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Multidomain Modifiable Dementia Risk Factors Are Associated With Poorer Cognition in Midlife

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Objective: Studies of modifiable dementia risk factors (MDRFs) generally consider MDRFs individually, despite strong evidence that they co-occur in adult populations. In a large sample of middle-aged adults, this study aimed to determine the frequency and co-occurrence of MDRFs, spanning five domains (mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, cognitive/social engagement, sleep disorders/symptomatology). The relationship between number of domains in which MDRFs were reported with cognitive performance and subjective cognitive concerns was then determined. ***Method:*** Middle-aged adults ($n = 1{,}610$) enrolled in the Healthy Brain Project and completed self-report surveys about their health and lifestyle. Participants also completed the Cogstate Brief Battery and the Cognitive Function Instrument, a measure of subjective ratings of cognition. Participants were classified according to number of domains (mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, cognitive/social engagement, sleep disorders/symptomatology) in which they reported at least one MDRF (0–5). Age, sex, education, and ethnicity were adjusted for in analyses. ***Results:*** Most individuals (66.5%) reported MDRFs in two or more domains. Compared with individuals displaying no MDRFs, individuals with MDRFs in 3–5 domains showed worse learning/working memory performance and greater subjective cognitive concerns, with the magnitude of these differences moderate-to-large ($d = 0.30$–0.93). Individuals displaying MDRFs in five domains also showed worse attention/psychomotor function ($d = 0.58$) compared to those displaying no MDRFs. ***Conclusions:*** These findings may suggest that multidomain MDRFs are highly frequent in middle-aged adults and are related to poorer cognition. This supports that modifiable dementia risk is multidimensional and raises the possibility that multidomain behavioral intervention trials in middle-aged adults may be useful to delay or prevent cognitive impairment or decline.

Key Points

Question: What is the frequency or burden of modifiable dementia risk factors (MDRFs) spanning five domains (mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, cognitive/social engagement, sleep disorders/symptomatology) in middle-aged adults, and how are they related to cognition? ***Findings:*** Multidomain MDRFs were reported by most middle-aged adults (66.5%) and were associated with poorer cognitive performance and greater subjective cognitive concerns. ***Importance:*** In middle-aged adults, multidomain MDRFs are highly frequent and may be associated

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continued

with subtle negative neurological changes indicated by poorer cognitive outcomes. ***Next Steps:*** Future research should investigate the association between multidomain MDRFs with cognitive decline and whether multidomain behavioral intervention trials targeting MDRFs in middle-aged adults can preserve cognition and delay future cognitive impairment and dementia.

Keywords: modifiable dementia risk factors, cognition, multidomain, midlife

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Dementia is a leading cause of disability and mortality worldwide, and Alzheimer's disease (AD) is the most common cause. Efforts to forestall dementia include the development of pharmacological and behavioral therapies and the identification and modification of factors that increase the risk for dementia. The strongest risk factors for sporadic AD dementia are age and carriage of the apolipoprotein E ε4 allele (Riedel et al., 2016), but neither can be modified. There is accumulating evidence that increased dementia risk is also associated with some medical conditions (e.g., diabetes), lifestyle behaviors (e.g., physical inactivity), and environmental contexts, each of which is modifiable. Epidemiological studies estimate that modifiable dementia risk factors (MDRFs) may account for 40% of dementia cases (Livingston et al., 2020), raising the possibility that targeting MDRFs could reduce dementia risk in later life. This is supported by the observation that dementia incidence in developed countries is declining, likely through initiatives targeting smoking and cardiovascular disease (Wolters et al., 2020).

Most programs seeking to modify MDRFs through behavioral intervention use dementia incidence as the main outcome (Kivipelto et al., 2018). Given the long duration and large sample sizes necessary to test hypotheses using this endpoint, clinical trials of similar interventions often use as outcomes markers of brain function such as cognitive performance or subjective ratings of cognition (Lim et al., 2021; Ngandu et al., 2015). Importantly, the use of cognitive outcomes as markers of brain function also allows investigation of the effects of MDRFs in midlife when individuals are unlikely to present with, or progress to, dementia, but may be at risk of subtle neurological changes. Hence, understanding the relationships between MDRFs and cognition in midlife could inform brain–behavior models of modifiable dementia risk as well as the design of behavioral interventions trials.

Many individual MDRFs have been targeted in behavioral intervention trials aimed at reducing risk for dementia on the basis of being shown consistently in observational studies to be associated with greater cognitive decline and increased risk for dementia (see Table 1, for summary; Almeida et al., 2017; Anstey et al., 2007, 2017; Becker et al., 2018; Cao et al., 2016; de Almondes et al., 2016; Kaup et al., 2016; Machado et al., 2014; McGrath et al., 2017; Shi et al., 2018; Singh-Manoux et al., 2018; Sommerlad et al., 2019; Tan et al., 2017). However, the extent to which multiple MDRFs can simultaneously influence cognition and dementia risk remains unclear, despite it being increasingly recognized that dementia risk is multifactorial (Peters et al., 2019). Consequently, dementia risk models that include several MDRFs rely on the meta-aggregation of findings of individual MDRFs from different studies with different designs (Livingston et al., 2020). This is despite epidemiological studies showing that modifiable risk factors for morbidity and mortality in adults (18–65+ years) co-occur, such that many adults (5%–42%) exhibit multiple simultaneous risk factors (Conry et al., 2011; Morris et al., 2016; Schuit et al., 2002). In addition, the few studies that have considered multiple MDRFs are commonly biased toward MDRFs that reflect cardiovascular conditions and/or risky lifestyle behaviors, such as physical inactivity and poor diet (Dhana et al., 2020; González et al., 2018; Peters et al., 2019). Therefore, there is a need to develop empirical models that could improve the understanding of how multiple MDRFs influence cognition and dementia risk. However, given the large number of individual MDRFs identified to date, this aim is accompanied by methodological and statistical challenges.

One approach that can aid parsimony and interpretability would be to classify MDRFs into risk domains and then investigate the contribution of those to cognition and, in turn, dementia risk (Tables 1 and 2). Based on their theoretical commonalities (Dhana et al., 2020; Knopman et al., 2018; Lavretsky et al., 2009), individual MDRFs can be classified into at least five risk domains, such as mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, low cognitive/social engagement, and sleep disorders/symptomatology, which are defined in Table 2. As described in Table 2, despite being strongly linked, risky lifestyle behaviors (e.g., physical inactivity) are classified separately from cardiovascular conditions (e.g., hypertension) to differentiate lifestyle behaviors from health conditions.

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Analysis code is available upon request. Given the nature of the raw data (which contain participant health information), it is available upon evidence of ethics approval and a signed data use agreement. This study design and its analysis were not preregistered.

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Table 1

Details on Selected Modifiable Dementia Risk Factors, Domain Classification, Measures, Outcomes, and Groupings

MDRF	Measure	Outcome	Risk classification
Mood symptomatology			
Depression symptomatology (Almeida et al., 2017)	DASS-42	Sum of depression items	Depression symptomatology: score of 10 or more
Anxiety symptomatology (Becker et al., 2018)	DASS-42	Sum of anxiety items	Anxiety symptomatology: score of 8 or more
Stress symptomatology (Machado et al., 2014)	DASS-42	Sum of stress items	Stress symptomatology: score of 15 or more
Risky lifestyle behaviors			
Poor adherence to MIND diet (Morris et al., 2015)	FFQ	MIND diet adherence (Morris et al., 2015)	Low MIND diet adherence: below 60th percentile (9.5; Dhana et al., 2020)
Physical inactivity (Tan et al., 2017)	IPAQ	Total number of MET minutes per week	Physically inactive: does not meet IPAQ criteria for moderate or high activity
Current smoking status (Anstey et al., 2007)	Self-report of smoking status	Current smoker: yes or no	Current smoker: yes
Cardiovascular conditions			
Hypertension (McGrath et al., 2017)	Self-report of diagnosis	Hypertension: yes or no	Hypertension: yes
Diabetes (Biessels et al., 2006)	Self-report of diagnosis	Diabetes: yes or no	Diabetes: yes
Hypercholesterolemia (Anstey et al., 2017)	Self-report of diagnosis	Hypercholesterolemia: Yes or no	Hypercholesterolemia: Yes
Obesity (Singh-Manoux et al., 2018)	Self-report of BMI	BMI	Obesity: BMI of 30 or higher
Cognitive and social engagement			
Low variety of leisure activities (Krell-Roesch et al., 2019)	CELA survey	Variety of leisure activities score from PCA (Bransby et al., 2022)	Low variety: median split was performed due to no predefined cutoff; score of 2 or less
Low social engagement (Sommerlad et al., 2019)	GSS	Sum of all items relating to frequency of engagement with friends and family	Low social engagement: median split was performed due to no predefined cutoff; score of 19 or less
Sleep disorders and symptomatology			
Excessive daytime sleepiness (Merlino et al., 2010)	ESS	Sum of all items	Excessive daytime sleepiness: score over 10
Insomnia symptomatology (de Almondes et al., 2016)	ISI	Sum of all items	Insomnia symptomatology: score of 15 or more
OSA (Dunietz et al., 2021)	Self-report of diagnosis	OSA: yes or no	OSA: yes

Note. MDRF = modifiable dementia risk factors; DASS-42 = Depression, Anxiety, and Stress Scale 42 items; MIND = Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay; FFQ = Food Frequency Questionnaire; IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent of task; BMI = body mass index; CELA = cognitive engagement in leisure activities; PCA = principal component analysis; GSS = general social survey; ESS = Epworth Sleepiness Scale; ISI = Insomnia Severity Index; OSA = obstructive sleep apnea.

Table 2
Operational Definition/Inclusion Criteria and Exclusion Criteria for Five Domains of MDRFs

MDRF domain	Definition/inclusion criteria	Exclusion criteria
Mood symptomatology	• Experience or presence of symptomatology that indicates poor mood or worsening mental health	• Lifestyle behaviors, health conditions, or other symptomatology (e.g., sleep) that may be related to poor mood symptomatology but do not reflect actual experience/presence of mood symptoms • Symptomatology, lifestyle behaviors, or health conditions that are not related to mood symptomatology
Risky lifestyle behaviors	• Health behaviors or habits that reflect risky lifestyle choices that relate to poorer health outcomes (e.g., cardiovascular)	• Symptomatology or health conditions that are related but do not reflect behaviors/habits • Lifestyle activities that are also related to poorer health outcomes but more strongly reflect other domains with different mechanisms (e.g., cognitive engagement)
Cardiovascular conditions	• Health conditions that reflect or increase risk for poor cardiovascular health	• Lifestyle behaviors or activities regardless of relationship to cardiovascular health • Symptomatology relating more strongly to other domains (e.g., mood, sleep) • Health conditions that are more strongly associated with different domains (e.g., sleep) regardless of indirect relationship to cardiovascular health (e.g., OSA)
Cognitive/social engagement	• Low engagement in activities that are cognitively or socially stimulating	• Health conditions or symptomatology • Lifestyle activities that may not directly reflect cognitive and social stimulation
Sleep disorders/symptomatology	• Symptomatology or disorders that are specific to sleep or sleep-related breathing and either influence or are influenced by sleep quality and duration	• Symptomatology or disorders that are not specific to sleep • Lifestyle behaviors or activities regardless of link to poor sleep symptomatology/disorders

Note. MDRFs = modifiable dementia risk factors; OSA = obstructive sleep apnea.

In the Healthy Brain Project (HBP), a large study of middle-aged adults with 50% reporting a family history of dementia, frequency of MDRFs in individual domains of cardiovascular risk (Yassi et al., 2022), mood (Perin et al., 2022), cognitive/social engagement (Bransby et al., 2022), and sleep symptomatology (Nicolazzo et al., 2021) have each been associated with poorer cognitive performance and subjective ratings of cognition. Integration of MDRFs across these multiple risk domains to determine their contribution to cognitive outcomes can now be investigated. This can be determined by defining MDRF burden as the number of risk domains in which MDRFs are reported and then estimating how MDRF burden influences cognition. In addition, to provide evidence for the importance of considering risk domains beyond the most considered cardiovascular conditions and risky lifestyle behaviors, an additional approach is to first only consider the extent to which these two domains are related to cognition, and then to estimate whether considering additional domains (e.g., mood, cognitive/social engagement, sleep) contributes greater information on how MDRFs are related to cognition.

The first aim of this study was to describe the frequency of MDRFs across multiple domains, including mood, lifestyle behaviors, cardiovascular conditions, cognitive/social engagement, and sleep disorders/symptomatology, and demonstrate the extent to which multidomain MDRFs co-occur in a large cohort of community-based middle-aged adults, with 50% reporting dementia family history. The second aim was to determine the relationship between MDRF burden (the number of domains in which MDRFs are reported) with cognitive performance and subjective cognition. It was hypothesized that reporting risk across a greater number of MDRF domains would be associated with poorer cognitive performance and greater subjective cognitive concerns. To distinguish the value of considering MDRF domains beyond those typically considered (i.e., cardiovascular and lifestyle), the third aim involved comparison of results of the previous analysis with results from an additional analysis to determine the relationship between risk in the cardiovascular conditions and/or risky lifestyle behaviors domains with cognitive performance and subjective cognition. The final aim was to explore individual associations between each MDRF domain and poorer cognitive performance and subjective cognitive concerns.

Method

Participants

The study sample (N = 1,610) comprised cognitively normal middle-aged adults enrolled in the HBP who had completed at least 75% of baseline MDRF assessments (Supplemental Figure 1; Lim et al., 2019). The HBP is a prospective cohort study that uses an online remote assessment platform and seeks to understand midlife risk factors for dementia. Recruitment of HBP participants was conducted via traditional means such as media announcements, social media posts, and distributing flyers and has been detailed previously (Lim et al., 2019). Briefly, participants were included if they resided in Australia, were fluent in English, and aged between 40 and 70 years. This age range was chosen to be inclusive of early and late middle-aged individuals. Participants were excluded if they self-reported a history of major 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 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. Recruitment for the HBP is ongoing, so the present study uses data collected up to the third formal DataFreeze (May 2020). In addition, as participants do not have to complete all assessments in one sitting, different sample sizes may be reported for different measures. The HBP was approved by the human research ethics committee at Monash University, Melbourne, Australia, and participants provided informed consent via the online platform prior to their involvement.

MDRF Selection and Measurement

Table 1 summarizes the MDRFs included in the present study, their risk domain classification, method of measurement, and operational definition of risk. Information on all MDRFs was obtained via self-report measures. Individual MDRFs were classified into five domains: mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, cognitive and social engagement, and sleep disorders and symptomatology (Tables 1 and 2). Table 2 summarizes the domain definition/inclusion criteria and exclusion criteria for classification of each individual MDRF into each domain. These domains were derived by identifying theoretical commonalities between individual MDRFs. The process of categorizing individual MDRFs into each domain was guided by previous literature (Dhana et al., 2020; Knopman et al., 2018; Lavretsky et al., 2009). Lifestyle risk factors were classified separately from cardiovascular risk factors because they reflect lifestyle behaviors rather than medical conditions.

Classification of MDRFs

Participants were classified as exhibiting risk in an MDRF domain if they reported at least one MDRF (based on risk classification in Table 1) present in 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 was then summed to create groupings based on how many domains participants reported at least one MDRF in (ranging from 0 to 5). This approach was taken as it reflects any risk associated with each domain rather than individual risk factors. Due to the large number of individual MDRFs ($n = 15$) included in this study, this synthesis of MDRF domain classification was adopted to aid parsimony and interpretability. Furthermore, this approach facilitates characterization of the nature and magnitude of the relationship between reporting MDRFs in an increasing number of domains and cognition. An alternative approach of assigning one point per MDRF yielded similar results (Supplemental Figures 3 and 4); however, this approach does not provide any information on the added value of considering MDRFs across multiple domains.

Assessment of Cognition

Unsupervised online cognitive testing was completed by participants using the Cogstate Brief Battery (CBB), a brief cognitive screening tool (Perin et al., 2020). The CBB has previously been shown to have high sensitivity to dysfunction and decline in attention, working memory, and learning, and AD-related cognitive impairment and decline (Maruff et al., 2013). Furthermore, delivery and instructions for remote assessment using the CBB have been adapted, and the psychometric properties of the online version have been demonstrated previously (Perin et al., 2020). The CBB includes four tests—Detection (DET), Identification (IDN), One Card Learning (OCL), and One-Back (OBK), which have been detailed previously (Lim et al., 2012). Briefly, the DET test is a simple reaction time paradigm measuring psychomotor function. The IDN test is a choice reaction time paradigm measuring visual attention. The OBK test is a one-back paradigm measuring working memory. The primary outcome measure for the DET, IDN, and OBK tests is reaction time in milliseconds (speed), which was normalized using a logarithmic base 10 ($\log_{10}$) transformation. The OCL test is a continuous visual recognition learning paradigm measuring visual learning within a pattern separation model. The primary outcome measure for the OCL test is the proportion of correct answers (accuracy), which is normalized using an arcsine square-root transformation. Raw scores for each outcome measures were standardized using the baseline mean and standard deviation of the current sample. All speed outcomes were reverse scored so that higher values indicate better cognitive performance. An attention/psychomotor composite was created by averaging the standardized DET and IDN scores. A learning/working memory composite was created by averaging the standardized OCL and OBK scores. These cognitive composite scores have been validated previously to be sensitive to AD-related cognitive decline and impairment (Maruff et al., 2013) and have been used in several previous studies (Lim et al., 2012, 2013, 2015, 2016). Furthermore, studies suggest that these composite scores may have greater sensitivity when compared to the individual CBB tests (Maruff et al., 2013).

Assessment of Subjective Cognitive Concerns

The Cognitive Function Instrument (CFI; Amariglio et al., 2015) was used to measure subjective ratings of cognitive concerns. As the CFI was initially designed for administration in older adults, some items were adapted to better reflect subjective assessment of cognition in midlife (Lim et al., 2019). Examples of items in the CFI include, "Thinking back over the past year, have you been misplacing things more often?" and "Thinking back over the past year, have you been requiring more written reminders than you needed a year ago?" Scores on each item range from 0 ("no/not applicable to me") to 2 ("yes and I find it concerning"). Internal consistency of the CFI for the current sample was, by convention, good ($\alpha = 0.88$), which is comparable to the internal consistency of the CFI in other samples (Amariglio et al., 2015). The CFI has previously been validated to be sensitive to cognitive decline in older adults as well as progression to MCI or dementia (Amariglio et al., 2015; Gifford et al., 2014). The sum of all responses (total score) was used as the outcome of subjective cognitive concerns and was standardized using the baseline mean and standard deviation derived from the current sample. The standardized score was reverse scored so that higher scores indicate fewer subjective cognitive concerns.

Data Analysis

All analyses were conducted using R Version 4.0.1. A series of analyses of variance and chi-square tests of independence were

conducted to determine any demographic differences between groups of participants with 0–5 MDRF domains.

To illustrate the frequency of MDRF domains and the extent to which they overlapped in the sample, a five-way Venn diagram was constructed using InteractiVenn (Heberle et al., 2015). The frequency of MDRFs within each domain and the extent to which they overlapped were also illustrated (Supplemental Figure 2). The degree of multicollinearity between each MDRF was estimated using the Variance Inflation Factor (VIF). A conservative VIF threshold cutoff that is generally accepted is a VIF score of above five for a predictor which indicates that the variable is moderately correlated with other predictors and that multicollinearity should be addressed (O'brien, 2007). Bivariate correlations were also estimated between individual MDRFs and the coefficients (r) are presented in Supplemental Table 2.

To determine the relationship between MDRF burden (reporting risk in an increasing number of MDRF domains) and cognitive performance and subjective cognitive concerns, a series of analyses of covariance (ANCOVAs) were conducted with group (risk in 0–5 MDRF domains) as the fixed factor and age, sex, years of education, and ethnicity entered as covariates. Estimated marginal means (EMMs) were calculated for each group, and the magnitude of difference between groups was expressed as Cohen's d effect sizes and 95% confidence intervals. Individuals who reported no MDRFs were used as the reference group for effect sizes estimating the magnitude of difference between this group and each group reporting MDRFs in one to five domains.

To determine whether considering MDRF domains beyond cardiovascular conditions and lifestyle behaviors provides additional information about the relationship between MDRFs and cognition, a series of ANCOVAs was also conducted to determine differences in cognitive outcomes comparing the group of participants that reported no MDRFs in the cardiovascular or lifestyle domains with groups that reported cardiovascular and/or lifestyle risk factors (and not considering any other MDRF domain). EMMs were calculated for each group, and the magnitude of difference between groups was expressed as Cohen's d effect sizes and 95% confidence intervals. The group that reported no MDRFs in the cardiovascular and lifestyle domains was used as the reference group. Results from this analysis were then compared to the results of any differences between the group that reported no MDRFs (across any domain) with the group that reported risk in all five domains when all five domains were considered.

An additional approach was also taken that included combining the groups that reported MDRFs in no or one domain and comparing this group with four groups reporting MDRFs in 2–5 domains on the cognitive outcomes. This approach was taken to create a larger reference group for comparison, given the group with no MDRFs was relatively small (7% of the total sample), while still evaluating the relationship between multidomain MDRFs and cognition and was compared with the original approach (i.e., comparison of no MDRFs group to 1–5 MDRF domain groups).

To explore the simultaneous contribution of individual MDRF domains to cognitive performance and subjective ratings of cognitive concerns, categorical variables of whether participants reported at least one MDRF in each domain or not were entered as simultaneous predictors in a series of ANCOVA models with each cognitive outcome.

All statistical analyses were adjusted for self-reported age, sex, ethnicity, and years of education. Statistical significance for all comparisons was set at $p < .05$. No corrections for Type I error were implemented because of the novel and experimental nature of this study, the potential to describe important contributions of MDRFs to cognition, and the use of effect sizes (Cohen's d) to contextualize magnitude of differences between groups of participants with risk in 0–5 MDRF domains.

Results

Demographic Characteristics

Table 3 summarizes the demographic characteristics of the total sample and of participants who reported MDRFs present in 0–5 domains. Overall, groups reporting MDRFs in more domains had a lower proportion of female participants, had fewer years of education, and had a lower proportion of participants of European ethnicity compared to the groups reporting fewer or no domains of MDRFs. Groups were equivalent in all other demographic characteristics.

Frequency of MDRFs in Middle-Aged Adults

Figure 1 illustrates the proportion of participants who reported MDRFs in each of the five domains. A total of 1,503 participants (93.4% of total sample) reported at least one MDRF. There was a considerable degree of overlap across MDRF domains with 66.5% of participants reporting risk in two or more domains (Figure 1).

Figure 2 illustrates the frequency of reported risk in each MDRF domain across groups that reported MDRFs in 1–5 domains. In groups that reported MDRFs in two or more domains, the most frequent domains were lifestyle, cardiovascular, and cognitive/social engagement (Figure 2).

VIF scores for all MDRFs were below the predefined cutoff of five indicating moderate correlations between each MDRF and suggesting no need to address multicollinearity (Supplemental Table 1).

Relationships Between Number of MDRF Domains With Cognitive Performance and Subjective Ratings of Cognition

An increasing number of domains on a continuous MDRF domain score (0–5) was significantly associated with worse performance on the attention/psychomotor function composite and learning/working memory composite and greater subjective cognitive concerns (Supplemental Figure 5). Adjusted mean (*SE*) performance on each cognitive outcome for each group is summarized in Table 4. When all five MDRF domains were considered, individuals who reported MDRFs in five risk domains performed significantly worse on the attention/psychomotor composite than those reporting no MDRFs, with a moderate magnitude of difference (Figure 3). Individuals who reported MDRFs in 3–5 risk domains performed significantly worse on the learning/working memory composite and reported greater subjective cognitive concerns than those reporting no MDRFs, with the magnitude of difference moderate to large (Figure 3).

When only considering cardiovascular and lifestyle domains of MDRFs, compared to the group that reported no MDRFs in these

Table 3
Demographic Characteristics of the Total Sample and Individuals That Reported at Least One Modifiable Dementia Risk Factor in 0–5 Domains

	Total sample	Number of reported MDRF domains									
		0		1		2		3		4		5	
Demographic characteristics	*M* (*SD*) or *N* (%)	*M* (*SD*) or *N* (%)		*M* (*SD*) or *N* (%)		*M* (*SD*) or *N* (%)		*M* (*SD*) or *N* (%)		*M* (*SD*) or *N* (%)		*M* (*SD*) or *N* (%)	*p*
N	1,610	107		433		535		357		133		45	
Age (years)	57.42 (7.07)	57.83 (7.02)		57.12 (6.98)		57.2 (7.07)		57.89 (7.29)		57.97 (6.82)		56.71 (6.81)	.434
Female sex	1,222 (75.9%)	98 (91.6%)		356 (82.2%)		416 (77.8%)		239 (66.9%)		83 (62.4%)		30 (66.7%)	**<.001**
Education (years)	15.93 (3.49)	16.85 (3.40)		16.84 (3.35)		15.83 (3.47)		15.20 (3.39)		15.20 (3.39)		14.22 (3.71)	**<.001**
Regional living	448 (27.8%)	32 (29.9%)		102 (23.6%)		149 (27.9%)		106 (29.7%)		44 (33.1%)		15 (33.3%)	.176
European ethnicity	1,313 (81.6%)	94 (87.9%)		374 (85.5%)		433 (80.9%)		283 (79.3%)		97 (72.9%)		32 (71.1%)	**.001**
Family history of dementia	1,126 (69.9%)	76 (71.0%)		304 (70.2%)		396 (74.0%)		231 (64.7%)		89 (66.9%)		30 (66.7%)	.082
Family history of CVD	1,302 (80.9%)	90 (84.1%)		355 (81.9%)		432 (80.7%)		280 (78.4%)		106 (79.7%)		39 (86.7%)	.616

Note. Bolded *p* values indicate statistically significant differences between MDRF domain groups on demographic characteristics at $p < .05$. MDRF = modifiable dementia risk factor; CVD = cardiovascular disease.

domains, the group that reported MDRFs in cardiovascular or lifestyle domains (without considering any other domains) did not differ on any cognitive outcome. The group that reported MDRFs in both cardiovascular and lifestyle domains showed worse performance on the learning/working memory composite ($d = 0.26$, $p = .001$) and greater subjective cognitive concerns ($d = 0.26$, $p = .001$) compared to the group reporting no MDRFs in these domains with the magnitude of difference small.

Combining the groups reporting MDRFs in no or one domain and comparing them with groups reporting 2–5 domains yielded comparable results. Compared with participants reporting MDRFs in no or one domain, participants reporting MDRFs in three or more domains had worse performance on the learning/working memory composite ($d = 0.22$–0.71) and greater subjective cognitive concerns ($d = 0.27$–0.71). Participants with risk across all five domains also had worse performance on the attention/psychomotor composite ($d = 0.48$) when compared to participants reporting MDRFs in no or one domain.

Reanalysis of participants that had 100% complete data did not change the results substantially. Participants who reported MDRFs in three or more domains had worse performance on the learning/working memory composite ($d = 0.25$–0.87) and greater subjective cognitive concerns ($d = 0.36$–0.90) compared to participants reporting no MDRFS. Those that reported risk in all five domains also had worse performance on the attention/psychomotor composite ($d = 0.61$).

Contribution of Individual MDRF Domains to Cognitive Performance and Subjective Ratings of Cognitive Concerns

When individual modifiable risk domains were considered as simultaneous predictors in ANCOVA models, risk in the mood and cardiovascular domains was significantly associated with worse performance on the learning/working memory composite (Table 5). Risk in the mood, cardiovascular, and sleep domains was significantly associated with greater subjective cognitive concerns. No other domains were significantly associated with any cognitive outcome when adjusting for age, sex, education, and ethnicity.

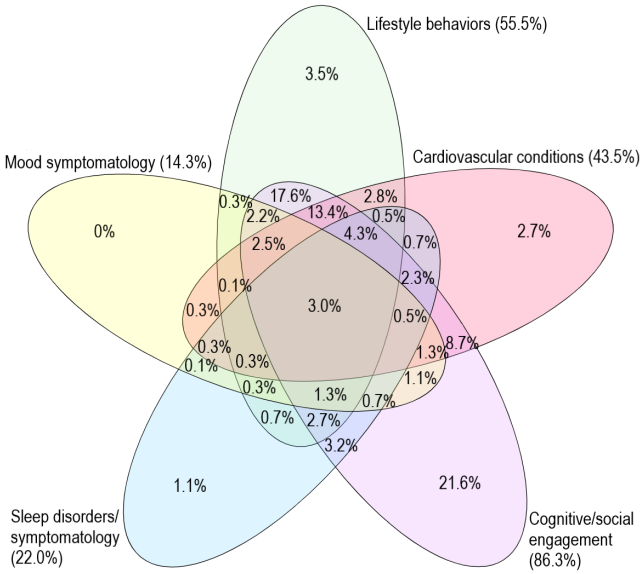
Exclusion of participants who completed assessments during the COVID-19 pandemic ($n = 42$) did not change any results substantially.

Discussion

This study investigated the relationship between MDRFs across multiple domains and cognition in middle-aged adults. The hypothesis that displaying MDRFs in more domains would be associated with poorer cognitive performance and greater subjective cognitive concerns was supported. Most middle-aged adults (66.5%) in this sample displayed at least one MDRF in two or more domains. Individuals who reported at least one MDRF in three or more domains showed worse cognition, compared to individuals who reported no MDRFs, with these differences moderate to large in magnitude for learning/working memory ($d = 0.30$–0.90) and subjective cognitive concerns ($d = 0.38$–0.92). Compared with those reporting no MDRFs, individuals who reported MDRFs across all domains also showed moderately worse attention/psychomotor function ($d = 0.58$). Consideration of how reporting MDRFs from different risk domains simultaneously relates to cognition showed that MDRFs in mood and cardiovascular domains

Figure 1

Frequency and Degree of Overlap Between Modifiable Dementia Risk Factor (MDRF) Domains (Mood, Lifestyle, Cardiovascular, Cognitive and Social Engagement, and Sleep) in Which Participants Reported at Least One MDRF



Note. Percentages next to domain labels represent the proportion of participants reporting MDRFs in that domain out of participants reporting any MDRFs ($N = 1{,}503$). See the online article for the color version of this figure.

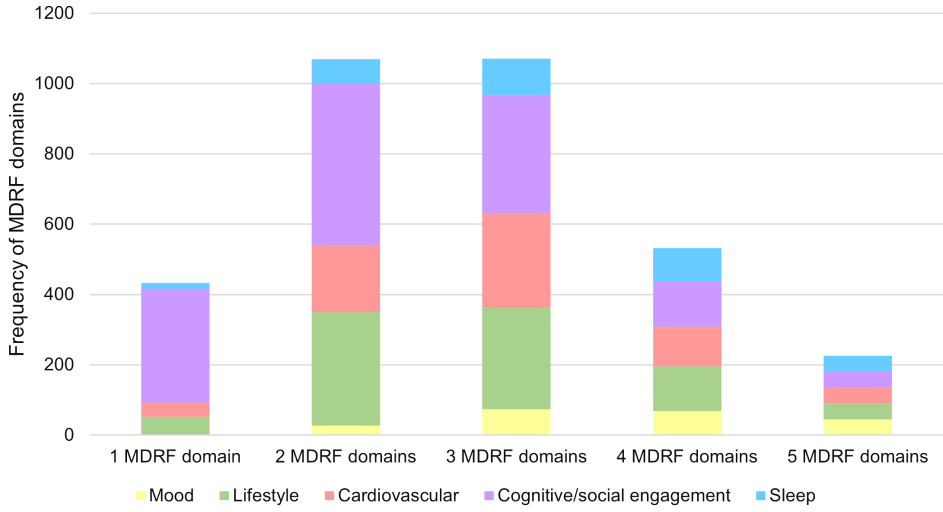
were most strongly and uniquely associated with poorer learning/working memory. Furthermore, greater subjective cognitive concerns were most strongly associated with risk factors in the mood, cardiovascular, and sleep domains. Together, these results suggest that multidomain MDRFs are highly frequent in middle-aged adults and are associated with worse cognition.

The finding that most middle-aged adults in this sample endorsed one or more MDRFs across multiple domains is in line with other reports showing consistent co-occurrence of similar risk factors for morbidity and mortality in adults (Conry et al., 2011; Morris et al., 2016; Schuit et al., 2002). To our knowledge, however, this is the first study to describe the frequency and degree of overlap between MDRFs across multiple domains in middle-aged adults.

To date, few studies have also sought to understand the simultaneous influence of MDRFs from multiple domains on cognitive impairment or dementia incidence in older or middle-aged adults (Livingston et al., 2020). These studies have mainly used dementia risk assessment scores, such as the Cardiovascular Risk Factors, Ageing, and Incidence of Dementia (CAIDE) score (Kivipelto et al., 2006) and the Australian National University–Alzheimer's Disease Risk Index (Anstey et al., 2014). Most of these scores also include nonmodifiable risk factors such as age or sex. The Lifestyle for Brain Health (LIBRA) index is distinct in that it is based on the measurement of MDRFs only across multiple domains (Vos et al., 2017). Consistent with results of the present study, previous studies have shown that an increased LIBRA index (indicating higher modifiable dementia risk) is related to worse cognitive performance and greater risk of cognitive impairment and dementia in older and middle-aged adults (Schiepers et al., 2018; Vos et al., 2017). However, the majority of MDRFs included in the LIBRA index represent cardiovascular conditions and related lifestyle behaviors (10 of 13; Schiepers et al., 2018). Thus, it is possible that studies using the LIBRA index, similar to other studies of modifiable dementia risk (Dhana et al., 2020; González et al., 2018) that focus on cardiovascular and lifestyle risk factors, may not be capturing risk present from other domains for some individuals. This criticism is based on the hypothesis that consideration of MDRFs beyond those in the cardiovascular and lifestyle domains would increase the accuracy of

Figure 2

Frequency of Reporting Risk in Each MDRF Domain (Mood, Lifestyle, Cardiovascular Conditions, Cognitive/Social Engagement, Sleep) in Groups That Reported Risk in 1–5 MDRF Domains



Note. MDRF = modifiable dementia risk factor. See the online article for the color version of this figure.

Table 4

Associations Between Number (0–5) of Domains in Which Individuals Reported at Least One MDRF With Cognitive Performance and Subjective Ratings of Cognition

			Number of MDRF domains					
			0	1	2	3	4	5
Cognition outcomes	β (*SE*)	*p*	EMM (*SE*)	EMM (*SE*)	EMM (*SE*)	EMM (*SE*)	EMM (*SE*)	EMM (*SE*)
Attention/psychomotor	**−0.078 (0.024)**	**.001**	0.106 (0.110)	0.093 (0.060)	0.005 (0.054)	−0.008 (0.061)	−0.141 (0.093)	−0.473 (0.160)
Learning/working memory	**−0.124 (0.025)**	**<.001**	0.206 (0.115)	0.138 (0.063)	0.067 (0.056)	−0.101 (0.063)	−0.114 (0.098)	−0.709 (0.169)
Subjective cognition	**−0.191 (0.024)**	**<.001**	0.281 (0.131)	0.179 (0.096)	0.121 (0.089)	−0.109 (0.093)	−0.543 (0.115)	−0.638 (0.187)

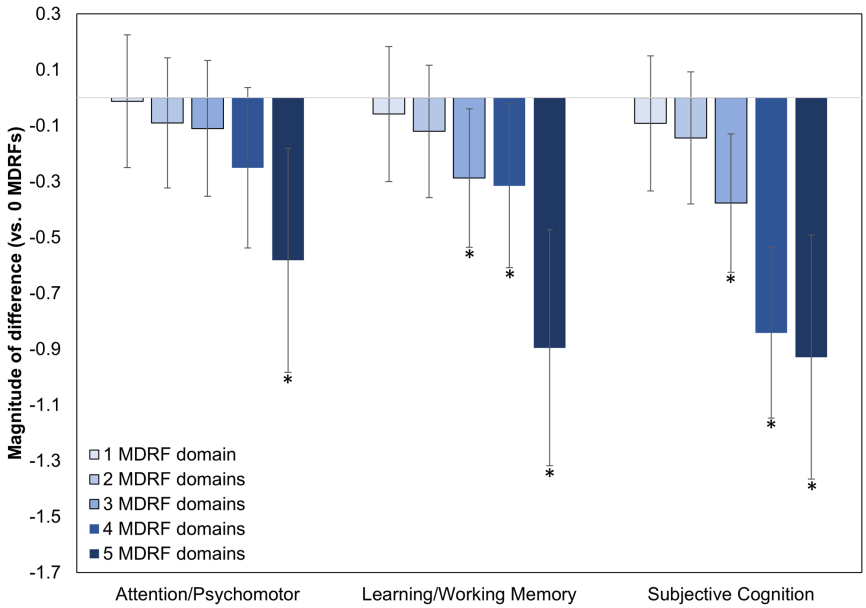
Note. Beta-coefficients are standardized, and each has been adjusted for age, sex, years of education, and ethnicity. Bold values are significant at $p < .05$. MDRF = modifiable dementia risk factor; EMM = estimated marginal means; *SE* = standard error.

modifiable dementia risk models. This hypothesis is supported by data from the present study, which, to our knowledge, is the first study of multidomain MDRFs to additionally consider multiple MDRFs in the mood and sleep domains. When only cardiovascular and/or lifestyle domains of MDRFs were considered in their relationship with cognition, only small, or no, relationships were observed. In contrast, when all five domains of MDRFs were considered, there was a moderate-to-large difference (d = 0.58–0.92) in all cognitive outcomes between individuals who reported MDRFs across all five domains and those with no MDRFs in any domain. These findings suggest that by considering domains of MDRFs beyond the most commonly considered cardiovascular and lifestyle domains, more information can be gained about the extent to which MDRFs may contribute to worse cognition. In the present study, a greater number of MDRF domains was associated with poorer attention/psychomotor function and learning/working memory, and greater subjective cognitive concerns. This was also observed in an additional comparison of individuals reporting multidomain MDRFs (2–5 domains) and no or single domain MDRFs. Thus, models of modifiable dementia risk may be more comprehensive and accurate when multiple domains of MDRFs are considered.

Higher burden of MDRFs across multiple domains may hasten the effects of early underlying neurological changes associated with AD or other dementias such that they are apparent as early as midlife (Merrill et al., 2016). The strong relationship observed in this study between risk in a higher number of MDRF domains and greater subjective cognitive concerns may indicate that middle-aged adults

Figure 3

Magnitude of Difference (Cohen's d) in Attention/Psychomotor Function, Learning/Working Memory and Subjective Ratings of Cognition Between Individuals Reporting No MDRFs and Those Who Reported at Least One MDRF in 1–5 Domains



Note. MDRF = modifiable dementia risk factor. Error bars represent 95% confidence intervals. See the online article for the color version of this figure.
Effect sizes marked by * are statistically significant at $p < .05$.

Table 5
Associations Between Risk in Individual MDRF Domains With Cognitive Performance and Subjective Ratings of Cognition

MDRF domains	Attention/psychomotor		Learning/working memory		Subjective cognition	
	β (*SE*)	*p*	β (*SE*)	*p*	β (*SE*)	*p*
Mood symptomatology	−0.137 (0.080)	.088	**−0.214 (0.084)**	**.011**	**−0.791 (0.079)**	**<.001**
Risky lifestyle behaviors	−0.038 (0.054)	.480	−0.050 (0.056)	.371	−0.042 (0.053)	.436
Cardiovascular conditions	−0.072 (0.055)	.189	**−0.197 (0.057)**	**.001**	**−0.116 (0.054)**	**.032**
Cognitive/social engagement	−0.043 (0.067)	.521	−0.083 (0.069)	.230	−0.074 (0.066)	.259
Sleep disorders/symptomatology	−0.118 (0.067)	.078	−0.084 (0.069)	.227	**−0.221 (0.066)**	**.001**

Note. Beta-coefficients are standardized and have been adjusted for age, sex, years of education, and ethnicity. Bold values are significant at $p < .05$. MDRF = modifiable dementia risk factor; *SE* = standard error.

with MDRFs spanning several domains are already perceiving changes to their own cognition. This reinforces the importance of understanding the manifestation of MDRFs in midlife even with dementia potentially decades away for some individuals. The results of this study also support that multidomain interventions for reducing MDRFs may already be needed in midlife (Lim et al., 2021).

Pathological changes associated with AD, such as the accumulation of amyloid-beta (Aβ) and tau have been detected in midlife, decades before dementia onset (Sutphen et al., 2015). Some studies in middle-aged and older adults have demonstrated associations between individual MDRFs such as depression/anxiety symptomatology, low adherence to the Mediterranean diet, physical inactivity, and obesity with elevated cortical Aβ and tau (Lavretsky et al., 2009; Merrill et al., 2016). Others have also found that midlife cardiovascular risk factors are associated with cerebrovascular disease and increased neurodegeneration in later life (Lane et al., 2020). However, the contribution of MDRFs across multiple domains to biomarker outcomes remains unknown. In this sample, through simultaneous consideration of all risk domains, it was observed that worse learning/working memory and greater subjective cognitive concerns were related most strongly to MDRFs from the mood, cardiovascular, and sleep domains. The relationships between MDRFs in these domains and worse cognition have been observed previously and are well established (Dux et al., 2008; Paradise et al., 2011; Tsapanou et al., 2019). It is possible that MDRFs across these different domains are exacerbating early neurological changes through multiple parallel biological mechanisms, such as neuroinflammation (McKenzie et al., 2017), overexposure to cortisol (Green et al., 2006), or disruption to neurotoxic waste clearance in the brain (Xie et al., 2013). Future research should investigate the influence of MDRFs in multiple domains on pathological markers for AD and other dementias in middle-aged adults. This will enhance understanding of how modifiable dementia risk may worsen cognition in midlife and inform efforts to delay or prevent cognitive decline and dementia progression.

A strength of this study is the large sample of community-dwelling middle-aged adults with 50% reporting a family history of dementia. There are limitations to the present study that warrant consideration. The HBP sample is highly educated, and the majority of participants report that they are of European ethnicity, which limits the generalizability of results. Findings of the present study will therefore need to be replicated in other more representative samples. As this study was cross-sectional and observational in design, it was not possible to determine whether MDRFs cause cognitive dysfunction or decline. Multidomain behavioral intervention trials are needed to determine whether targeting MDRFs can lead to better cognition. Although a comprehensive range of MDRF measures was included in this study, all assessments relied on self-report and were completed remotely via the HBP platform. Whilst self-report questionnaires are the most common way of assessing MDRFs, this method of assessment combined with the unsupervised context may have resulted in inaccurate (e.g., overestimated/underestimated) responses relating to MDRFs or subjective cognitive concerns. Furthermore, responses of individuals with greater subjective cognitive concerns to MDRF questionnaires may be shaped by their cognitive concerns rather than reflecting their true answers or performance. Remote assessment platforms for research studies are increasingly being tested and used, and studies within the HBP (Bransby et al., 2022; Nicolazzo et al., 2021; Perin et al., 2022; Yassi et al., 2022) have shown comparable relationships to others that were conducted in clinic (Jonaitis et al., 2013; Mascherek et al., 2020; Tsapanou et al., 2019; Yaffe et al., 2020). However, additional studies are needed to further understand differences in the accuracy of data, if any, collected between remote and in-clinic assessments. The HBP was designed to be as flexible as possible for participants, and as such, participants were only required to complete all assessments within a 6-month assessment window. As participants did not have to complete all assessments in one sitting, the time between various questionnaires and tests completed may vary for participants. Cognitive functions measured by the CBB are limited and not as comprehensive as a standard neuropsychological assessment; however, the validity of the CBB to measure cognitive domains disrupted by AD has been previously demonstrated (Maruff et al., 2013). Medication use and adherence were not examined in this study, and future studies seeking to further clarify the contribution of cardiovascular conditions on cognition should determine whether pharmaceutical treatment for cardiovascular conditions such as hypertension and hypercholesterolemia mitigates relationships between multidomain MDRFs and cognition. An important consideration is that many of the MDRFs included in the present study may be associated with external factors such as social determinants of health (e.g., race, socioeconomic neighborhood advantage). As such, it will be important to investigate the extent to which external factors influence the relationship between MDRFs and cognition.

There is currently no consensus on the best approach to operationalize and synthesize MDRFs. Several methods have been used previously such as considering MDRFs individually (Jonaitis et al., 2013), weighted risk scores (e.g., CAIDE; Kivipelto et al., 2006), and data-driven approaches (Katayama et al., 2020). Methods other

than the categorization of MDRFs into domains have also been attempted in the current sample (Supplemental Figures 3 and 4). There is also currently no consensus on which MDRFs are most important to include. A systematic review of studies investigating combinations of MDRFs demonstrated that no MDRF was measured consistently across all studies (Peters et al., 2019). The variety of approaches reflects the complexity of MDRF measurement and heterogeneity in the field, as well as the issue that many MDRFs are highly related. By classifying a wide range of MDRFs into broad risk domains that are well defined and operationalized, the approach used in the present study offers one potential method to standardize the operationalization and synthesis of multiple MDRFs and address the heterogeneity in the field.

Limitations notwithstanding, our results suggest that MDRFs across multiple domains are highly frequent in middle-aged adults at risk for dementia and are associated with worse cognition. This supports that modifiable dementia risk is multidimensional and may be associated with negative neurological outcomes potentially evident even in midlife. These findings can inform brain–behavior models of modifiable dementia risk as well as the design of multidomain behavioral intervention trials targeting MDRFs to preserve cognition and delay dementia.

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