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RESEARCH ARTICLE

The relative contribution of modifiable and non-modifiable factors for determining cognition in mid-life individuals at risk for late-life Alzheimer's disease

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Abstract

INTRODUCTION: It remains unknown whether cognitive reserve contributors can protect against dementia from mid-life, in the context of several modifiable and non-modifiable risk factors, including family history and inherited risk for late-life dementia.

METHODS: We leveraged PREVENT Dementia, a large multisite study of healthy mid-life at-risk individuals ($N = 700$) and used canonical correlation analysis (CCA) to investigate multivariate associations between 13 cognitive tasks, 10 modifiable and four non-modifiable risks, and three reserve contributors.

RESULTS: The CCA identified a significant canonical mode ($r = 0.486$, $p_{(FWE)} < 0.001$) between dementia risk, reserve contributors, and cognition. The key finding was that modifiable stimulating activities showed the strongest positive association with cognition. Depressive symptoms and traumatic brain injury were the top two modifiable risk factors negatively associated with cognition.

Bolin Cao and Qing Qi contributed equally to this work.

DISCUSSION: These results highlight the strong potential of early, cost-effective, and multifactorial dementia prevention interventions that target both modifiable risk reduction and boosting of cognitive reserve from mid-life.

KEYWORDS
cognition, cognitive reserve contributors, dementia, mid-life, modifiable risk factors, non-modifiable risk factors

Highlights

- Stimulating activities were the top reserve factor positively associated with cognition.
- Depressive symptoms were the top risk factor negatively associated with cognition.
- Male sex was associated with weaker cognition in mid-life.
- Memory functions were significantly associated with risks and reserve factors.

1 | BACKGROUND

Dementia is a global epidemic that presents profound challenges to individuals, families, healthcare systems, and societies throughout the world, and there is an urgent need to reduce its rising worldwide prevalence.[1] Notably, the neuropathological processes underlying dementia begin in mid-life, with subtle cognitive decrements emerging decades before clinical symptoms manifest.[2–4]

Up to 45% of dementia cases could potentially be prevented or delayed by addressing modifiable medical and lifestyle risk factors.[1,5] As exposure to many modifiable risk factors for dementia begins in mid-life,[6] as do early pathological changes of the main causes of dementia such as Alzheimer's disease (AD), interventions must be implemented from middle age, if not earlier,[2–4,7] prior to the manifestation of substantial brain damage.

Higher cognitive reserve is linked to a reduced risk of dementia, so building cognitive reserve is a crucial preventive approach. Studies show that individuals with greater cognitive reserve experience slower age-related cognitive decline[8] and can tolerate higher levels of age-related and dementia-related brain pathology[1,9] before functional cognitive impairment becomes evident. Education, stimulating avocational activities (physical, social, and intellectual), and high occupational attainment are key contributors to cognitive reserve.[10,11] Engagement in these activities can help offset brain pathology and genetic predispositions by fostering greater neural connectivity and enhancing information processing capacity.[12]

The role of stimulating activities and occupational attainment in offsetting dementia risk as early as mid-life, in individuals who are presently healthy but carry the inherited risk, such as Alipopoprotein ε4 (*APOE* ε4) genotype, and other, modifiable risks of future dementia remains largely unknown. The majority of studies investigating the contribution of dementia-related risk and protective factors focus on older or already symptomatic cohorts.[8,9] Studies examining both dementia risk and protective factors in the mid-life population are limited, predominantly examine single or limited numbers of factors (a summary of previous studies is presented in Table S1),[7,13–16] and/or focus on narrowly defined cognitive outcomes,[17,18] often overlooking their complex interactions.

To address this important gap, we examined the multivariate association between dementia risks, reserve contributors, and cognition in mid-life, years before the potential onset of dementia symptoms. Nine modifiable risks were based on the early and mid-life risk factors identified in the 2024 Lancet Commission report[1] and included hyperlipidemia, hypertension, obesity, diabetes, hearing impairment, depressive symptoms, smoking status, alcohol intake, and traumatic brain injury (TBI). Poor sleep, which is emerging as an important risk factor for brain health in mid and late life,[19,20] was also included. The four non-modifiable risk factors included were *APOE* ε4, family history of dementia (FHD), sex, and age. Three key contributors to cognitive reserve were examined: education, stimulating avocational activities (physical, social and intellectual), and occupational attainment.[10,11] Cognitive domains were examined via the Cognito neuropsychological battery[21] and the Visual Short-Term Memory Binding task (VSTMBT).[22] We hypothesized that a higher cumulative burden of risk factors would be associated with poorer cognitive outcomes, while reserve contributors would show the opposite effect. We were particularly interested in examining the relative contributions of different risk and reserve contributors, to identify the key deleterious and protective factors in cognition in mid-life individuals.

2 | METHODS

2.1 | Participants

We leveraged the PREVENT Dementia program, a large, multisite study investigating the origins and early diagnosis of dementia in mid-life at-risk individuals ($N = 700$).[2] Participants aged 40 to 59 years were recruited across five study sites: Imperial College London, the University of Edinburgh, the University of Cambridge, the University

of Oxford, and Trinity College Dublin. All participants were cognitively normal at baseline, as confirmed through comprehensive clinical evaluations. Exclusion criteria included a diagnosis of mild cognitive impairment (MCI) or dementia and any contraindications for magnetic resonance imaging (MRI). The full protocol has been described elsewhere.[3] The recruitment target was 50% with and 50% without parental dementia family history. For this analysis, we excluded individuals with incomplete cognitive ($n = 31$) or clinical ($n = 82$) assessments (Figure S1). The current findings are based on Wave 1 (baseline) data, with ongoing follow-up assessments in Waves 2 and 3.

2.2 | Standard protocol approvals, registrations, and patient consent

The study was approved by the London–Camberwell St Giles National Health Service Ethics Committee (REC reference: 12/LO/1023), 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.

2.3 | Cognitive assessments

Cognitive function was evaluated using the Cognito neuropsychological battery[21] and the VSTMBT,[22] resulting in 13 summary variables (Table S2). The Cognito battery assesses a broad spectrum of cognitive functions across all adult age groups, not limited to those typically associated with dementia detection in older adults. It measures multiple domains, including attention (visual attention task), memory (narrative recall, description recall, implicit memory, name-face association, and working memory tasks), language (phoneme comprehension and verbal fluency tasks), and visuospatial abilities (geometric figure recognition task).[18,21] Eleven summary variables used in this study were derived from the Cognito battery, capturing these functions. The VSTMBT, a computer-based task, evaluates visual short-term memory binding, testing recognition of single features (e.g., complex shapes or colors) and feature conjunctions (e.g., shape-color combinations). Two summary variables from the VSTMBT were included, representing the percentage of correctly recognized items in each condition (see the Supplementary Information [SI] for full details of how variables were calculated and used in the analysis).

2.4 | Modifiable risk factors assessments

Ten modifiable risk factors associated with dementia risk, including hyperlipidemia, hypertension, obesity (body mass index), diabetes, hearing impairment, depressive symptoms, smoking status, alcohol intake, TBI, and poor sleep, were examined. These factors were assessed through clinical measurements (e.g., blood pressure, fasting glucose, and cholesterol levels), standardized questionnaires (e.g., Center for Epidemiologic Studies Depression Scale [23] for depressive symptoms, Pittsburgh Sleep Quality Index[24] for sleep quality, and Brain Injury Screening Questionnaire [BISQ][25] for TBI), and self-reports (e.g., lifestyle interviews for smoking and alcohol intake and medical history taking for hearing impairment) (see SI).

RESEARCH IN CONTEXT

1. **Systematic review**: Whether cognitive reserve contributors can protect against dementia from mid-life, in the context of several modifiable and non-modifiable risk factors, including family history and inherited risk for late-life dementia, remains unknown, as shown by a systematic review of PubMed.
2. **Interpretation**: Stimulating activities showed a strong positive association with mid-life cognition that was larger than that of every modifiable risk factor assessed and of the inherited (*APOE* ε4) risk, suggesting a central role of stimulating activities in boosting cognition, regardless of dementia risk factors.
3. **Future directions**: Future studies from the ongoing testing waves (8 years after baseline) of this multisite study will determine the longitudinal impact of risk and protective factors on cognitive trajectories of middle-aged individuals at risk for late-life dementia. Results suggest that future studies should investigate early, cost-effective, and multifactorial interventions that target both risk reduction and boosting of cognitive reserve for dementia prevention from mid-life.

2.5 | Non-modifiable risk factor assessments

Apolipoprotein E (*APOE*) genotyping was performed using blood-derived genomic DNA, with *APOE* ε4 carriership defined as having at least one *APOE* ε4 allele.

FHD was determined by self-reported parental diagnosis of dementia during the clinical interviews, classifying participants as FHD+ if at least one parent was diagnosed with dementia. These non-modifiable factors were included because they are well-established contributors to dementia risk,[26,27] influencing both the likelihood of late-life dementia and cognitive decline trajectories.[1] Detailed assessment methods are provided in the SI.

2.6 | 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 BISQ.

2.7 | Cognitive reserve contributors

Protective factors contributing to cognitive reserve were assessed using the Lifetime of Experiences Questionnaire (LEQ).[28] We focused on their assessment with relevance to the mid-life age group in particular, capturing the two relevant factors for mid-life, as provided by the LEQ: (a) socially, physically, and intellectually stimulating activities and (b) occupational attainment. (a) Stimulating activities were evaluated based on the frequency of engagement in seven physical, social, and intellectual activities, scored on a 6-point Likert scale (0 to 35, higher scores indicating greater engagement). (b) Occupational attainment was derived from two subscores, occupational complexity (based on the International Standard Classification of Occupations) and managerial responsibility (reflecting the number of people supervised), which were summed and normalized. Education was measured as the total number of years of formal schooling (see SI).

2.8 | Statistical analyses

To quantify the multivariate association between (1) dementia risk factors and reserve contributors and (2) cognitive measures, and to describe the relative contribution of each variable, we used canonical correlation analysis (CCA),[29] a multivariate statistical technique that identifies linear combinations (canonical modes) of two sets of variables that are maximally correlated with each other. CCA was used to identify maximally correlated linear combinations between dementia risk/reserve contributors ($n = 17$) and cognitive measures ($n = 13$). Statistical significance was assessed using permutation testing (5000 permutations), with family-wise error (FWE) correction applied to canonical correlations and variable loadings ($p_{(FWE)} < 0.05$) (see SI for full details).

Because the primary CCA indicated that the stimulating activities had the largest positive loading among the dementia risk factors and cognitive contributor sets, a post hoc additional analysis was conducted to determine which specific activities contributed to this pattern (see SI). The CCA was reestimated after replacing the stimulating activities with its seven individual items entered simultaneously, while retaining education and occupational attainment and keeping all other variables identical to the primary analysis.

TABLE 1 Summary of characteristics of mid-life individuals ($n = 587$).

	Variable	Mean ± SD or (%)
Lifetime of Experiences Questionnaire	Occupational attainment	13.00 ± 4.65
	Stimulating activities	18.48 ± 3.57
	Years of education[a]	16.71 ± 3.53
Modifiable	Hyperlipidemia[a]	137 (23.33%)
	Hypertension[a]	135 (22.99%)
	Body mass index (BMI) [a]	27.70 ± 5.49
	Diabetes[a]	19 (3.24%)
	Hearing impairment[a]	65 (11.07%)
	Depressive symptoms[a]	9.16 ± 8.48
	Smoking status[a]	33 (5.62%)
	Alcohol intake[a]	9.63 ± 16.62
	Traumatic brain injury (TBI) [a]	3.82 ± 5.31
	Poor sleep quality	303 (51.61%)
Non-modifiable	Age	51.14 ± 5.50
	Sex (M)	228 (38.8%)
	APOE ε4 carriers	218 (37.1%)
	Family history of dementia (FHD)	289 (49.2%)
Cognitive tests	Description recall (accuracy)	13.29 ± 4.41
	Narrative recall (accuracy)	13.91 ± 4.30
	Name-face association (accuracy)	5.26 ± 2.13
	Verbal fluency (accuracy)	27.64 ± 6.62
	Form perception (latency)	5740.60 ± 1507.43
	Phoneme comprehension (latency)	1469.42 ± 285.30
	Form perception (accuracy)	6.34 ± 1.16
	Phoneme comprehension (accuracy)	8.61 ± 0.60
	VSTMBT shape (accuracy)	0.86 ± 0.17
	VSTMBT shape-color binding (accuracy)	0.49 ± 0.22
	Working memory (accuracy)	9.80 ± 0.64
	Implicit memory (accuracy)	1.03 ± 0.69
	Working memory (latency diff)	7.20 ± 3068.56

Abbreviations: APOE, apolipoprotein E; diff, difference; M, male; SD, standard deviation; VSTMBT, Visual Short-Term Memory Binding task.
[a]These variables shown correspond to the early and mid-life risk factors identified by the 2024 Lancet Commission on Dementia Prevention, Intervention, and Care.

3 | RESULTS

The cohort characteristics are shown in Table 1. Descriptive statistics of the cognitive measures, stratified by sex and *APOE* ε4 status, are reported in Supplementary Results and Table S3.

After using FWE correction, only the first canonical mode was significant ($r = 0.486$, $p_{(FWE)} < 0.001$; Figure 1A); all subsequent modes were non-significant. We found that in the first canonical mode, the dementia risk factors of depressive symptoms, TBI, diabetes, hypertension, hearing impairment, and poor sleep showed significantly negative loadings, suggesting that higher levels of these risk factors are linked to poorer cognitive performance across nine of the 13 cognitive measures (verbal fluency, name-face association, description recall, form perception [accuracy], working memory, phoneme comprehension [accuracy], VSTMBT shape, form perception [latency], and phoneme comprehension [latency]) (Figure 1B,C). Of these six modifiable factors, depressive

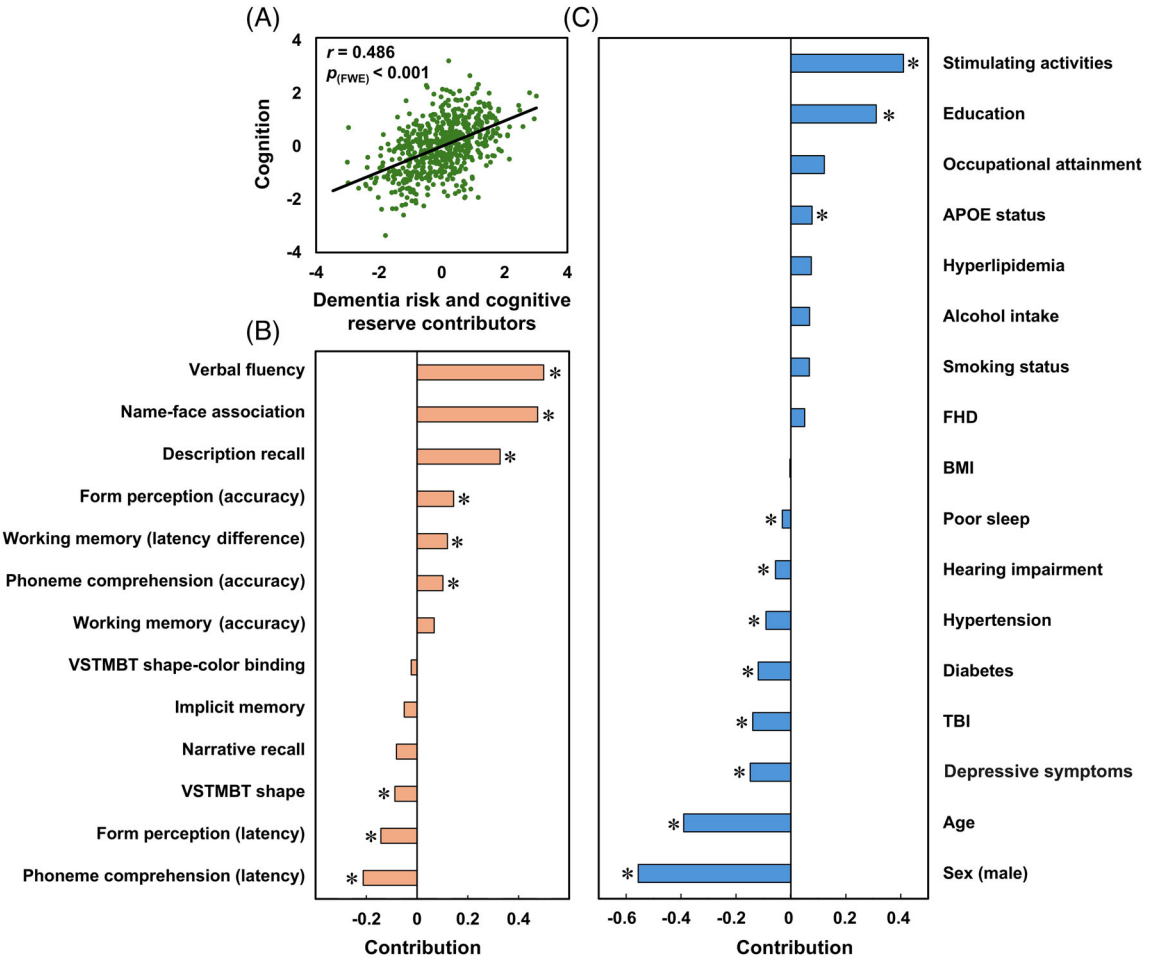

FIGURE 1 Multivariate association of cognition with dementia risk factors and reserve contributors in mid-life. (a) Canonical correlation between cognitive measures and dementia risk and cognitive reserve contributors in mid-life ($r = 0.486$, $p_{(FWE)} < 0.001$). The *x*-axis represents the canonical variable scores for dementia risk and cognitive reserve contributors, and the *y*-axis represents the canonical variable scores for cognitive performance measures. (b) Loadings of 13 cognitive measures in the canonical mode. The *x*-axis indicates the loading values (ranging from negative to positive), reflecting the direction and strength of each measure's contribution, and the *y*-axis lists the cognitive measures (e.g., verbal fluency, name-face association, and VSTMBT shape). (c) Loadings of dementia risk and cognitive reserve contributors in the canonical mode. The *x*-axis shows the loading values (ranging from negative to positive), indicating the direction and strength of each variable's contribution, and the *y*-axis lists the variables, including modifiable risk factors (e.g., depressive symptoms, TBI, hypertension, and poor sleep), non-modifiable risk factors (e.g., age, sex, *APOE* status, and FHD), and cognitive reserve contributors (e.g., stimulating activities and education). Asterisks (*) indicate that loadings are significant after family-wise error rate correction. *APOE*, apolipoprotein E; BMI, body mass index; FHD, family history of dementia; TBI, traumatic brain injury; VSTMBT, Visual Short-Term Memory Binding task; acc, accuracy.

symptoms had the highest negative contribution to cognition, followed closely by TBI, diabetes, and hypertension. Two non-modifiable factors, sex and older age, also showed significantly negative loadings, suggesting they were linked to poorer cognitive scores. Specifically, males performed worse than females across the same nine cognitive measures, and older age was similarly associated with poorer performance in those nine cognitive measures. *APOE* ε4 showed significantly positive loadings, suggesting that carriers performed better on these nine cognitive measures. The loadings of cognitive measures, dementia risk, and reserve contributors are listed in Table S4.

Conversely, socially, physically, and intellectually stimulating activities followed by years of education were the two of three reserve contributors that had significantly positive loadings, indicating that greater engagement in these areas is associated with better cognitive performance. When the contribution of the seven stimulating activities was modeled individually, six out of seven showed a significant positive relationship to cognition (see Figure S2 and Table S5 for details on these loadings).

The top three cognitive tasks that showed a significant relationship with risk factors and reserve contributors tap into episodic and relational memory functions and correspond to the top three cognitive variables that we have shown in independent analyses to be positively associated with cognitive reserve contributors in mid-life.[13] The other tasks, in order of loading strength, that showed a positive relationship tap into visuospatial abilities, working memory, and language functions.[21] The positive loadings for cognitive tasks where accuracy

was the variable of interest suggest that better performance in these areas is associated with a higher presence of reserve contributors and a lower burden of risk factors. For tasks where response latency was the variable of interest (i.e., working memory, form perception, and phoneme comprehension), the loading reflects a time-related metric where a shorter latency indicates better performance. For example, despite the negative loading for the phoneme comprehension task, the significant loading suggests that better performance was associated with high presence of reserve contributors and low risk burden. The task of VSTMBT shape exhibited a significantly negative loading, suggesting that poorer performance is more likely when there is a higher burden of risk factors, highlighting susceptibility to these risks.

Because the composite stimulating activities score showed the strongest positive loading in the primary CCA, we conducted a follow-up analysis in which the seven constituent activities were entered simultaneously in place of the composite score. Six of the seven activities showed significant positive loadings on cognition, indicating that the observed effect reflects a broad pattern of engagement rather than being driven by a single activity (see Figure S2 and Table S5).

4 | DISCUSSION

This study examined the relative contributions of ten modifiable risks, two non-modifiable risks, and three cognitive reserve contributors to identify the key risk and protective factors in cognition in a cohort of currently cognitively healthy mid-life individuals ($N = 700$), half with FHD and 37% with inherited (*APOE* ε4) risk of late-life dementia. Physically, socially, and intellectually stimulating activities were the top reserve contributor, with a significant positive relationship with cognition in this age group, whereas depressive symptoms and TBI were the top two modifiable risk factors negatively associated with cognition in mid-life. Episodic and relational memory functions were the top cognitive domains that showed a significant relationship with risk and reserve contributors, suggesting that modifiable lifestyle factors significantly impact cognitive functions that are vulnerable to early dementia and, thus, may be promising cost-effective interventions for protecting against AD-related cognitive impairment in mid-life. These results highlight a strong potential for early and cost-effective multifactorial interventions, targeting both risk reduction and boosting of cognitive reserve, with a strong focus on engagement in a variety of stimulating activities for dementia prevention in mid-life.

Two modifiable reserve contributors – socially, physically, and intellectually stimulating activities and education – showed a significant positive relationship with cognition, suggesting that higher engagement in these activities boosts cognition in mid-life. The observed effect of education reflects long-term effects set in motion from early life and young adulthood. The central question, however, related to the effect on cognition of lifestyle activities undertaken in mid-life that are, therefore, unlike education, substantially modifiable in mid-life.

The key novel finding was that stimulating activities showed a strong positive association with mid-life cognition, in the context of 17 factors. These results suggest a central role of stimulating activities in boosting cognition in mid-life regardless of the presence of dementia risk factors. This result is consistent with that of other studies we have published,[13–15] which considered stimulating activities independently of other risk and protective factors. Remarkably, here we show a very strong role for stimulating activities that was larger, in absolute terms, than that of 12 other modifiable factors, including that of non-modifiable factors, such as inherited (*APOE* ε4) risk, for late-life AD. These comprised a variety (seven) of activities, including socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in physical activities, reading, practicing a second language, and traveling.

When the contribution of each of these seven stimulating activities was modeled individually, six out of seven showed a significant positive relationship to cognition, demonstrating that this association was distributed across multiple forms of physical, social, and intellectual engagement rather than being attributable to a single activity, supporting the interpretation of a cumulative lifestyle effect in mid-life. Each had a lower positive loading on the relationship to cognition than education, further suggesting that together they have a stronger impact on cognition than each does individually. This further suggests that a variety of stimulating avocational activities is important for cognition in mid-life. We caution that the observational cross-sectional data (from the baseline visit) presented in this study limit conclusions on causality. For example, it is possible that cognitive abilities determine engagement in stimulating activities, rather than the inverse. However, the effect of stimulating activities on mid-life cognition here was captured additionally to that of the total years of education, which suggests that the observed relationship cannot be reduced to long-standing cognitive advantage alone. In previous studies we also showed the effect of stimulating activities on cognition independently of education,[13–15] which further supports this interpretation. Furthermore, the cohort comprises cognitively normal mid-life individuals (ages 40 to 59) without MCI or dementia and, thus, is specifically designed to precede the stage at which neurodegenerative disease typically drives marked withdrawal from activities. While subtle preclinical changes may be present, the proportional disengagement characteristic of symptomatic neurodegeneration is unlikely to explain the strength and consistency of the observed multivariate association in this age group. Future studies from the ongoing testing Waves 2 and 3 (2 and 8 years after baseline, respectively) of this multisite study will be critical for determining the longitudinal and causal impact of risk and protective factors on cognitive trajectories of middle-aged individuals at risk for late-life dementia.

Episodic and relational memory are two of the earliest cognitive functions that show changes in presymptomatic AD.[30,31] Impairment of episodic memory is the hallmark of AD in the majority of cases,[32] and studies have found it to be strongly associated with conversion from MCI to AD[33] in older adults. Similarly, relational memory tasks, especially with a semantic memory aspect, have been used to differentiate between MCI and healthy aging,[34] again in older adults. Importantly, our results extend previous literature in older adults and suggest that, well before a potential AD diagnosis, modifiable lifestyle activities can strengthen cognitive functions that are vulnerable to early

AD neuropathology and, thus, may build cognitive reserve and help maintain cognitive function despite underlying neuropathology. This is consistent with a previous study where we showed that higher engagement in stimulating activities was associated with stronger cognition, particularly in individuals with a FHD.[15]

APOE ε4 genotype showed a positive association with episodic and relational memory functions, visuospatial abilities, working memory, and language functions. The positive association of *APOE ε4* genotype with cognition is counterintuitive but aligns with other findings for *APOE ε4* carriers in mid-life cohorts, including stronger cognition,[14,35] cerebral hyperperfusion,[36,37] and hyperconnectivity within the default mode network (DMN),[38] relative to non-carriers. Our finding adds to these previous findings that are consistent with the antagonistic pleiotropy hypothesis of aging,[39] which proposes that genes that are deleterious in late life, such as the *APOE ε4* gene allele, have survived through evolution because they might confer an advantage early in life, when humans are reproductively fit.

Six modifiable risk factors showed significantly negative association with cognitive performance, suggesting that higher levels of these risks negatively impact cognition in mid-life. These included, in order of contribution, depressive symptoms, TBI, diabetes, hypertension, hearing impairment, and poor sleep. This order replicates that shown in the Lancet Commission report,[1] with the exception of hearing impairment, which shows a lower contribution to cognition in this study, potentially due to the narrower range of deficits captured here, as our participants did not exhibit "hearing loss," which is the variable included in Livingston et al.[1] Furthermore, this study advances the literature and extends findings from the Livingston et al. study[1] by showing the relative contribution of poor sleep in the context of other well-established mid-life risk factors for late-life dementia. Previous studies in older adults showed that depressive symptoms could lead to cognitive decline through elevated cortisol levels, vascular dysregulation, and diminished neurotrophic support,[40] whereas TBI negatively impacted cognition through mechanisms, such as white matter damage,[41] neuroinflammation,[42,43] and blood–brain barrier disruption.[44] Cardiovascular risk factors, such as those captured here (i.e., diabetes, hypertension), may accelerate cognitive decline by disrupting cerebral perfusion, inducing microvascular pathology, and creating metabolic disturbances that undermine neural networks integral to memory and perceptual processing.[45]

Male sex and older age emerged as significant non-modifiable factors with negative loadings, indicating heightened vulnerability to weak cognition in mid-life. Previous studies found poorer cardiovascular health in men relative to women in mid-life.[46,47] We also previously showed in this cohort that male participants carried a larger dementia risk burden than females, with higher rates of hearing loss, hypertension, overweight, current smoking, TBI, alcohol use, and diabetes.[2] These disparities likely contribute to a higher cardiovascular disease load in middle-aged men, including cerebral small vessel disease, which is associated with white matter damage,[48,49] and may explain the observed negative association of male gender with cognition.

4.1 | Methodological considerations

The lifestyle activity scores were obtained from self-report answers to the LEQ,[28] which is an internationally validated and widely used instrument but may, nevertheless, include some level of recall bias in reporting. The study population is made up mainly (95%) of White Caucasians, not unlike the historic racial mix of older people in the UK and Ireland, which limits the generalizability of findings beyond individuals of European ancestry.

5 | CONCLUSION

The majority of previous studies focused on old-age or symptomatic cohorts when investigating the contribution of dementia-related risk and protective factors. The very few studies that focused on the mid-life age range investigated individual risk factors or reserve contributors independently of one another. This study overcomes these limitations by combining 17 diverse risk and protective factors into a unified analysis to reveal how these factors collectively shape cognition for middle-aged individuals.

The key novel finding was a strong positive contribution of stimulating avocational activities to mid-life cognition, in the context of 17 factors, including 14 risks and three reserve contributors. Physically, socially, and intellectually stimulating activities were the top reserve factor, with a significant positive relationship to episodic and relational memory, followed by education, suggesting they boost cognitive reserve in mid-life regardless of the presence of risk factors for dementia. We highlight a strong potential for early, cost-effective, and multifactorial dementia prevention interventions that target both risk reduction and boosting of cognitive reserve, with a strong focus on engagement with physically, socially, and intellectually stimulating activities in mid-life.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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