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48 Years of Research on Health and Lifestyle Risk Factors Associated with Dementia in Latin America: Systematic Review, Meta-Analysis, and Meta-Regression[1]

48 Años de Investigación sobre Factores de Riesgo de Salud y Estilo de Vida Asociados con la Demencia en América Latina: revisión sistemática, metaanálisis y metarregresión.

Eduardo Reynoso-Arellano[2]; Vinicius Maia-Azevedo[3]; Nicolas Silva-Magalhães[4]; Hugo Marte-Santana[5]
Corresponding author: Eduardo Reynoso-Arellano; eduardoreynosoarellano@gmail.com, Institute of Applied Neuroscience, Universidad Iberoamericana (UNIBE), Santo Domingo, Dominican Republic.

Review

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ABSTRACT

Introduction: Latin America is one of the regions with the highest prevalence of dementia worldwide. Despite this epidemiological situation, there is almost no evaluation of the evidence on health and lifestyle risk factors for the development of dementia in the region. Our objective was to review the evidence on these risk factors. **Methods:** A literature search was conducted between 1977 and 2025 following PRISMA guidelines. We conducted a random-effects meta-analysis and meta-regression, and the methodological quality of the studies was assessed using RoBINS-I. **Results:** The meta-analysis revealed a statistically significant association between

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[2] Eduardo Reynoso-Arellano, MA. Institute of Applied Neuroscience, Universidad Iberoamericana (UNIBE). Santo Domingo, Dominican Republic. https://orcid.org/0000-0002-6001-6990. eduardoreynosoarellano@gmail.com

[3] Vinicius Maia-Azevedo, BS. Universidade Una Contagem, Contagem – Minas Gerais, Brasil. . https://orcid.org/0009-0001-5834-1209 vinicius.maia2011@gmail.com

[4] Nicolas Silva-Magalhães, BS. Universidade Federal Rural de Pernambuco. Recife, Brasil. nicolasdellano@gmail.com

[5] Hugo Marte-Santana, PhD. Institute of Applied Neuroscience, Universidad Iberoamericana (UNIBE). Santo Domingo, Dominican Republic. https://orcid.org/0000-0003-0971-0423. h.marte@unibe.edu.do

the evaluated risk factors and the development of dementia. However, in the quality assessment of the evidence, we observed "serious" and "critical" risks of bias. The meta-regression analysis identified depression as the only significant moderator. **Conclusion:** Although an association between risk factors and dementia was identified, the low methodological quality of the studies limits these findings.

KEYWORDS: Dementia; Risk Factors; Latin America; Meta-analysis; Metaregression

RESUMEN

Introducción: *América Latina es una de las regiones con mayor prevalencia de demencia a nivel mundial. A pesar de esta situación epidemiológica, prácticamente no existe una evaluación de la evidencia sobre los factores de riesgo de salud y estilo de vida para el desarrollo de demencia en la región. Nuestro objetivo fue revisar la evidencia sobre estos factores de riesgo.* ***Métodos****: Se realizó una búsqueda de literatura entre 1977 y 2025 siguiendo las directrices PRISMA. Se llevó a cabo un metaanálisis de efectos aleatorios y una metarregresión, y la calidad metodológica de los estudios fue evaluada mediante la herramienta RoBINS-I.* ***Resultados****: El metaanálisis reveló una asociación estadísticamente significativa entre los factores de riesgo evaluados y el desarrollo de demencia. Sin embargo, en la evaluación de la calidad de la evidencia se observaron riesgos de sesgo "serios" y "críticos". El análisis de metarregresión identificó la depresión como el único moderador significativo.* ***Conclusión****: Aunque se identificó una asociación entre los factores de riesgo y la demencia, la baja calidad metodológica de los estudios limita estos hallazgos.*

PALABRAS CLAVES: *Demencia; Factores de Riesgo; Latinoamérica; Metanálisis; Metarregresión*

INTRODUCTION

Dementia (DE) is a disease characterized by acquired impairment of one or more brain functions, usually accompanied by behavioral alterations and a degree of severity sufficient to produce loss of autonomy[1,2]. According to the latest figures we had access to, around 41 million people live with undiagnosed dementia worldwide, which represents approximately 75% of those who suffer from it[3].

Currently, DE constitutes one of the major public health callenges in Latin America (LATAM), with a growing impact on disability, mortality, and the socioeconomic burden of the region[3]. According to a report by the World Health Organization and Alzheimer's Disease International[4], Latin America and the Caribbean have some of the highest prevalence rates of dementia worldwide. The same report also indicates that 66% of people with dementia live in developing countries. This phenomenon is influenced by substantial socioeconomic and cultural variability, which complicates its prevention and management[5,6].

Recent evidence has identified potentially modifiable risk factors that tend to cluster in profiles linked to social disadvantages[7,8,9]. Their association with low educational level and reduced family income highlights the urgency of implementing targeted public health interventions[10]. Complementarily, it is noted that the structural inequalities of the region are related to reductions in brain volume and alterations in temporo-cerebellar, fronto-thalamic, and hippocampal connectivity[11].

In this scenario, Latin America faces an unprecedented dementia epidemic, with clinical, epidemiological, economic, and human repercussions[12]. Given this reality, it is essential to integrate the available evidence to estimate the magnitud of the association between modifiable health and lifestyle risk factors and DE in the region. This type of synthesis not only facilitates the identification of factors with greater relative weight but also allows exploration of sources of heterogeneity, establishment of prevention priorities, and guidance of public health policies based on contextualized evidence.

MATHERIAL AND METHODS

Protocol and Reporting Standars

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13]. The review protocol was not prospectively registered in PROSPERO or other registries, which is acknowledged as a methodological limitation.

Research Questions

The purpose of this systematic review was to identify and synthesize studies published between 1977 and 2025 on health and lifestyle risk factors associated with the development of

dementia in Latin America, as well as to estimate the magnitude of their association through meta-analysis and explore potential moderators through meta-regression.

To establish the review question, the PICO model proposed by the Cochrane Library was implemented[14]. Based on this analysis, the research question guiding the systematic review was: What health and lifestyle risk factors are associated with the development of dementia in the population of Latin America, and what is the magnitude of their association according to the available evidence? (Table 1).

Table 1. Definition of variables using the PICO model

Model	Variables
(P) - Population	Population in Latin America
(I) - Intervention	Health and lifestyle risk factors
(C) - Comparison	Absence or lower exposure to risk factors
(O) - Outcome	Development or diagnosis of dementia.

Eligibility Criteria

Eligibility studies included cohort, case-control, and cross-sectional designs conducted exclusively in Latin America. Studies were required to evaluate health-related lifestyle-related risk factors for dementia, including groups with and without exposure to such factors.

Health-related risk factors were defined as clinical or medical conditions assessed at the individual level (e.g., depression, cardiovascular or metabolic diseases), whereas lifestyle-related risk factors referred to modifiable behaviors (e.g., smoking, alcohol consumption, physical inactivity, and dietary patterns). Only factors explicitly analyzed as exposures in relation to dementia risk were considered.

Studies were required to report measures of association and to evaluate the relationship between risk factors and dementia at the individual level. Only articles published in peer-reviewed scientific journals, with or without open access, were included.

Exclusion criteria included studies with designs other than cohort, case-control, or cross-sectional; studies conducted outside Latin America or including countries from other regions; studies that did not evaluate health- or lifestyle-related risk factors; studies lacking comparison groups; studies that did not report measures of association; studies that did not assess dementia outcomes at the individual level; and studies not published in peer-reviewed journals.

Information Source and Search Startegy

A comprehensive literature search was conducted in PubMed, Scopus, Redalyc, Dialnet, LILACS, and SciELO. The following search terms were used in English and Spanish: "risk factors" AND "dementia" AND ("Latin America" OR "Latinoamerica"); "dementia" AND ("Latin America" OR "Latinoamerica") AND ("cohort" OR "case-control" OR "cross-sectional"); "factores de riesgo" AND "demencia" AND ("América Latina" OR "Latinoamérica"); "demencia" AND ("América Latina" OR "Latinoamérica"); and ("factores de riesgo" OR "causas" OR "determinantes") AND "demencia" AND ("América Latina" OR "Latinoamérica").

The temporal range was unrestricted, including studies published between 1977 and 2025. The search strategy prioritized studies that explicitly described exposures as "risk factors" in the title or abstract. Consequently, studies evaluating specific exposures (e.g., depression, smoking, or cardiovascular conditions) without explicitly labeling them as risk factors may not have been captured. This methodological decision is acknowledged as a limitation of the review. Two reviewers independently screened titles and abstracts, followed by full-text assessment. Discrepancies were resolved through discussion, with consultation of a third reviewer when necessary.

We acknowledge that this approach may have excluded studies evaluating specific exposures (e.g., depression, cardiovascular disease, smoking, diet) not labeled as "risk factors," representing a potential source of bias.

Study selection

The initial search yielded 4,292 records. After removal of duplicates (n = 17), titles were screened, resulting in the exclusion of 4,223 records not related to the review objective. Twenty records were excluded after abstract screening, and 28 articles were excluded following

full-text assessment for not meeting the inclusion criteria. A total of four studies were included in the final systematic review and quantitative synthesis (Figure 1).

Data extraction

Data were extracted using a standardized form and included study characteristics (author, year, country, study design), sample characteristics , type of risk factor , diagnostic criteria for dementia, reported measures of association, and variables included in adjusted statistical models.

Risk of bias assessment

Risk of bias was assessed using the ROBINS-I tool, according to study design. The assessment was performed independently by two reviewers, and disagreements were resolved by consensus.

Statistical analysis

Effect sizes (OR, HR, sHR) were transformed to the natural logarithm scale to allow pooling under a random-effects model. We acknowledge that these effect measures have distinct interpretations (OR: odds, HR: time-to-event hazard, sHR: competing risks) and combining them represents an approximation for exploratory purposes.

Quantitative synthesis was conducted when at least two studies reported comparable measures of association. Given the limited number of eligible studies, all additional analyses beyond the primary meta-analysis were considered exploratory.

Meta-analysis

The same studies included in the systematic review were incorporated into the meta-analysis. Effect sizes were pooled using a random-effects model, which accounts for between-study variability arising from differences in study design, population characteristics, and contextual factors. Meta-regression was performed as an exploratory, hypothesis-generating analysis due to the small number of included studies (n=4) and high predictor-to-observation ratio, acknowledging the high risk of overfitting. Effect sizes were modeled on the log scale, with type of risk factor as moderator. Findings from this analysis should not be interpreted as causal.

Effect estimates were transformed to the natural logarithm scale prior to pooling. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Heterogeneity estimates were interpreted cautiously due to the small number of included studies.

Meta-regression (exploratory)

An exploratory meta-regression was conducted to investigate potential sources of heterogeneity across studies. Given the limited number of included studies, this analysis was considered hypothesis-generating rather than confirmatory and was interpreted with caution. Effect sizes were modeled on the natural logarithm scale to stabilize variances, improve normality of the sampling distribution, and ensure linearity of model assumptions, using a weighted least squares approach with inverse-variance weighting. The type of risk factor was included as a moderator variable. Due to the small number of observations relative to the number of predictors, no causal inferences were drawn from this analysis, and results were not used for formal hypothesis testing.

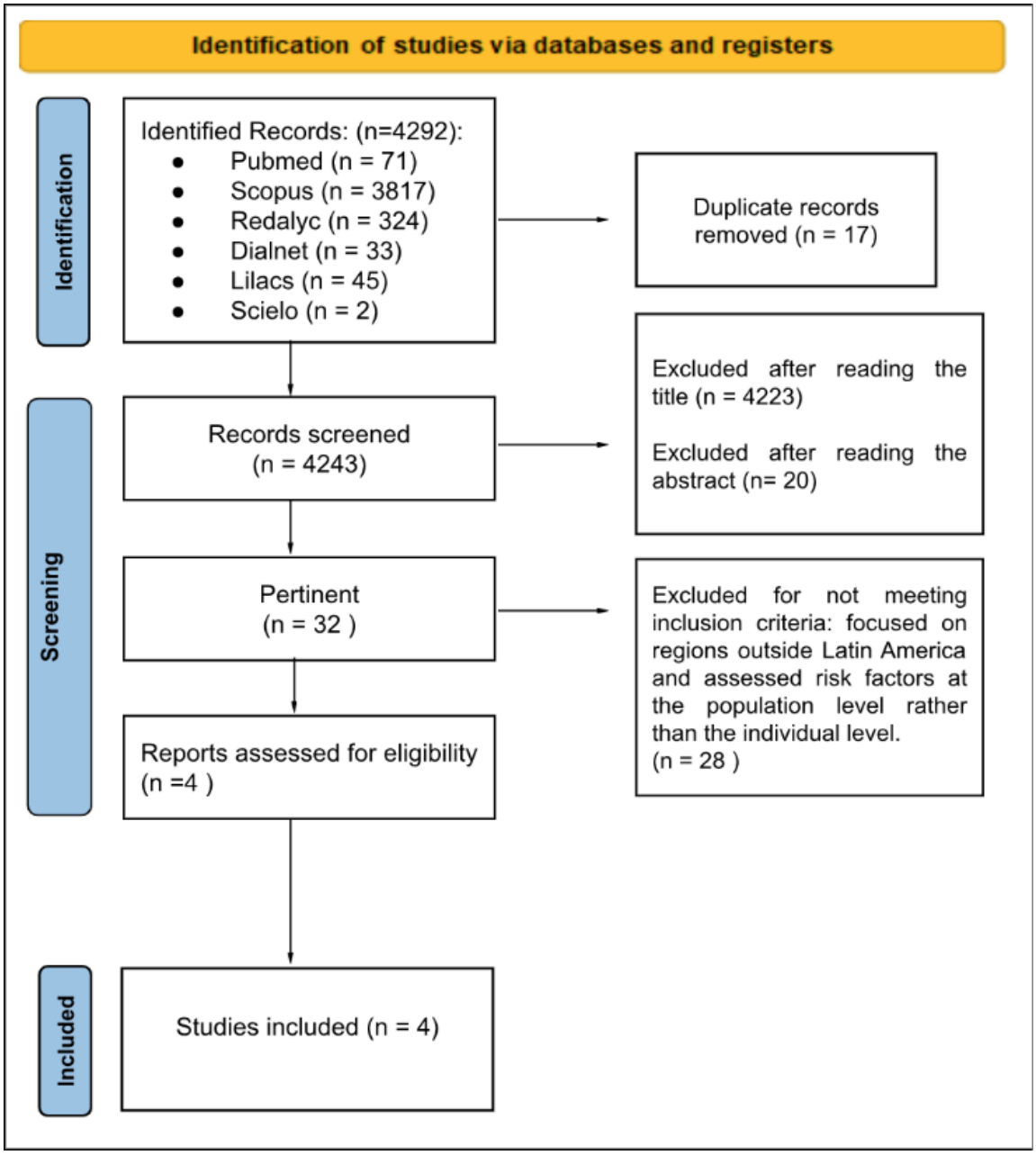
Assessment of publication bias

Formal assessment of publication bias (e.g., funnel plots or statistical tests) was not performed due to the small number of included studies, as such methods are unreliable and potentially misleading when fewer than ten studies are available. This limitation is acknowledged.

Software

Statistical analyses were performed using Jamovi (version 2.7.3.0) for meta-analysis and heterogeneity assessment. Meta-regression analyses were conducted in Python (version 3.13.0) using the statsmodels library, with pandas and matplotlib for data handling and visualization. Sensitivity analyses were not conducted due to the limited number of included studies and the high risk of bias identified across studies. As a result, all quantitative findings should be interpreted with caution.

Figure 1. PRISMA Flow Diagram



RESULTS

Study selection and general characteristics.

A total of four studies met the inclusion criteria and were incorporated into the systematic review and quantitative synthesis, comprising an overall sample of 17,389 participants. Among them, 1,746 individuals developed dementia during follow-up, while 15,643 did not. Regarding geographical distribution, Cuba was the most frequently represented

country (27%), followed by the Dominican Republic, Peru, Mexico, Puerto Rico, and Venezuela (14% each), and Brazil (7%). All included studies involved human participants and evaluated dementia incidence as the primary outcome

Characteristics of evaluated risk factors.

Across the included studies, a wide range of health-related and lifestyle-related risk factors were examined. Depression was the most frequently studied factor (21.43%), followed by cardiovascular health, physical activity, and fruit and vegetable consumption (14.28% each). Less frequently evaluated factors included cognitive impairment without dementia, obesity, stroke, fish consumption, and smoking status (7.14% each) (Table 2).

Table 2. General Description of the Studies

Database	Authors	Study Type	Risk Factor	Country	Sample	Age Range	Sampling	Scope	Design	Conclusion
Pubmed	Perales-Puchalt et al. (2019)	Empirical	Cardiovascular Health	CU, DR, PE, VE, MX & PR	6447	65-74	Cluster	Explanatory-correlational	Cohort	Moderate cardiovascular health is associated with lower dementia in older adults.
Pubmed	Johansson et al. (2019)	Empirical	Depression	CU, DR, PE VE, MX & PR	9312	≥65	Cluster	Explanatory-correlational	Cohort	Depression in older adulthood increases the risk of developing dementia.
Pubmed	César-Freitas et al. (2021)	Empirical	Cognitive impairment without dementia	BRA	630	≥60	Stratified random sampling	Explanatory	Cohort	Dementia is more common in older people, with low education or initial cognitive problems

Scopus	Peeters et al. (2020)	Empirical	Obesity; Stroke; Depression; Sleep complaints; Physical activity; Fish, fruit/vegetable consumption; Smoking status	CU	1846	≥65	Geographical cluster sampling	Descriptive-correlational	Cohort	Stroke, depression, low level of physical activity, low fish consumption, low fruit and vegetable consumption, and smoking are associated with a higher risk of dementia, while obesity and sleep complaints are related to a lower risk.

Abbreviations (CU, Cuba); (DR, Dominican Republic); (PE, Peru); (VE, Venezuela); (MX, Mexico); (PR, Puerto Rico); (BRA, Brazil)

Methodological characteristics of included studies

All included articles were cohort studies published in peer-reviewed journals and written in English. Most studies were identified through PubMed (75%), with the remainder retrieved from Scopus (25%). Sampling strategies varied, with cluster sampling being the most common (50%), followed by stratified random sampling and population-based sampling within geographically defined clusters (25% each).

In terms of analytical approaches, the studies employed heterogeneous statistical techniques. One quarter used descriptive methods combined with survival analysis, another quarter applied multivariate models alongside survival analysis, 25% incorporated group comparison tests, multivariate regression, survival analysis, and count data models, and the remaining studies relied on descriptive statistics, multiple imputation, and logistic regression. The most frequently reported measure of association was the odds ratio (67%), followed by the subhazard ratio (27%) and the hazard ratio (6%) (Table 3).

Table 3. Methodological Characteristics

Code	Authors	Methods	Techniques	Incident Group	Non-incident group	Measures of Association	Effect Size	CI	Estimated variance	Estimated standard error	P-value
1	Perales-Puchalt et al. (2019)	Adapted Life Simple 7	Descriptive methods and survival analysis	605	4996	Subhazard Ratio (sHR)	0.73	0.54-0.97	0.0222	0.1097	0.03
1	Perales-Puchalt et al. (2019)	Adapted Life Simple 7	Descriptive methods and survival analysis	605	4996	Subhazard Ratio (sHR)	0.66	0.46-0.96	0.0353	0.188	0.031
2	Johansson et al. (2019)	Semi-structured interview on geriatric mental status	Multivariate methods and survival analysis	862	8450	Subhazard Ratio (sHR)	1.63	1.26-2.11	0.0174	0.132	0.001
2	Johansson et al. (2019)	Semi-structured interview on geriatric mental status	Multivariate methods and survival analysis	862	8450	Subhazard Ratio (sHR)	1.28	1.09-1.51	0.0071	0.084	0.05
3	César-Freitas et al. (2021)	Neuropsychological tests	Group comparison tests, multivariate regression models, survival analysis techniques, and count data models Reintentar	110	520	Hazard Ratio (HR)	4.10	1.92 - 8.76	0.1496	0.3868	0.001

4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	2.21	1.17–4.16	0.1032	0.3213	< 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.81	1.00–3.28	0.0922	0.3036	≈ 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.39	0.96–2.00	0.0326	0.1806	> 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	0.62	0.42–0.90	0.0364	0.1908	< 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.81	1.13–2.90	0.0606	0.2461	< 0.05
4	Peeters et al. (2020)	Health factors, demographic variables,	Descriptive statistics, multiple imputation,	169	1,677	Odds Ratio (OR)	2.29	1.49–4.16	0.0727	0.2696	< 0.001

		cognitive measures, and lifestyle habits	and logistic regression								
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.77	1.06–2.95	0.0714	0.2672	< 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.26	0.72–2.21	0.0821	0.2866	> 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	1.96	1.15–3.35	0.0731	0.2704	< 0.05
4	Peeters et al. (2020)	Health factors, demographic variables, cognitive measures, and lifestyle habits	Descriptive statistics, multiple imputation, and logistic regression	169	1,677	Odds Ratio (OR)	2.21	1.17-4.16	0.1032	0.3213	< 0.05

Abbreviations (CI; Confidence Interval)

Individual study findings

Perales-Puchalt et al.[15] evaluated cardiovascular health as a risk factor for dementia using an adapted version of the American Heart Association's Life's Simple 7 index. In a

sample of 6,447 older adults aged 65–74 years from six Latin American countries (Cuba, Dominican Republic, Peru, Venezuela, Mexico, and Puerto Rico), 605 participants developed dementia. Moderate and ideal cardiovascular health levels were associated with a lower incidence of dementia, with effect sizes of 0.73 (95% CI: 0.54–0.97, p = 0.03) and 0.66 (95% CI: 0.46–0.96, p = 0.031), respectively.

Johansson et al.[16] examined depression as a risk factor for dementia in a cohort of 9,312 individuals aged 65 years and older from the same six countries. Using multivariate models and survival analysis, they reported that late-life depression was associated with an increased risk of dementia, with effect sizes of 1.63 (95% CI: 1.26–2.11, p = 0.001) and 1.28 (95% CI: 1.09–1.51, p = 0.05).

César-Freitas et al.[17] investigated cognitive impairment without dementia as a predictor of dementia incidence in Brazil. The study included 630 participants aged over 60 years, of whom 110 developed dementia. Non-demented cognitive impairment was associated with a substantially increased risk of dementia (HR = 4.10; 95% CI: 1.92–8.76, p = 0.001). Additional associations with advanced age and lower educational level were also reported.

Peeters et al.[18] analyzed a broad range of health, demographic, cognitive, and lifestyle factors in a Cuban cohort of 1,846 participants aged over 65 years, among whom 169 developed dementia. Several factors were identified as protective, including obesity (OR = 0.63; 95% CI: 0.43–0.91; p < 0.05) and sleep complaints (OR = 0.62; 95% CI: 0.42–0.90; p < 0.05). In contrast, increased dementia risk was observed for history of stroke (OR = 1.81; 95% CI: 1.00–3.28; p ≈ 0.05), lower levels of physical activity, lack of regular fish consumption, low fruit and vegetable intake, and current smoking. Depression showed a positive association with dementia risk (OR = 1.39; 95% CI: 0.96–2.00), although this did not reach statistical significance.

Risk of bias assessment

According to the ROBINS-I tool, all included studies exhibited important methodological limitations. Perales-Puchalt et al.[15] and Johansson et al.[16] were rated as having a serious overall risk of bias, primarily due to issues related to confounding, exposure

classification, and outcome measurement. The studies by César-Freitas et al.[17] and Peeters et al.[18] were judged to have a critical overall risk of bias, mainly attributable to missing data, exposure misclassification, and strong residual confounding (Figures 2 and 3).

Figure 2. Traffic Light Plot

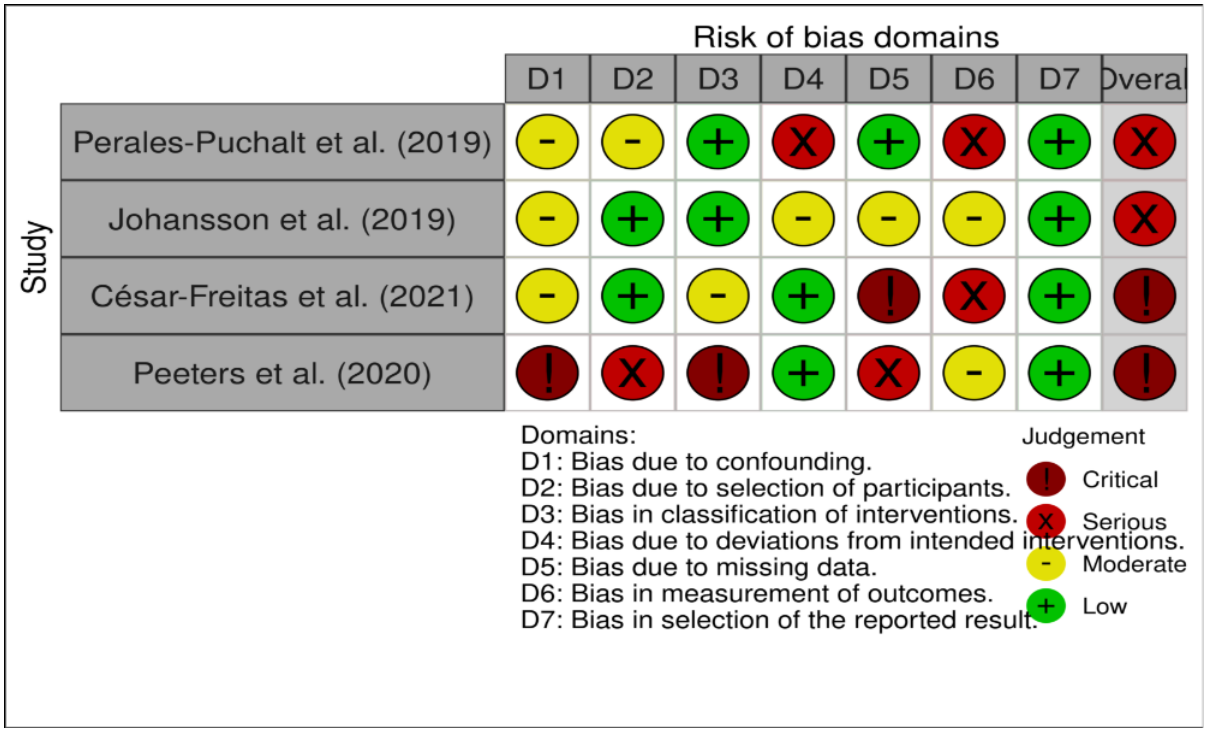
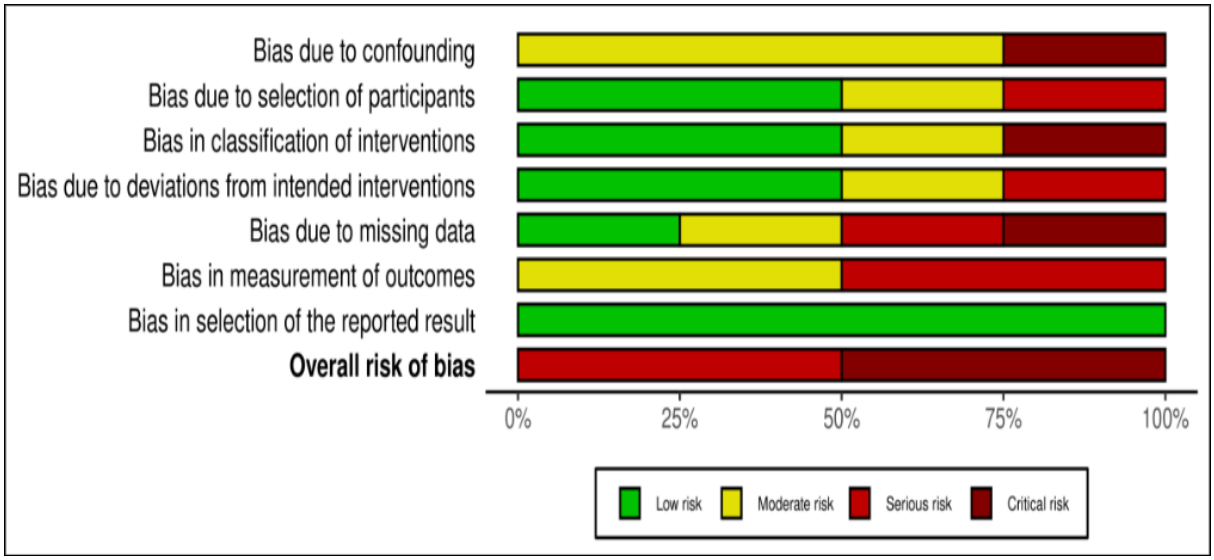


Figure 3. Graphical Summary

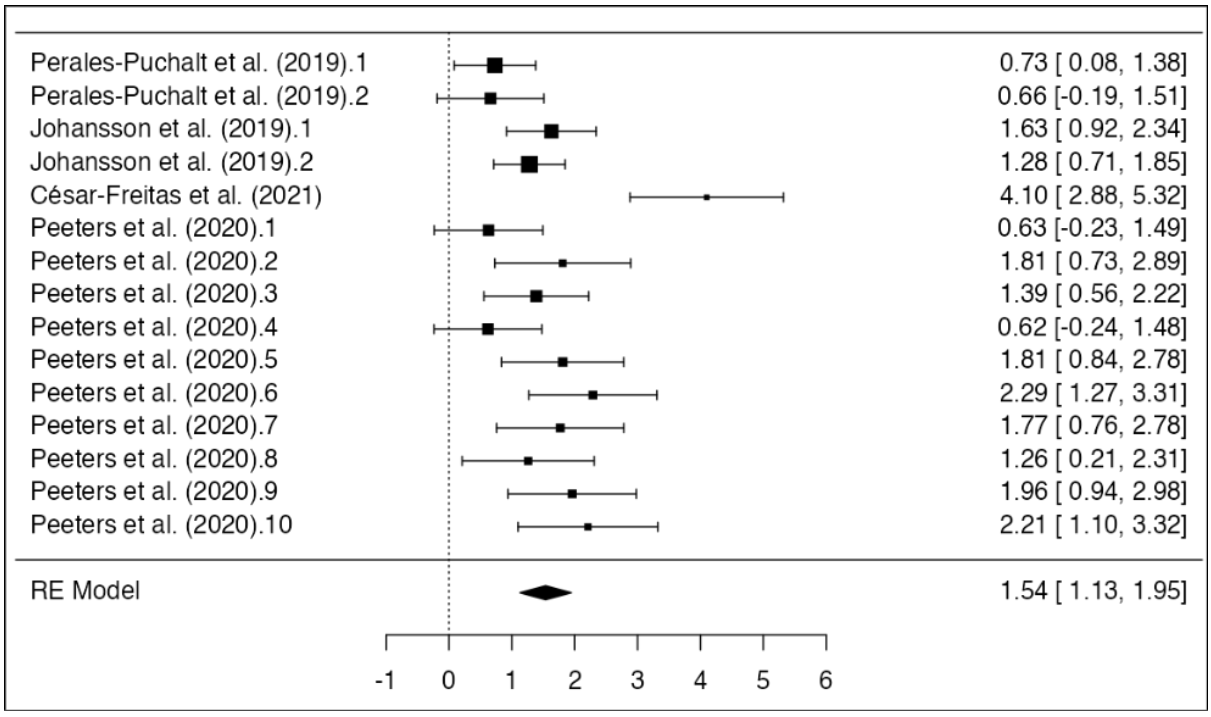


Meta-analysis

The random-effects meta-analysis showed a statistically significant overall association between exposure to the evaluated risk factors and the development of dementia (RR = 1.54; 95% CI: 1.13–1.95). Individual study estimates varied in both magnitude and direction, with some suggesting protective effects and others indicating increased risk. Substantial heterogeneity was observed across studies, reflecting differences in the type of risk factors assessed, study populations, and methodological quality (Figure 4).

However, due to the extremely limited number of eligible studies, the quantitative synthesis should be interpreted as an exploratory approximation intended to illustrate the general direction and magnitude of the associations reported in the available literature, rather than as a precise estimate of the combined effect.

Figure 4. Forest Plot



Meta-regression

An exploratory meta-regression was performed to examine potential sources of heterogeneity. The model explained a large proportion of the observed variability in effect sizes ($R^2 = 0.968$; adjusted $R^2 = 0.777$). The type of risk factor emerged as the main contributor to heterogeneity, with depression being the only moderator significantly associated with larger

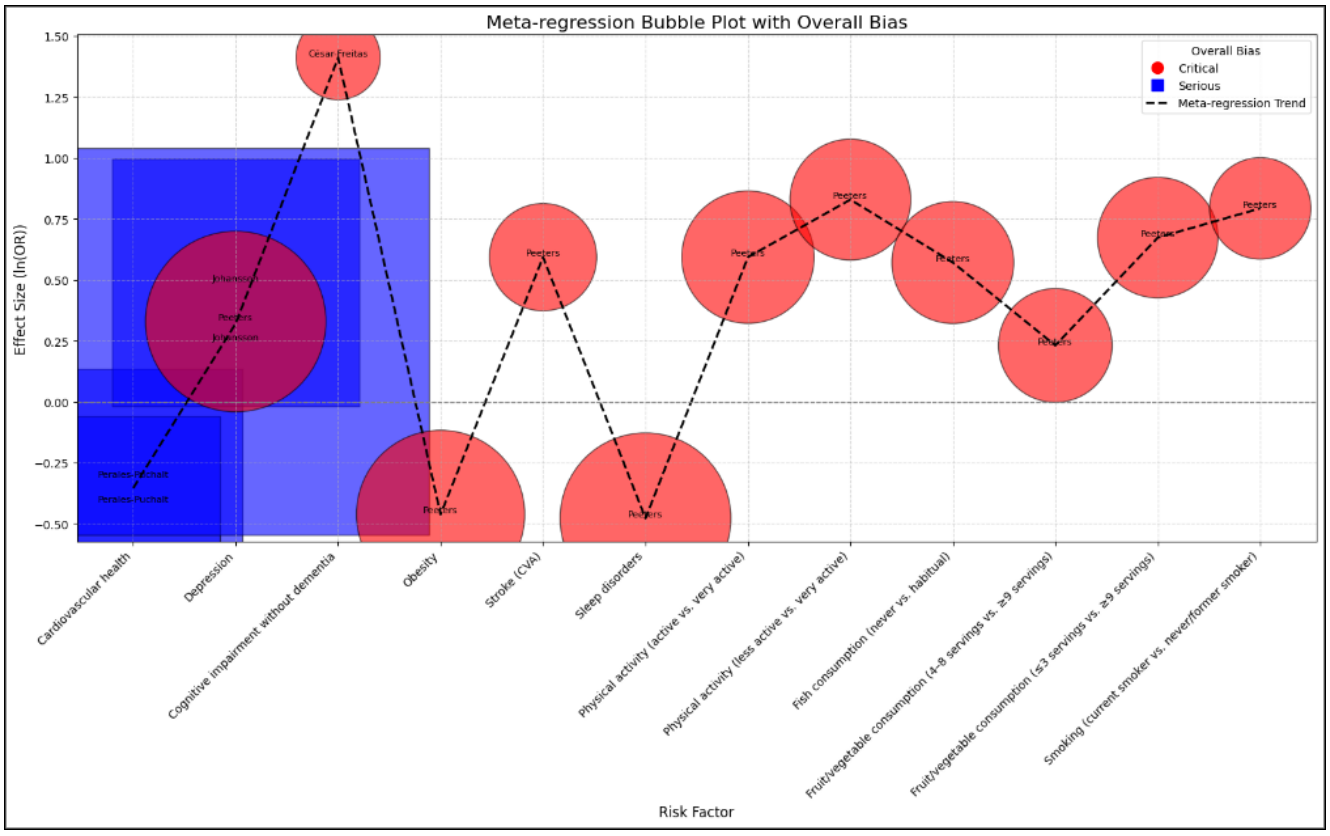
effect sizes. Overall risk of bias was not significantly associated with effect size. Despite the high explained variance, the overall model was not statistically significant ($F(2,12) = 5.056$, $p = 0.177$), and the results should therefore be interpreted cautiously (Table 3; Figure 5). Given the limited number of available studies and the ratio between predictors and observations, the model is subject to a high risk of overfitting and unstable estimates; therefore, the results should be interpreted strictly as hypothesis-generating.

Table 4. Meta-regression Results

R-squared	Adj. R-squared	Prob (F-statistic		Coef	Std err	T	P>|t|)	[0.025	0.975]
0.968	0.777	0.177							
			const	-03421	0.257	-1.333	0.314	-1.446	0.762
			Cognitive impairment without dementia	1.7531	0.508	3.452	0.075	-0.432	3.938
			Depression	0.6711	0.155	4.335	0.049	0.005	1.337
			Fish consumption (never vs habitual)	0.9131	0.397	2.301	0.148	-0.794	2.621
			Vegetable/fruit consumption (4–8 servings vs. ≥9 servings)	0.5731	0.414	1.385	0.300	-1.207	2.354
			Fruit/vegetable consumption (≤3 servings vs. ≥9 servings)	1.0151	0.400	2.540	0.126	-0.704	2.734
			Obesity	-0.1199	0.338	-0.355	0.756	-1.572	1.333

Physical activity (active vs. very active)	0.9351	0.379	2.467	0.132	-0.696	2.566
Physical activity (less active vs. very active)	1.1711	0.399	2.935	0.099	-0.545	2.888
Sleep complaints	-0.1359	0.335	-0.405	0.725	-1.579	1.308

Figure 5. Meta-regression Plot



DISCUSSION

The present systematic review and meta-analysis identified a statistically significant overall association between the evaluated health- and lifestyle-related risk factors and the development of dementia in Latin American populations. Under a random-effects model, the pooled estimate indicated a 54% higher probability of developing dementia among exposed individuals. While this finding suggests a meaningful relationship between modifiable and

clinical risk factors and dementia incidence, it must be interpreted with caution due to the substantial heterogeneity observed and the methodological limitations of the included studies.

The assessment of methodological quality using the ROBINS-I tool revealed important threats to internal validity across all included studies. Two studies were classified as having a serious overall risk of bias[15,16], while the remaining two reached a critical level[17,18]. The most frequent sources of bias included residual confounding, limitations in participant selection, inadequate handling of missing data, and imprecision in outcome measurement. These limitations substantially reduce the certainty of the pooled estimate and indicate that the observed associations should not be interpreted as causal.

Given the substantial heterogeneity detected in the meta-analysis, an exploratory meta-regression was conducted to examine whether specific study characteristics could explain variability in effect sizes. Although the model explained a high proportion of variance (R^2 = 0.968), the overall model was not statistically significant and showed evidence of overfitting, as reflected by the low residual degrees of freedom and the discrepancy between R^2 and adjusted R^2. This result was expected given the limited number of included studies relative to the number of predictors and underscores the exploratory nature of this analysis.

Despite these limitations, the examination of individual moderators yielded a notable finding: depression emerged as the only statistically significant moderator of effect size. Studies that included depression as a risk factor tended to report larger effect estimates compared with studies focusing on other exposures. This observation is consistent with current neurobiological models linking depression and dementia through shared mechanisms, including chronic neuroinflammation, dysregulation of the hypothalamic–pituitary–adrenal axis, and cumulative neuronal vulnerability[19–21]. Proinflammatory cytokine activity has been implicated in both depressive symptomatology and neurodegenerative processes, suggesting a plausible biological pathway through which late-life depression may increase susceptibility to dementia.

However, this result must be interpreted in conjunction with the risk of bias assessment. The study primarily contributing to the depression signal was rated as having a serious risk of bias[16], mainly due to confounding and participant selection issues. Therefore, although depression appears to be a consistent source of heterogeneity and a potentially relevant risk

factor, the current evidence does not allow firm conclusions regarding its magnitude or causal role in dementia development in Latin American populations.

Other evaluated factors, including obesity, sleep complaints, and certain lifestyle behaviors, did not emerge as significant moderators in the meta-regression. Some of these factors showed counterintuitive associations in individual studies, such as an apparent protective effect of obesity or sleep complaints[18]. These findings are likely influenced by residual confounding, reverse causality, and measurement limitations, and should not be interpreted as evidence of true protective effects. Instead, they highlight the complexity of risk factor profiles in older populations and the methodological challenges inherent in observational research on dementia.

The relevance of these findings is amplified by the epidemiological context of Latin America, a region currently exhibiting one of the highest global prevalences of dementia and projections indicating a marked increase in disease burden over the coming decades[22]. This situation is compounded by high rates of cardiovascular disease, depression, diabetes, socioeconomic inequality, and limited access to early diagnostic and preventive services. Accelerated population aging, fragmented health systems, and constrained resources further increase vulnerability and underscore the need for robust, region-specific evidence to inform prevention strategies.

Importantly, the available evidence in this review is largely derived from individual-level observational studies and does not include population-level analyses. This restricts the ability to assess how risk factors operate across broader social and structural contexts, which may be particularly relevant in Latin America given pronounced socioeconomic and cultural heterogeneity. The absence of high-quality longitudinal studies with rigorous control of confounding limits the precision of current estimates and represents a critical gap in the regional literature.

The scarcity of high-quality longitudinal studies in Latin America partly reflects structural limitations in the region's epidemiological research capacity. Unlike Europe or North America, where large population-based cohorts with long-term follow-up are well established, many Latin American countries lack sustained research infrastructures capable of examining the evolution of risk factors over time. As a result, a substantial portion of the available knowledge derives either from analyses embedded within international cohorts or from local

studies with relatively small sample sizes, which constrains the ability to generate precise and generalizable estimates of dementia risk in the region.

From a broader epistemological perspective, this systematic synthesis also contributes to the emerging field of meta-science within neuroscience research. By systematically evaluating the methodological quality, sources of heterogeneity, and structural limitations of the available literature, the present review highlights not only empirical findings but also the underlying architecture of knowledge production in dementia research in Latin America. Such meta-scientific analyses are essential for identifying gaps in study design, measurement consistency, and regional research capacity.

In this sense, the value of the present work extends beyond the estimation of pooled associations. The systematic mapping of available evidence provides a framework for guiding future research priorities, emphasizing the need for large-scale longitudinal cohorts, harmonized measurement of risk factors, and improved methodological rigor in observational studies of dementia across Latin America. Strengthening these foundations will be critical for advancing both the scientific understanding of dementia risk and the development of effective prevention strategies in the region.

CONCLUSION

This systematic review and meta-analysis suggests that health- and lifestyle-related factors are associated with dementia risk in Latin America, with depression and cardiovascular health emerging as the most consistently reported contributors across studies. However, the overall certainty of the evidence is low to very low due to the limited number of studies, substantial heterogeneity, and high risk of bias. These findings highlight a critical gap in high-quality epidemiological research on dementia risk factors in the region and underscore the need for well-designed longitudinal studies that integrate clinical, behavioral, and population-level data. Strengthening the regional evidence base is essential to inform context-specific prevention strategies and public health policies aimed at reducing the growing burden of dementia in Latin America.

LIMITATIONS

This review has several important limitations. Only four observational studies met the inclusion criteria, which limits statistical power, generalizability, and the robustness of secondary analyses. All included studies presented serious or critical risk of bias according to

the ROBINS-I tool, mainly due to residual confounding, imprecise exposure classification, missing data, and limitations in outcome measurement.

Substantial heterogeneity was observed across studies, reflecting differences in design, populations, exposure definitions, and measures of association, which restricts the interpretability of the pooled estimates despite the use of a random-effects model. Additionally, the search strategy prioritized studies explicitly labeling exposures as "risk factors," potentially omitting relevant studies on depression, cardiovascular disease, smoking, diet, and other exposures, and the review protocol was not prospectively registered. Formal assessment of publication bias was not performed due to the small number of included studies.

The meta-regression analysis was exploratory and hypothesis-generating, conducted with a small number of studies relative to the number of predictors, resulting in a high risk of overfitting and Type I error. The reported association between depression and dementia should therefore be interpreted cautiously. Finally, effect measures pooled in the meta-analysis (OR, HR, sHR) have distinct interpretations, and combining them represents an approximation for exploratory purposes only. All included studies evaluated dementia at the individual level; future research integrating individual- and population-level approaches is needed to better characterize dementia risk in Latin America, accounting for clinical, behavioral, and socioeconomic factors.

AUTHOR CONTRIBUTIONS

ER-A conceived and designed the study, conducted the literature search, data extraction, statistical analysis, interpretation of results, and drafted the initial manuscript. VM-A contributed to the methodological design, conducted the literature search, validated the statistical analyses, and participated in the critical review of the manuscript. N-SM & HM-S participated in the critical review of the intellectual content of the manuscript and provided academic supervision. All authors approved the final version of the manuscript and assume responsibility for the integrity and accuracy of the work.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no financial, personal, or competing interests/conflicts of interest.

CONSENT STATEMENT

We confirm that it was not necessary to obtain consent for this work.

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