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Associations between sex and lifestyle activities with cognitive reserve in mid-life adults with genetic risk for Alzheimer's disease

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Abstract

Background Females have a higher age-adjusted incidence of Alzheimer's Disease (AD) than males, even when accounting for longer lifespan and, therefore, stand to benefit the most from dementia prevention efforts. As exposure to many modifiable risk factors for dementia begins in mid-life, interventions must be implemented from middle-age. Building cognitive reserve, particularly through stimulating avocational activities and occupational attainment presents a crucial, underexplored, dementia prevention approach for mid-life. It is currently unknown, however, whether modifiable lifestyle factors can protect against AD processes, from mid-life, differentially for females and males who carry inherited risk for late-life dementia. To address this gap, this study investigated the impact of biological sex and APOE4 carrier status on the relationship between stimulating activities, occupational attainment, and cognition in mid-life.

Methods We leveraged the PREVENT–Dementia program, the world's largest study investigating the origins and early diagnosis of dementia in mid-life at-risk individuals ($N = 700$; 40–59 years). Cognitive performance was measured using the Cognito Battery and the Visual Short Term Memory Binding task. Mid-life specific reserve contributors were assessed via the Lifetime of Experiences Questionnaire.

Results Females had significantly better episodic and relational memory ($p < 0.001$), and lower occupational attainment than males ($p < 0.001$). Engagement in stimulating activities was positively associated with episodic and relational memory, regardless of sex and APOE4 status (β = 0.05, CI 0.03–0.07, $p < 0.001$). APOE4 carriers showed significant sex differences in the association between occupational attainment and episodic and relational memory (β = 0.38, CI 0.12–0.63, $p = 0.003$). APOE4 carrier females with higher occupational attainment showed better cognition (β = 0.16, CI -0.002–0.32, $p = 0.053$), whereas APOE4 carrier males showed the opposite effect (β = -0.20, CI -0.40 – -0.001, $p = 0.049$).

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Conclusion Our findings suggest that occupational attainment in mid-life contributes to cognitive reserve against inherited risk of dementia in females, but not males. They highlight the need for high precision approaches that consider biological sex and APOE4 carrier status to inform Alzheimer's disease prevention strategies and clinical trials.

Keywords Alzheimer's disease, Sex differences, Cognitive reserve, APOE4, Modifiable, Mid-life, Lifestyle factors, Occupation

Background

Dementia is a global epidemic that presents profound challenges to individuals, families, health care systems, and societies throughout the world, and there is an urgent need to reduce the rising worldwide prevalence [1]. Evidence suggests that up to 45% of future dementia cases can be prevented by modifying medical and lifestyle risk factors [2]. As exposure to many modifiable risk factors for dementia begins in mid-life, interventions must be implemented from the middle-age, if not earlier [3–10], prior to the manifestation of substantial brain damage.

Higher cognitive reserve is linked to a reduced risk of dementia and, therefore, building cognitive reserve is a crucial preventative approach. Research indicates that individuals with greater cognitive reserve experience slower age-related cognitive decline [11] and can tolerate higher levels of age-related and dementia-related brain pathology [2, 12, 13], before functional cognitive impairment becomes evident. Education, stimulating avocational activities (physical, social and intellectual), and occupational attainment are key contributors to cognitive reserve [14, 15]. Research indicates that cognitive reserve in older adults is developed through participation in activities that enhance cognitive function. These activities range from early-life education and hobbies to employment and social interactions. Engaging in such activities can help offset brain pathology and genetic predispositions by fostering greater neural connectivity and enhancing information processing capacity [16–18].

It remains unknown whether stimulating activities and occupational attainment can offset dementia risk as early as mid-life, in individuals who are presently healthy but carry the inherited risk (APOE4 genotype) of future dementia. Education has garnered a lot of attention, but it's not substantially modifiable in mid-life. Therefore, the additional contribution of stimulating activities and occupational attainment, which are modifiable in mid-life, is of central importance to preventative strategies in this life stage. It is also not clear who benefits the most from these different reserve contributors. For example, evidence suggests that older females and males benefit differently from interventions aimed at reducing dementia risk [19], e.g., vascular risk factors [20]. Females stand to benefit the most from dementia prevention efforts, due to their elevated incidence of all-type dementia, even when accounting for longer lifespan [21, 22]. Furthermore, historically, females have had restricted access to advanced education and opportunities for cognitively stimulating activities, or prolonged employment. These limited opportunities to build cognitive reserve may, in and of themselves, contribute to the higher incidence of dementia in females [23]. Mounting evidence suggests that sex and APOE4 interact on risk for Alzheimer's disease and related dementias. Compared to males, females exhibit greater penetrance of the APOE4 allele [24], an increased risk of dementia if they carry this genetic variant, and faster cognitive decline [25, 26]. Compared with noncarrier females or APOE4 carrier males, females with an APOE4 allele have increased lifetime risk for AD [27, 28], smaller adjusted hippocampal volumes [29–31], more pathologic levels of CSF abeta and tau [32, 33], more senile plaques and neurofibrillary tangles postmortem [34], and poorer cognition [29, 30]. Recent studies also indicate that APOE4 carrier females also have greater tau burden based on CSF and tau PET imaging [35, 36], and have steeper rates of cognitive decline [37] than females without an APOE4 allele.

Only a limited number of recent studies in older adults have investigated the interactions of sex and APOE4 genotype on cognition and cognitive reserve in older adults. Pa et al. [38] found that higher physical activity was associated with greater cognitive reserve for speed in older females but not in males (mean age=76.11±6.31 years), but APOE4 carrier status attenuated these associations in females. Alty et al. [39] found that cognitive reserve, measured through IQ, moderated the rate of age-related cognitive decline in males but not in females. Only males with higher cognitive reserve experienced a slower decline in cognitive functions compared to those with lower cognitive reserve. No interaction between APOE4 genotype and sex on cognitive trajectories was found [39]. These limited studies highlight the poorly understood, complex interplay between sex, genetic factors, and lifestyle activities in shaping cognitive reserve.

Crucially, whether sex and APOE4 interact to affect the impact of stimulating activities and occupational attainment on cognition in middle-aged individuals remains uncharted territory. To address this gap, this study investigated the impact of biological sex and APOE4 carrier status on the relationship between stimulating activities, occupational attainment, and cognition, in a large cohort of middle-aged and cognitively healthy individuals (N=700, 40–59 years). This will enable high precision

approaches that consider biological sex and APOE4 carrier status to inform strategies for Alzheimer's disease prevention and clinical trials.

Methods

Participants

700 participants were recruited in the PREVENT–Dementia program, a multi-site, prospective longitudinal study investigating the origins and early diagnosis of dementia in mid-life at-risk individuals [8]. Cognitive, clinical and lifestyle assessments were carried out in the five study sites: Imperial College London, the University of Edinburgh, the University of Cambridge, the University of Oxford and Trinity College Dublin (See Supporting Information [SI]; SFigure 1). Participants were aged between 40 and 59 years and were cognitively normal at the time of recruitment, as determined during a thorough clinical examination. Exclusion criteria for the study were a diagnosis of MCI or dementia and known MRI contraindications. The recruitment target was 50% with, and 50% without parental dementia family history. More details on the study population can be found in Ritchie and Ritchie [9] and Ritchie et al. [40]. Individuals with incomplete cognitive (N=31) or clinical (N=9) data were excluded (See SI; SFigure 1 and STable 1). The study reports the wave 1 (baseline) testing data, which were completed at the time of manuscript preparation. Wave 2 and 3 of testing are currently ongoing.

Standard protocol approvals, registrations, and patient consents

The study was approved by the London-Camberwell St Giles National Health Service Ethics Committee (REC reference: 12/LO/1023), by the Trinity College Dublin School of Psychology Research Ethics Committee (SPREC022021–010), and the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee, all of which operate according to the Helsinki Declaration of 1975 (and as revised in 1983). All participants provided written informed consent.

APOE genotyping

In brief, genomic DNA was isolated from blood samples and APOE genotyping was performed. All members of the research and clinical teams were blind to the result of APOE genotyping. In this study, APOE4 risk was determined by ≥1 APOE4 allele. 264/700 carried≥1 APOE4 allele (See Table 1). For further details, see Ritchie et al. [41].

Biological sex

While the dichotomies of sex and gender are no longer considered to be sharply discrete, in this study 'sex' was defined as an individual's natal or biological sex, and was self-reported in the Brain Injury Screening Questionnaire.

Menopausal status

Self-reported menopausal status was determined from the pregnancy and menstruation survey administered during the clinical assessments, particularly the answer to the question: "Are you postmenopausal?". 'Yes' were categorized as postmenopausal, 'No' as premenopausal. Of the 433 female participants, 149 (34.41%) were postmenopausal, 233 were premenopausal. 51 participants who answered 'don't know' were excluded from further

Table 1 Participant characteristics

Participant characteristics	All	Females	Males	*p* value	Effect size
N	660	408	252	–	–
Age (y)	52.0 (9.0)	52.0 (8.0)	53.0 (10.0)	0.03	0.08
Race (% Caucasian)	95.9%	95.8%	96.0%	0.99	< 0.001
BMI	27.0 (6.5) (n = 659)	26.3 (7.2) (n = 407)	27.8 (4.7) (n = 252)	< 0.001	0.15
Hypertension (%)	17.1%	11.3%	26.6%	< 0.001	0.19
Hyperlipidemia (%)	23.4% (n = 644)	21.3% (n = 395)	26.9% (n = 249)	0.12	0.06
Poor sleep (%)	51.8% (n = 657)	52.6% (n = 407)	50.4% (n = 250)	0.64	0.02
Current smoker (%)	5.8% (n = 657)	4.7% (n = 405)	7.5% (n = 252)	0.18	0.05
High alcohol intake (%)	17.4% (n = 655)	12.1% (n = 405)	26.0% (n = 250)	< 0.001	0.17
APOE4 (% Carriers)	38.2%	38.0%	38.5%	0.96	0.002
Years of education	17.0 (5.0)	17.0 (5.0)	17.0 (3.0)	0.18	0.05
Stimulating activities	18.0 (5.0)	18.0 (5.0)	18.0 (4.0)	0.19	0.05
Occupational attainment	13.8 (6.3)	12.6 (7.1)	15.0 (6.3)	< 0.001	0.21
Episodic and relational memory	0.001 (1.0)	0.17 (1.0)	-0.28 (1.0)	< 0.001	0.47
Multisensory processing	-4e-5 (1.0)	0.01 (1.0)	-0.02 (1.1)	0.70	0.03
Short-term memory binding	0.12 (1.1)	0.09 (1.1)	0.15 (1.0)	0.39	0.03

Note: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Effect size was determined using r for Mann-Whitney U test, Cohen's d for independent samples t-test and φ for the Chi-Square test. Abbreviations: BMI, body mass index; APOE4, Apolipoprotein E4 genotype

analyses. As this prospective longitudinal study commenced in 2014, it was not designed to include detailed assessments of menopausal status.

Clinical and lifestyle-bases assessments

Blood pressure was measured after five minutes of supine rest. Blood samples were collected from overnight fasted participants and immediately analysed for standard biochemistry and haematology measures at local laboratories. Hypertension and hyperlipidemia were analyzed as binary variables. Hypertension was defined as an average diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥ 140 mmHg, or a positive history of hypertension as reported during the medical history interview. Hyperlipidemia was defined as total cholesterol > 6.5 mmol/L or a positive history of hyperlipidemia reported in the medical history interview. Body mass index (BMI) was analyzed as a continuous variable, calculated by dividing weight (kg) by height (m^2).

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) [42]. The PSQI score ranges from 0 to 21, whereby higher scores indicate poorer sleep quality. 'Poor' sleep was binarized at a cut-off of PSQI score > 5 [10]. Smoking status and alcohol intake were assessed through a lifestyle interview. Participants were first asked if they were nonsmokers/nondrinkers, ex-smokers/ex-drinkers, or current smokers/drinkers. Smoking status was binarized if they were current smokers. Ex-drinkers and current drinkers were asked to estimate the number of glasses of wine, beer, and stronger alcohol consumed per week, and the total number of units per day/week was calculated. 'High' alcohol intake was defined as consuming more than 21 units per week.

Cognitive reserve contributors

Lifetime education was measured by the total number of years each participant had engaged in formal schooling, with reported values ranging from 0 to 38 years. The Lifetime of Experiences Questionnaire (LEQ) [43] was used to measure engagement in a broad range of lifestyle activities across three distinct stages of life: young adulthood (13–29 years), mid-life (30–64 years), and late life (65 years onwards), and only the mid-life activities were examined. For each life-stage, the LEQ provides two sub-scores that capture (a) "specific" activities – the primary activity undertaken in that stage, i.e., in mid-life this constitutes occupational attainment – and, (b) "non-specific" activities – engagement in physical, social and intellectual activities, in each stage. The LEQ comprises a standardized scoring approach, as follows. The mid-life stimulating activities (i.e., 'non-specific score') were assessed by the frequency of engagement in 7 physically, socially and intellectually stimulating activities, scored on a 6-point Likert scale of frequency (never, less than monthly, monthly, fortnightly, weekly, daily). Scores range from 0 to 35, with higher scores reflecting more frequent engagement in such activities. The items included in the scale are socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in physical activity that is mildly, moderately, or vigorously energetic, reading, practicing a second language and travel. The travel item asks participants if they have visited any of a list of continents between the ages of 30–54. Responses were scored on a 6-point scale as follows: none, 1–2 regions, 3–4 regions, 5 regions, 6 regions, 7 regions.

The mid-life occupational attainment (i.e., 'specific score') is comprised of two sub-scores that measure (a) occupational complexity and (b) managerial responsibility. For the first, participants were asked to record their primary occupation in each 5-year interval from age 30 to age at assessment. Each reported occupation was scored on a scale of 0–9, according to the International Standard Classification of Occupations (ISCO 08) guidelines (https://www.ilo.org/public/english/bureau/stat/isco/isco08/) and relating to the skill level associated with occupations, where managers score 1, professionals 2, technicians and associate professionals score 3, and so on. Participant scores were inverted and summed. The second sub-score measured the managerial responsibility associated with reported occupations. The managerial complexity score was based on participants' responses to the LEQ question: "Did any of your jobs require you to be in charge of or responsible for other people? If yes, indicate job title, number of years in position, and an estimate of the number of people you were in charge of." Participants were instructed to provide information on up to four occupations where they had managerial responsibilities. If participants indicated that they were employed in a managerial capacity, the number of people that they oversaw in four of their reported occupations was documented. Managerial responsibility was scored as follows: 0 people = 8, 1–5 people = 16, 5–10 people = 24 and 10 + people = 32. The highest score across occupations was recorded as the managerial responsibility sub-score, thus capturing the maximum level of leadership responsibility achieved during the participant's midlife career. Occupational attainment was derived by summing the occupational complexity and managerial sub-scores and multiplying them by a normalization factor of 0.25, to ensure that mid-life specific and non-specific scores have comparable mean values [43].

Cognitive assessments

Cognitive function was assessed with the Cognito neuropsychological battery [44], and the Visual Short-Term Memory Binding task (VSTMBT) [45], yielding 13 summary variables. The Cognito battery examines

information processing across a wide range of cognitive functions in adults of all ages and is not restricted to those functions usually implicated in dementia detection in the elderly. It tests several aspects of cognition, including attention (task: visual attention), memory (tasks: narrative recall, description recall, implicit memory, name-face association, working memory), language (tasks: phoneme comprehension, verbal fluency) and visuospatial abilities (task: geometric figure recognition) [46, 44]. 11 summary variables from the Cognito battery capturing the above functions [46, 44] were used [see SI]. The VSTMBT [45] is a computer-based task that assesses visual short-term memory binding of single features, e.g., complex shape or colour combinations, or feature conjunctions, e.g., shape and colour combinations. The two summary variables used from the VSTMBT were the percentage of correctly recognized items from the two conditions (see SI).

Cognitive analyses

Based on our previously published method [47], rotated principal component analysis clustered the above-mentioned multiple cognitive measures (13 summary variables) into related cognitive domains (see SI). Parallel analysis and plotted scree plots determined the number of components that best represented the original 13 cognitive measures. The eigenvalues of the first three components were larger than 95th percentile of the randomly generated eigenvalues (See SI; SFigure 2 A), thus showing that the three components (C) solution best represented the data. The three components were then rotated to be uncorrelated with each other, and could cumulatively explain a total of 40% percentage of the variance (C1 = 16%, C2 = 12%, C3 = 11%) (SFigure 2B).

Statistical approach

The statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS V.27) and R software (https://www.R-project.org/). Outlier assessment was summarized in the SI (SFigure 3). The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort were analysed across sexes using chi-square (χ^2 tests) for categorical variables (Race, hypertension, hyperlipidemia, poor sleep, current smoker, high alcohol intake, APOE4), and Mann-Whitney U tests or independent samples t-tests for continuous variables (*Mann-Whitney U test*: age, BMI, years of education, stimulating activities, occupational attainment, and short-term memory binding; *independent samples t-test*: episodic and relational memory, and multisensory processing), depending on whether they met the assumption of normality in this cohort. Multicollinearity assessment for the three reserve contributors showed no significant collinearity (SI, STable 4).

Independent hierarchical regression models investigated the effects of reserve contributors (education, stimulating activities, and occupational attainment) on each cognitive domain and the moderating role of sex and APOE4. First the models examined the main effects of reserve contributors and sex on cognitive domains, then the 2-way interaction term of contributor × sex was added to examine the moderation effect of sex, with age and the other two contributors included as covariates. For any observed significant 2-way interactions, the moderating role of APOE4 was tested with 3-way interactions of APOE4 × sex × reserve contributor on cognition, with age and the other two contributors included as covariates. The effect of lifetime education was controlled for when considering the impact of stimulating activities and occupational attainment on cognition. Further analyses controlling, in addition to age, for other potential confounds (i.e., BMI, race, hypertension, hyperlipidemia, sleep, alcohol, smoking status) corroborated the results (see SI, STables 5–7). Simple slope analyses tested the significance of the slopes of the regression lines for any significant interactions. The Bonferroni correction was used to correct for multiple comparisons in the analyses of main effects of reserve contributors and sex on cognition. We followed up significant main effects that were in line with previous literature by performing one three-way interaction model, between sex × occupational attainment × APOE4, that directly investigated the study question.

Data availability

Data are available to access through a data request on the study website (www.preventdementia.co.uk); the ADDI platform (DOI: https://doi.org/10.34688/PREVENTMAIN_BASELINE_700V1); Dementia Platforms UK; and the Global Alzheimer's Association Network.

Results

Demographics

Demographic variables, cognition, and reserve contributors scores of the cohort are summarized in Table 1. Females and males did not differ significantly in APOE4 carrier status, years of education, stimulating activities, and 2/3 cognitive domains. Females were slightly younger than males (on average by 1 year), and had significantly lower occupational attainment, and significantly higher episodic and relational memory. Females and males also differed significantly in BMI, hypertension and alcohol intake.

Cognitive performance

A unique set of cognitive measures from the initial 13 (with high coefficients; criterion threshold > 0.4) was closely related to each cognitive component (C1–C3). The mapping of cognitive functions invoked by the highest loading measures (Fig. 1), determined the cognitive functions in each domain. The four measures that loaded strongly on C1 reflected memory recall with a strong episodic element (3/4: descriptive recall, narrative recall, name-face association [recall of relations]) in different modalities (i.e., verbal, visuo-spatial); thus, this domain was labelled 'episodic and relational memory.' The four measures that loaded strongly on C2 reflected processing of visual, auditory/linguistic and multisensory integration of audio-visual information; thus, this domain was labelled 'multisensory processing.' The two measures that loaded strongly on C3 reflected the visual short term memory binding task (VSTMBT), which involved recalling of single features (shape) or feature binding (shape and colour); thus, this domain was labelled 'short-term memory binding' (Fig. 1). The cognitive loading of the first component, labelled the episodic and relational memory domain, replicated a previous finding (with an independent pilot sub-group, $N=210$) of the PREVENT–Dementia cohort [47], demonstrating that the analysis is robust in capturing the most varying cognitive functions for this mid-life cohort.

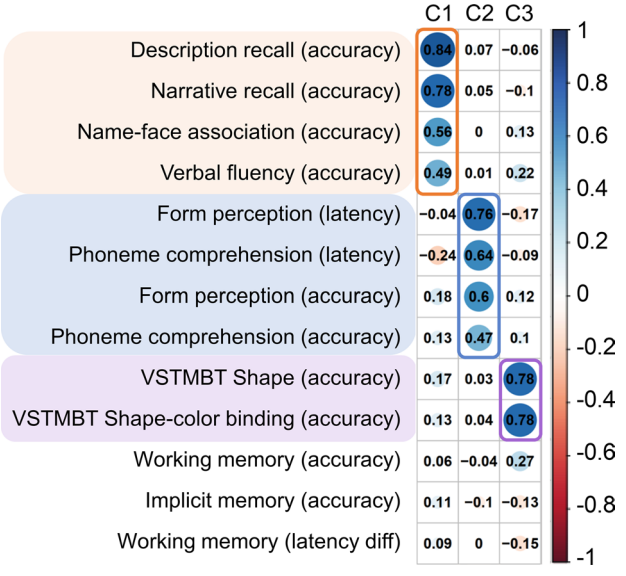

Fig. 1 Cognitive data reduction. The figure shows the loadings of each cognitive measure (in rows) on each cognitive component (in columns). A larger absolute coefficient (darker colors and larger solid circles) represents a closer relationship between the cognitive measure and the corresponding component. Cognitive measures with a coefficient > 0.4 on each component were used to interpret the cognitive functions contributing to each component. Cool/warm colors represent the positive/negative relationships between cognitive measures and components, as shown in the color-bar scale. The color-bar indicates loading values, and higher loading values indicate stronger contribution to corresponding components. Abbreviations: C, component; VSTMBT, visual short-term memory binding task; diff, difference. C1: Episodic and relational memory; C2: Multisensory processing; C3: Short-term memory binding

Sex differences in cognition and reserve contributors

Females had better episodic and relational memory compared to males ($p=8.82\times10^{-9}$) (Fig. 2A). Females had significantly lower occupational attainment than males ($p=1.33\times10^{-7}$) (Fig. 2B).

Reserve contributors and cognition in mid-life

Education was significantly positively associated with episodic and relational memory (β (SE) = 0.05 (0.01), 95% Confidence Interval [CI] 0.03–0.07, $p=5.64\times10^{-5}$; corrected for multiple comparisons), independently of stimulating activities, occupational attainment, sex, and age (Table 2). No sex × education interaction was observed. No association with education was observed for the other two cognitive domains.

Stimulating activities were significantly positively associated with episodic and relational memory (β (SE) = 0.05 (0.01), CI 0.03–0.07, $p=4.68\times10^{-6}$; corrected for multiple comparisons) (Table 2; Fig. 3A), independently of education, occupational attainment, sex, and age (Table 2). No sex × stimulating activities interaction was observed. No association with stimulating activities was observed for the other two cognitive domains (Fig. 3A).

Occupational attainment was not significantly associated with cognition for the whole cohort (Fig. 3B) in any of the three cognitive domains.

Sex differences in the association between occupational attainment and cognition in APOE4 carriers

Based on significant differences observed between females and males in episodic and relational memory (Table 2; Fig. 2A), and in occupational attainment (Fig. 2B), the impact of sex on the association between this cognitive ability and occupational attainment was investigated. A trend interaction sex × occupational attainment was found (β (SE) = 0.14 (0.08), CI -0.007–0.29, $p=0.06$) (Table 3 – Model A, Fig. 4A). There was a significant three-way interaction APOE4 × sex × occupational attainment (β (SE) = 0.33 (0.16), CI 0.02–0.64, $p=0.037$; Table 3 – Model B), which can be explained by the presence of a significant interaction sex × occupational attainment only for APOE4 carriers (β (SE) = 0.38 (0.13), CI 0.12–0.63, $p=0.003$; Fig. 4B–C). Simple slope analyses for APOE4 carrier showed a trend positive relationship for females (β (SE) = 0.16 (0.08), CI -0.002–0.32, $p=0.053$), and a significantly negative association (β (SE) = -0.20 (0.10), CI -0.40 – -0.001, $p=0.049$) for males (Fig. 4B), between occupational attainment and episodic and relational memory. As the cohort's age group covers the menopause transition, a post-hoc analysis was

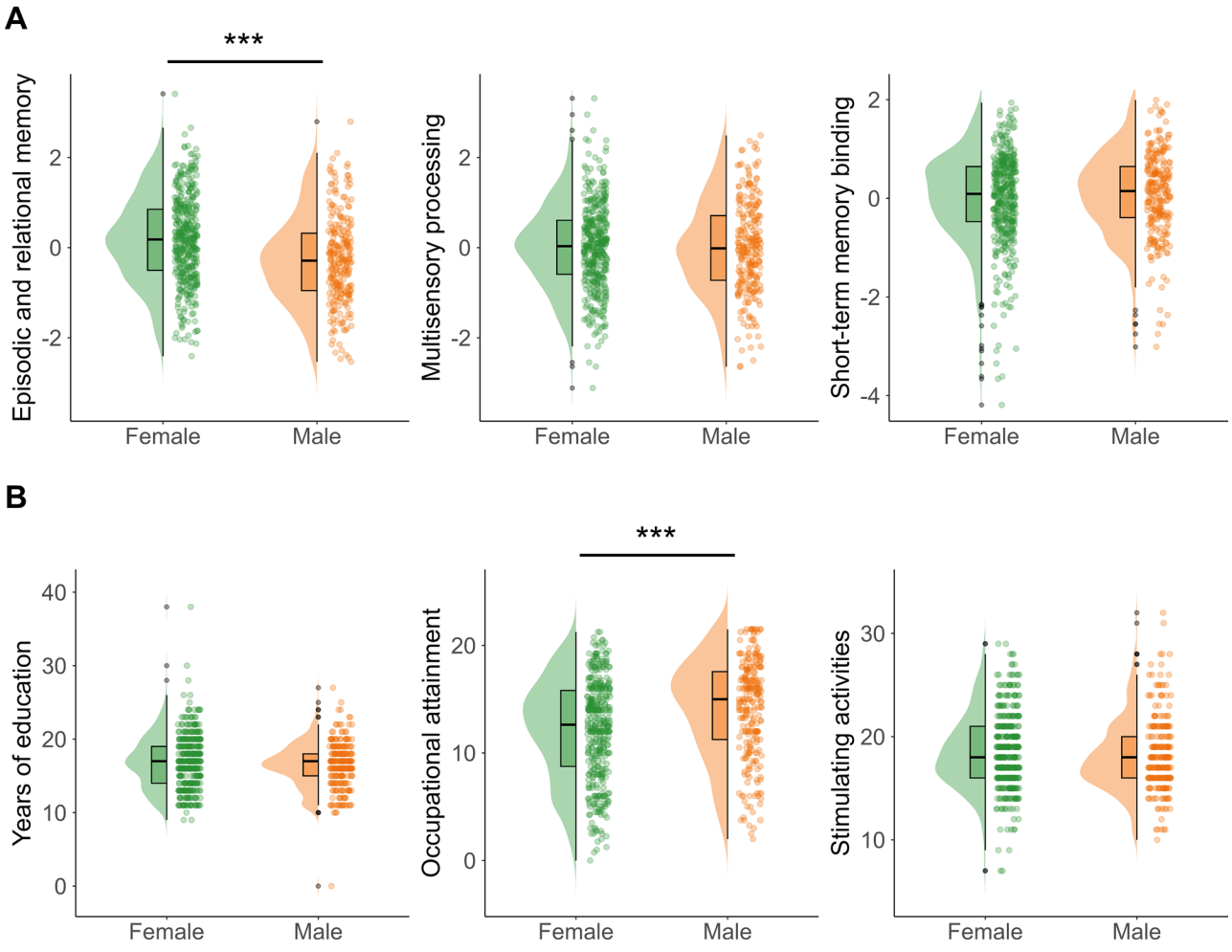

Fig. 2 Sex differences on cognition and reserve contributors. (**A**) Sex differences on cognitive domains. (**B**) Sex differences on reserve contributors. Females had significantly better episodic and relational memory than males. Females have significantly lower occupational attainment than males. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1−1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. *** = $p < 0.0005$

Table 2 Regression coefficients for the main effects of reserve contributors on episodic and relational memory

Model summary		**R^2**	**F**	***p* value**
		0.14	**20.53**	**< 0.001**
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Episodic and relational memory	Years of education	0.05 (0.01)	[0.03, 0.07]	< 0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	< 0.001
	Occupational attainment	0.003 (0.01)	[-0.01, 0.02]	0.71
	Sex	0.41 (0.08)	[0.26, 0.56]	< 0.001
	Age	-0.02 (0.01)	[-0.03, -0.01]	0.008

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals

conducted to investigate whether menopause impacted the association between occupational attainment and cognition in females. No effect of menopause was found (See SI; STable 3).

Discussion

This study investigated the impact of sex and APOE4 carrier status on the relationship between mid-life stimulating activities, occupational attainment, and cognition, in a cohort of individuals (N=700), who were presently cognitively healthy, but carried genetic risk for late-life AD. We leveraged the PREVENT–Dementia program

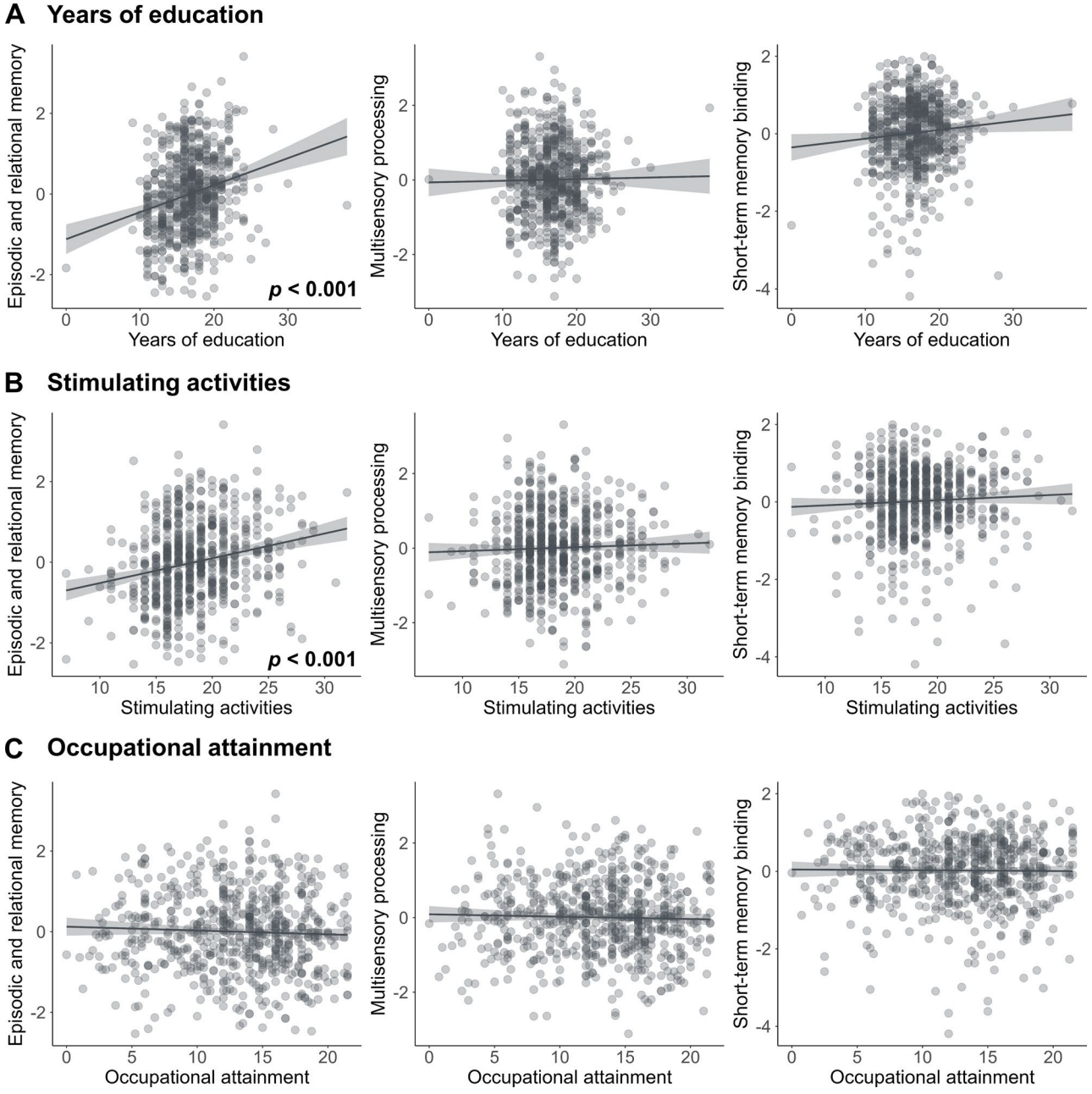

Fig. 3 Association of reserve contributors with cognition. (**A**) The effects of education, (**B**) stimulating activities, and (**C**) occupational attainment on each of the three cognitive domains are shown. Higher education was significantly associated with better episodic and relational memory. Higher engagement in stimulating activities was significantly associated with better episodic and relational memory. The effect of each reserve contributor was estimated after controlling confounding variables, as well as the other two contributors. On the x axis, higher scores represent greater education/stimulating activities/occupational attainment, and on the y axis, higher scores represent better cognition

[9], the world's largest study investigating the origins and early diagnosis of dementia in mid-life at-risk individuals. After controlling for the effect of education, we found that individuals with higher engagement in physically, socially and intellectually stimulating activities showed better episodic and relational memory, regardless of biological sex and APOE4 status. Significant sex differences in APOE4 carriers were found in the association between occupational attainment and cognition. APOE4 carrier females with higher occupational attainment showed better cognition, whereas APOE4 carrier males with higher occupational attainment showed worse cognition. These findings suggest that cognitive reserve contributors that are modifiable in mid-life boost cognition in middle-age, with sex and APOE4 status significantly affecting this relationship. They highlight the urgent need for high

Table 3 Regression coefficients for models including 2-way or 3-way interactions of IVs on episodic and relational memory

Model A: 2-way interaction				
Model summary		R^2	F	*p* value
		0.14	17.76	< 0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Episodic and relational memory	Occupational attainment	-0.08 (0.06)	[-0.20, 0.05]	0.23
	Sex	0.40 (0.08)	[0.25, 0.55]	< 0.001
	Years of education	0.05 (0.01)	[0.03, 0.07]	< 0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	< 0.001
	Age	-0.02 (0.01)	[-0.03, -0.004]	0.01
	Sex*Occupational attainment	0.14 (0.08)	[-0.007, 0.29]	0.06
Model B: 3-way interaction				
Model summary		R^2	F	*p* value
		0.15	11.75	< 0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Episodic and relational memory	APOE4	0.03 (0.12)	[-0.22, 0.27]	0.83
	Sex	0.31 (0.10)	[0.12, 0.51]	0.001
	Occupational attainment	-0.01 (0.08)	[-0.17, 0.14]	0.87
	APOE4*Sex	0.22 (0.16)	[-0.08, 0.53]	0.16
	APOE4*Occupational attainment	-0.19 (0.12)	[-0.43, 0.06]	0.13
	Sex*Occupational attainment	0.03 (0.09)	[-0.16, 0.21]	0.78
	APOE4*Sex*Occupational attainment	0.33 (0.16)	[0.02, 0.64]	0.037
	Years of education	0.05 (0.01)	[0.02, 0.07]	< 0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	< 0.001
	Age	-0.02 (0.01)	[-0.03, -0.002]	0.03

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals

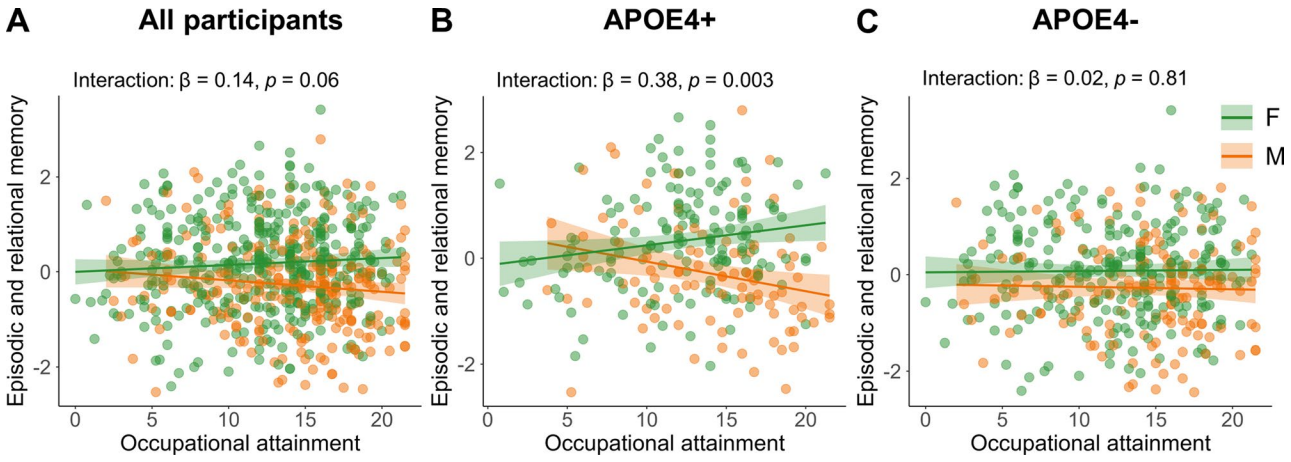

Fig. 4 Sex differences in the associations between occupational attainment, cognition and APOE4 genotype in mid-life. (**A**) A trend effect interaction is shown between sex and occupational attainment on episodic and relational memory. (**B**) A significant interaction is shown between sex and occupational attainment on episodic and relational memory in APOE4 carriers. (**C**) APOE4 non-carriers showed no significant interactions between sex and occupational attainment. On the x axis, higher scores represent greater occupational attainment, and on the y axis, higher scores represent better episodic and relational memory

precision approaches that consider biological sex and APOE4 carrier status to inform Alzheimer's disease prevention strategies and clinical trials.

Higher engagement in physically, socially and intellectually stimulating activities in mid-life was associated with stronger cognition in a composite domain capturing episodic and relational memory, independently of sex, age, years of education and occupational attainment. This result replicates a previous finding [48] with a pilot sub-group (N=210) of the PREVENT–Dementia cohort. These activities comprised socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading, practicing a second language and travel, suggesting that cognition in mid-life can benefit from the combination of a wide variety of stimulating activities.

Effects were seen only in the domain of episodic and relational memory, two of the earliest cognitive functions that show changes in pre-symptomatic AD [49–51]. Impairment of episodic memory is the hallmark of AD in the majority of cases [52], and studies have found it to be strongly associated with conversion from MCI to AD [53], in older adults. Similarly, relational memory tasks, especially with a semantic memory aspect, have been used to differentiate between MCI and healthy aging [54], again in older adults. To the best of our knowledge, effects of stimulating activities on episodic and relational memory (or multisensory processing and short-term memory as tested here) have not previously been reported in mid-life individuals. We caution that the interpretability of the effect of lifestyle activities on each individual cognitive function is limited by their composite assessment in this study and requires individuation in future studies. Furthermore, the stimulating activities reported here are a composite score of seven discrete items. Conversely, the aggregate consideration of cognitive domains and avocational lifestyle activities may increase the power to detect early and subtle cognitive changes due to lifestyle in at-risk mid-life individuals, an estimated 23 years from dementia onset [3]. Importantly, our results extend previous literature in older adults and suggest that, well before a potential AD diagnosis, modifiable avocational activities can strengthen cognitive functions that are vulnerable to early AD neuropathology, and, thus, are promising cost-effective interventions for building cognitive reserve from mid-life.

The key question in this study, however, was to investigate the impact of sex and APOE4 carrier status on the association between reserve contributors and cognition in mid-life. To the best of our knowledge this is the first study to report a sex-specific effect of occupational attainment on cognitive ability, in individuals who are presently cognitively healthy but carry the genetic risk (APOE4) for late-life AD. Why do APOE4 carrier females with higher occupational attainment in mid-life show stronger cognitive ability? While the precise mechanism is unclear, multidimensional vulnerability influences to AD in middle-aged APOE4 carrier females likely render them more responsive to protective lifestyle activities. First, in mid-life, multi-system vulnerabilities set in motion by the menopausal transition [55], can lead to metabolic deficiencies and ultimately cognitive decline [56], thus exposing middle-aged females to higher risk for AD. Second, historically, females have accrued higher vulnerability to neurodegeneration, relative to males, through barriers to key reserve contributors, such as educational and occupational opportunities, leading to lower cognitive reserve [57]. Third, these female-specific vulnerabilities may be further exacerbated [58] by interactions with genetic risk for late-onset AD [59]. A recent review study in older adults [age>65 years] found that females benefited from reserve contributors more than males [60]. Our finding advances the state-of-the-art understanding by suggesting that occupational attainment may offset the impact of APOE4 genetic risk in females from mid-life, by boosting cognitive abilities that are both vulnerable to AD risk and early AD neuropathology [49, 50, 61].

APOE4 carrier males showed a negative association between occupational attainment and episodic and relational memory. Previous studies in older adults have found that high job strain was associated with worse cognition [62] and cognitive decline [63] in males, but not in females. One potential explanation for these findings may be the substantial sex differences in both the magnitude and the duration of stress response, shaped by male (e.g., testosterone) and female (e.g., estradiol) sex hormones [64]. In light of the observed males' significantly higher occupational attainment, our results further suggest that APOE4 carriership in males may be associated with a domain-general cognitive resource limitation, leading to a dose effect on the relationship between occupational attainment and episodic and relational memory. The significantly weaker episodic and relational memory relative to females, observed in the male cohort, suggests a cognitive vulnerability in this domain, which may explain why episodic and relational memory decreases with stronger engagement of domain-general cognitive resources in high strain occupational duties.

The above interpretations relating to biological (sex hormones, menopausal transition, AD biomarkers) variables are plausible but as-of-yet untested, given that these data were not directly measured in this study. Thus, future studies are needed to understand the underlying mechanisms associated with divergent effects of lifestyle factors in middle-aged females versus males with inherited dementia risk.

Methodological considerations

The lifestyle activity scores were obtained from self-report answers to the LEQ [43], which is an internationally validated and widely used instrument, but may, nevertheless, include some level of recall bias in reporting. The scoring of occupational complexity is affected by length of work history. This limitation was mitigated by controlling for age in statistical analyses. The data presented is from PREVENT–Dementia, an ongoing longitudinal program commenced in 2014, that did not include detailed assessment of menopause status. Detailed and objective measurements, including hormonal assays are necessary to investigate in future studies the interactions between menopause status and dementia risk factors in middle-aged females. The possibility that higher education may determine high avocational activities,

occupational attainment, and cognition has been considered but is not likely. We found that the effect of lifestyle activities on cognitive ability was independent of the total years of education, which shows that education does not directly drive this effect. Furthermore, mid-life occupational attainment was associated with improved cognitive performance only in APOE4 carrier females, who were not more educated than APOE4 non-carrier females, or males. We caution that the interpretability of the effect of lifestyle activities on each individual cognitive function is limited by their composite assessment in this study and requires individuation in future studies. The study population are mainly (95%) of white Caucasian ethnicity, not dissimilar to the historic ethnic mix of older people in the UK and Ireland, which limits generalizability of findings beyond individuals of European ancestry. Finally, the observational cross-sectional data (from the baseline visit) presented in this study limit conclusions on causality. Future studies from the ongoing testing waves two and three (2 and 8 years post baseline respectively) of this multi-site study will determine the longitudinal impact of modifiable lifestyle activities in middle-aged individuals at risk for late life AD.

Conclusion

The majority of previous studies have focused on the effect of reserve contributors on cognition or AD pathology in late life [65–67]. One recent study, including individuals aged from 50 to 80 years, showed sex-specific effects of IQ, as a proxy of cognitive reserve, on age-related cognitive decline [39]. The current study makes a novel contribution by showing interactions between sex, APOE4 and reserve contributors on cognition in mid-life. We show a positive effect of stimulating activities on cognition in middle-aged individuals regardless of sex and inherited risk, and of occupational attainment in individuals with inherited risk for late-life AD, while controlling for educational differences. Our findings demonstrate that occupational attainment in mid-life contributes to cognitive reserve against inherited risk of dementia in females, but not males, at risk for late-life AD. They suggest that sex and APOE4 carrier status are important variables to consider for building high precision dementia prevention strategies and clinical trials.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01610-9.

Supplementary Material 1

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Author contributions
Study concept or design: Q.Q., F.D., R.S., L.N. Major role in the acquisition of data: Q.Q., F.D., R.S., K.R., G.M-T., I.K., P.M., S.H., D.R., J.T.O., C.W.R., B.L., L.N. Analysis or interpretation of data: Q.Q., F.D., R.S., L.N. Drafting/revision of the manuscript: Q.Q., F.D., R.S., L.N.

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Data availability
Data are available to access through a data request on the study website (www.preventdementia.co.uk); the ADDI platform (DOI: https://doi.org/10.34688/PREVENTMAIN_BASELINE_700V1); Dementia Platforms UK; and the Global Alzheimer's Association Network.

Declarations

Ethics approval and consent to participate
The study was approved by the London-Camberwell St Giles National Health Service Ethics Committee (REC reference: 12/LO/1023), by the Trinity College Dublin School of Psychology Research Ethics Committee (SPREC022021–010), and the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee, all of which operate according to the Helsinki Declaration of 1975 (and as revised in 1983). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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