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

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ABSTRACT

Latin America has the highest prevalence of dementia worldwide. Despite this epidemiological situation, there is 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. A literature search was conducted between 1977 and 2025 (PRISMA). We conducted a random-effects meta-analysis and meta-regression. The methodological quality of the studies was assessed using RoBINS-I. The meta-analysis revealed a statistically significant association between 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. 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

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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 main public health crises in Latin America (LATAM), with a growing impact on disability, mortality, and the socioeconomic burden of the region [3]. In the report by the World Health Organization and Alzheimer's Disease International [4], the highest prevalence worldwide is found in Latin America and the Caribbean. This same report notes that 66% live in developing countries. This phenomenon is influenced by great socioeconomic and cultural variability that complicates its 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, LATAM 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 magnitude 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.

METHODS

Sistematic Review

For the present review, the recommendations and guidelines of the PRISMA method were followed [13]. For the collection of articles, the PubMed, Scopus, Redalyc, Dialnet, Lilacs, and Scielo

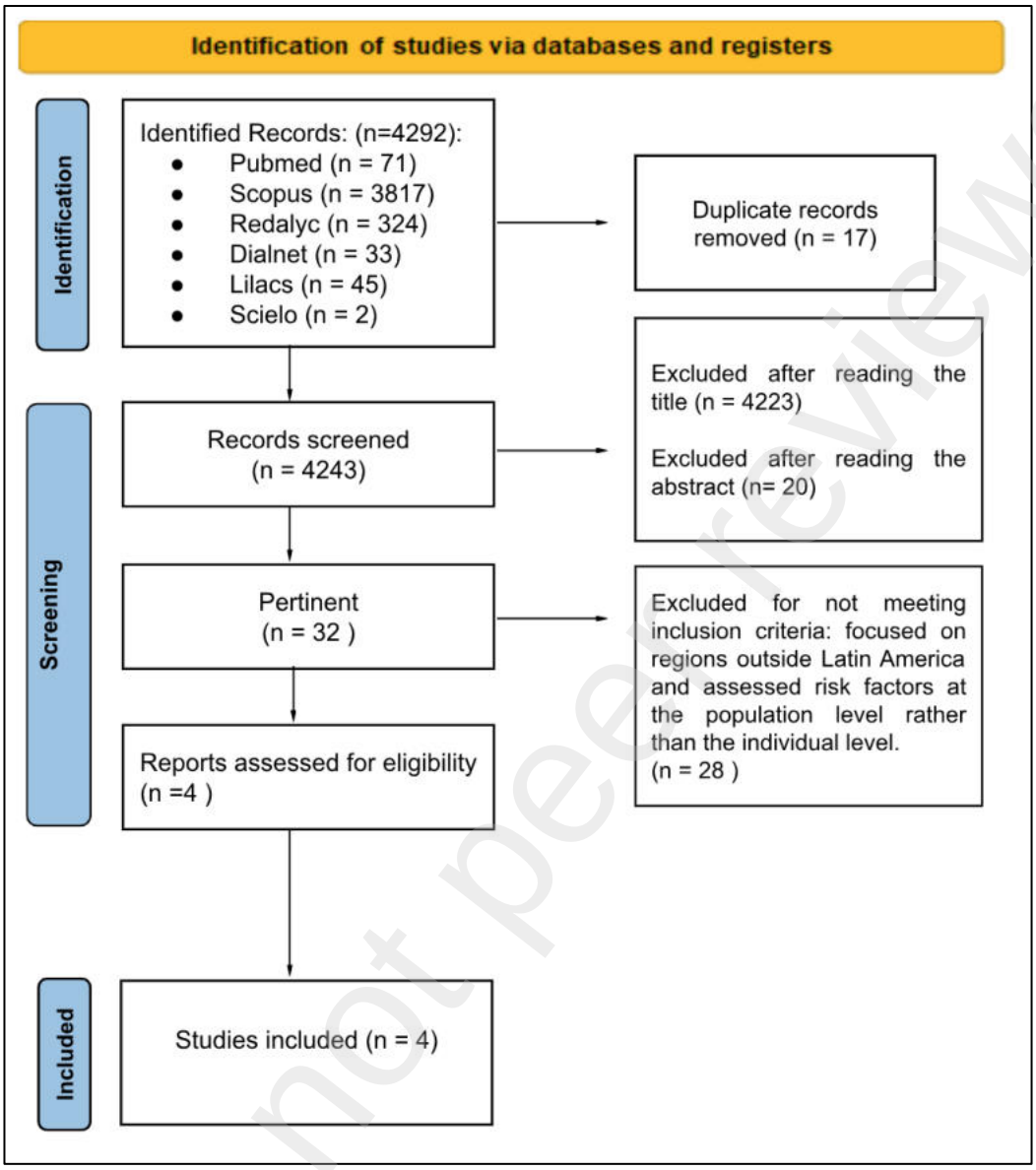
databases were used with the keywords: "risk factors" AND "Dementia" AND ("Latin America" OR "Latinoamerica"), "Dementia" AND ("Latin America" OR "Latinoamerica") AND ("cohort" OR "case-control" OR "cross-sectional"), "factores de riesgo" AND "Demencia" AND ("América Latina" OR "Latinoamérica"), "Demencia" AND ("América Latina" OR "Latinoamérica"), y ("factores de riesgo" OR "causas" OR "determinantes") AND "Demencia" AND ("América Latina" OR "Latinoamérica"). The temporal range was open, including studies from 1977 to 2025.

The inclusion criteria comprised all cohort, case-control, and cross-sectional studies conducted exclusively in LATAM, which evaluated risk factors related to health and lifestyle, including groups with and without exposure to such factors. The studies had to have measures of association and evaluate the relationship between risk factors and dementia at the individual level, published in peer-reviewed scientific journals, with or without open access.

The exclusion criteria included all studies that were not cohort, case-control, or cross-sectional studies, those conducted outside LATAM or that included countries from other regions, those that did not evaluate risk factors related to health or lifestyle, that did not include groups with and without exposure to risk factors, that lacked measures of association or that did not evaluate the relationship of risk factors with dementia at the individual level, as well as studies not published in peer-reviewed scientific journals.

With the previously specified search criteria, a total of 4,292 articles were obtained. After applying the inclusion and exclusion criteria, a sample of 4 studies was obtained. Seventeen were discarded due to duplication, 4,223 articles after reading the titles for not being related to the objective of the review, 20 after reading the abstracts, and 28 for not meeting the inclusion criteria.

Figure 1. PRISMA Flow Diagram



Meta-analysis

The studies included in the meta-analysis were the same ones selected for the systematic review, ensuring that the quantitative synthesis was performed on the same sample of articles evaluated qualitatively. To combine the study results, a random-effects model was employed. This model is appropriate when it is assumed that the effect sizes of the studies do not come from a single population, but from a distribution of different populations, which reflects the intrinsic variability in study type, population, and context.

Heterogeneity among the studies was assessed with the I^2 statistic, which indicated a value of 68.72%. This value, which is considered substantial, means that almost 69% of the observed variability in the results is not due to chance, but to real differences among the studies. Cochran's Q test, with a p-value of less than 0.001, confirmed that this heterogeneity was statistically significant.

Meta-regression

To explore the sources of heterogeneity, a meta-regression was conducted. In this analysis, the effect sizes were transformed to their natural logarithm (ln(OR)) to normalize the data distribution and meet the model assumptions. The type of risk factor was used as a moderator variable in a weighted least squares (WLS) regression model. In this model, each study was assigned a weight based on the inverse of its variance. This ensures that studies with more precise results (lower variance) have greater influence on the model, reducing bias. The R-squared (R^2) of the meta-regression showed that the moderator variable explained a significant portion of the variability among the studies.

Software

For the statistical analyses, Jamovi software (version 2.7.3.0) was used for the initial meta-analysis and heterogeneity assessment. Subsequently, Python (version 3.13.0) was employed for the meta-regression, using the statsmodels library for the analysis, and pandas and matplotlib for data manipulation and visualization, respectively.

RESULTS

Of the total sample of 4 studies, all involved human participants, gathering a total of 17,389 participants, of whom 1,746 developed dementia and 15,643 did not develop it, considering the combined samples of the articles. Regarding geographical distribution, Cuba was the most analyzed country (27%), followed by the Dominican Republic, Peru, Mexico, Puerto Rico, and Venezuela (14% each), and Brazil (7%).

Regarding the risk factors evaluated, the most studied was depression (21.43%), followed by cardiovascular health, physical activity, and fruit-vegetable consumption (14.28% each). To a lesser extent, cognitive impairment without dementia, obesity, stroke, fish consumption, and smoking status were analyzed (7.14% each) (Table 1).

For the combination of results and statistical analysis, the variances and standard error of the association measures were calculated. The variance of the logarithm of the odds ratio was estimated

using the formula Var(ln(OR)) = 1/a + 1/b + 1/c + 1/d, where a, b, c, and d represent the number of events and non-events in the study groups. For the hazard ratio and subhazard ratio, the variance was calculated from the 95% confidence interval reported in each study using the expression Var(ln(HR/SHR)) = (2×1.96 / [ln(upper CI limit) − ln(lower CI limit)])². The standard error was obtained from the variance by taking its square root. In cases where the p-value was not reported, it was calculated by transforming the effect sizes (OR or sHR) to the logarithmic scale, dividing them by their standard error to obtain a Z value, and then converting Z to p according to the standard normal distribution.

In methodological terms, 75% of the articles came from PubMed and 25% from Scopus. One hundred percent corresponded to outcomes on dementia development, cohort designs, empirical articles, and publications in English. The most used sampling method was cluster sampling (50%), followed by stratified random sampling and population sampling within geographically defined clusters (25% each). Regarding the scope of the studies, the most employed was explanatory-correlational (50%), followed by explanatory (25%) and correlational-descriptive (25%).

Regarding the analytical techniques employed, 25% used descriptive methods and survival analysis, another 25% applied multivariate methods and survival analysis, 25% employed group comparison tests, multivariate regression models, survival analysis techniques, and count data models, while the remaining 25% relied on descriptive statistics, multiple imputation, and logistic regression. The most used measure of association was the odds ratio, applied to the majority of risk factors (67%), followed by the subhazard ratio (27%) and the hazard ratio (6%). (Table 2)

Table 1. 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)

Table 2. 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, cognitive	Descriptive statistics, multiple imputation, and logistic	169	1,677	Odds Ratio (OR)	2.29	1.49–4.16	0.0727	0.2696	< 0.001

		measures, and lifestyle habits	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)

Risk factors evaluated

Perales-Puchalt et al. [14], studied cardiovascular health as a risk factor for dementia through an adaptation of the American Heart Association's Life's Simple 7 index. They employed descriptive methods and survival analysis in a sample of 6,447 participants, selected through cluster sampling, of

whom 605 developed dementia and 4,996 did not, with ages ranging from 65-74 years. The results showed that moderate and ideal levels of cardiovascular health were associated with lower incidence of dementia in older adults from six Latin American countries: Cuba, Dominican Republic, Peru, Venezuela, Mexico, and Puerto Rico. The effect size was 0.73 (95% CI: 0.54–0.97, p = 0.03). Consistently, a similar association was observed with an effect size of 0.66 (95% CI: 0.46–0.96, p = 0.031), confirming that maintaining moderate or ideal cardiovascular health reduces the risk of dementia in this population.

Johansson et al. [15], studied depression as a risk factor for dementia, using the Geriatric Mental State Semi-structured Interview. They employed multivariate methods and survival analysis in a sample of 9,312 participants, selected through cluster sampling, of whom 862 developed dementia and 8,450 did not, including people over 65 years of age. The results showed that depression in old age is associated with an increased risk of developing dementia in older adults from six Latin American countries: Cuba, Dominican Republic, Peru, Venezuela, Mexico, and Puerto Rico. The effect size was 1.63 (95% CI: 1.26–2.11, p = 0.001), indicating a significantly elevated risk. Consistently, an effect size of 1.28 (95% CI: 1.09–1.51, p = 0.05) was observed, reaffirming that depression in old age constitutes a significant risk factor for the incidence of dementia in this region.

César-Freitas et al. [16], investigated cognitive impairment without dementia as a risk factor for the incidence of dementia in Brazil. The neuropsychological assessment included the Mini-Mental State Examination (MMSE), the Brief Cognitive Screening Battery (BCSB), a phonemic verbal fluency test, the Functional Activity Questionnaire (FAQ), and the Cornell scale for depressive symptoms. They employed group comparison tests, multivariate regression models, survival analysis, and count data models in a sample of 630 participants over 60 years of age, selected through stratified random sampling, of whom 110 developed dementia and 520 did not. The results showed that non-demented cognitive impairment is associated with a significantly higher risk of developing dementia, with a Hazard Ratio of 4.10 (95% CI: 1.92–8.76, p = 0.001). Likewise, it was observed that the incidence of dementia in this sample is significantly related to advanced age and low educational level.

Peeters et al. [17] studied health factors, demographic variables, cognitive measures, and lifestyle behaviors as predictors of dementia in Cuba. They used descriptive statistics, multiple imputation, and logistic regression in a sample of 1,846 participants over 65 years of age, selected

through population sampling based on geographically defined clusters, of whom 169 developed dementia and 1,677 did not. The results showed significant associations of both risk and protection.

Among the protective factors, they found that 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; $p < 0.05$) were associated with a lower risk of dementia. Among the risk factors, they identified that a history of stroke (OR = 1.81; 95% CI: 1.00–3.28; $p \approx 0.05$), depression (OR = 1.39; 95% CI: 0.96–2.00; $p > 0.05$), lower level of physical activity—active vs. very active (OR = 1.81; 95% CI: 1.13–2.90; $p < 0.05$) and minimally active vs. very active (OR = 2.29; 95% CI: 1.49–4.16; $p < 0.001$)—, not consuming fish regularly (OR = 1.77; 95% CI: 1.06–2.95; $p < 0.05$), low fruit and vegetable consumption (≤3 servings vs. ≥9: OR = 1.96; 95% CI: 1.15–3.35; $p < 0.05$), and current smoking (OR = 2.21; 95% CI: 1.17–4.16; $p < 0.05$). Overall, the findings suggest that both unhealthy lifestyles and certain clinical factors significantly increase the risk of dementia, while some unexpected factors, such as obesity and sleep complaints, were associated with a protective effect in this Cuban sample.

Bias risk assessment

In the bias risk assessment using the RoBINS-I tool, the included studies showed methodological limitations that reduce the certainty of the evidence. The work of Perales-Puchalt et al. [14], which concluded that moderate cardiovascular health is associated with lower risk of dementia, presented a serious overall risk, mainly due to problems in the classification of interventions and in the measurement of outcomes. Similarly, Johansson et al. [15], which reported that depression in older adulthood increases the risk of dementia, was also assessed with a serious risk, with biases related to confounding and selection of participants (Figure 2).

In contrast, the studies by César-Freitas et al. [16], and Peeters et al. [17] reached a critical overall risk. In the case of César-Freitas, whose results showed that dementia is more common in older people, with low education or initial cognitive impairment, the main limitations were related to missing data and outcome measurement. The study by Peeters, which reported unconventional associations—such as an apparent protective effect of obesity and sleep complaints—presented a critical risk due to strong confounding and problems in the classification of exposures, which considerably reduces confidence in its findings.

Overall, studies with serious risk provide signals of association consistent with prior literature (cardiovascular health and depression), but should be interpreted with caution. Those with critical risk present severe methodological limitations that threaten the internal validity of their results. Therefore, the overall certainty of the available evidence on risk and protective factors for dementia in these studies is low to very low (Figure 3).

Figure 2. Traffic Light Plot

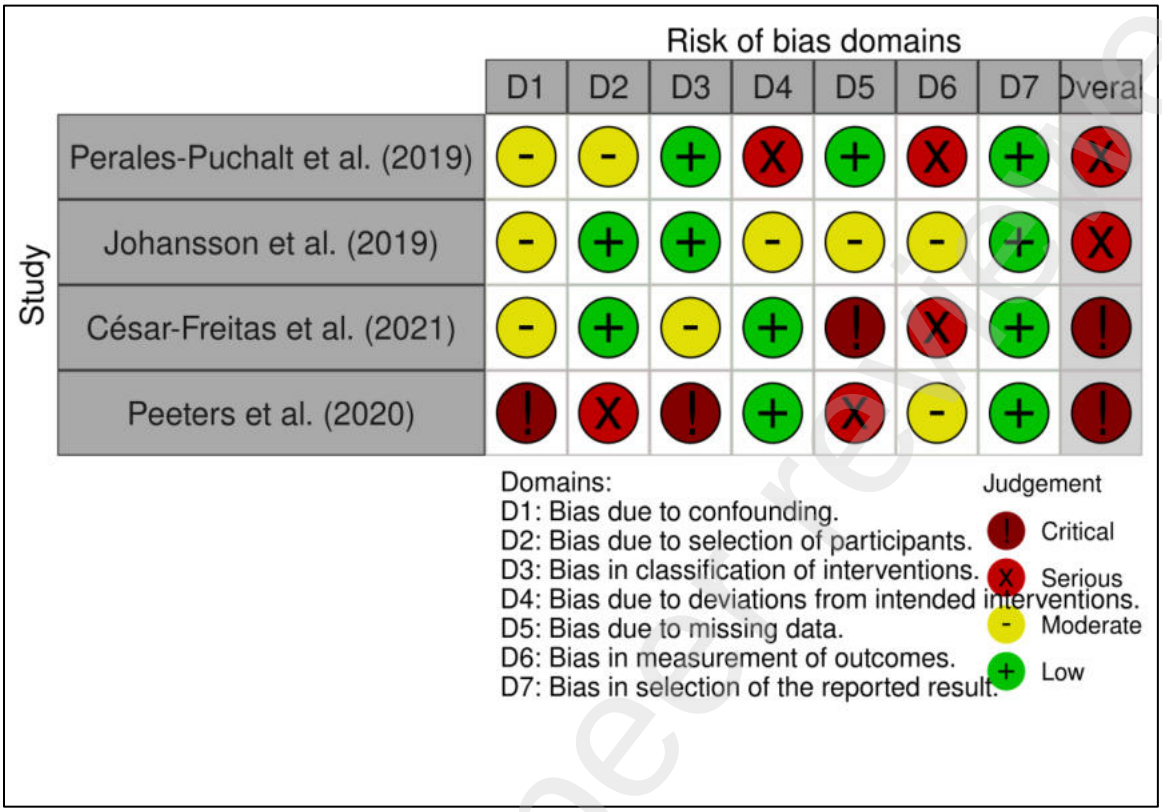
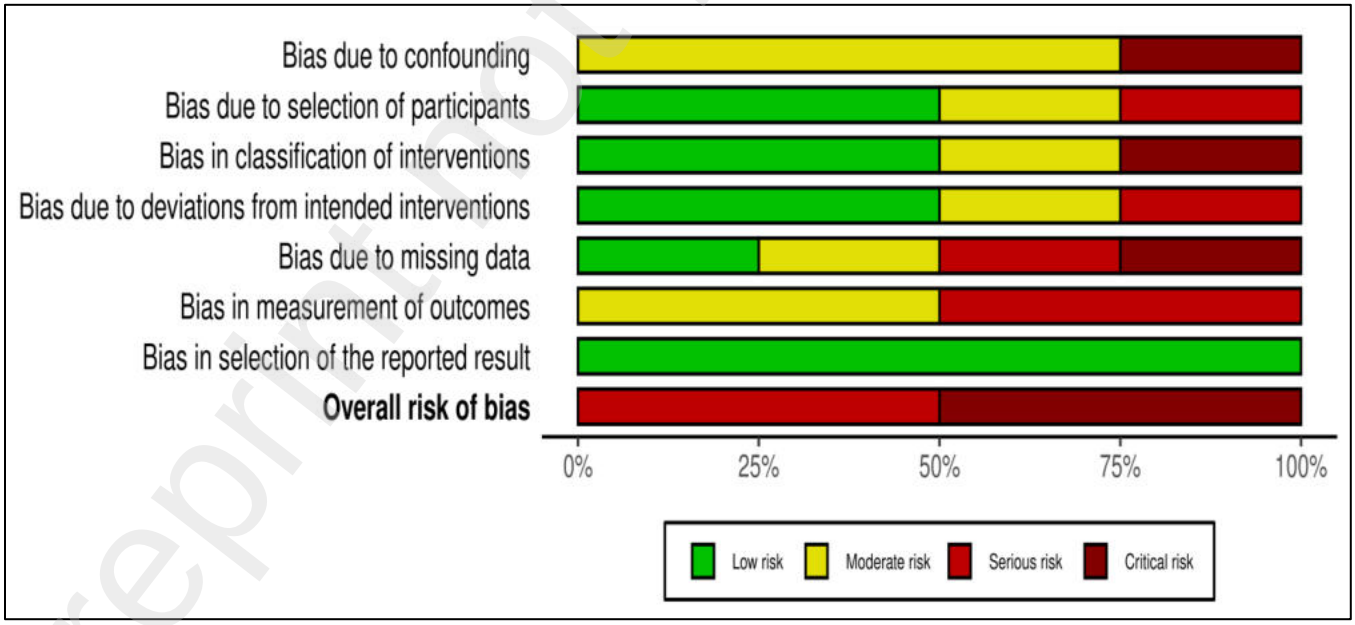


Figure 3. Graphical Summary



Meta-analysis

The meta-analysis under a random-effects model showed a significant overall association between the studied factors and the risk of dementia (RR = 1.54; 95% CI: 1.13–1.95), indicating a 54% higher probability of developing dementia in exposed individuals. In other words, if all exposed individuals in the included studies are considered together, this group presents a 54% higher risk of developing dementia compared to the non-exposed. However, individual studies showed heterogeneous results, with some suggesting a protective effect and others a higher risk, and several with confidence intervals that included the null value. This heterogeneity reflects that the analyzed factors do not act uniformly and that their impact may vary according to the population, context, and methodological quality of the study.

It is relevant to highlight that, although the overall result is statistically significant, the strength of the evidence is limited. Most studies presented serious or critical risk of bias according to RoBINS-I, mainly due to residual confounding, problems in the classification of exposures, and limitations in outcome measurement. These aspects affect the internal validity of the findings and reduce the certainty of the evidence, which is classified as low to very low.

From a clinical and public health perspective, the findings suggest that the presence of cardiovascular, behavioral, and psychological factors could increase the risk of dementia, which reinforces the importance of preventive strategies in older populations. However, the interpretation should be cautious, as the results reflect average associations and not individual cumulative risks, and cannot be directly extrapolated to a predictive model without further validation (Figure 4).

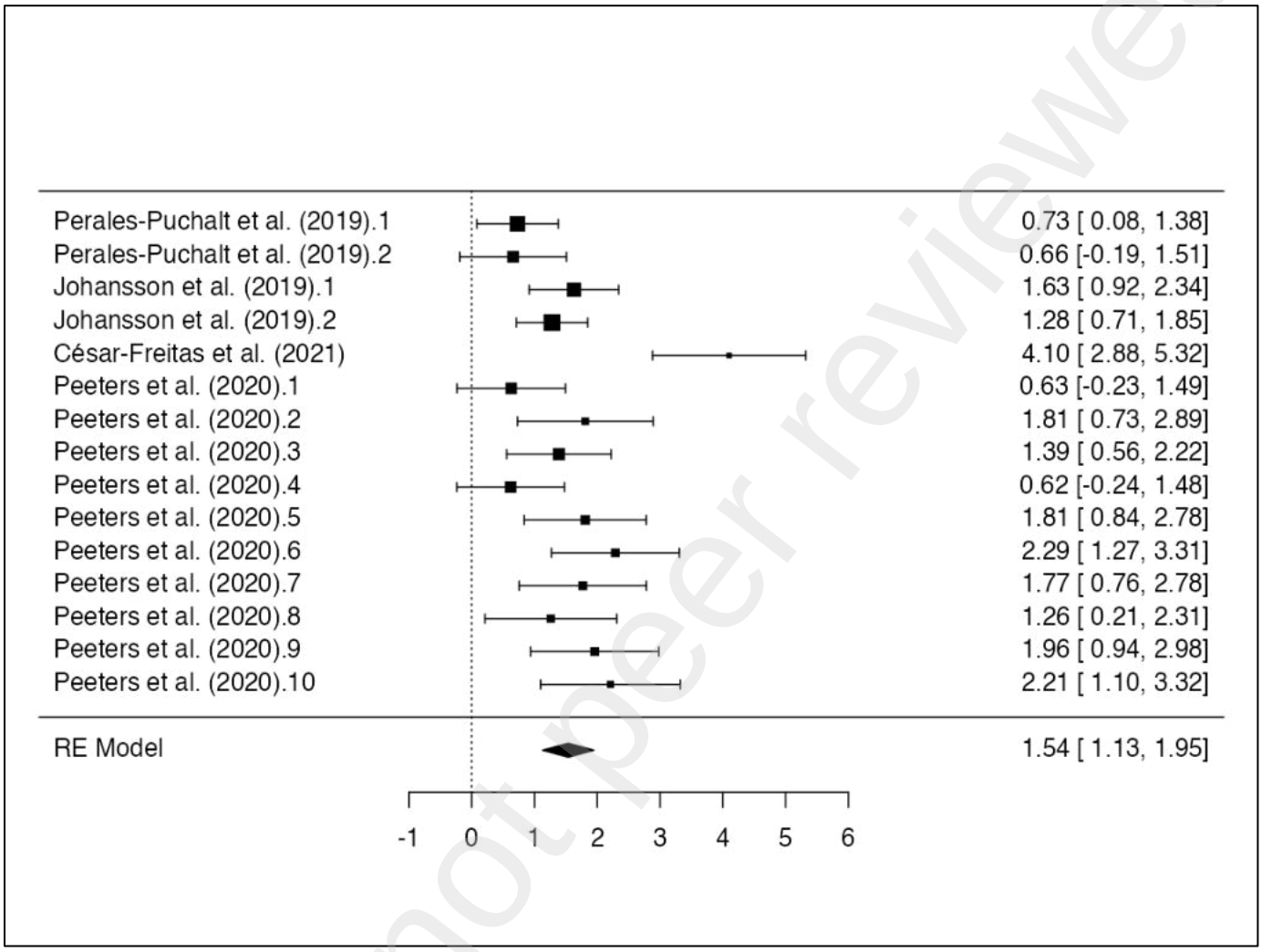


Figure 4. Forest Plot

Meta-regression

A meta-regression analysis was conducted using Weighted Least Squares (WLS) with the aim of examining the influence of potential moderator variables on the effect size and, thus, explaining the heterogeneity observed among the studies. The model included 12 predictors and was based on 15 studies, managing to explain a high proportion of the variability among studies, as indicated by an R^2 of 0.968. This suggests that approximately 96.8% of the variability in effect size can be attributed to the risk factors considered and the overall risk of bias.

However, the adjusted R^2, which penalizes the inclusion of multiple predictors, was considerably lower (0.777), indicating that, although the model is robust, part of its explanatory capacity could be due to the high number of variables included. The main source of heterogeneity among studies was the type of risk factor analyzed. In particular, the Depression variable emerged as a statistically significant predictor of effect size, while the overall risk of bias did not show a significant association (Table 3).

Despite this, the overall model significance test (F-statistic) did not reach significance ($F(2, 12) = 5.056$, $p = 0.177$). This discrepancy, together with the reduced number of residual degrees of freedom (Df = 2) and the relatively lower adjusted R^2, suggests possible model overfitting, probably derived from the model's complexity in relation to the small number of studies included. Therefore, although the model effectively explains the variability of the data from the analyzed sample, the conclusions should be interpreted with caution and cannot be generalized without additional validation in larger samples.

It is worth noting that, within the evaluated factors, depression was the only statistically significant moderator variable, indicating that its association with a larger effect size (i.e., higher risk of dementia) is reliable and not attributable to chance. Other factors, such as cognitive impairment or obesity, did not show significant effects; although their coefficients might suggest some relevance, the high p-values and confidence intervals that cross zero indicate that these results could be coincidences and, therefore, should not be interpreted as evidence of a real relationship.

Table 3. 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 shows the bubble plot of the meta-regression analysis, where risk factors are represented on the X-axis and effect size (ln[OR]) on the Y-axis; the size of each bubble indicates the study weight and the color reflects the overall risk of bias ('Serious' in blue, 'Critical' in red). The dispersion of the bubbles evidences the heterogeneity among studies, which the model largely explains, while the regression line illustrates the predicted average effect. Despite the predominance of studies with 'Critical' risk of bias, no clear separation by category is observed, confirming that overall risk of bias is not a significant moderator. The plot also highlights that Depression is consistently associated with a larger effect size, supporting its significance as the only relevant predictor.

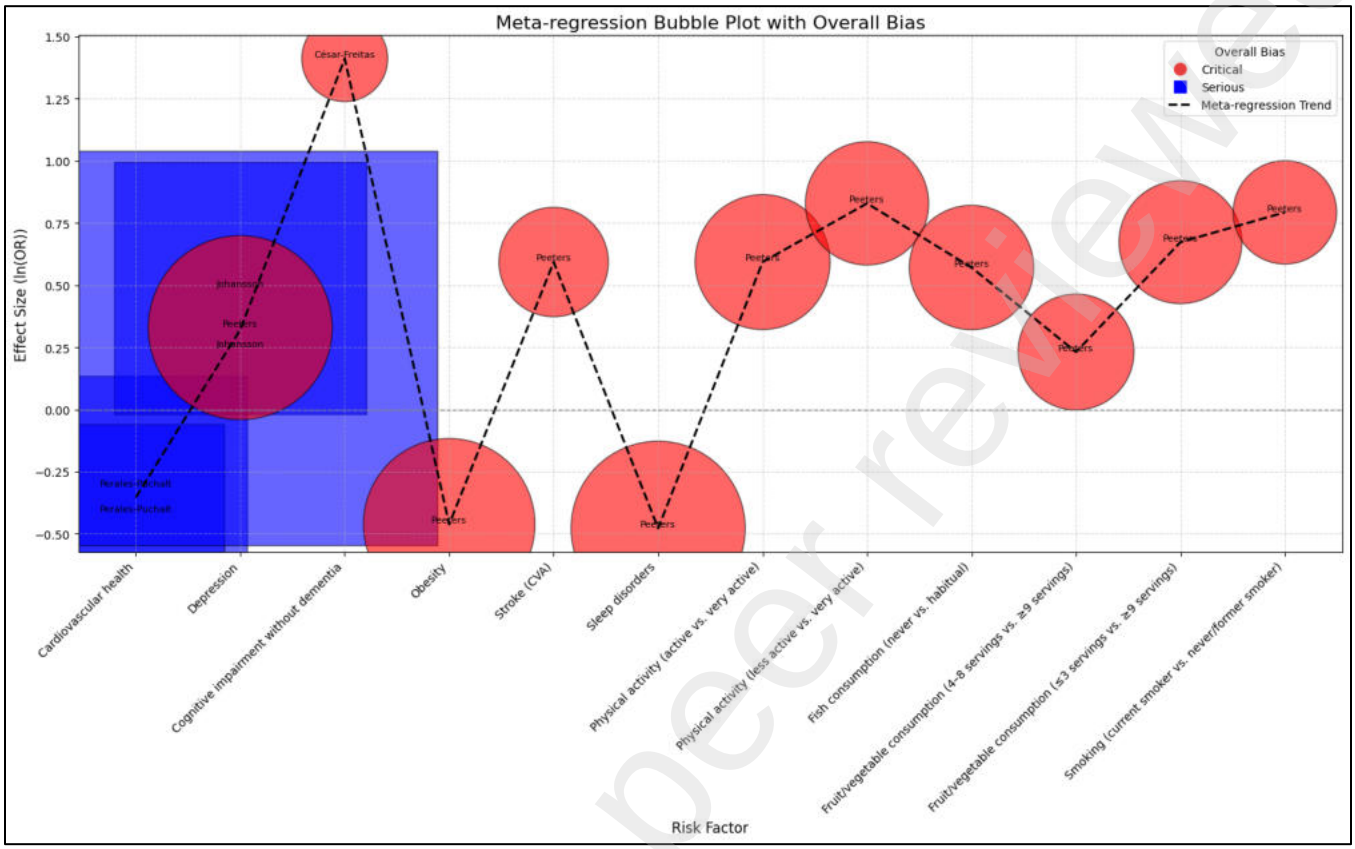


Figure 5. Meta-regression Plot

DISCUSSION

The present study identified, through a random-effects meta-analysis, a statistically significant overall association between the evaluated risk factors and the development of dementia, with a relative risk of 1.54 (95% CI: 1.13–1.95). This result indicates that joint exposure to these factors increases the probability of developing dementia by 54%. However, this main finding should be interpreted with great caution due to the significant methodological limitations identified in the included studies, which compromise the certainty of the evidence.

The assessment using the RoBINS-I tool classified the overall certainty of the evidence as low to very low. Specifically, two studies were rated with "serious" risk of bias [14, 15], while two others reached a "critical" level [16, 17]. These methodological deficiencies include confounding problems, inadequate participant selection, poor handling of missing data, and limitations in outcome

measurement. Such elements directly threaten the internal validity of the findings and, consequently, the reliability of the combined effect.

Given the high heterogeneity and low methodological quality observed, a meta-regression analysis was conducted to explore whether specific study characteristics could explain the variability in effect sizes. The meta-regression model, although it explained a high percentage of the variance (R^2 = 0.968), was not statistically significant as a whole (p=0.177) and showed signs of overfitting. This limitation was foreseeable considering the small number of studies in relation to the analyzed predictors. In itself, this model reflects the inconsistency and inherent limitations of the primary evidence.

Despite the limitations of the overall model, the analysis of individual moderators revealed a relevant finding: depression was the only factor that proved to be a statistically significant moderator (p=0.049) of effect size. This suggests that studies that include depression as a risk factor tend to report effects of consistently different magnitude than those that do not consider it. This finding has neurobiological coherence when considering the complex relationship between neuroinflammation, depression, and dementia. Neuroinflammation contributes to the development of depressive symptoms through the release of proinflammatory cytokines, while depression can exacerbate existing inflammatory responses. This process generates a vicious cycle that perpetuates both depressive symptoms and neuronal damage, potentially contributing to the subsequent development of dementia [18, 19, 20].

However, this result should be analyzed in conjunction with the bias assessment, since the study by Johansson et al. [15], focused precisely on depression, was rated with "serious" risk. Therefore, although depression emerges as a key source of heterogeneity, the evidence supporting it comes from studies with significant methodological weaknesses. In contrast, other factors such as obesity or sleep disturbances did not prove to be significant moderators.

Our results pose important challenges considering that the prevalence of dementia in LATAM is the highest in the world (8.5%) and is projected to reach 19.3% by 2050 [21]. This critical epidemiological situation is aggravated by specific sociodemographic characteristics of the region that can influence both exposure to risk factors and access to preventive and therapeutic interventions. The region presents high rates of cardiovascular diseases, diabetes, depression, and marked socioeconomic

inequalities, factors that are strongly associated with the development of dementia. Additionally, accelerated population aging in the region, combined with fragmented health systems and limited resources for early detection and management of DE, amplifies the urgency of having robust evidence on modifiable risk factors.

The presence of methodologically limited evidence restricts opportunities to develop evidence-based prevention strategies and public health policies specifically adapted to regional reality. It is important to highlight that the studies used for this research focused on individual development of dementia and did not contemplate studies focused on the development of dementia at the population level. Population-level studies could shed greater light on this situation, as individually focused studies in the region are biased.

This limitation is particularly concerning given that risk factors may manifest differently in populations with different genetic, socioeconomic, and cultural profiles. Without high-quality evidence that allows for adequate identification and quantification of risk factors in the Latin American context, prevention efforts and clinical decisions may lack the necessary precision, which represents a critical missed opportunity to mitigate the growing burden of dementia in an already vulnerable region.

CONCLUSION

In summary, although the meta-analysis points toward an association between the studied factors and the risk of dementia, this conclusion is fragile. The low methodological quality of the primary studies, evidenced by the high risk of bias, severely limits confidence in the overall effect. The meta-regression reinforces this caution, being a statistically non-significant model, but manages to identify depression as an important source of variability among studies. The main implication of these findings is the urgent need to conduct studies focused on the development of dementia at the individual level with more robust and rigorous designs in order to establish with greater certainty the true risk and protective factors for dementia in the region.

LIMITATIONS

The included studies focused on articles evaluating dementia development at an individual level. Considering the importance of population-level data, future research should combine both approaches, as population-level investigations could shed greater light on this relationship.

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. 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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