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Associations between multidomain modifiable dementia risk factors with AD biomarkers and cognition in middle-aged and older adults

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ABSTRACT

This study aimed to determine associations between modifiable dementia risk factors (MDRF), across domains mood symptomatology, lifestyle behaviors, cardiovascular conditions, cognitive/social engagement, sleep disorders/symptomatology, with cognition, beta-amyloid (Aβ) and tau, and brain volume. Middle-aged/older adults (n=82) enrolled in a sub-study of the Healthy Brain Project completed self-report questionnaires and a neuropsychological battery. Cerebrospinal fluid levels of Aβ 1–42, total tau (t-tau), and phosphorylated tau (p-tau$_{181}$) (Roche Elecsys), and MRI markers of hippocampal volume and total brain volume were obtained. Participants were classified as no/single domain risk (≤1 domains) or multidomain risk (≥2 domains). Compared to the no/single domain risk group, the multidomain risk group performed worse on the Preclinical Alzheimer's Cognitive Composite (d=0.63, p=.005), and Executive Function (d=0.50, p=.016), and had increased p-tau$_{181}$ (d=0.47, p=.042) and t-tau (d=0.54, p=.021). In middle-aged/older adults, multidomain MDRFs were related to increases in tau and worse cognition, but not Aβ or brain volume. Findings suggest that increases in AD biomarkers are apparent in midlife, particularly for individuals with greater burden, or variety of MDRFs.

1. Introduction

The incidence of Alzheimer's disease (AD) dementia and all-cause dementia is estimated to be reducing by 16% and 13% respectively per decade in high income countries (Wolters et al., 2020). This raises the possibility that some risk for dementia is modifiable and that key modifiable dementia risk factors (MDRFs) may influence AD pathogenesis, cognitive decline and/or dementia onset (Livingston et al., 2020). Multiple clinical studies have demonstrated that individual MDRFs are moderately associated with dementia risk and with cognitive decline (Cherbuin et al., 2015; Gottesman et al., 2017a; Morris et al., 2015; Santabárbara et al., 2019; Sommerlad et al., 2019). Consistent with this, animal models indicate that MDRFs can promote abnormal accumulation of beta-amyloid (Aβ) and tau, and consequent neurodegenerative processes through biological pathways such as neuroinflammation (Gregor and Hotamisligil, 2011), increases in glucocorticoids (Green et al., 2006) and disruption to normal neurotoxic clearance processes (Lin et al., 2016). Biomarker studies conducted in older adults also indicate that MDRFs such as depressive or anxiety symptoms (Lavretsky et al., 2009), poor diet, physical inactivity and obesity (Merrill et al., 2016) are each associated with elevated Aβ and tau levels. A recent study of both middle-aged and older adults found no associations between a range of individual MDRFs and plasma levels of tau collected remotely (Roccati et al., 2023), however, the validity and sensitivity of plasma biomarkers collected remotely still remains unclear.

There is increasing epidemiological evidence that many MDRFs co-occur and likely cluster together (Conry et al., 2011; LaPlume et al.,

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2022; Morris et al., 2016; Poortinga, 2007), such that many adults may exhibit multiple simultaneous MDRFs. Despite this, there remains little data on the extent to which the combined contribution of multiple simultaneous MDRFs might relate to AD biomarkers. Studies that have considered multiple MDRFs have most commonly only considered cardiovascular risk factors, often defined using validated risk scores such as the Framingham Heart Study – Cardiovascular Risk Score (FHS-CRS) or Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) score (Bos et al., 2019; Rabin et al., 2019; Song et al., 2020). These studies showed that greater cardiovascular risk, indicated by higher composite risk scores, is associated with increased brain atrophy over time in cognitively unimpaired (CU) older adults, and greater tau accumulation in CU older adults in the preclinical stage of AD (i.e., surpassed established threshold for Aβ positivity). However, the combined contribution of a wider range of MDRFs, beyond cardiovascular risk factors, to AD biomarkers remains unclear. Further, as the pathophysiological process of AD begins in midlife (Sutphen et al., 2015), it is important for these relationships to be clarified in middle-aged adults.

Recently, in a large group of middle-aged and older adults (40–70 years old) enrolled in the Healthy Brain Project (HBP), we demonstrated that 67% of the sample reported MDRFs in two or more risk domains including mood symptomatology, risky lifestyle behaviors such as smoking and physical inactivity, low cognitive and/or social engagement, cardiovascular conditions, and sleep symptomatology/disorders (Bransby et al., 2023a). Further, reporting MDRFs across a greater number of these domains was associated with poorer learning and working memory, and attention, and greater subjective cognitive concerns (Bransby et al., 2023a). These results suggest that even in midlife, reporting a greater burden or variety of MDRFs may be associated with poorer brain health. However, as this sample from the HBP was assessed remotely via an online platform, it was not possible to determine the extent to which multiple MDRFs were related to AD biomarkers. Recently, cerebrospinal fluid (CSF) samples and brain MRIs were collected from a sub-sample of the HBP, enabling clarification of the association between MDRFs spanning multiple risk domains and AD biomarkers in middle-aged adults. This investigation will inform current models of AD pathogenesis and the design of dementia prevention strategies.

The first aim was to confirm relationships between multidomain MDRFs and cognitive performance assessed remotely in a larger sample of middle-aged and older adults from the HBP, using in person neuropsychological assessment in the smaller sub-sample of participants. In line with our previous study (Bransby et al., 2023a), it was hypothesized that individuals with multidomain MDRFs would have poorer cognitive performance compared to individuals with no or single domain MDRFs. The second aim was to determine the relationship between multidomain MDRFs and CSF levels of $A\beta_{42}$, total tau, and phosphorylated tau ($p\text{-}tau_{181}$), as well as total brain and hippocampal volumes determined from magnetic resonance imaging (MRI). It was hypothesized that individuals with multidomain MDRFs would have lower levels of CSF $A\beta_{42}$, higher levels of CSF total tau and $ptau_{181}$, and reduced total brain and hippocampal volume, compared to individuals with no or single domain MDRFs.

2. Methods

2.1. Participants

Participants (N=82) were cognitively unimpaired middle-aged and older adults enrolled in the HBP who had agreed to attend detailed in-person assessments. Recruitment details of the HBP have been detailed previously (Lim et al., 2019). Briefly, participants were included in the HBP if they were aged between 40 and 70 years, residents of Australia and fluent in English. Participants were excluded if they self-reported a history of severe traumatic brain injury or other major neurological disease/insult, psychiatric condition (i.e., schizophrenia, uncontrolled current major depression, or other uncontrolled Axis I psychiatric disorder), any prior use of Therapeutic Goods Administration approved medications for Alzheimer's disease (AD; e.g., donepezil, memantine, or other approved medications), or a diagnosis of mild cognitive impairment (MCI), AD, Parkinson's disease or other known diagnosis of dementia. HBP participants who had completed all online baseline measures, saliva sampling for *APOE* genotyping, had expressed interest in participating in more comprehensive in-person assessments and were residents of Victoria, Australia (or willing to travel) were contacted to establish interest in participating in in-person assessments. The process of recruitment and data collection has been detailed previously (Lim et al., 2023). Briefly, interested participants underwent comprehensive medical and safety screening and were excluded if they had any health conditions that would make biomarker assessments unsafe (e.g., incompatible metallic implant, blood clotting abnormalities). If participants passed screening, they attended a visit at the Royal Melbourne Hospital between November 2018 and February 2020 and underwent a series of assessments in a single visit including a comprehensive neuropsychological battery, MRI, and a lumbar puncture to obtain a sample of CSF. *APOE* status was blinded to research assistants that conducted assessments, and to participants. All participants who underwent in-person assessments completed the neuropsychological assessments (n=82), 95% of participants provided a CSF sample (n=78), and 94% of participants underwent MRI (n=77). This HBP Biomarker sub-study was approved by the human research ethics committee at Melbourne Health in Melbourne, Australia (HREC/17/MH/322) and participants provided written informed consent in person with a trained research assistant prior to any procedures.

2.2. Modifiable dementia risk factor selection and measurement

MDRFs were selected for inclusion based on evidence of associations with worse cognition, and/or increased risk for cognitive decline and dementia (Cherbuin et al., 2015; Gottesman et al., 2017b; Morris et al., 2015; Santabárbara et al., 2019; Sommerlad et al., 2019), and being readily modifiable by middle-aged and older individuals (Bransby et al., 2023b). Measurement and classification of risk for each MDRF has been detailed and operationally defined elsewhere (Bransby et al., 2023a). Furthermore, the theoretical and statistical rationale for aggregation of MDRF into risk domains has also been described in detail previously (Bransby et al., 2023a). Briefly, individual MDRFs (n=15) were classified into five broad domains: mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, low cognitive and social engagement and sleep disorders and symptomatology. Increased depressive or anxiety symptoms and psychological stress were classified into the mood symptomatology domain as these MDRFs indicate poor mood or worsening mental health. Physical inactivity, poor diet, and current smoking status were classified into the risky lifestyle behaviors domain as these MDRFs reflect health behaviors or habits that relate to increased risk for poorer health outcomes. Hypertension, hypercholesterolemia, diabetes and obesity were classified into the cardiovascular conditions domain as these MDRFs reflect health conditions that are associated with poorer cardiovascular health. Social isolation and low engagement in cognitively stimulating leisure activities were classified into the low cognitive and social engagement domain as these MDRFs reflect low engagement in activities that are socially and cognitively stimulating. Insomnia symptoms, excessive sleepiness and obstructive sleep apnea were classified into the sleep disorders/symptomatology domain as these MDRFs reflect symptoms or disorders specific to sleep or sleep-related breathing that are associated with sleep quality and duration.

2.3. Classification of modifiable dementia risk factors

Consistent with previous attempts to synthesize a wide range of MDRFs (Bransby et al., 2023a), participants were classified as having risk in a MDRF domain if they reported at least one individual MDRF

within that domain. Each domain was given a score of one point such that a participant with one or more MDRFs in that domain would only receive one point. The number of points across domains were then summed to create groups based on how many domains in which participants reported at least one MDRF (0−5). Due to the large number of individual MDRFs considered in the current study, this approach was selected to promote parsimony and interpretability. The benefit of this approach, that is, consideration of MDRFs beyond those which fall within the cardiovascular/lifestyle domain, has also been previously demonstrated (Bransby et al., 2023a). Participants were grouped into: (1) no/single domain risk, when no MDRFs are reported, or when MDRFs are reported only in a single domain; and (2) multidomain modifiable risk, when MDRFs are reported in two or more domains. These groupings were selected to provide information on whether reporting multidomain MDRFs is associated with worse cognition and increased biological markers of AD, compared to reporting no MDRFs or MDRFs in a single domain. Additionally, as the sample size in the current study was relatively small (N=82), there was insufficient power to compare groups reporting MDRFs across 0–5 domains or to include the number of MDRF domains (0−5) as a continuous score, due to being positively skewed (skewness=0.434, kurtosis=2.601).

2.4. Cognitive assessments

Participants underwent a comprehensive neuropsychological test battery which lasted ~60 min. Table 1 summarizes the range of neuropsychological tests from which outcomes were selected to calculate cognitive composite scores in the current study. These measures were used to compute three cognitive composite scores: (1) Preclinical Alzheimer's Cognitive Composite (PACC); (2) Episodic Memory; and (3) Executive Function. Raw scores for each outcome measure were standardized using the baseline mean and standard deviation of the sample. The standardized scores for each test were then averaged to create each composite score (Table 1). Higher cognitive composite scores indicate better performance. These cognitive composite scores are well-validated and have been shown to be sensitive to AD-related cognitive deficits or decline (Bransby et al., 2019; Lim et al., 2014). The Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) Scale were used to assess general cognition. The Cognitive Function Instrument (CFI) was used to assess subjective ratings of cognition and the National Adult Reading Test (NART) was used as an estimation of intelligence.

2.5. CSF biomarker assessments

CSF was collected by lumbar puncture with most samples collected between 13:00 and 14:30 h. The protocol for CSF sample collection and processing is well-established and has been described previously (Li et al., 2015). Briefly, CSF samples were transferred for processing on wet ice and were spun at 2000 x g at +4 ∘C for 10 min. Supernatant was pipetted off to a new polypropylene tube and gently inverted a few times to avoid possible gradient effects. Samples were then aliquoted in 0.5 mL portions into screw-cap polypropylene tubes (Sarstedt cat# 72.730.007) and stored at −80 ∘C pending biochemical analyses. CSF concentrations of amyloid-beta 1–42 ($A\beta_{42}$), total tau (t-tau), and tau phosphorylated at threonine 181 ($p\text{-}tau_{181}$) were measured by immunoassay (Roche Elecsys®). All CSF sample analyses were conducted at the National Dementia Diagnostics Laboratory (The Florey Institute, University of Melbourne, Australia). As 26 (33%) participants had $A\beta_{42}$ levels above the maximum limit of detection indicating extremely low levels of Aβ burden in the brain, they were assigned the top range score (1700 pg/mL) (Doecke et al., 2020). There were no statistically significant demographic or clinical differences between participants that had $A\beta_{42}$ levels above the maximum limit of detection and those with $A\beta_{42}$ levels below the maximum limit of detection (Supplementary Table 1). The threshold for Aβ abnormality (Aβ+) was classified when CSF $A\beta_{42}$ levels were less than 1000, in accordance with standardized cut-offs established by Roche.

Table 1
Neuropsychological test outcomes in each cognitive composite.

Composite score	Neuropsychological tests
PACC	MMSE, Logical memory delayed recall, ISLT delayed recall, WAIS-R digit symbol (number correct)
Episodic memory	Logical memory delayed recall, ISLT delayed recall, GMLT recall (moves per second)
Executive function	GMLT (errors), TMT – B (seconds), category fluency (fruit/ furniture)

Note. PACC=Preclinical Alzheimer's Cognitive Composite; MMSE=Mini-mental state examination; ISLT=International shopping list test; WAIS-R=Wechsler Adult Intelligence Scale-Revised; GMLT=Groton maze learning test; CVLT-II=California verbal learning test second edition; TMT-B=Trail making test B.

2.6. Brain MRI

Participants underwent MRI using a 3 T Siemens Prisma system (Siemens, Erlangen, Germany). To attain data on brain volume, T1-weighted MRI was used with the following acquisition parameters: voxel size 0.8×0.8×0.8 mm, repetition time (TR) = 2400 ms, echo time (TE) = 2.31 ms, flip angle = 8°. To determine that the images were free of major motion artefact, all images were visually inspected. To calculate hippocampal and total brain volume, FreeSurfer's recon-all pipeline (v6.0.0) (Dale et al., 1999; Fischl and Dale, 2000) was used which includes motion correction, bias field correction, skull stripping, Talairach transformation and segmentation to white and grey matter (Fischl et al., 2002). Following this was a tessellation of the white and grey matter boundary, topology correction and surface warping to enhance the grey-white and grey-CSF borders (Dale et al., 1999; Fischl and Dale, 2000). Surface inflation, spherical atlas transformation and parcellation of the cerebral cortex were then performed once the cortical models were generated (Fischl et al., 2004). Throughout the entire processing pipeline, visual inspections were completed. Total brain volume and hippocampal volume (average of left and right hippocampal volumes) were corrected for intracranial volume.

2.7. APOE genotyping

Participants provided a saliva sample via Genotek Oragene (OG-500) 2 mL saliva kits (including instructions on saliva collection) that were mailed to their postal address. Saliva samples were sent to GenoFIND Services laboratory (Salt Lake City, USA), where they were processed to obtain targeted SNPs including *APOE* (rs429358, rs7412) using TaqMan GTXpress Master Mix (Life Technologies) as per manufacturer's instructions.

2.8. Data analysis

All analyses were conducted using R Version 4.0.1. A series of analyses of variance (ANOVA) and chi square tests of independence were conducted to determine any demographic differences between multidomain and no/single domain risk groups.

To determine the relationship between multidomain MDRFs and cognitive performance, ANCOVAs were conducted with group (multidomain / no/single domain risk) as the fixed factor. Estimated marginal means (EMM) were calculated for both groups and the magnitude of difference between groups on each cognitive composite was expressed as Cohen's d effect sizes and 95% confidence intervals. The no/single domain risk group was used as the reference group.

To determine the relationship between multidomain MDRFs and biomarkers of AD and neurodegeneration, a series of analyses of covariance (ANCOVAs) were conducted with group (multidomain / no/

single domain risk) as the fixed factor. EMMs were calculated for both groups and the magnitude of difference between groups on each biomarker was expressed as Cohen's d effect sizes and 95% confidence intervals. The no/single domain risk group was used as the reference group.

In all statistical models, age, sex, years of education and presence or absence of an *APOE* ε4 allele were entered as covariates, given their known influence on cognition and AD biomarkers (Buckley et al., 2022; Gonneaud et al., 2020; Jack et al., 2015; Lim et al., 2015). Statistical significance for all comparisons was set at $p < .05$. The potential for Type I error was minimized through the computation of effect sizes (Cohen's d) for each statistical comparison between multidomain and no/single domain risk groups. Effect sizes were used to contextualize the importance of outcomes, with effect sizes classified as small ($d \leq 0.2$), moderate ($d = 0.3–0.7$), and large ($d \geq 0.8$) (Brydges, 2019). Effect sizes classified as small were not interpreted, irrespective of their level of statistical significance.

2.8.1. Post-hoc analysis

To explore the relationship between reporting multidomain MRDFs and cognitive performance when the influence of AD biomarkers was accounted for, ANCOVAs with group (multidomain / no/single domain risk) as the fixed factor and each cognitive composite as outcomes were repeated with $A\beta_{42}$, p-tau_{181} and t-tau entered as covariates in addition to age, sex, years of education and presence or absence of an *APOE* ε4 allele. EMMs were calculated for both groups and the magnitude of difference between groups on each biomarker was expressed as Cohen's d effect sizes and 95% confidence intervals. The no/single domain risk group was used as the reference group.

Given the inclusion of older adults (aged over 65 years) in the current sample, a sensitivity analysis was conducted to determine whether the outcome of the statistical analyses was influenced by the presence of the older participants in the sample. Participants aged over 65 years (n=10) were excluded from the sample and original ANCOVAs that yielded differences between no/single domain and multidomain risk groups on biomarker and cognitive outcomes were repeated, with age, sex, years of education and presence or absence of an *APOE* ε4 allele as covariates. The cut-off of over 65 years was selected due to the inclusion of age 65 in midlife in previous models of dementia risk (Livingston et al., 2020) and to avoid further limiting statistical power. An exploratory analysis investigating the relationship between age and main cognition and biomarker outcomes (i.e., $A\beta_{42}$, p-tau_{181}, t-tau, and PACC) in the multidomain risk and no/single domain groups separately was conducted using linear regression (Table S3).

To explore whether any individual MDRF domains are driving associations with cognitive and biomarker outcomes, a series of ANCOVAS were conducted with the five individual domains (reporting at least one MDRF within a domain or not) as simultaneous predictors.

Finally, 33% of the current sample has CSF $A\beta_{42}$ values above the maximum limit of detection (i.e., 1700 pg/mL) which restricts the range of Aβ levels that can be estimated. A sensitivity analysis was conducted to determine whether this may influence results of the analysis of the relationship between multidomain MDRFs and Aβ. An ANCOVA with group (multidomain / no/single domain risk) as the fixed factor was repeated with CSF $A\beta_{42}$ relative fluorescence units as the outcome, which indicates the concentration of the protein and does not have an upper limit.

2.9. Data availability

HBP data and biospecimens can be accessed by formal application. A data use agreement and an approved Human Research Ethics Committee application will be required. For access to biospecimens, a Materials Transfer Agreement will also be required.

3. Results

3.1. Demographic and clinical characteristics

Table 2 summarizes the demographic and clinical characteristics for multidomain and no/single domain risk groups. On average, the no/single domain risk group had ~2 more years of education compared to the multidomain risk group. There were no other statistically significant differences between groups on demographic or clinical characteristics.

3.2. Modifiable dementia risk factors and cognitive performance

After adjusting for age, sex, years of education and *APOE* ε4, cognitive performance on the PACC and the Executive Function composite was significantly worse in the multidomain risk group compared to those with no/single domain risk, with these differences moderate in magnitude (Table 3, Fig. 1). While the difference in the Episodic Memory composite between groups was also moderate in magnitude, it did not reach statistical significance (Table 3, Fig. 1).

3.3. Modifiable dementia risk factors and AD biomarkers

After adjusting for age, sex, years of education and *APOE* ε4, CSF t-tau and p-tau_{181} levels were significantly different between multidomain and no/single domain risk groups (Table 3). Compared to the no/single domain risk group, the multidomain risk group had greater CSF t-tau and p-tau_{181} levels, with the magnitude of these differences moderate (Table 3, Fig. 1). There were no differences between groups on CSF $A\beta_{42}$ levels, or hippocampal and total brain volumes, and the magnitude

Table 2
Demographic and clinical characteristics of the total sample and no/single domain and multidomain risk groups.

	Total sample	No/single domain risk	Multidomain risk	
	M(SD) or N (%)	M(SD) or N(%)	M(SD) or N(%)	p
N	82	34	48	
Age (years)	58.17 (6.87)	58.73 (6.95)	57.77 (6.86)	.536
Sex (women)	54 (65.85%)	29 (85.29%)	25 (52.08%)	.217
Education (years)	16.48 (3.40)	**17.41 (3.34)**	**15.81 (3.33)**	**.035**
European ethnicity	69 (84.15%)	33 (97.06%)	36 (75%)	.062
Family history dementia	62 (75.61%)	23 (67.65%)	39 (81.25%)	.158
***APOE* ε4 carrier**	31 (37.80%)	11 (32.35%)	20 (41.67%)	.392
CSF Aβ+	13 (15.85%)	7 (20.59%)	6 (12.50%)	.356
MMSE	28.80 (1.18)	28.85 (1.23)	28.77 (1.15)	.758
CDR-SB	0.04 (0.15)	0.06 (0.20)	0.02 (0.10)	.270
NART total score	34.39 (6.65)	36.03 (6.42)	33.23 (6.63)	.060
CFI total score	5.77 (5.69)	4.88 (4.76)	6.40 (6.25)	.237

Note. Chi squares of independence were conducted to determine whether there was a statistically significant difference between no/single domain risk and multidomain risk groups on categorical outcomes (sex, European ethnicity, family history of dementia, *APOE* ε4 carriage and CSF Aβ+); ANOVA was used to determine significant differences on continuous outcomes (age, education, MMSE, CDR-SB, NART total score, CFI total score). Bolded values are statistically significant at p<.05. No/single risk domain=MDRFs in no or one domain; multidomain risk=MDRFs in two or more domains; *APOE* = apolipoprotein; CSF = cerebrospinal fluid; Aβ+ = CSF $A\beta_{42}$ <1000 pg/mL; MMSE = Mini-Mental State Examination; CDR-SB = Clinical Dementia Rating Scale sum of boxes; NART = National Adult Reading Test; CFI = Cognitive Function Instrument.

Table 3
Associations between reporting MDRFs across multiple domains with cognition, AD biomarkers and neurodegenerative markers in middle-aged and older adults.

			No/single domain risk	Multidomain risk
	β (SE)	*p*	EMM (SE)	EMM (SE)
PACC (z-score)	**-0.567 (0.196)**	**.005**	0.172 (0.160)	-0.394 (0.125)
Episodic memory (z-score)	-0.373 (0.218)	.091	0.117 (0.177)	-0.256 (0.138)
Executive function (z-score)	**-0.489 (0.217)**	**.027**	0.144 (0.176)	-0.345 (0.138)
$A\beta_{42}$ (pg/mL)	0.304 (0.241)	.211	1329 (65.1)	1432 (51.2)
p-tau_{181} (pg/mL)	**0.461 (0.224)**	**.043**	14.6 (1.082)	17.4 (0.849)
t-tau (pg/mL)	**0.519 (0.222)**	**.022**	175 (11.20)	208 (8.79)
Hippocampal volume (mm^3)	0.079 (0.255)	.758	8.13 (0.116)	8.17 (0.086)
Total brain volume (mm^3) ('000 s)	-0.114 (0.239)	.637	644 (4.69)	642 (3.48)

Note. Beta-coefficients are standardized and have been adjusted for age and sex, years of education and *APOE* ε4. EMMs were calculated on raw outcome values to enhance clinical meaning. Hippocampal and total brain volume outcome values are adjusted for intracranial volume and divided by 1000. Bolded values indicate statistically significant values at $p<.05$. No/single risk domain=MDRFs in no or one domain; multidomain risk=MDRFs in two or more domains; MDRF = modifiable dementia risk factor; PACC = Preclinical Alzheimer's Cognitive Composite; AD = Alzheimer's disease; EMM = estimated marginal means; p-tau_{181} = tau phosphorylated at threonine 181; t-tau = total tau.

of these differences was small. Re-analysis with log transformed values for biomarkers did not alter results.

3.4. Post-hoc analysis

When Aβ and tau biomarkers were accounted for in addition to age, sex, years of education and *APOE* ε4 in investigations of the relationship between multidomain MDRFs and cognitive performance, the magnitude of difference in cognitive performance between groups with multidomain risk and no/single domain risk remained moderate for the PACC (d=0.54) and Episodic Memory composite (d=0.42), however, it became slightly weaker and non-significant for the Executive Function composite (d=0.38) composite. ANCOVA model results can be found in Table S2.

When individuals aged over 65 years were excluded, the magnitude of difference between the no/single domain and multidomain risk groups on outcomes of tau and cognition remained moderate. Compared to the no/single domain group, the multidomain group had higher levels of t-tau (d=0.45, p=.039) and p-tau_{181} (d=0.43, p=.051), and worse performance on the PACC (d=0.63, p=.011) and Executive Function composite (d=0.69, p=.006). The difference between groups on the Episodic Memory composite remained not statistically significant (p=.064), however, it was moderate in magnitude (d=0.44). Further, an exploratory analysis of the relationship between age and main cognition and biomarker outcomes in multidomain risk and no/single domain risk groups separately revealed that age was not associated with CSF $A\beta_{42}$ in either group. However, increased age was associated with increased p-tau_{181} and t-tau levels in both groups. Increased age was also associated with worse PACC performance in the multidomain risk group but not the single domain risk group. These results can be found in Table S3.

Exploration of the contribution of individual MDRF domains to cognitive performance demonstrated that no individual MDRF domains were associated with performance on the PACC, Episodic Memory or Executive Function composites. Exploration of the contribution of

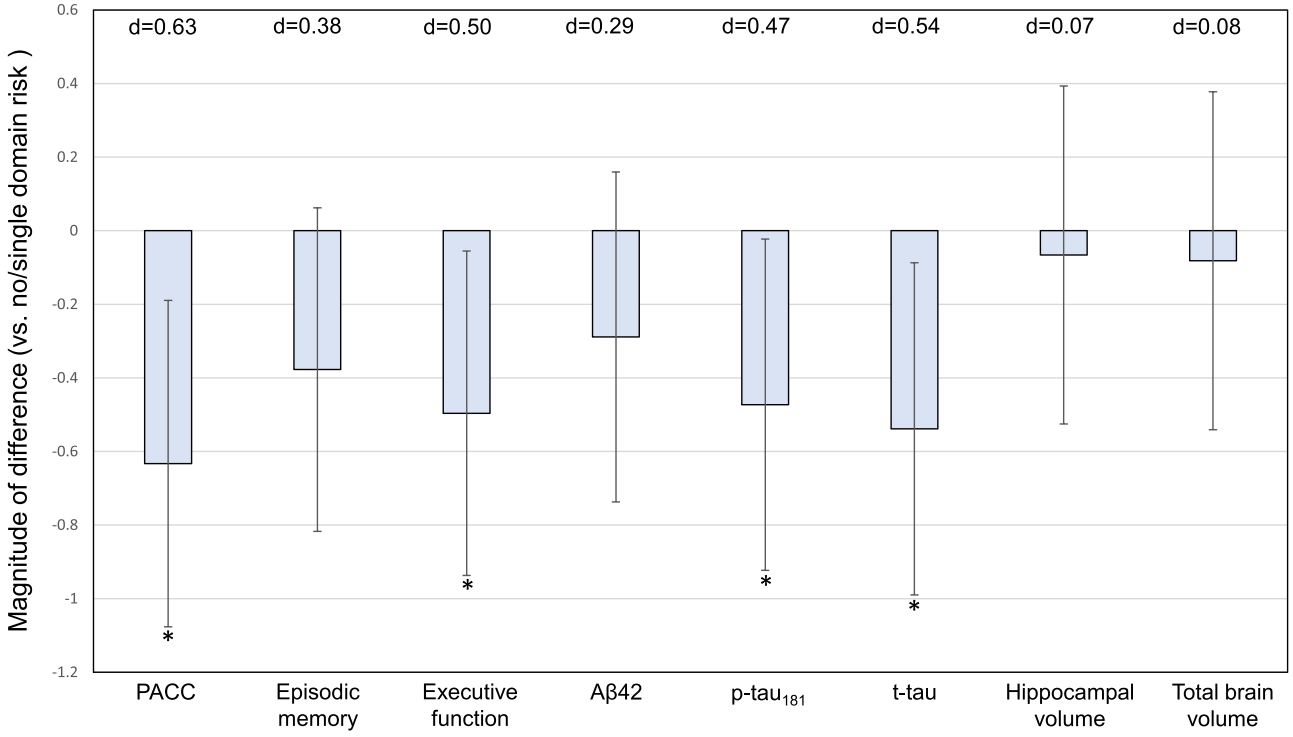

Fig. 1. Magnitude of difference (Cohen's d) in cognitive performance and biomarkers of AD and neurodegeneration between multidomain and no/single domain risk groups (with no single/domain risk as reference group; represented by the '0' line). No/single risk domain=MDRFs in no or one domain; multidomain risk=MDRFs in two or more domains; MDRF=modifiable dementia risk factor; PACC=Preclinical Alzheimer's Cognitive Composite; p-tau_{181}=tau phosphorylated at threonine 181; t-tau=total tau; Error bars represent 95% confidence intervals; Effect sizes marked by * are statistically significant at $p<.05$.

individual MDRF domains to biomarker outcomes suggested that reporting at least one MDRF in the risky lifestyle behaviors domain, β(SE)=0.481(0.223), p=.034, and cognitive/social engagement domain, β(SE)= 0.481(0.229), p=.039, were associated significantly with greater CSF t-tau and p-tau$_{181}$ levels, compared to not reporting any MDRFs in those domains. No significant associations were observed for any other individual MDRF domains.

Re-analysis of the difference between the multidomain risk group and no/single domain risk group on Aβ using CSF Aβ_{42} relative fluorescence units, which indicates the concentration of the protein and does not have an upper limit, also yielded a non-significant result (p=.06).

4. Discussion

The results of this study support and extend that of previous findings (Bransby et al., 2023a) by demonstrating that multidomain MDRFs are related to poorer cognition. Compared to the no/single domain risk group, the multidomain risk group demonstrated moderately worse cognitive performance on the PACC and Executive Function composite. Further, when AD biomarkers were controlled statistically in post-hoc sensitivity analyses, the magnitude of these differences in cognition between modifiable risk groups were largely unchanged. The second hypothesis that multidomain MDRFs would be associated with increases in AD biomarkers was partially supported. Compared to the no/single domain risk group, the multidomain risk group had higher levels of CSF p-tau181 and t-tau, with these differences moderate in magnitude. However, levels of CSF Aβ_{42}, and total brain and hippocampal volumes were not different between multidomain and no/single domain risk groups. Together, these results suggest that in middle-aged and older adults, multidomain MDRFs are associated with increased levels of tau and worse cognitive performance. The relationship between MDRFs and worse cognitive performance was independent of Aβ or tau levels suggesting that the presence of multidomain MDRFs may relate to reduced brain function through pathways that are not specific to AD.

Previously, in a large sample of middle-aged and older adults, we demonstrated that multidomain MDRFs were associated with worse attention and memory, albeit measured remotely in an unsupervised context (Bransby et al., 2023a). The results of this study confirm those observed previously by demonstrating that differences in cognitive performance between individuals with multidomain and no/single domain risk are also evident when well-established in-clinic neuropsychological measures are used. Thus, it may be likely that with biomarker collection and analysis of the larger sample of middle-aged and older adults from HBP, similar relationships would also be observed between multidomain MDRFs and increased tau. The absence of a statistically significant relationship between MDRFs and the Episodic Memory composite in this study is likely due to a lack of statistical power as the magnitude of difference between multidomain and no/single domain risk groups was moderate (d=0.38). Further, in the larger HBP sample, the magnitude of difference between the no MDRF group and multidomain risk groups on a Learning/Working Memory composite ranged from moderate to large in magnitude (d=0.30–0.90) (Bransby et al., 2023a). The results of this study also accord with that of others that have sought to synthesize MDRFs in a risk index. For example, higher scores on the Lifestyle for Brain Health (LIBRA) index were associated with greater cognitive impairment and greater decline across multiple tests in middle-aged and older adults (Cody et al., 2022; Deckers et al., 2019; Heger et al., 2021). Additionally, in the current study, statistical control of AD biomarkers did not change the nature or magnitudes of relationships between multidomain MDRFs with worse cognitive performance, and the magnitude of difference between groups remained moderate. While the relationship between tau and cognition has been demonstrated consistently in this sample and others (Brier et al., 2016; Lim et al., 2023), this may suggest that the relationship between multidomain MDRFs and poorer cognition in middle-aged and older adults reflects involvement of other neurodegenerative pathways. These pathways may be pathophysiological, such as increases in cerebrovascular disease (Wang et al., 2020), or functional, such as diminished cognitive reserve (Jia et al., 2021). For example, the multidomain risk group may have reduced cognitive reserve, possibly associated with engaging in fewer cognitively stimulating activities or healthy lifestyle behaviors (Jia et al., 2021; Stern, 2012). This may have contributed to their worse cognitive performance in comparison to the no/single domain risk group. Future studies are required to further elucidate the mechanisms underlying the relationship between multidomain MDRFs and poorer cognition.

The finding that multidomain MDRFs were associated with increased tau levels in middle-aged and older adults is consistent with other reports of relationships between cardiovascular risk factors and tau (Bos et al., 2019; Rabin et al., 2019). These studies showed that greater cardiovascular risk, determined by the FHS-CRS, was associated with increased cortical and CSF tau levels in older adults with preclinical AD (Bos et al., 2019; Rabin et al., 2019). Other studies have observed that higher levels of cortical tau in older adults is associated with individual MDRFs such as hypertension (Petrovitch et al., 2000), depressive symptomatology (Babulal et al., 2020), and repetitive negative thinking (Marchant et al., 2020). Results of the current study support these findings by demonstrating that multidomain MDRFs may increase risk of AD dementia via increases in tau, and extend them by suggesting that these relationships become apparent in midlife. This is further supported by the observation that findings in the current study remained when older adults were excluded. Further, a causal inference study which computed polygenic risk scores (PRS) for 22 MDRFs examined their associations with a range of AD-related phenotypes, including CSF tau and neuropathological burden of neurofibrillary tangles in older adults (Andrews et al., 2021). The results of this study indicated that the PRS for moderate-to-vigorous physical activity was causally related to fewer neurofibrillary tangles, and the PRS for high low-density lipoproteins were causally related to higher levels of CSF tau. Taken together, the results of previous studies and the current study suggest that increases in AD pathophysiology, particularly tau, are apparent as early as midlife, and that this may be exacerbated by greater burden or variety of MDRFs.

The observation that multidomain MDRFs was not associated with Aβ is consistent with a recent study reporting no association between higher scores on the LIBRA index and cortical Aβ accumulation in cognitively unimpaired middle-aged and older adults (Cody et al., 2022). Other studies also found no relationships between cardiovascular risk factors, measured by the FHS-CRS, and both CSF and PET Aβ levels in older adults (Bos et al., 2019; Lane et al., 2020). This suggests that the contribution of cardiovascular risk factors to cognitive decline and dementia may be independent of Aβ. This is supported by a recent study that showed that a composite of cardiovascular risk factors was only associated with episodic memory decline in Aβ- older adults, but not in Aβ+ older adults (Rosenich et al., 2022). Conversely, some studies in older adults have shown that MDRFs such as low cognitive and social engagement (Biddle et al., 2019; Landau et al., 2012), sedentary behavior (Law et al., 2018), and poor sleep (Sprecher et al., 2015) are individually associated with increased cortical Aβ and lower CSF Aβ_{42}. It is possible that MDRFs in domains other than cardiovascular conditions may increase risk for dementia through AD-related processes (i.e., decreased CSF Aβ), and that these more specific relationships between MDRFs and AD biomarkers are diluted by synthesizing MDRFs into domains or a composite score. One other possible explanation for the findings of these other studies (Biddle et al., 2019; Landau et al., 2012; Law et al., 2018; Sprecher et al., 2015) is that in older adults, MDRFs such as low cognitive and social engagement or poor sleep may reflect withdrawal from activities or symptoms associated with underlying pathology and incipient dementia (i.e., reverse causation). Finally, it is also possible that the lack of relationship detected between multidomain MDRFs and Aβ in the current study may be due to limited statistical power, and range restriction, as CSF Aβ_{42} levels in younger adults are typically at the highest detectable level. The relationship between

multidomain MDRFs and Aβ will need to be clarified by future studies with sufficient sample size to examine the contribution of each individual MDRF domain.

In the current study, multidomain MDRFs were also not associated with hippocampal or total brain volume. This is inconsistent with studies showing relationships between composite cardiovascular risk scores and smaller total brain volumes (Lane et al., 2020; O'Brien et al., 2020). However, whilst these studies measured MDRFs in midlife, the reduction in brain volume was observed over a very long period of time, for example, from midlife to late-life. As only cross-sectional brain volume was measured in the current study, it is likely that the observed association between multidomain MDRFs and increased total tau, a marker of general neurodegeneration, is indicative of early emerging neurodegenerative processes and that brain volume loss may only be detectable later and over time. As CSF samples for the HBP have been bio-banked, there is an opportunity for future studies to examine relationships between MDRFs and other markers of neurodegeneration. Further, future processing of existing MRI scans will enable investigation into the contribution of non-AD pathologies, such as cerebrovascular disease, to relationships between MDRFs, cognition and dementia risk.

By classifying a wide range of MDRFs into risk domains, findings of the current study form a basis for understanding how multidomain MDRFs may influence AD pathogenesis and brain function. The results of this study suggest that in middle-aged and older adults, multidomain MDRFs relate to increases in AD pathophysiology and worse cognition. The influence of multidomain MDRFs on poorer cognition may be a result of both AD and non-AD pathways (Jia et al., 2021; Merrill et al., 2016; Wang et al., 2020), and future prospective clinicopathological and interventional studies are required to test this hypothesis. To our knowledge, this is the first study to examine relationships between such a comprehensive range of MDRFs and AD biomarkers and cognition in middle-aged adults. The importance of these relationships in midlife was supported by the observation that they remained largely unchanged after older adults were excluded from analysis. These results have implications for the design of dementia prevention strategies, and support behavioral intervention efforts that target multidomain MDRFs to preserve cognition or delay cognitive decline beginning in midlife (Lim et al., 2021).

There are several limitations to the current study that warrant consideration. First, this study was cross-sectional in design so prospective studies are required to determine the longitudinal associations of multidomain MDRFs with biomarker, neurodegenerative and cognitive changes over time. Further, reverse causality is a possibility for current findings, such that individuals with worse cognitive performance or increased tau levels may be more likely to have more MDRFs across multiple domains. Another possible interpretation is that the no/single domain risk group demonstrated improved cognitive performance and reduced tau levels compared to the multidomain risk group. Future intervention trials that target multidomain MDRFs are needed to determine whether reducing MDRFs can delay or prevent cognitive impairment or decline. Second, 33% of the current sample had CSF $A\beta_{42}$ values above the maximum limit of detection (i.e., 1700 pg/mL) which restricts the range of Aβ levels that can be estimated and may have influenced the lack of finding for Aβ. However, re-analysis using CSF $A\beta_{42}$ relative fluorescence units, which indicates the concentration of the protein and does not have an upper limit, also yielded a non-significant difference between the multidomain risk group and no/single domain risk group. Further, the current sample was small, with the majority of participants Caucasian and highly educated, and had a greater proportion of individuals with a higher risk of developing dementia (~38% *APOE* ε4 carriers vs. 25% in the general population) (Gharbi-Meliani et al., 2021). To aid the generalizability of these results, it will be important to replicate these findings in a larger, more population-based sample. Finally, MDRFs are often associated with a range of other socioeconomic and external factors, such as race, income, and environment. For instance, the no/single domain group in the current study reported more years of formal education compared to the multidomain risk group. Higher education may relate to socioeconomic factors (e.g., higher income) that are associated with a lower chance of developing MDRFs, or better management of health and lifestyle behaviors (Dotson et al., 2009). Due to the limited sample size, these considerations were outside of the aims of the current study. However, a more comprehensive consideration of these external factors will be important in refining and clarifying the role of MDRFs in increasing risk of cognitive dysfunction and AD biomarker abnormality.

These limitations notwithstanding, the results of this study suggest that in middle-aged and older adults, multidomain MDRFs are associated with increased CSF t-tau and p-tau_{181} levels, and poorer cognition. These findings suggest that increases in AD biomarkers are apparent even in midlife, particularly for individuals with a greater burden or variety of MDRFs. As controlling for AD biomarkers did not substantially diminish the moderate relationship between multidomain MDRFs and cognition, this also suggests the involvement of mechanisms non-specific to AD in this relationship. These findings support the inclusion of multidomain MDRFs in brain-behavior models of AD and suggest that multidomain behavioral intervention trials that target MDRFs starting in midlife may be useful to delay or prevent the onset of cognitive decline or dementia.

Verification

As the corresponding author, I verify that this manuscript has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Declaration of Competing Interest

L Bransby, N Yassi, E Rosenich, RF Buckley, QX Li, M Pase and YY Lim have no relevant conflicts of interest to disclose. Paul Maruff is a consultant of Cogstate Ltd.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.02.015.

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