
| | High | 0.01 (−0.10-0.12) | .871 | −0.05 (−0.16-0.06) | .350 | −0.08 (−0.18-0.03) | .137 | −0.08 (−0.19-0.03) | .157 | −0.06 (−0.17-0.05) | .304 | −0.06 (−0.17-0.05) | .272 | −0.11 (−0.22-0.00) | .055 | 0.00 (−0.11-0.11) | .955 |
| Demand (REF: low) * FU * FU | Medium | 0.01 (−0.00-0.02) | .160 | −0.00 (−0.01-0.01) | .985 | −0.00 (−0.01-0.01) | .908 | −0.00 (−0.02-0.01) | .596 | −0.00 (−0.01-0.01) | .964 | 0.00 (−0.01-0.02) | .525 | 0.00 (−0.01-0.02) | .536 | 0.00 (−0.01-0.02) | .670 |
| | High | 0.00 (−0.01-0.02) | .806 | 0.01 (−0.01-0.02) | .254 | 0.01 (−0.00-0.03) | .079 | 0.01 (−0.00-0.03) | .074 | 0.01 (−0.00-0.03) | .121 | 0.01 (−0.01-0.02) | .220 | 0.02 (0.00-0.03) | .014 | 0.00 (−0.01-0.01) | .969 |
| APOE (REF: non-carrier) | e4 allele | −0.09 (−0.35-0.17) | .491 | −0.08 (−0.34-0.19) | .571 | −0.06 (−0.33-0.20) | .653 | −0.10 (−0.37-0.16) | .443 | −0.06 (−0.32-0.20) | .649 | 0.09 (−0.18-0.36) | .516 | −0.08 (−0.34-0.18) | .549 | −0.09 (−0.36-0.17) | .492 |
| APOE (REF: non-carrier) * FU | e4 allele | 0.09 (−0.06-0.23) | .230 | 0.07 (−0.08-0.22) | .345 | 0.06 (−0.09-0.21) | .426 | 0.08 (−0.07-0.23) | .305 | 0.07 (−0.08-0.22) | .341 | −0.02 (−0.17-0.13) | .813 | 0.08 (−0.07-0.23) | .292 | 0.07 (−0.08-0.22) | .361 |
| APOE (REF: non-carrier) * FU * FU | | −0.03 (−0.05- -0.01) | .005 | −0.03 (−0.05- -0.01) | .003 | −0.03 (−0.05- -0.01) | .007 | −0.03 (−0.05- -0.01) | .002 | −0.03 (−0.05- -0.01) | .003 | −0.02 (−0.04-0.00) | .107 | −0.03 (−0.05- -0.01) | .004 | −0.03 (−0.05- -0.01) | .004 |
| Demand (REF: low) * APOE | Medium | −0.04 (−0.41-0.34) | .850 | 0.11 (−0.28-0.49) | .587 | 0.13 (−0.25-0.51) | .493 | 0.22 (−0.16-0.59) | .265 | 0.09 (−0.29-0.47) | .644 | −0.23 (−0.61-0.16) | .245 | 0.19 (−0.19-0.57) | .335 | 0.06 (−0.32-0.44) | .756 |
| | High | 0.25 (−0.13-0.63) | .195 | 0.04 (−0.34-0.41) | .839 | −0.03 (−0.41-0.35) | .877 | −0.02 (−0.39-0.36) | .931 | 0.01 (−0.37-0.38) | .975 | −0.13 (−0.51-0.25) | .509 | −0.01 (−0.39-0.36) | .943 | 0.14 (−0.24-0.52) | .480 |
| Demand (REF: low) * APOE * FU | Medium | −0.05 (−0.26-0.17) | .676 | −0.15 (−0.37-0.06) | .160 | −0.17 (−0.38-0.05) | .125 | −0.19 (−0.41-0.02) | .081 | −0.15 (−0.37-0.07) | .171 | 0.07 (−0.14-0.29) | .518 | −0.21 (−0.43-0.00) | .055 | −0.08 (−0.29-0.13) | .434 |
| | High | −0.23 (−0.44- -0.01) | .039 | −0.04 (−0.25-0.18) | .743 | 0.01 (−0.20-0.23) | .922 | −0.01 (−0.23-0.20) | .904 | −0.04 (−0.25-0.17) | .732 | 0.02 (−0.19-0.23) | .886 | −0.01 (−0.23-0.19) | .891 | −0.09 (−0.31-0.12) | .407 |
| Demand (REF: low) * APOE * FU * FU | Medium | 0.01 (−0.01-0.04) | .292 | 0.04 (0.01-0.06) | .012 | 0.03 (0.01-0.06) | .014 | 0.04 (0.01-0.07) | .004 | 0.04 (−0.01-0.07) | .009 | 0.01 (−0.02-0.03) | .697 | 0.04 (0.01-0.07) | .004 | 0.03 (−0.00-0.05) | .067 |
| | High | 0.03 (0.01-0.06) | .017 | 0.02 (−0.01-0.04) | .273 | 0.01 (−0.02-0.04) | .535 | 0.01 (−0.02-0.04) | .372 | 0.01 (−0.01-0.04) | .285 | 0.00 (−0.02-0.03) | .726 | 0.01 (−0.02-0.04) | .532 | 0.02 (−0.01-0.05) | .134 |
| AIC | | 27 525 | | 27 513 | | 27 515 | | 27 535 | | 27 501 | | 27 518 | | 27 506 | | 27 515 | |

*Notes:* * FU, rate of change over follow-ups (positive values indicate a flatter rate of decline, negative values indicate a steeper rate of decline); * FU * FU, change in the rate of change over follow-ups (positive values indicate a slowing of the rate of decline throughout the study period, negative values indicate an acceleration of the rate of decline throughout the study period); APOE, apolipoprotein e4 genotype; b, coefficient; CI, 95% confidence interval; p, level of significance; REF, reference group.

[a]Without unstructured covariance because the hessian of the model was not negative semidefinite.

dementia risk, the intensity of information processing might be the occupational aspect most relevant for cognitive health in old age. Human information processing comprises the perception and interpretation of stimuli, which requires working memory and long-term memory, as well as response selection.[17] High demands in language and knowledge might train the retrieval of information from long-term memory, which is usually impaired in dementia.[18] High demands in pattern detection might train the ability to hold content in working memory and working memory ability is a predictor for progression to dementia.[19] Service-oriented jobs, as any type of social interaction, require the processing of a lot of different kind of information.[20] Processing complex information could enhance the brain's network efficiency, which is a predictor for conversion to dementia.[21]

People with an APOE e4 allele tend to have a faster cognitive decline, but seem to experience a greater benefit from having a medium compared to low level of mental work demands than non-carriers. Other studies noted a cognitive gain for APOE e4-allele carriers through intellectual lifestyle activities. For instance, Rodriguez et al.[22] found associations between higher occupational attainment and better cognitive functioning. Wirth et al.[23] and Arenaza-Urquijo et al.[24] observed a lower amount of Alzheimer pathology in APOE e4 carriers if they had higher lifetime cognitive activity. Dekhtyar et al.[25] observed a significant reduction in dementia risk if people with an APOE e4 allele engaged in intellectual lifestyle activities, such as occupation, that enhanced cognitive reserve. Importantly, their findings indicate that the magnitude of the risk reduction is similar between carriers and non-carriers.[25] Similarly, Garibotto et al.[26] observed no difference between APOE e4 carriers and non-carriers in the protective effect of occupational attainment on cognitive performance and brain metabolism. If the APOE gene is something like a "plasticity" gene that determines to what extent a person is susceptible to the effects of environmental factors, then APOE e4-allele carriers experience a gain in cognitive functioning through this factor but not necessarily a greater gain than non-carriers.

Overall, our results are in favor of the differential preservation hypothesis,[27] as cognitively stimulating occupations seem to build up a cognitive reserve equally in APOE e4 allele carriers and non-carriers. Then again, the preserved differentiation hypothesis argues that prior cognitive abilities such as intelligence drive cognitive engagement, which then explains lower prevalence rates.[27] Findings from the Lothian birth cohorts confirm that intelligence at the age of 11 is significantly associated with cognitive ability in old age (but not with cognitive decline[28]), which also explains a large part of the effect of socio-intellectual activity participation.[29] If an APOE e4 allele had a similar effect as childhood intelligence, then we would observe that carriers would have worse cognitive abilities at baseline and lower levels of demands at work. However, we did not. A genetic predisposition in terms of an APOE e4 allele does not seem to be due to preserved differentiation.

Whether lifestyle factors can help to decrease the risk for cognitive impairments in genetically high-risk groups is a central question. Findings from the UK Biobank indicate additive effects of smoking status, alcohol consumption, diet, and physical activity on dementia risk in people with a genetic predisposition.[30] The results from our study suggest that high mental demands at work might have the same effect. However, an analysis of the Rotterdam study indicated that only people with low genetic risk might benefit from a healthy lifestyle such as physical activity, diet, and absence of diabetes or depression.[31] As their cohort was older at baseline, it is possible that, for genetically predisposed people, the positive effects of lifestyle might be stronger at a younger age and lose their efficiency in old age. Moreover, it is important to distinguish the lifestyle factors under investigation. The effects of intellectual stimulation might behave completely different from the effects of physical activity and diet.

There are limitations underlying out study. First, we worked with mixed-models that have the advantage that they estimate the participant's trend across time without placing restrictions on the number of observations per person.[32] However, statistical constraints forced us to model fixed effects for covariates so that possible random effects could not be accounted for within the same models. Second, our study included only individuals aged 75 and older. The effect might be different in younger ages. Third, we experienced a loss to follow-up. Even though we used fixed-effects models to avoid biases in the reported effect, the dropout cases might have changed the variance and underestimate the true effect. Fourth, mental demands at work were operationalized via a standardized classification system O*NET. Even though this is a well-recognized classification system, the values may not necessarily reflect the exact level of demands that the individuals experienced. Fifth, we used the MMSE for indicator of cognitive functioning, which might have ceiling effects. Lastly, we tested eight different types of mental work demands. With Bonferroni correction, the significant level would be $P < .006$ but it is meant to be employed when researchers test different hypotheses on the same data,[33] which is not the case in our study and can lead to Type II error.[34]

In conclusion, our study suggests that engaging in intellectual activities at work that involve the active processing of information in the form of language, knowledge, and patterns could help us maintain cognitive functioning for a longer lifetime period, even in people who carry the dementia risk variant of the APOE gene. As our results are based on exposure-intensity throughout the occupational history, we suggest that APOE e4 allele carriers and non-carriers increase these types of intellectual activities already in younger age to build up a protective effect.

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## CONFLICTS OF INTERESTS

The authors have no conflicts of interest to declare.

## PREVIOUS PUBLICATIONS

None.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions (contractual obligations of the members of the study team).

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## SUPPORTING INFORMATION

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