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Original Research

Cardiovascular Risk Scales Association with Cerebrospinal Fluid Alzheimer's Disease Biomarkers in Cardiovascular Low Cardiovascular Risk Regions

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Abstract

BACKGROUND: Cardiovascular risk factors are associated with Alzheimer's Disease (AD) development. However, few studies compare the overall cardiovascular risk with AD biomarkers, and when done, they are mainly performed in moderate cardiovascular risk regions.

OBJECTIVES: To determine whether cardiovascular risk in older adults is associated with pathological cerebrospinal fluid (CSF) biomarkers of AD in a low cardiovascular risk population.

DESIGN: This is a cross-sectional study performed between 2017 and 2020.

PARTICIPANTS: The present work included patients between 50 and 75 years old who were negative for CSF AD biomarkers and had minimum cognitive alterations (controls) and patients with positive CSF AD biomarkers and in early stages of AD (cases).

MEASUREMENTS: CSF biomarkers included total tau, phosphorylated tau 181 and amyloid ß42 (Aß42). Analytical variables were obtained. ERICE, SCORE2 and Framingham scales were used to calculate the overall patient's cardiovascular risk. The Aß42/Aß40 ratio and neurofilaments were explored when available.

RESULTS: Two hundred and thirty-three patients were included. Nearly 76% of the sample had AD. AD patients had higher cardiovascular risk than controls (p-value < 0.05). ERICE and SCORE2 were associated with AD presence. Framingham was not. A correlation between elevated cardiovascular risk and higher total tau and NfL levels was observed when adjusted by age.

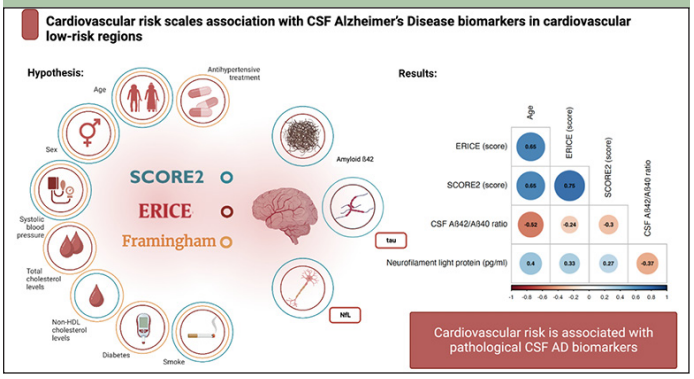
CONCLUSION: Cardiovascular risk assessment may be helpful in neurodegenerative disorders detection, as it is associated with CSF total tau and NfL. ERICE and SCORE2 may be useful scales in low cardiovascular risk regions to improve cardiovascular control and prevent neurodegenerative pathologies.

Key words: Alzheimer's disease, neurodegeneration, Cardiometabolic Risk Factors.

Introduction

Alzheimer's Disease (AD) is a prominent contributor to global dementia cases (1). It is distinguished by a decline in various cognitive domains and manifests primarily as amnesia. This condition is characterized by acquired and irreversible changes that result in a notable deterioration of cognitive functions and interference with routine daily activities (1–3).

Central figure. Hypothesis and key findings regarding the association between cardiovascular risk and Alzheimer's Disease cerebrospinal fluid biomarkers



The figure showcases colored circles, each aligned with a corresponding scale denoted by its name in the center. Blue: correlates with SCORE2; Yellow: correlates with Framingham; Red: Correlates with ERICE; Bold: Statistically significant after age-adjustment.

The diagnosis of AD is based on the [AT(N)] classification (amyloid, tau, neurodegeneration) (2), or the alteration of the cerebrospinal fluid (CSF) AD biomarkers Amyloid ß42 (Aß42) and total tau (t-tau), or phosphorylated tau (p-tau), since they are currently the best predictor of AD diagnosis (4). Briefly, the reduction of CSF Aß42 has been suggested as an early event in AD dementia, followed by abnormalities in other biomarkers (2, 5). While Aß40 represents the predominant type of Aß peptide, the ratio of Aß42/Aß40 is used to gauge pathological amyloidosis, serving as an early CSF indicator for AD presence (2, 5). In addition, although tau proteins typically stabilize microtubules and are found in neurons under normal circumstances (5, 6), the level of t-tau has been shown to rise in the presence of chronic degenerative disorders or acute neuronal damage (5). This increase leads to the formation of p-tau, disrupting

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microtubules, hindering axoplasmic flow, and ultimately contributing to the loss of neuronal synapsis (2). Lastly, the use of neurofilament light chain (NfL) as a diagnostic tool for axonal degeneration in AD is also worth noting. Although NfL is not exclusive to AD, it indicates axonal damage due to its association with the presence and severity of AD-related symptoms (7).

In terms of AD risk factors, it is essential to note that nearly 40% of dementia risk is modifiable, and approximately 30% of the total modifiable risk aligns with cardiovascular disease (CVD) risk factors, such as diabetes mellitus type 2 (DMT2), hypertension, and obesity (8). CVD covers a range of harmful changes affecting both heart function and blood vessels, making it the leading global cause of mortality (9). Moreover, CVD (10) and AD are more common as we age, especially among older patients. Interestingly, there seems to be a two-way connection between cerebrovascular disorders and the severity of AD (9). In this context, CVD can lead to cerebral hypoperfusion, triggering metabolic disorders. It can also cause acidosis, oxidative stress and activate mechanisms linked to AD (11). Additionally, CVD risk factors can potentially increase inflammation and blood-brain barrier dysfunction, which worsens AD pathogenesis (9, 11). In contrast, amyloid dysregulations may promote similar mechanisms, potentially exacerbating CVD factors (9). Thus, whether AD and CVD act as causes or consequences remains elusive; although a clear relationship between the both is evident (9).

Due to the fact that the period between the initial pathological mechanisms of AD and the appearance of the initial symptoms is prolonged (8), a better understanding of the modifiable risk factors to potentially intervene is needed. Among older patients, it is common to observe comorbidities, such as DMT2, hypertension or obesity, all of which impact on the presence of AD. Hence, the simultaneous presence of multiple metabolic disorders can culminate in a more pronounced elevation of pathological pathways (9).

Several cardiovascular risk assessment tools have been recently developed to estimate the ten-year risk of developing CVD. The Framingham scale, based on the American population (12), the Systematic Coronary Risk Evaluation (SCORE2) scale and SCORE2-OP for older individuals, both based on European patients data (10, 13), are the most used. Others, like The Life's Simple 7 of the American Heart Association (14), or the Spanish REGICOR (15), are also widely known. Moreover, international guidelines establish the necessity of adapting the cardiovascular risk scales to geographical areas (16, 17). For instance, the "Ecuación de Riesgo Cardiovascular Española" (ERICE) scale quantifies the cardiovascular risk for Spanish people (16). At the same time, the low risk SCORE2 category considers regions in Europe with low CVD risk, including Spain (10, 13).

Previous studies linked elevated cardiovascular risk with impaired cognitive performance (8, 11, 18). However, these analyses predominantly rely on cognitive tests or the diagnosis of cognitive decline. Additionally, they often utilize the Framingham scale, which is based on populations with moderate cardiovascular risk (19), and limited research explore whether higher levels of a particular cardiovascular risk scale is linked to pathological CSF AD biomarkers (14, 20). Lastly, there is a lack of studies based on low cardiovascular risk regions that elucidate the impact of cardiovascular pathology on AD. Thus, to consider the variation of cardiovascular risk assessment across geographical regions due to different lifestyle and demographic factors (16) is imperative.

Therefore, this study aims to determine whether elevated cardiovascular risk among older adults corresponds to AD presence, particularly in regions considered of low cardiovascular-risk. Moreover, the study aims to evaluate if cardiovascular risk scales correlate with CSF AD biomarkers.

Methods

Participants and study design

The present work is a cross-sectional study conducted at the Neurology Unit of the Hospital Universitari I Politècnic La Fe de València, Spain, between January 2017 and December 2020 contemporary. It was carried out in accordance with the guidelines of the Declaration of Helsinki. It received the approval from the Research Ethics Committee of our University, register CEI21/052, and the Research Ethics Committee of our Hospital, approval 202-705-1.

We included participants who signed the informed consent, were aged between 50 and 75 years, and accepted a lumbar puncture for CSF AD biomarkers (t-tau, p-tau, Aß42) analysis. Additionally, their medical records included data on total cholesterol levels, high-density lipoprotein (HDL) cholesterol levels, and blood pressure measured within six months of the CSF sampling. Exclusion criteria were defined by other neurological disorders such as multiple sclerosis, epilepsy brain injury, or primary psychiatric disorders, like bipolar disorder or schizophrenia.

The AD diagnosis was based on the CSF ratio t-tau/Aß42 (AD when ratio t-tau/Aß42 >0.51) and the ratio Aß42/Aß40 (AD when <0.069) when available. If patients tested positive for Aß42/Aß40 and had a t-tau/Aß42 ratio < 0.51, we relied on the Aß42/Aß40 ratio as a reference due to its higher sensitivity. Patients who did not meet the previous CSF criteria were considered non-AD. Only those non-AD patients who failed one neuropsychological test (score lower than the minimum threshold) or did not fail any of them were included. Neuropsychological evaluations for assessing the cognitive status of patients are detailed in the supplementary material.

Regarding AD patients, only those with mild cognitive impairment and mild dementia were included. As a result, patients with minimal cognitive alteration (controls) and those in the early stages of AD were selected for the present work.

CSF biomarkers, including Aβ42, t-tau, p-tau, and the t-tau/Aß42, and Aß42/Aß40 ratios, along with NfL, were quantified via chemiluminescence immunoassay (21) following the protocols of the Neurology Unit of the Hospital. The inclusion of Aß42/Aß40 and NfL was delayed for specific patients due to its later implementation in the hospital's techniques. This work used these biomarkers to improve the understanding between cardiovascular risk assessment and AD biomarkers. The cut-off points were >485, >56, <725, and >0.807 pg/ml for p-tau, t-tau, Aß42, and NfL, respectively.

Conversely, patients' medical records were thoroughly examined to record analytical variables, including total and HDL cholesterol, systolic blood pressure (SBP), and diastolic blood pressure (DBP). In cases where multiple points for of the same variable were available, an average was calculated to get accurate results. The presence of DMT2 diagnosis, antihypertensive treatment, smoking habits, and the number of concomitant medications was ascertained through a combination of medical records review and patient interviews. Medications were listed by Yes/No, following the Anatomical Therapeutical Chemical (ATC) code of the WHO Collaborating Centre for Drug Statistic Methodology (WHO) (https://www.whocc.no/atc_ddd_index/) in 2021.

Cardiovascular risk assessment

Cardiovascular risk assessment was obtained with the European SCORE2 (13) and SCORE2-OP 10 table scales, the Spanish ERICE scale (16) and the American Framingham scale (12).

SCORE2 and SCORE2-OP calculate the ten-year risk of cardiovascular events. The difference between them is that SCORE2 is valid for patients aged from 40 to 69 years and SCORE2-OP is used for patients between 70 and 89 years (10, 13). For this study, both scales were treated as the same, henceforth referred to SCORE2. SCORE2 was included in this study because it is the proposed one by the European Society of Cardiology and indeed it has different risk estimations depending on the region where cardiovascular risk is assessed (10, 13). This Scientific Society classifies regions' cardiovascular risk according to the age and sex-adjusted cardiovascular mortality rates published by the World Health Organization (WHO). Regions with less than 100 deaths per 100,000 population are classified as low cardiovascular risk areas (13). Since Spain is considered a low-risk region according to this scale, we used the low cardiovascular risk tables for this study. Regarding its variables, this scale considers patients age, sex, smoking habits, SBP, and non-HDL cholesterol (10, 13). In addition, the scale assigns scores from 1 to 49 to indicate ten-year cardiovascular risk, which is categorized into three stages: low, medium, or high CVD risk (see Supplementary Table 1) (10, 13).

ERICE was added as it is validated in the same country as the study's population. This scale considers factors such as antihypertensive treatment, DMT2 presence, smoking habits, age over 40, SBP, and total cholesterol levels (16). The scores on this scale range from 1 to 84, and are categorized into six levels: low, mild, moderate, moderate-high, high, and very high ten-year absolute risk of a first fatal or non-fatal cardiovascular event (16). To compare ERICE categories with SCORE2, the categories of ERICE were grouped as low, moderate, and high cardiovascular risk categories (see Supplementary Table 1).

Framingham was chosen due to its widespread use in cardiovascular risk and its prevalent role in cognitive impairment prevention risk initiatives. This scale includes age, sex, SBP, smoking habits, HDL, total cholesterol levels and antihypertensive treatment (12). We categorized this scale into three stages: low, medium, or high CVD (see Supplementary Table 1).

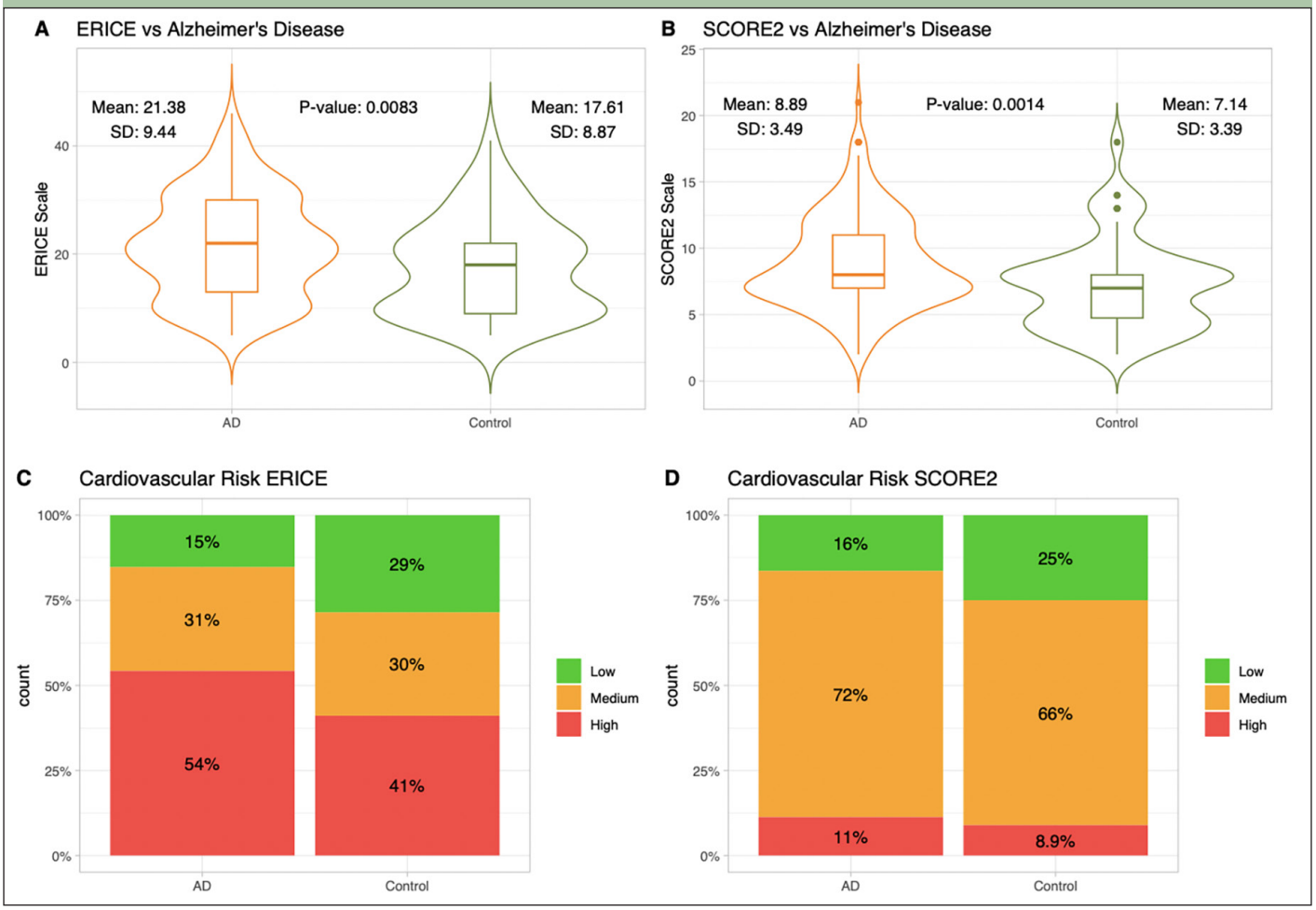
To compare the cardiovascular risk scales with the AD variables, cardiovascular scales were analyzed quantitatively (using the score of the scales) and qualitatively (using the categories of the scales). Finally, we created a new category (cardiovascular alert) to perform dichotomous analysis. The cardiovascular alert was "yes" when patients' cardiovascular risk was "moderate" or "high" and "no" when patients' cardiovascular risk was "low". A summary of the main differences between these three scales is presented in Supplementary Table 1.

Statistical analysis

After the completion of the follow-up of the subjects, all the information was stored in a database designed specifically for this study. Subjects' medical records were reviewed during the overall process, and a posterior data cleansing was conducted to check the completeness and correctness of the dataset. Finally, the statistical analysis was conducted using different libraries of the advanced statistical treatment RStudio@ program (22).

The sample size to conduct the study was calculated using G*Power statistical software (23). Two-sample t-tests were conducted after testing compliance with the assumptions of normality (Shapiro-Wilk test) and homogeneity of variances (Levene's test) to check statistical significance differences between both groups. An equivalent non-parametric alternative to the t-test was employed if such assumptions were not met. In that sense, the Wilcoxon rank-sum method or Welch two-sample t-test was checked. As a result, the significance level was established at 0.05 for all tests. Moreover, Pearson's Chi-squared tests were conducted to discover if AD depends on several qualitative factors. Fisher's exact

Figure 1. Distribution of cardiovascular risk in AD and non-AD patients



Comparison of the scale's score between AD patients and the control group, depicted using violin plots: (A) ERICE; (B) SCORE2. Comparison of risk categories between AD patients and the control group, shown using by stacked chart bars: (C) ERICE; (D) SCORE2.

test was also employed to analyze the corresponding contingency tables for the sub-study, where the sample size was reduced. The parameters were established as a one-sided test with a medium effect size, a power of 0.9, and a significance level of 0.05, which concluded with a minimum sample size of 156 subjects.

Additionally, logistic regression analysis was conducted to investigate the association between AD presence and cardiovascular risk scales, considering the potential influence of age by incorporating patient age as a covariate. Secondly, correlation analyses were performed between the components of the cardiovascular scales, the cardiovascular risk scales, and the CSF biomarkers as continuous variables. Thirdly, and since the CSF AD biomarkers did not have a normal distribution, they were categorized into three equal groups based on their tercile placement (high, medium, or low categorizations). Lastly, a multinomial logistic regression was conducted on each AD biomarker group to determine whether there were differences among groups, corrected by age.

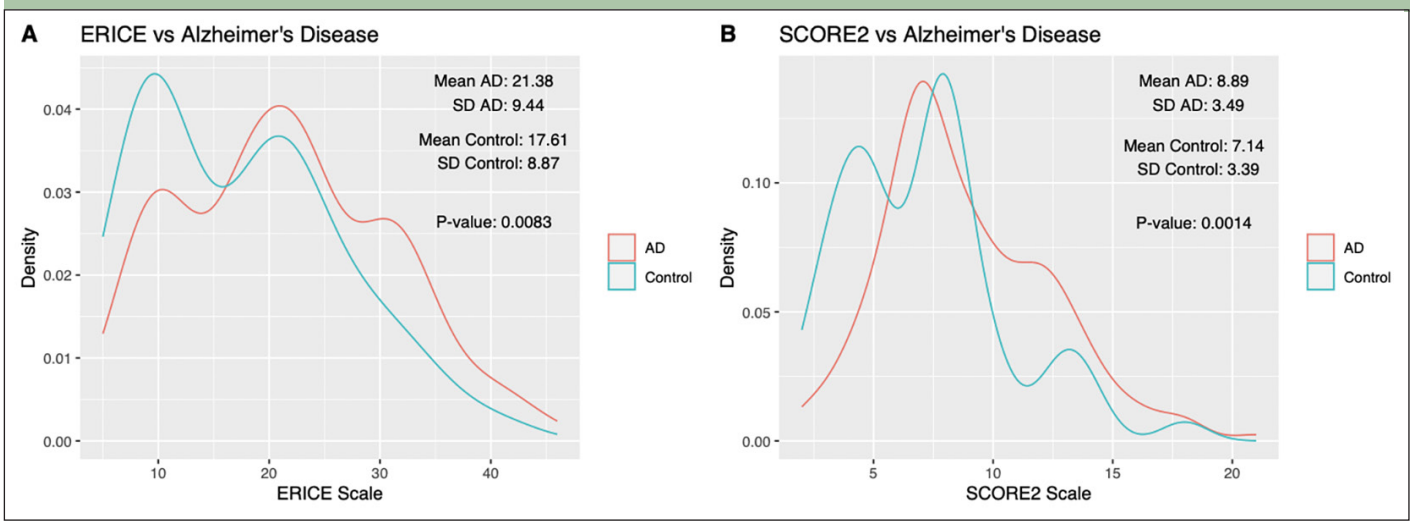
Finally, two sub-studies addressed age differences and other AD CSF biomarker's roles in CVD. For the first one, patients between 50 and 66 years were included (no age differences between AD and non-AD patients). We performed a two-sample t-test and Pearson's Chi-squared for descriptive analysis and logistic regression to compare AD presence with ERICE and SCORE2 scores (Model 1) and age as a covariable (Model 2). For the second sub-study, the sample size was restricted to subjects with recorded data for CSF biomarkers Aß42/Aß40 and NfL, regardless of their age. In this context, the study's statistical power was computed for this reduced sample, revealing a medium effect size and a statistical power of 0.86. As a result, the statistical significance of the results remains statistically relevant. Similar to previous approaches, logistic regression analyses were performed, with adjustments made for age.

Results

Demographic and clinical description of participants

The present work included 233 patients aged between 50 and 75, with a mean age of 68.5 ± 5.3 years. Among

Figure 2. Population density of cardiovascular risk based on Azheimer's Diasease diagnosis



Distribution of cardiovascular risk using (A) the ERICE scale; (B) the SCORE2 scale.

these, 177 patients were diagnosed with AD (75.97%) and 56 were control subjects (24.03%). The AD group was older than the control group (p-value: <0.0001)). Additionally, demographic and clinical details for both groups are provided in Supplementary Table 2. As expected, there was a positive correlation between CSF AD biomarkers and the diagnosis of AD.

Cardiovascular risk score: A key alert for Alzheimer's Disease screening in older adults

ERICE, SCORE2, and Framingham scales were applied within the specified cohort to explore associations with cardiovascular risk (Supplementary Table 3 and Figure 1). A clear association was detected between elevated cardiovascular risk score and an increased likelihood of AD development using ERICE and SCORE2. However, Framingham did not show any association with AD. As a result, our subsequent in-depth analysis was focused on ERICE and SCORE2.

Figures 1A and 1B reveal that both scales assigned higher scores to AD patients and lower scores to controls. When examining across different cardiovascular risk categories (low, medium, high), ERICE displayed a comparable distribution of moderate risk for both groups. Notably, more individuals with low cardiovascular risk were found in the control group, while over half of the AD patients exhibited high cardiovascular risk (Figure 1C). On ERICE, there were noteworthy differences between alert levels and the presence of AD. However, SCORE2's alert did not exhibit significant differences between AD patients and controls, nor did it reveal distinctions within its cardiovascular risk categories (Supplementary Table 3). In SCORE2, most patients in both groups had a moderate cardiovascular risk profile, resulting in a broader "intermediate risk area" for classifying the risk of cardiovascular disease. It could mean that this scale underestimates the cardiovascular risk or the ERICE overestimates. Lastly, similar to what we observed with ERICE, the control group had a higher percentage of low cardiovascular risk profiles than patients with AD (Figure 1D).

Regarding the distribution of cardiovascular risk based on population density for each scale, Figure 2 displays two patterns on ERICE. In the control group, the scores were around 10, indicating a low cardiovascular risk. Conversely, most AD patients' scores clustered around 20, indicating a high cardiovascular risk profile (Figure 2A). On the other hand, when we examined the distribution of SCORE2 scores (Figure 2B), both groups appeared intertwined, showing the AD group a clear peak between the two highest points of the control group's distribution.

The influence of age as a confounding factor

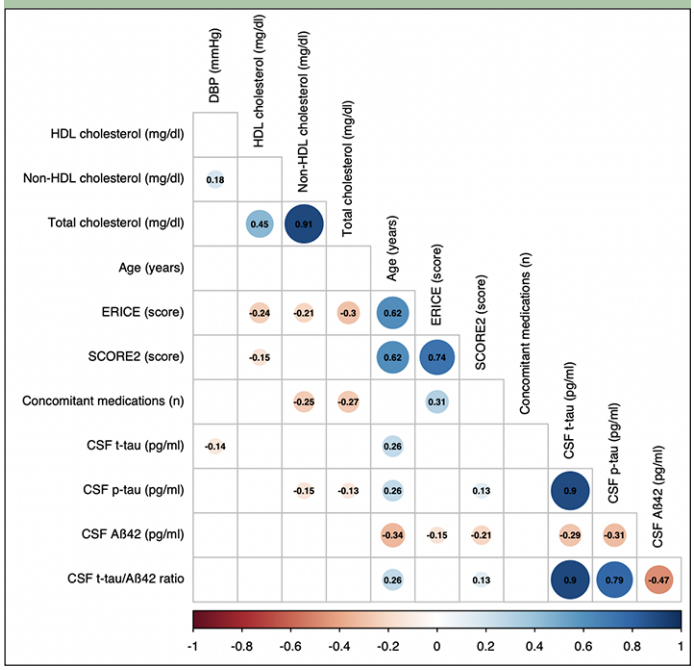
Since age is a significant confounding factor in determining AD risk, a logistic regression analysis was conducted to assess differences between cardiovascular risk and AD presence (Supplementary Table 4). Upon accounting for age, the differences between cardiovascular risk and AD presence lost statistical significance. In addition, no differences were observed when including sex on the models.

Subsequently, a sub-analysis was carried out with patients between 50 and 66 years (n=69, Supplementary Table 5). In this case, no age differences were found and a trend was observed when adjusting for age in ERICE, which considers DMT2 presence and antihypertensive treatment consumption (Supplementary Table 6, Model 2).

Cardiovascular risk association with Alzheimer's Disease biomarkers

The correlation between the scales mentioned above, including their variables, and the CSF AD biomarkers p-tau, Aß42, and t-tau/Aß42 were examined (Figure 3).

Figure 3. Pairwise correlations among the scores of the cardiovascular risk scales, their variables and CSF Amyloid ß42, t-tau, p-tau and the t-tau/Aß42 ratio



Blue indicates positive correlation; red indicates negative correlation. Abbreviations: Aß42: ß amyloid 42; CSF: Cerebrospinal fluid; dl: decilitre; HDL: high-density lipoprotein; mg: milligram; ml:millimetres; mmHg: millimetres of mercury; n: number of patients; pg: picogram; p-tau: phosphorylated tau; std: standard deviation; t-tau: total tau

ERICE positively correlated with a higher number of concomitant medications intake, SBP, and age. In contrast, a negative correlation emerged when comparing this scale with Aß42 levels, HDL, and total cholesterol (Figure 3). Similarly, SCORE2 demonstrated a positive correlation with age, SBP, p-tau, and the r t-tau/Aß42 ratio, whereas the opposite effect was observed concerning HDL cholesterol and Aß42.

As depicted in Figure 3, age exhibited a consistent correlation across both cardiovascular risk scales (0.62). Yet, these scales did not show the same degree of correlation with CSF AD biomarkers. This finding could imply that while age remains an essential factor to consider, other components linked to cardiovascular disease play a role in shaping the overall risk of AD.

Lastly, multinomial logistic regression was used to compare the categorized AD CSF biomarkers with the overall cardiovascular risk on each scale. In this case, the inclusion of sex in the models was not relevant, prompting its removal. As observed in Supplementary Table 7, a higher cardiovascular risk, according to ERICE, was associated with increased odds of medium t-tau and p-tau levels compared to the low category. Moreover, patients with greater cardiovascular risk exhibited a 3% and 4% higher likelihood of belonging to the group with elevated t-tau/Aß42 and p-tau levels, but differences disappeared when age was introduced into the model as a covariate. Curiously, higher t-tau levels diminish with an increased ERICE score when adjusted for age (0.95 (95%CI [0.091, 0.99], p-value=0.022)).

When the same models were applied using SCORE2 (Supplementary Table 8), a higher cardiovascular risk was associated with lower levels of Aß42 compared to those with high Aß42. In addition, an elevated SCORE2 score increased the likelihood of having higher p-tau and t-tau/Aß42 levels when age was not considered. Matching ERICE's results, the greater cardiovascular risk decreased the likelihood of having high t-tau, compared to low t-tau, by 0.89 (95% CI [0.78, 0.99], p-value=0.04) when adjusting for age.

Cardiovascular risk variables associated with Aß42/Aß40 and neurofilament CSF AD biomarkers

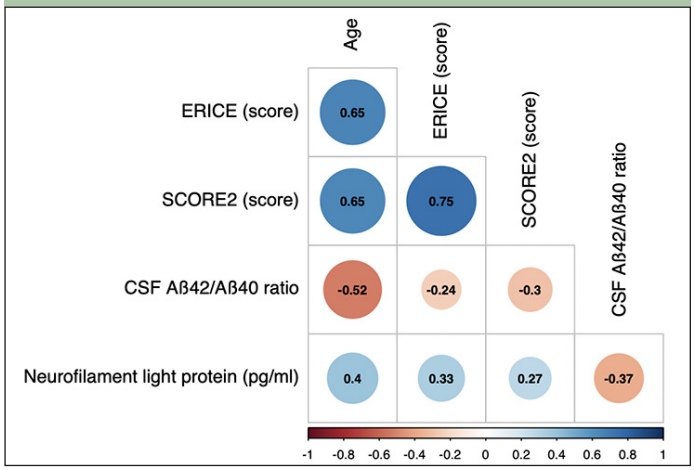
A more in-depth analysis of additional AD CSF biomarkers (Aß42/Aß40, NfL) and cardiovascular scales was conducted as a sub-study involving 106 participants, of which 75.47% had AD (Supplementary Table 9). The cardiovascular risk profile of AD patients and controls resembled the earlier findings, and the alerts from both cardiovascular risk scales were associated with the presence of AD (Supplementary Table 10).

ERICE and SCORE2 scores were associated with Aß42/Aß40, a primary AD biomarker, and impaired NfL levels (Supplementary Table 11). However, the significance of the associations diminished when the cardiovascular risk scores were adjusted for age.

A correlation was evident between NfL and the Aß42/Aß40 ratio (-0.37), alongside a robust correlation between cardiovascular risk scales (0.75), wherein age emerged as the most influential explanatory variable.

Subsequently, correlations were examined between the scales, the CSF ratio Aß42/Aß40, and NfL levels (Figure 4). The Aß42/Aß40 negatively correlated with both scales, especially with SCORE2 (-0.30). In contrast, NfL had a positive correlation with the scales, with ERICE displaying a more robust association (0.33). When partial correlations were calculated, these correlations became smaller and NfL remained significant. These findings highlight the modifying effect of cardiovascular risk variables on obtaining altered biomarkers.

Figure 4. Pairwise correlations among the scores of the cardiovascular risk scales, the ratio Aß42/Aß40, and neurofilaments



Blue: Positive correlation; Red: Negative correlation. Abbreviations: ß40: ß amyloid 40; ß42: ß amyloid 42; CSF: Cerebrospinal fluid; dl: deciliter; ml: millimeters; pg: picogram.

Discussion

The current study underscores the association between biomarkers of neurodegeneration and increased cardiovascular risk. We observed that lower t-tau levels and elevated NfL correlated with higher cardiovascular risk scores, even after accounting for age adjustments.

Each cardiovascular risk factor is associated with AD, but its independent evaluation often does not give us representative information about the total risk of AD development, since they act synergistically (14, 24, 25). However, cardiovascular risk scales include a comprehensive range of cardiovascular risk factors, offering a more robust estimation of the overall cardiovascular risk. Consequently, this study examines the potential link between global scores derived from cardiovascular risk scales and the presence of AD.

To compare the overall cardiovascular risk with AD presence, we used ERICE, SCORE2, and the Framingham scales, which predict a 10-year CVD event (10, 13, 16). Our observations reveal that AD patients had a greater cardiovascular risk than controls when we used ERICE and SCORE2 scales. Nevertheless, the statistical differences disappeared when the Framingham scale was applied to our population.

As observed in Supplementary Table 1, one of the main differences between these scales is the interpretation of cholesterol. SCORE2 includes non-HDL cholesterol (10, 13), whereas ERICE is based on total cholesterol (16) and Framingham considers levels of HDL and total cholesterol (12). The introduction of non-HDL cholesterol estimation for CVD marks a significant change from the previous SCORE cardiovascular risk score (26). Total and HDL cholesterol are considered a more reliable indicator of cardiovascular disease (10, 13), whereas HDL cholesterol is decreased in the neurons of AD patients (27), possibly contributing to its pathology (24, 27). Additionally, the role of LDL cholesterol in dementia seems to have a limited impact (28) and it is considered in SCORE2 for therapy recommendations but not a factor in its final score algorithm. Another difference between the mentioned is the presence of DMT2, a well-known AD risk factor for later-life (8, 9, 11). Neuronal insulin receptors and insulin expression are diminished in AD patients (9). Moreover, the insulin-degrading enzyme (IDE) is involved in Aß clearance, potentially impacting on its disruption and amyloid deposition (11). Nevertheless, when DMT2 was analyzed separately in our study, it did not show statistical differences.

Regarding the common variables in both scales, age and sex are the main influential factors, whereas smoking status is included to complete the cardiovascular risk assessment tools (10, 12, 13, 16). In addition, age and sex also play an important role when assessing AD risk. Elevated age is linked to greater cardiovascular risk, emerging as the predominant factor across all the cardiovascular risk scales examined. We noticed that the correlation between age and the cardiovascular risk score was the same for ERICE and SCORE2. However, the association between the score of both scales and the AD presence or the CSF biomarkers was different. Consequently, it becomes apparent that age does not act alone, so cardiovascular factors emerge as pivotal modifiable risk factors for AD. These findings led to earlier research that emphasized how age, in conjunction with other components such as cardiovascular factors, enhances the likelihood of AD presence (14, 24, 25).

To reduce the confounding effect of the variable age, we introduced it into our logistic regression models. We conducted a subgroup analysis with individuals aged between 50 and 66 years. Despite not identifying statistically significant differences, we observed that ERICE almost correlates with cardiovascular risk when adjusted by age (Supplementary Table 6). These results could be attributed to the small sample size of this sub-study (n=69) or the life stage of the patients. Notably, the patients in the sub-study are in midlife, and certain factors, such as DMT2, tend to have a more significant influence in later-life (8). As a result, exploring the association of ERICE with AD presence in patients 65 years or older may be of interest for future research.

Several studies suggest that hypertension, particularly SBP, is a mid-life risk factor for AD (8, 11, 29) and for early cognitive decline symptoms (11). Patients under antihypertensive treatment have an increased CVD risk on ERICE and Framingham compared to those not undergoing that treatment (12, 16), whereas SCORE2 does not consider antihypertensive treatments or lipid-lowering agents as variables, despite the European Society of Cardiology prompts healthcare practitioners to assess its implications through hazard ratio adjustments (10). Furthermore, antihypertensives may affect neurodegenerative processes (30), so its consideration on cardiovascular risk scales is of interest. Nonetheless,

no significant differences were detected in our cohort, possibly due to its low impact in late-life (8, 11) or because we did not analyze the antihypertensives subgroups or the treatment duration.

Regarding the overall cardiovascular risk with AD presence, Framingham scale did not show statistical differences. This phenomenon could be attributed to the fact that the Framingham CVD risk scale is validated on the American population, classified as a moderate risk region by SCORE2, whereas the Spanish population is classified as a low-risk group by the same scale. Secondly, we hypothesize that the absence of association between Framingham and AD is due to the fact that this scale does not represent accurately the factors that most impact AD presence, but further research is needed to confirm this hypothesis. Previous research shows an association between cardiovascular risk assessed through Framingham and imaging AD biomarkers, such as white matter hyperintensities and FDG-PET (18), as well as smaller hippocampus volumes, diminished grey matter, and total brain volume (19). A 20-year follow-up study showed that patients with higher cardiovascular risk according to Framingham had worsen cognition (19). Additionally, in the study by Viticchi et al. 2015, the Framingham Risk Score accurately predicted cognitive decline with an AUC of 0.63 in general analysis and an AUC of 0.77 when accounting for APOEe4, a variable that we could not test. Nevertheless, we did not detect differences using this cardiovascular risk scale, so we primarily focused on ERICE and SCORE2 , adapted and validated for low cardiovascular risk regions.

We compared the ERICE and the SCORE2 cardiovascular risk scales. ERICE showed a higher discriminatory capacity for identifying AD and neurodegenerative biomarkers than SCORE2. In the case of ERICE, control patients had a total cardiovascular risk score of 10, while it was the double for AD patients. These differences were not observed with the SCORE2 scale (Figure 2). As previously discussed, differences might arise from variations in the cardiovascular factors considered and how each of them contributes to the overall cardiovascular risk within the scale.

Concerning AD CSF biomarkers, SCORE2 showed a stronger association with Aß42 burden than ERICE. Recent findings from the CABLE study suggest that higher cardiovascular levels are linked to an increased Aß42/Aß40 ratio when APOE4 is present (14). In addition, other investigations have correlated higher cardiovascular risk factors in midlife with elevated brain amyloid accumulation. According to the longitudinal Harvard Aging Brain Study, Aß burden and higher cardiovascular risk act synergistically and are associated with accelerated cognitive decline. However, these associations were not observed in the cross-sectional analysis (18), which matches our results, in which we did not find any association between cardiovascular risk and AD presence when adding age to the models. Finally, a longitudinal study focusing on individuals with low to moderate cardiovascular risk did not find an association between cardiovascular risk and Aß42, even in the cross-sectional analysis (32).

As per other AD biomarkers, there was a modest association between cardiovascular risk and tau phosphorylation, as well as the t-tau/Aß42 ratio. This finding supports the idea that lower cardiovascular risk is associated with reduced CSF t-tau and p-tau levels, which are directly interconnected (14). Other investigations have reported contrasting results, suggesting that patients with cerebrovascular changes, directly associated with higher cardiovascular risk factors, exhibited lower Braak Stages (25). Our study identified a decrease in the likelihood of high t-tau presence with an increase in cardiovascular risk, even after adjusting for age. Moreover, a longitudinal study has established that cardiovascular risk is independently associated with AD biomarkers and cognitive decline. Since these effects act additively (20), it is worth considering that CVD may impact on cognitive outcomes through brain injuries.

Elevated NfL levels indicate neurodegeneration and neuronal death. This biomarker is non-specific for advanced stages of AD. In this context, ERICE showed a stronger and significant association with NfL than SCORE2 (0.33 vs. 0.27), even after adjusting for age. CSF NfL correlates with plasma NfL (33) and is highly accurate and less invasive screening method. Our findings also reveal a correlation between NfL and the CSF ratio Aß42/Aß40. Given that blood NfL may rise years before the onset of symptomatic manifestations (33), an elevated cardiovascular risk and increased plasma NfL concentrations could serve as vital indicators for cognitive impairment screening.

Strengths and limitations

The present study has some limitations. Firstly, the time frame of the study. Cardiovascular risk scores primarily predict future cardiovascular events and may not accurately reflect the current cardiovascular health of the patients. Additionally, the impact of each cardiovascular risk factor on the risk of dementia varies across different life stages. Furthermore, we recognize that the number of control patients is relatively low. The reason is that CSF sampling is an invasive and uncomfortable procedure that is not typically recommended for population screening. A lumbar puncture is a procedure that involves discomfort and some side-effects, so it cannot be performed in the general population. However, it is worth noting that this limitation can also be considered a strength, as very few studies exist comparing AD patients with CSF biomarkers to individuals without cognitive decline, which are generally challenging to find. Our patients were carefully chosen since CSF biomarkers and neuropsychological evaluations were both assessed.

Finally, we would like to highlight the clinical utility of employing cardiovascular risk scales for identifying individuals at risk of neurodegenerative pathologies, especially in regions with a low cardiovascular risk profile. There is a scarcity of studies investigating the relationship between cardiovascular risk and AD within low risk regions, and our study contributes substantiating evidence to this domain by comparing two valid scales. Future studies must include larger cohorts and explore different life courses to analyze these associations comprehensively and to delve deeper into factors like sex differences, ethnicity, or race, which we could not explore in our study.

Conclusion

In our study, ERICE and SCORE2 were associated with AD presence, whereas Framingham was not. Although they were low, there were different correlations between ERICE and SCORE2 scores and AD CSF biomarkers. Both cardiovascular risk scales showed a significant association with t-tau and NfL, which are related to neurodegenerative processes. Therefore, using cardiovascular risk scales adapted to the objective population may be helpful to improve cardiovascular control and prevent neurodegenerative pathologies.

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