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REVIEW ARTICLE

Cardiovascular disease as a mediator in the relationship between lifestyle risk factors and cognitive outcomes: a scoping review

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Abstract

Dementia is a major global health challenge and lifestyle modification is a key prevention strategy. Cardiovascular disease (CVD) is hypothesized to mediate lifestyle–dementia relationships, but empirical evidence is unclear. Mediation analysis offers insight into causal mechanisms beyond traditional associations. This scoping review synthesizes the limited available studies applying mediation analysis to examine whether CVD mediates associations between lifestyle factors (smoking, alcohol use, diet, physical activity) and cognitive outcomes in adults aged 45 and older. Of 1309 records screened, five studies met the inclusion criteria, reflecting a small, heterogeneous evidence base. Most examined physical activity ($n = 4$), with two reporting partial

mediation by composite CVD risk scores. Evidence for diet ($n = 2$) and alcohol ($n = 1$) was inconclusive, and no studies assessed smoking. Overall, evidence for CVD as a mediator remains tentative, sparse, and inconsistent, highlighting major methodological gaps and an urgent need for robust studies to clarify whether cardiovascular health underpins lifestyle-related dementia risk.

KEYWORDS
aging, cardiovascular diseases, dementia, mediation analysis, risk factors

Highlights

- Five studies were identified that used mediation analysis to explore the role of cardiovascular disease in the relationship between lifestyle risk factors and dementia.
- Cardiovascular disease may partially mediate the impact of physical activity on brain health.
- Diet and alcohol consumption showed no clear mediation effects by cardiovascular disease on cognition.
- Longitudinal, well-powered studies with robust mediation frameworks are urgently needed to evaluate vascular pathways and optimize dementia prevention strategies targeting modifiable lifestyle factors.

1 | INTRODUCTION

Dementia represents a major global health concern, with rising prevalence driven by aging populations and limited effective treatments.[1–3] Over 50 million individuals worldwide live with dementia, including Alzheimer's disease and vascular dementia, with this number expected to rise to 153 million by 2050.[4] In addition to neurodegenerative processes, such as amyloid beta accumulation and tau pathology, increasing evidence points to a significant role for vascular contributions to dementia.[5–8] Vascular dementia is the second most common form of dementia after Alzheimer's disease, and cerebrovascular pathology frequently coexists with Alzheimer's pathology in mixed dementia cases.[9,10] This convergence suggests that cardiovascular disease (CVD) may not only increase dementia risk directly but also act as an intermediary in pathways linking other risk factors to cognitive decline.

Modifiable lifestyle-related risk factors – including poor diet, physical inactivity, smoking, and excessive alcohol consumption – are strongly associated with CVD[11–15] and have also been identified as potentially modifiable dementia risk factors,[16–20] as highlighted in the most recent Lancet Commission report for dementia.[19,20] These relationships form the basis of the vascular hypothesis of dementia, which proposes that harmful lifestyle behaviors contribute to vascular pathology, which in turn accelerates or triggers cognitive decline through mechanisms such as cerebral hypoperfusion, microinfarcts, and blood–brain barrier dysfunction.[21,22] While these pathways are conceptually well established, the extent to which CVD actually mediates the association between lifestyle and dementia risk remains unclear.

Despite analytic methods designed to explore causal pathways, current evidence largely comes from correlational or association-based studies, which cannot determine whether CVD truly functions as a mediator rather than a co-occurring risk factor.[23] Most systematic reviews have summarized direct associations between lifestyle factors and cognitive outcomes or between CVD and cognitive outcomes,[24–26] but few have examined the combined pathway. This lack of mechanistic clarity represents an important gap that effective prevention strategies depend on to understand how risk factors exert their influence. For example, if the protective effect of physical activity on cognition operates primarily through cardiovascular pathways, then interventions targeting vascular health could maximize cognitive benefits.

Mediation analysis provides a methodological framework for formally testing these pathways. Unlike traditional analyses that assess direct associations, mediation analysis estimates indirect effects and quantifies the extent to which an exposure influences an outcome via an intermediate variable, in this case CVD[27] (Figure 1). By applying causal inference principles, mediation analysis moves beyond whether associations exist to address how and through what mechanisms they occur.[28–30] Despite its potential value, the degree to which mediation analysis has been used to study lifestyle–CVD–dementia pathways, and what it reveals about these relationships, remains unknown.

To address this gap, we conducted a scoping review to identify and synthesize studies that have applied mediation analysis to examine whether CVD mediates the relationship between lifestyle risk factors

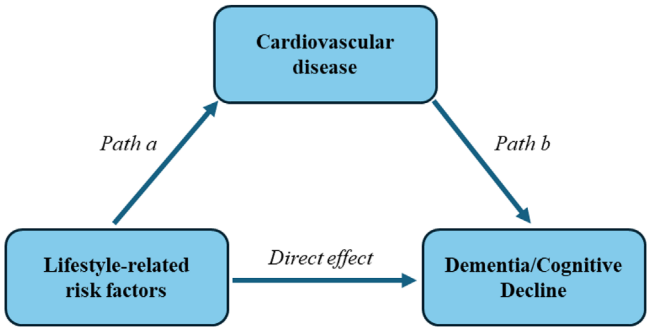

FIGURE 1 Conceptual model of mediating pathway between lifestyle-related risk factors (e.g., physical inactivity, diet, smoking, alcohol consumption) and dementia. The indirect effect is the product of paths a (effect from intervention to mediator) and b (effect from mediator to outcome). The total effect is the sum of direct and indirect effects.

and cognitive outcomes, including dementia. For the purpose of this review, cognitive outcomes were broadly conceptualized to include both clinical diagnoses of dementia and measures of cognitive decline, reflecting the range of outcomes used in the literature. By mapping existing evidence and identifying key gaps, this review aims to clarify what is currently known about these mediation pathways and inform future research priorities.

1.1 | Objectives

The purpose of this scoping review was to map and synthesize the existing literature that has applied mediation analysis to examine whether CVD acts as a mediator in the relationship between lifestyle-related risk factors and cognitive outcomes. Specifically, this review aimed to:

1. Identify studies that have formally tested mediation pathways involving lifestyle risk factors (diet, physical inactivity, smoking, and alcohol consumption), CVD as a potential mediator, and cognitive outcomes, including dementia;
2. Summarize the extent and characteristics of this evidence, including which risk factors and cardiovascular conditions have been studied and the types of cognitive or dementia outcomes assessed; and,
3. Highlight gaps in the literature and methodological limitations to inform future research directions for understanding causal pathways linking lifestyle, vascular health, and cognitive aging.

2 | METHODS

2.1 | Protocol and registration

A scoping review protocol was published a priori on OSF.io.[31] Reporting of methodology and results followed the Joanna Briggs Institute Evidence Synthesis Reporting Guide for Protocols and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[32] (Appendix A).

2.2 | Search strategy and selection criteria

Using the multifile option and deduplication tool on the Ovid platform, we searched Ovid MEDLINE All, Embase Classic+Embase, and APA PsycINFO. We also searched CINAHL (Ebsco) and Web of Science (core databases). We performed all searches on July 12, 2024, using a combination of controlled vocabulary (e.g., "smoking," "cardiovascular diseases," "cognitive dysfunction," "mediation analysis") and keywords (e.g., "sedentary lifestyle," "CVD," "Alzheimer," "causality"). There were no date or language restrictions, but animal-only records were removed. The search strategy was developed in consultation with an information specialist and peer-reviewed in accordance with Peer Review of Electronic Strategies (PRESS) guidelines.[33] Results were downloaded and deduplicated using EndNote version 9.3.3 (Clarivate Analytics) and uploaded to Covidence (Veritas Health Innovation Ltd.). A manual search of the reference lists of included studies was performed to identify any literature that was not identified in the original search. Our full search strategy can be found in Appendix B.

2.3 | Eligibility criteria

We included empirical studies (i.e., cross-sectional studies, longitudinal studies, and randomized controlled trials) that conducted formal mediation analysis to examine whether CVD mediated the association between at least one lifestyle-related risk factor (diet, physical inactivity, smoking, and alcohol consumption) and cognitive outcomes in adults aged 45 years and older. The lower cut-off of 45 years was chosen because midlife is a critical exposure window for dementia risk, with numerous studies demonstrating that cardiovascular and lifestyle-related risk factors during this period are strongly associated with late-life cognitive decline and dementia.[19,20]

Cognitive outcomes were broadly defined to capture the range of dementia-related endpoints studied in the literature, including clinical diagnoses of dementia (e.g., Alzheimer's disease, vascular dementia, all-cause dementia), intermediate outcomes such as mild cognitive impairment, and cognitive decline measures, including validated neuropsychological test scores (e.g., memory, executive function) and imaging-based markers of brain aging when explicitly linked to cognition.

2.4 | Exclusion criteria

Case studies, narrative reviews, editorials, book chapters, descriptive studies, and qualitative studies were excluded. The reference lists and bibliographies of relevant systematic reviews, scoping reviews, and meta-analyses were scanned to identify relevant studies; however, the reviews themselves were excluded. Additionally, we excluded stud-

ies if they included animal populations or adults younger than 45 years or did not conduct formal mediation analysis using appropriate methodologies.

2.5 | Data screening, extraction, and synthesis

Titles, abstracts, and full-text articles were screened independently and in duplicate by four reviewers (A.L.J.H., T.C., P.R., R.A.) using Covidence. There was a high level of inter-rater agreement at both the title/abstract stage (87% to 98% proportionate agreement) and full-text screening stage (95% proportionate agreement). Discrepancies were resolved through consensus discussion, ensuring consistent application of inclusion criteria across reviewers.

Data extraction was conducted independently by one reviewer (A.L.J.H.) using a piloted extraction form and verified by a second reviewer (T.C.). This approach was chosen to balance methodological rigor with feasibility given the small number of included studies. Although this process introduces a potential risk of extraction error, verification minimizes this risk and is acknowledged as a limitation.

Extracted variables included study design, population characteristics, exposure(s), mediator(s), outcome(s), statistical methods for mediation analysis, and mediation estimates (direct, indirect, and total effects; proportion mediated, when available). Where possible, effect estimates were noted as reported; no transformations or standardization was applied because of substantial heterogeneity in mediation models, effect scales, and statistical techniques across studies. Instead, we narratively synthesized findings and explicitly described differences in analytic approaches.

Methodological variability – such as differences in mediation models (e.g., structural equation modeling, counterfactual-based approaches), handling of exposure–mediator interactions, and bootstrapping for confidence intervals – was documented and considered in the interpretation of findings rather than pooled, given the conceptual and statistical heterogeneity of included studies.

2.6 | Quality assessment

The assessment of methodologic quality was conducted using the tool proposed by Vo et al.[34] One author (A.L.J.H.) independently applied the criteria and scored "yes" or "no" for each item. Items deemed not applicable to a specific study were scored as "not applicable."

3 | RESULTS

3.1 | Literature search

A total of 1309 articles were identified in the initial search. After screening by title and abstract, 1274 were excluded. The most common reason for exclusion was not conducting mediation analysis or not assessing CVD as a mediator. After evaluating the full text of 35 articles, a total of five studies met the inclusion criteria for the current review. Manual screening of the reference lists of relevant literature reviews did not identify additional studies for inclusion. Details of the article screening process are outlined in the PRISMA diagram (Figure 2).

3.2 | Overview of included studies

The search identified five studies that applied mediation analysis to evaluate the role of CVD in the association between lifestyle risk factors and cognitive outcomes.[35–39] The mean age of participants ranged from 53 to 65 years old, and 39% to 67% of the participants in these studies were female. These studies varied substantially in design, exposure and mediator definitions, cognitive outcome measures, and analytic methods (Table 1). Three were cohort studies,[37–39] one was a cross-sectional analysis of randomized controlled trial baseline data,[35] and one was a secondary analysis of randomized controlled trial data.[36] Sample sizes ranged widely from 160 to over 260,000 participants, and follow-up periods, where reported, ranged from 2 years to more than 15 years.

3.3 | Heterogeneity in exposure and mediator measures

Both exposures and mediators were operationalized inconsistently across studies, complicating synthesis. For physical activity – the most frequently studied exposure – approaches ranged from self-reported activity and sedentary time to objective measures of aerobic fitness. Dietary exposures included adherence to the Dietary Approaches to Stop Hypertension (DASH) diet or Mediterranean diet, while alcohol exposure was assessed as a clinical diagnosis of alcohol use disorder. No included study evaluated smoking. Similarly, CVD mediators were highly variable, spanning composite risk scores (e.g., Framingham Stroke Risk Profile [FSRP]), individual diagnoses (e.g., heart disease), and cardiac structural measures (e.g., left atrial function). These differences in measurement introduce conceptual heterogeneity that limits comparability across findings.

3.4 | Methodological approaches to mediation

Mediation analysis approaches also differed considerably. Two studies, Blumenthal et al. and Spartano et al., used bootstrapped estimates of indirect effects, Gonzalez Casanova et al. applied the Valeri and Vanderweele approach,[40] Hu et al. employed counterfactual-based mediational g-formula modeling, and Kraal et al. reported traditional estimates of direct and indirect effects. Most studies adjusted for mediator-outcome confounders, but none conducted sensitivity analyses for unmeasured confounding. Notably, none of the studies reported

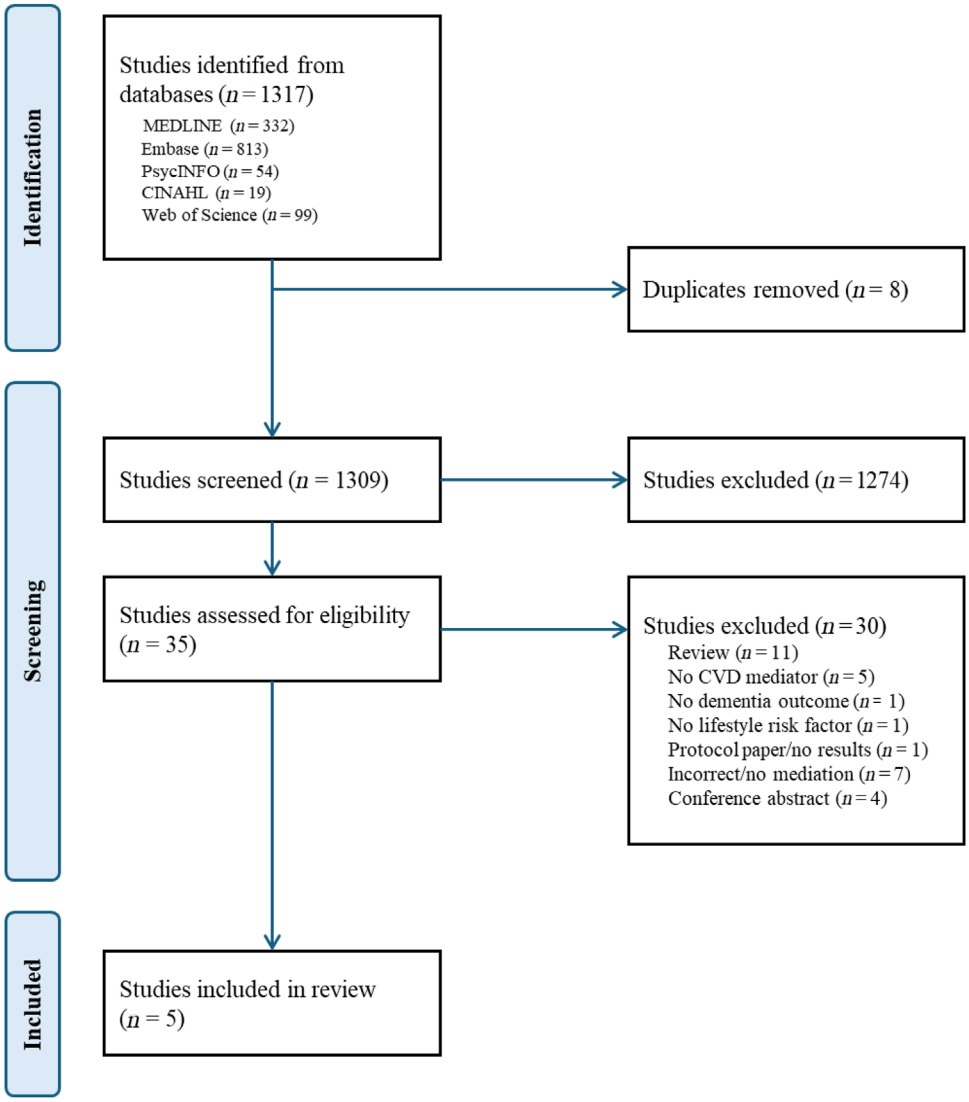

FIGURE 2 PRISMA diagram of results for each stage of search strategies.

repeated measurement of mediators, and only Kraal et al. included model goodness-of-fit indices.

3.5 | Summary of mediation findings

Overall, evidence that CVD mediates lifestyle-cognition relationships was sparse and inconsistent, with most studies reporting null or negligible indirect effects (Table 2). Across the three main risk factors represented (physical activity, diet, and alcohol), no robust mediation effect emerged.

3.5.1 | Physical activity

Four studies examined this exposure. Gonzalez Casanova et al. and Kraal et al. reported no significant mediation via CVD. Blumenthal et al. found that the FSRP partially mediated the association of aerobic fitness with executive functioning and verbal memory. Similarly, Spartano et al. found that composite cardiovascular risk (via FSRP) explained between 8.3% and 22.0% of the association between physical activity or sedentary time and neuroimaging markers of brain aging. However, effects were modest, and the reliance on risk scores rather than clinical endpoints limits interpretation.

3.5.2 | Diet

Two studies assessed diet, neither of which found evidence that CVD mediated associations with cognitive outcomes. In Gonzalez Casanova et al., adherence to the Mediterranean diet was not associated with cognitive decline. Conversely, Blumenthal et al. found that while adherence to the DASH diet was associated with better neurocognitive performance in adults with cognitive impairment, the association was not mediated by FSRP.

TABLE 1 Summary of eligible studies.

Author Year Country	Study design	Participant characteristics	Risk factor(s)	Outcome(s)	Mediator(s)	Mediation analysis method	Was CVD identified as a mediator?
Blumenthal et al. (2017)[35] USA	Cross-sectional analysis of baseline RCT data	$N = 160$; age, mean ± SD years = 65.4 ± 6.8; 67% female	DASH diet, PA, and aerobic fitness	Neurocognitive functioning	Stroke (FSRP)	Bootstrapped estimates of indirect effects	Partially
Gonzalez Casanova et al. (2023)[36] Spain	Secondary analysis of RCT	$N = 476$; age, mean ± SD years = 65.2 ± 4.9; 39% female	Mediterranean diet and PA	Cognitive functioning	Left atrial structure and function	Valeri and Vanderweele[40] approach	No
Hu et al. (2023)[37] Finland	Cohort study	$N = 262{,}703$; age (females), mean ± SD years = 59.4 ± 13.0; age (males), mean ± SD years = 56.7 ± 11.5; 53% female	Alcohol use disorder	Dementia (early-onset and late-onset)	Composite CVD measure of: - Atrial fibrillation - Cerebrovascular disease - Heart failure - Ischemic heart disease - Peripheral arterial disease	Mediational g-formula based on counterfactual causal inference framework	No
Kraal et al. (2021)[38] USA	Cohort study	$N = 5200$; age, mean ± SD years = 61.2 ± 5.6; 58% female	MVPA in early-adulthood and mid-adulthood	Episodic memory (baseline and 16-year follow-up)	Heart disease	Estimated direct and indirect effects	No
Spartano et al. (2023)[39] USA	Cohort study	$N = 2507$; age, mean ± SD years = 53.9 ± 13.6; 53% female	MVPA, sedentary time, and step count	Brain aging including TCBV, WMHV, free water, and PSMD	FSRP calculated using the following CVDs: - Atrial fibrillation - Congestive heart failure - Coronary artery disease - Peripheral artery disease	Bootstrapped estimates of indirect and direct effects	Yes

Abbreviations: CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; FSRP, Framingham Stroke Risk Profile; MVPA, moderate to vigorous physical activity; PA, physical activity; PSMD, peak width of skeletonized mean diffusivity; RCT, randomized controlled trial; TCBV, total cerebral brain volume; WMHV, white matter hyperintensity volume.

TABLE 2 Summary of mediator models.

Author Year	Exposure	Path a	Mediator	Path b	Outcome	Total effect (point estimate [95% CI])	Direct effect (point estimate [95% CI])	Indirect effect (point estimate [95% CI])	Proportion mediated (%)
Blumenthal et al. (2017)[35]	DASH diet	NS	Stroke (FSRP)	✓	Executive functioning	–	–	–	–
				✓	Verbal memory	–	–	–	–
	PA	NS		✓	Executive functioning	–	–	–	–
				✓	Verbal memory	–	–	–	–
	Aerobic fitness	✓		✓	Executive functioning	–	0.20 [0.02, 0.38]*	0.03 [–0.01, 0.10]	–
				✓	Verbal memory	–	0.14 [–0.01, 0.29]	0.03 [–0.01, 0.07]	–
Gonzalez Casanova et al. (2023)[36]	Mediterranean diet	–	LA volume index	–	Cognitive functioning	0.00 [–0.11, 0.11]	0.01 [–0.10, 0.13]	–0.01 [–0.03, 0.00]	–
		–	PSLS	–		–0.01 [–0.12, 0.09]	–0.02 [–0.13, 0.08]	0.01 [–0.01, 0.02]	–
		–	Conduit strain	–		–0.01 [–0.12, 0.10]	0.01 [–0.12, 0.09]	0.01 [–0.01, 0.01]	–
		–	Contractile strain	–		–0.01 [–0.11, 0.10]	–0.01 [–0.12, 0.10]	0.00 [–0.01, 0.01]	–
		–	LA stiffness index	–		–0.02 [–0.12, 0.02]	–0.02 [–0.12, 0.09]	0.00 [–0.02, 0.02]	–
	PA	–	LA volume index	–		–0.07 [–0.17, 0.03]	–0.05 [–0.16, 0.05]	–0.02 [–0.03, 0.00]	–
		–	PSLS	–		–0.05 [–0.15, 0.05]	–0.05 [–0.15, 0.05]	0.00 [–0.01, 0.01]	–
		–	Conduit strain	–		–0.05 [–0.15, 0.05]	–0.05 [–0.15, 0.05]	0.00 [–0.01, 0.01]	–
		–	Contractile strain	–		–0.05 [–0.15, 0.05]	–0.05 [–0.15, 0.05]	0.00 [–0.01, 0.01]	–
		–	LA stiffness index	–		–0.05 [–0.15, 0.05]	–0.06 [–0.15, 0.04]	0.01 [–0.01, 0.02]	–
Hu et al. (2023)[37]	AUD (males)	–	CVD	✓	Early-onset dementia	5.26 [3.48, 7.48]*	5.24 [3.38, 7.64]*	1.00 [0.95, 1.06]	–
		–		✓	Late-onset dementia	2.01 [1.41, 2.87]*	2.19 [1.61, 2.96]*	0.92 [0.79, 1.00]	–

(Continues)

TABLE 2 (Continued)

Author Year	Exposure	Path a	Mediator	Path b	Outcome	Total effect (point estimate [95% CI])	Direct effect (point estimate [95% CI])	Indirect effect (point estimate [95% CI])	Proportion mediated (%)
	AUD (females)	—		NS	Early-onset dementia	1.39 [0.35, 4.84]	1.46 [0.40, 4.86]	0.95 [0.79, 1.13]	—
		—		✓	Late-onset dementia	2.80 [1.70, 4.31]*	2.92 [1.86, 4.62]*	0.96 [0.83, 1.00]	—
	AUD (total)	—		✓	Early-onset dementia	4.46 [2.93, 6.25]*	4.40 [2.95, 6.12]*	1.01 [0.98, 1.06]	—
		—		✓	Late-onset dementia	2.31 [1.81, 3.05]*	2.39 [1.83, 3.13]*	0.97 [0.80, 1.00]	—
Kraal et al. (2021)[38]	Early-adulthood MVPA	NS	Heart disease	✓	Baseline memory	0.072 [0.041, 0.103]*	0.053 [0.015, 0.092]*	−0.001 [−0.002, 0.001]	—
				NS	16-year memory change	−0.021 [−0.072, 0.031]	−0.060 [−0.125, 0.005]	−0.000 [−0.002, 0.002]	—
	Mid-adulthood MVPA	✓		✓	Baseline memory	0.035 [−0.003, 0.073]	0.028 [−0.010, 0.066]	0.001 [−0.001, 0.002]	—
				NS	16-year memory change	0.064 [0.001, 0.128]*	0.067 [0.004, 0.131]*	0.000 [−0.002, 0.002]	—
Spartano et al. (2023)[39]	MVPA	✓	FSRP	✓	TCBV	0.039*	0.031	0.008*	20.5
				✓	PSMD	−0.050*	−0.039*	−0.011*	22.0
				✓	Free water	−0.071*	−0.033*	−0.003*	19.7
				✓	WMHV	−0.030	−0.016	−0.014*	n/a
	Sedentary time	✓		✓	TCBV	−0.036*	−0.033*	−0.003*	8.3
				✓	PSMD	0.039*	0.035*	0.004*	10.3
				✓	Free water	0.019	0.014	0.006*	n/a
				✓	WMHV	−0.036*	−0.041*	0.005*	n/a
	Step count	✓		✓	TCBV	0.030*	0.025	0.005*	16.7
				✓	PSMD	−0.039*	−0.032*	−0.006*	15.4
				✓	Free water	−0.028	−0.019	−0.009*	n/a
				✓	WMHV	0.003	0.011	−0.008*	n/a

Abbreviation: AUD, alcohol use disorder; CI, confidence interval; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; FSRP, Framingham Stroke Risk Profile; LA, left atrial; MVPA, moderate to vigorous physical activity; PA, physical activity; PSLS, peak systolic longitudinal strain; PSMD, peak width of skeletonized mean diffusivity; TCBV, total cerebral brain volume; WMHV, white matter hyperintensity volume.

✓ = Significant values for pathway.

NS = Non-significant values for pathway.

— = Information on pathway was not available.

n/a = Not applicable to estimate, as direct and indirect effects are in opposite directions or not significant.

* Significant (as indicated by absence of zero or one in 95% confidence intervals or $p < 0.05$).

TABLE 3 Summary of study quality.

	Blumenthal et al. (2017)[35]	Gonzalez Casanova et al. (2023)[36]	Hu et al. (2023)[37]	Kraal et al. (2021)[38]	Spartano et al. (2023)[39]
Planning					
Was the mediation analysis planned a priori in the trial protocol?	×	×	×	×	×
Were the mediators chosen based on the clinical rationale underlying the mechanisms in which the exposure affects the outcome?	✓	✓	✓	✓	✓
Was the choice of mediator(s) based on independent data?	✓	✓	✓	✓	✓
Was there a plan to collect pre- and post-randomization confounders of the exposure-mediator relationship?	n/a	n/a	n/a	n/a	n/a
Was there a plan to collect pre- and post-randomization confounders of the mediator-mediator relationship?	n/a	n/a	n/a	n/a	n/a
Was there a plan to collect pre- and post-randomization confounders of the mediator-outcome relationship?	n/a	n/a	n/a	n/a	n/a
Were the mediators measured prior to the outcome to assure the causal interpretation of the findings?	×	✓	✓	✓	✓
Were the mediators measured repeatedly?	×	×	×	×	×
Was a causal diagram reported underlying the causal relationship of the exposure(s), mediator(s), and outcome(s)?	✓	✓	✓	×	×
Was the sample size for the mediation analysis estimated?	×	✓	×	×	×
Conduct					
Were multiple imputations (or other valid approaches) used to handle missing data?	n/a	n/a	n/a	n/a	n/a
If a complete-case analysis was used, did they adjust for baseline covariates that were differentially distributed between responders and non-responders?	×	×	×	×	×
Was a sensitivity analysis conducted to assess the impact of different approaches on the findings?	×	×	×	×	×
Does the study report separate analyses for separate mediators?	n/a	✓	n/a	n/a	n/a
Does the study use an appropriate framework for analysis?	✓	✓	✓	✓	✓
Does the study evaluate the goodness of fit of each model?	×	×	×	✓	×
Does the study assess potential interaction(s) between exposure and confounding factors, exposure and mediator, mediator and mediator in the mediator and outcome models?	×	×	✓	×	×
Does the study adjust for exposure–mediator confounders?	n/a	n/a	n/a	n/a	n/a
Does the study adjust for mediator–mediator confounders?	n/a	×	n/a	n/a	n/a
Does the study adjust for mediator–outcome confounders?	✓	✓	✓	✓	✓
Does the study perform sensitivity analysis to assess sensitivity of the results to the assumption of no measured mediator-mediator or mediator–outcome confounder?	×	×	×	×	×
Does the study perform sensitivity analysis to assess sensitivity of the results to potential measurement errors of the mediator(s)?	×	×	×	×	×
Does the study use apt strategies when some of the mediator–mediator or mediator–outcome confounders are potentially affected by the exposure (e.g., by considering confounders as mediators themselves)?	×	×	×	×	×

(Continues)

TABLE 3 (Continued)

	Blumenthal et al. (2017)[35]	Gonzalez Casanova et al. (2023)[36]	Hu et al. (2023)[37]	Kraal et al. (2021)[38]	Spartano et al. (2023)[39]
Reporting					
Does the study report the approaches used for mediation analysis?	✓	✓	✓	✓	✓
Does the study provide a causal diagram that underlies the analysis?	✓	×	×	✓	✓
Does the study report the sample size calculation?	×	✓	×	×	×
Does the study report the actual sample size of the mediation analysis?	✓	✓	✓	✓	✓
Does the study report how missing data are handled?	×	×	×	✓	×
Does the study report all confounders considered and adjusted for in the analysis?	✓	✓	✓	✓	✓
Does the study report the model-building procedure and the final form of all models used in the analysis?	×	×	✓	✓	✓
Does the study report the goodness of fit of all the models?	×	×	×	✓	×
Does the study report the point estimates and the confidence intervals of the direct effect(s)?	✓	✓	✓	✓	×*
Does the study report the point estimates and the confidence intervals of the indirect effect(s)?	✓	✓	✓	✓	×*
Does the study report the point estimates and the confidence intervals of the total effect(s)?	×	✓	✓	✓	×*
Does the study report the methods and results of all sensitivity and other additional analyses (in the main paper or appendices)?	✓	✓	✓	✓	✓
Does the study discuss the validity of all causal assumptions underlying the analysis (in the main paper or appendices)?	✓	✓	✓	✓	✓

✓ (yes).
× (no).
n/a = Not applicable to score.
* Point estimates, but not confidence intervals, were reported.

3.5.3 | Alcohol

One large cohort study, conducted by Hu et al., evaluated alcohol use disorder and dementia. While alcohol use disorder increased the risk of both early- and late-onset dementia, the elevated risk of dementia associated with alcohol use disorder was not mediated by CVD.

3.5.4 | Smoking

No included study investigated smoking as an exposure, leaving this pathway entirely unexamined.

3.6 | Quality and reporting

Quality assessment revealed multiple methodological limitations (Table 3). None of the studies followed a pre-specified mediation protocol, and none performed sensitivity analyses for key assumptions. Only one study estimated sample size requirements, and none incorporated repeated mediator measurements, both of which are essential for robust causal inference. Furthermore, point estimates of indirect effects were often small and accompanied by wide confidence intervals, underscoring concerns about limited power and heterogeneity in analytic methods.

4 | DISCUSSION

This scoping review synthesized the limited literature using mediation analysis to examine whether CVD explained the relationship between lifestyle risk factors and dementia-related outcomes. Our review identified only five eligible studies, most of which focused on physical activity and employed diverse methodologies to explore mediation effects. The study findings provided very limited and inconsistent evidence for CVD as a mediator in these pathways. While two studies reported statistically significant indirect effects – primarily for physical activity and composite cardiovascular risk profiles – most findings

were null, and the observed mediation effects were modest and varied by outcome and analytic approach. Overall, these findings underscore the methodological and conceptual gaps in the existing evidence base.

Although some models demonstrated statistically significant mediation, the clinical and mechanistic implications of these small indirect effects are uncertain. For example, while FSRP scores explained up to 22% of the association between physical activity and neuroimaging markers of brain aging, these findings do not establish whether such effects are clinically relevant or whether they would translate into dementia prevention at the population level. The lack of sensitivity analyses, repeated mediator measurements, and standardized outcome definitions further complicates interpretation. These limitations make it premature to conclude that CVD meaningfully explains lifestyle–dementia relationships in practice.

The modest and inconsistent findings observed here offer, at best, tentative support for the vascular hypothesis of dementia. This hypothesis posits that vascular pathology mediates the effects of upstream risk factors on cognitive decline.[21,22] Partial mediation observed in a small subset of analyses identified in this review suggests that vascular health could play a role, but the current literature is too limited to fully substantiate these claims. Prior conceptual frameworks and reviews describing the lifestyle—vascular–cognition pathway assumed that vascular processes mediated the effects of lifestyle behaviors,[41–43] but our review reveals how rarely this hypothesis has been tested using formal causal modeling. Compared to existing reviews that largely summarize direct associations between lifestyle risk factors and dementia,[16,44–46] this review adds value by identifying how little empirical work has formally quantified mediation within this relationship and by highlighting methodological gaps that must be addressed before causal inferences can be drawn.

Notably, no mediation studies involving smoking were identified despite its well-established links to both CVD and cognition.[47–49] This absence likely reflects the scarcity of longitudinal datasets that capture smoking exposure, incident CVD, and cognitive outcomes over sufficient follow-up periods to enable mediation modeling. Alternatively, it is possible that smoking is more often treated as a covariate rather than a primary exposure, limiting its inclusion in formal mediation analyses. Future research should address this gap by incorporating robust measures of smoking exposure across midlife, when vascular damage most strongly influences dementia risk trajectories.

Several methodological issues limit confidence in the reported mediation effects. First, none of the limited number of included studies followed a pre-specified mediation protocol, and only one estimated sample size requirements, raising concerns about low statistical power and potential Type II error. Second, mediators and outcomes were rarely measured at multiple time points, and in several studies, the temporal ordering of exposure, mediator, and outcome was unclear, both of which raise questions to causal inference. Third, analytic approaches varied widely (e.g., bootstrapped indirect effects, counterfactual-based mediational g-formula, Valeri and Vanderweele approach), and none incorporated sensitivity analyses for unmeasured confounding. Finally, heterogeneity in the operationalization of both exposures (e.g., self-reported physical activity vs objective fitness) and mediators (e.g., composite risk scores vs structural cardiac measures vs individual CVD diagnoses) introduces additional complexity and reduces the comparability of findings. Together, these issues mean that existing findings should be viewed as exploratory rather than confirmatory.

5 | CONCLUSIONS

This review is the first to map evidence on vascular mediation using formal mediation analysis in lifestyle–cognition research, providing a foundation for future investigations. However, the evidence base remains extremely small ($n = 5$ studies), precluding any generalizable conclusions. The included studies exhibited substantial heterogeneity in design, follow-up duration, and analytic rigor, and most lacked essential features for causal inference. These limitations underscore the fact that while mediation analysis offers a powerful framework for understanding mechanisms, its potential has yet to be realized in this field. High-quality longitudinal studies with rigorous mediation frameworks are needed to clarify whether improving cardiovascular health is a viable strategy for reducing dementia risk through lifestyle modification.

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CONFLICT OF INTEREST STATEMENT

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

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