Cardiovascular health and dementia incidence among older adults in Latin America: results from the 10/66 Study.

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Abstract

OBJECTIVES: Growing evidence shows that cardiovascular health (CVH) is associated with brain health. Little is known about this topic among older adults in Latin America, where the number of people living with dementia is rising. This study aimed to assess the longitudinal association between cardiovascular health and dementia in six Latin American countries.

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METHODS: We analyzed longitudinal data from the 10/66 study which included non-demented residents at baseline aged 65+ in six Latin American countries (n=6447) and were followed up for three years. An index of modifiable CVH factors (ranging from 0 to 14) was calculated. Incident dementia was modeled using competing risks regression to adjust for risk of death.

RESULTS: The sample included 6.2% participants with poor (0–5), 81.0% with moderate (6–10) and 12.8% with ideal CVH (11–14). At follow-up, 9.4% had developed dementia and 13.1% had died. Compared to poor CVH, participants with moderate and ideal levels of CVH had a significantly lower risk of dementia both in the unadjusted (subhazard ratio for moderate: 0.77; ideal: 0.59) and adjusted models (moderate: 0.73; ideal: 0.66).

CONCLUSION: Moderate and ideal levels of CVH in old age may protect against dementia incidence. These findings may inform health promotion efforts within dementia national plans adopted recently in some Latin American countries.

Introduction

Dementia is a growing public health concern in Latin America. Life expectancy in Latin America has increased ~9 years in the last 30 years and the population 65 and older is projected to increase from 7.6% in 2015 to 19.4% in 2050. [1,2] Latin America has one of the highest dementia prevalence worldwide and the number of dementia cases is projected to result in a 346% increase from 2013 to 2050. [3–5] This increase will have serious consequences at multiple levels. At the individual level, mortality and disability will increase significantly. In fact, in Latin American countries, mortality rates among people with dementia are up to six times higher than for healthy older adults. [6] In addition, dementia disability burden has exponentially grown in Latin America compared to other health conditions in the last decades. [7] In these countries more so than most high-income countries, patients with dementia are mainly cared for by families and to a much lesser extent by public institutions. [3] Thus at the family level, dementia care will place a great burden on relatives, impacting the health of informal family caregivers. [8,9] At the social level in Latin America, costs for elder patients with dementia are seven times higher than for elder patients without dementia and are mainly accounted for by informal care. [3,10,11] In fact, in these countries the directly attributable cost of dementia exceeds that of depression, hypertension, diabetes, ischaemic heart disease and stroke. [5] Understanding factors that increase dementia risk among older adults in Latin America is paramount to develop effective public policies and prevention strategies in these countries.

Cardiovascular health (CVH) might play an important role in reducing dementia incidence in Latin America. Dementia incidence has declined in some high-income countries, which might be partly explained by CVH improvements in these countries. [12] However in Latin America, there is an increasing transition to urban settings and adaptation of lifestyles associated with cardiovascular and metabolic disease. [13,14] Abundant evidence from high-income countries and some from Latin America shows that single cardiovascular risk factors

and indices are associated with cognition and dementia. [12,14–16] A growing body of research is focusing on the cumulative impact of modifiable cardiovascular risk factors on brain health. [17] For example, the American Heart Association Life's Simple 7 CVH guidelines are based on four modifiable health behaviors: nonsmoking, healthy diet, physical activity, and body mass index (BMI); and three modifiable biological factors: blood pressure (BP), total cholesterol, and fasting glucose. [18] CVH indices such as the Life's Simple 7 represent an improvement over the assessment of single cardiovascular risk factors as these factors often coexist and affect the brain through common pathways. [18] These CVH indices also overcome limitations of other indices such as the Framingham index as it only focuses on modifiable risk factors and include different levels of severity within each factor. [18] While studies have shown that an index of modifiable CVH factors is associated with stroke, brain integrity and cognitive functioning and decline, [19–27] to our knowledge only two studies (the Framingham study and the INVADE-trial) have assessed its association with dementia incidence. [21,28] However, the sample in the Framingham study was highly educated, both studies were from high-income countries (USA and Germany) and their models did not account for competing risk of death, which may have biased associations as individuals with lower CVH have a higher mortality rate. [29]

The present study aimed to explore the longitudinal association between an index of modifiable CVH factors and dementia incidence among Latin American older adults using data from the 10/66 study. We hypothesized that higher levels of CVH would be associated with a lower incidence of dementia. We accounted for mortality by using competing risks survival analysis. Given the region's history of wealth inequalities, [30] we explored whether associations differed by wealth. Determining the association between CVH and dementia among older adults in Latin America will inform dementia prevention policies and practice in these countries.

Methods

Study design

Two publications have described the 10/66 study in detail previously. [31,32] In short, this is an observational cohort study recruiting all resident adults 65 and older from 11 specific rural and urban catchment areas in eight low- and middle-income countries in Latin America, Africa and Asia. The present secondary analysis included only Latino American countries: Cuba, Dominican Republic, Venezuela, Mexico, Peru and Puerto Rico. Literate participants gave written informed consent and illiterate participants gave verbal consent with an independent witness. The 10/66 study followed the ethical guidelines of the 1975 Declaration of Helsinki and Institutional Review Boards of the local sites and King's College London approved the study protocol. Study procedures for the secondary analysis were determined by the University of Kansas Medical Center's Institutional Review Board as not involving human subjects research.

Sample and procedure

Centers conducted the baseline survey between 2004 and 2010 and included a clinical participant and informant interview, and a physical examination, which gathered information

about dementia and risk factors, mental and physical health, anthropometrics, disability and use of services. [31,32] Phlebotomists took fasting blood samples at baseline from participants. Each full assessment lasted an average of 2–3 hours and centers translated, back-translated and adapted materials to the different languages as needed.

Centers conducted the follow-up assessments between 2007 and 2013 and aimed to re-interview all participants from baseline using the same measurements. [6,31,32] Interviewers attempted to locate participants up to four times at their household and if they were no longer present, contacted up to three non-cohabiting friends or relatives about their vital status and new location. Interviewers contacted relocated participants in person or by telephone irrespective of whether their new location was outside the catchment area or conducted a verbal autopsy with an informant if they had died, including the date of death and evidence of dementia-related cognitive decline and functioning impairment.

Measures

CVH index—We calculated a CVH index at baseline based on the Life's Simple 7 index with few modifications given data availability (Appendix 1). [18] Participants were asked whether they had ever smoked, if they were still smoking regularly and at what age they quit smoking. The average of two sitting blood pressure assessments were used to define blood pressure. Participants who had been told they had hypertension and were currently receiving treatment for it were considered to be under hypertension treatment. Phlebotomists collected fasting glucose and interviewers asked whether participants were being treated for diabetes and the type of treatment. Only participants who currently used insulin or oral hypoglycemics were considered as being treated for diabetes. Cholesterol values were obtained from fasting blood samples but they did not include questions on treatment for hypercholesteremia. Given the lack of data on participants' weight, obesity was defined using waist circumference and the World Health Organization cut-off points for risk of metabolic complications. [33] Participants were asked if they had gone for walks of half kilometer (10–15 minutes) or more and the number of times they had gone for walks of half a kilometer during the last month. A cutoff of 20 walks per month (5 walks per week) was used as a proxy indicator for 150 minutes of moderate physical activity per week. Only dietary intake of meat, fish and fruits and vegetables and frequency of intake were collected. Therefore, diet was calculated by adding points (0: inappropriate or 1: appropriate) using these three measures. The frequency of meat and fish consumption was measured with a four point Likert scale (never, some days, most days and every day). We considered meat consumption appropriate for values of never and some days. We considered fish consumption appropriate for values of some days, most days and every day. The survey also asked about the amount of servings of fruits and vegetables in the last 3 days. We considered values of 13.5 or more servings in the last 3 days (4.5 per day) appropriate. We scored the seven criteria individually as either 0 (poor), 1 (intermediate) or 2 (ideal). For the present analyses, the total score was the sum of all criteria ranging from 0 to 14, which we also categorized into three groups based on data distribution (0–5, 6–10, and 11–14) since studies show associations may not be linear. [23,26,34]

Covariates—To adjust for potential confounding, we selected baseline socio-demographic covariates that could be determinants of dementia and CVH. [8] These covariates included age (65–69; 70–75; 75–79; 80+), sex, educational level (did not complete primary, completed primary, completed secondary), wealth (top; bottom 50% out of a summary score of assets owned: motor vehicles, television, refrigerator and/or freezer, water utilities, electricity utilities, telephone, plumbed toilet, and plumbed bathroom) and country. The term sex was used to be coherent with the term used in the data collection method. However, we acknowledge that any effect of this variable might be related to either genetic (sex) or social (gender) factors. [35]

Dementia diagnosis—Dementia cases were defined using either 10/66 or DSM-IV criteria for which algorithms have been previously published and validated. [36–39] 10/66 dementia cases scored above a cut-point of predicted probability for dementia, calculated with coefficients derived from a logistic regression equation based on cognitive test, informant report scores and diagnostic output from clinical interviews. [36] DSM-IV dementia cases needed to have cognitive impairment, impairment in social or occupational functioning and cognitive deficits that did not occur exclusively during the course of delirium and that were not better explained by another mental disorder. [38]

We obtained information for dementia diagnosis from culturally and linguistically adapted cognitive tests (CSI'D', COGSCORE scale with CERAD's animal-naming verbal fluency, and modified CERAD ten word list learning task with delayed recall), [40,41] participant interview (Geriatric Mental State), [42] informant interview (CSI'D', RELSCORE scale and HAS-DDS) and neurological examination (including the Luria three step motor sequencing fist-edge-palm test). [40,43] Participants who died after baseline and had a score higher than two on RELSCORE from the post-mortem informant interview, with endorsement of either "deterioration in memory" or "a general deterioration in mental functioning", or both; an increase in RELSCORE higher than two points from baseline; and the onset of these signs being 6 months before death or later were diagnosed as probable incident dementia.

Cohort for analysis

Participants were included if 1) they were from countries in Latin America, including urban and rural sites in Mexico and Peru and urban sites in Cuba, Dominican Republic, Venezuela, and Puerto Rico, 2) had available blood test data, 3) did not have dementia at baseline using 10/66 and DSM-IV criteria and 4) had an existing value in either 10/66 or DSM-IV dementia diagnosis at follow-up.

Statistical analysis

Descriptive analyses of baseline characteristics are presented as frequencies and percentages. We calculated person-years at risk as the interval between baseline and follow-up assessment, or the estimated time of onset of dementia, or the time of death, whichever occurred first. Competing risks regression was used to model the impact of CVH on 10/66 and DSM-IV dementia incidence, [44] where competing events that occur prior to or instead of the event of interest cannot be treated as censored. The model estimates a cumulative incidence function, the probability of observing an event before a given time, for the failure

event of interest (dementia) while acknowledging the possibility of the competing event (death). We estimated subhazard ratios and their 95% confidence intervals for participants' CVH scores, which we modelled as both a discrete score and categorized based on data distribution (0–5, 6–10, and 11–14). Models adjusted for age, sex, level of education, wealth and country. Secondary analyses explored associations stratified by age, sex, education, asset ownership. We performed all analyses using Stata version 13 with statistical significance at p< 0.05. [45]

Results

Table 1 summarizes the baseline characteristics for all participants by CVH levels, dementia and deceased status. The final analytic sample consisted of 6,447 participants and included 400 (6.2%) participants with poor (0–5), 5,222 (81.0%) with moderate (6–10) and 825 (12.8%) with ideal CVH (11–14). There were 605 (9.4%) incident dementia and 846 (13.1%) participants died during follow-up. Those with poor baseline CVH levels were younger (65–69 years old: 30.8%), had not completed primary education (39.9%), and were in the bottom 50% of wealth (55.0%). Those with dementia at follow-up tended to be older (80+ years old: 40.5%), women (69.4%), and had not completed primary education (46.1%). Mortality was higher among individuals who were older (i.e. 80+: 26.2% vs 65–69: 7.0%), male (17.0% vs 11.1%), less educated (incomplete primary: 16.7% vs completed secondary: 6.1%), and less wealthy (14.6% vs 11.6%).

Figure 1 shows the cummulative incidence function of dementia by the three levels of CVH. Those with poor CVH levels had a higher cumulative incidence of dementia that those with moderate and ideal levels, which had a similar dementia incidence. Table 2 shows the unadjusted and adjusted subhazard ratios of dementia by baseline CVH and stratified by wealth levels. The risk of dementia was 4% lower with each additional point of the 0–14 continuous score of CVH in the unadjusted associations (p=0.04). However, this association attenuated slightly and was not statistically significant after adjusting for age, gender, education, assets and country. Compared to poor CVH, participants with moderate and ideal levels of CVH had a significantly lower risk of dementia both in the adjusted and unadjusted models. Maintaining moderate CVH conveyed a 27% (Adj. SHR: 0.73, 95% Confidence Interval [CI]: 0.54, 0.97) lower risk of dementia compare poor CVH. As well, participants with ideal CVH had a 34% (Adj. SHR: 0.66, 95% CI: 0.46, 0.96) lower risk of dementia than those with poor CVH.

In secondary analysis stratified by wealth, participants in the top 50% of wealth with ideal CVH had lower risk of dementa (Adj. SHR: 0.60, p=0.098) than those with poor CVH, after adjusting for covariates. Among those in the bottom 50% of wealth, unadjusted associations were statistically significant for both moderate and ideal CVH levels and the strength of the association remained after adjustment (Adj. SHRs: 0.57 & 0.65), although ideal CVH was only marginally significant (p=0.085). Those with moderate and ideal levels of CVH had 54–75% lower risk of dementia than those with poor levels.

Discussion

To our knowledge, this is the first study to explore the longitudinal association between an index of modifiable CVH risk factors and dementia incidence among Latin American older adults. This is also one of the first studies worldwide to study such associations. Our analyses build upon the Framingham study by assessing these associations among individuals in a wide spectrum of socioeconomic positions from low- and middle-income countries, which increases the external validity of our results. Another strength compared to previous research is that this study also accounts for competing risk of death, decreasing bias related to the associations between CVH, dementia and mortality. [29] Our findings suggest that CVH is inversely associated with dementia incidence in this population. These associations were mostly present among individuals in the bottom 50% of wealth.

We hypothesized that higher levels of CVH would be inversely associated with dementia incidence. In line with our hypothesis, we found that moderate and ideal levels of CVH were associated with a lower dementia incidence than poor levels. These findings are in line with a growing literature showing that cumulative indices of modifiable CVH factors are associated with stroke, cognitive functioning, decline, brain integrity and dementia. [19–27,34] Findings are consistent with the Framingham study in that the 0–14 continuous CVH index was not associated with dementia incidence. [21] Results are also similar to those in the REGARDS study, which found a lower cognitive impairment incidence among an ethnically diverse American middle age adult sample with moderate and ideal CVH levels in a diverse sample of middle agers. [26] In addition, the risk of dementia was similar among those with moderate and ideal CVH levels and the effect sizes were comparable to the ones found in this study.

Similar to findings from individual risk factors, [12] most studies exploring the association between indices of modifiable CVH factors and brain health have found associations among young or middle-aged individuals. [19,20,22–26,34] However, in the present study we found that such associations exist among individuals aged 65 and over. Whereas the earlier findings reinforce the importance of maintaining ideal levels of CVH decades before a potential dementia onset, our findings offer a rather optimistic picture for individuals and policy-makers in that even moderate levels of CVH are sufficient to reduce dementia risk.

This study shows that the association between CVH and dementia was mostly present among participants at the bottom 50% of wealth. The Study of Latinos in the USA had similar findings in which CVH was cross-sectionally associated with verbal learning scores among those with low levels of education. [19] However, the Study of Latinos found an interaction of education adjusted for income whereas in our analyses, we have found a differential association by wealth adjusted for education. These different findings might shed light into independent mechanisms interacting with CVH. CVH plays an important role in β-amyloid and other neurodegenerative protein deposition and clearance as well as vascular pathology development, which might interact with neurodegeneration. [46,47] The moderating effect of education found in the Study of Latinos might be related to cognitive reserve buffering the effects of poor CVH among those with higher levels of education. [48] However, since we adjusted for education in our study, an alternative explanation to our findings is that

the effect of poor CVH on the brain is aggravated by the well-established chronic stress driven by lower social standing. [49] Recent findings support this idea as comorbid depression and diabetes significantly increased risk for mild cognitive impairment and Alzheimer's disease among Mexican-Americans. [50]

These results are the first attempt to examine the longitudinal association between a Life's Simple 7-like index of modifiable CVH factors and dementia in the Latin American population. Our previous study found that a similar four-component index was associated with cognitive functioning cross-sectionally in a representative sample of Mexicans 50 and older. [34] Our study extends findings from the USA by demonstrating that an index of modifiable CVH risk factors is associated with dementia incidence in a diverse sample of Latin American older adults. This diverse sample reflects the population of catchment areas from six countries in Latin America, men and women, with different ancestries and varying levels of wealth. Besides the implications for Latin America, findings may also apply to some extent to the Latino population in the USA, where 17% of the population identify as Hispanic or Latino, mostly from Puerto Rico, Mexico and Cuba. [51] In fact the Study of Latinos found CVH to be associated with cognitive function among middle-aged Latinos of different origins. [19] However, generizability might be compromised by acculturation effects and the Hispanic paradox in which there is a positive selection of immigrants from Latin America to the USA. [52,53]

Study limitations

There are limitations to this study. First, the operationalization of CVH did not replicate the Life's Simple 7 index fully. [18] Differences in the operationalization might compromise the comparability between our study and others. Second, the CVH index has not been previously validated in Latin America although the individual CVH criteria used in the USA and Latin America are comparable. Third, the assessment of a CVH index gives the same weight to the different domains, which might not represent their real contribution to CVH.

Public health implications and future research recommendations

Regarding potential public health implications, this study highlights the importance of maintaining ideal or moderate levels of CVH to reduce the risk of dementia. Our findings convey a positive and important public health message that even moderate levels of CVH are enough to reduce dementia risk. Given that 94% of the study population of Latin Americans 65 and older have moderate or ideal levels of CVH, policy-makers should put a great effort in promoting maintenance of CVH. These policies may include media and educational campaigns, labeling and consumer information, taxation, subsidies, and other economic incentives, local environmental changes, direct restrictions, and mandates. [54] Strengthening the countries' welfare state might also diminish the differential association between CVH and dementia by wealth. Our findings may help inform a holistic CVH promotion at the primary care level in Latin American countries with an existing dementia national plan (i.e. Cuba, Mexico or Puerto Rico). [55] In Cuba for example, there are protocols in place to promote physical activity, smoking cessation and prevent hypertension and diabetes among older adults. However, Cuba's dementia risk-reduction program is not being implemented

equally in all regions and was approved without additional budget allocation, which may hinder the execution of some of the proposed measures. [56]

Further research is needed to better understand the differential association between CVH and dementia incidence by wealth. Potential effect modifiers such as social participation, social contact and loneliness should also be explored. [57] Further research should also aim to understand the effect of CVH maintenance across the lifespan in reducing dementia risk rather than studying CVH at a single point in time. Also, dementia risk-reduction clinical trials should aim to improve CVH among those with poor CVH levels.

Conclusion

These findings add to the growing evidence that CVH is important for optimal brain health [17] and is the first study in Latin America to address the association between CVH and dementia incidence using an index of modifiable levels of CVH. We found that moderate and ideal levels of CVH were associated with a lower incidence of dementia among older adults from six countries in Latin America. These results suggest that dementia-related policies in Latin America need to focus on reaching and maintaining at least moderate CVH levels in older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Key points:

- Few studies have explored the link between modifiable cardiovascular health indices and dementia risk

- Research linking heart and brain health is scarce in Latino America

- Dementia risk is lower among Latin American elders with moderate/ideal cardiovascular health

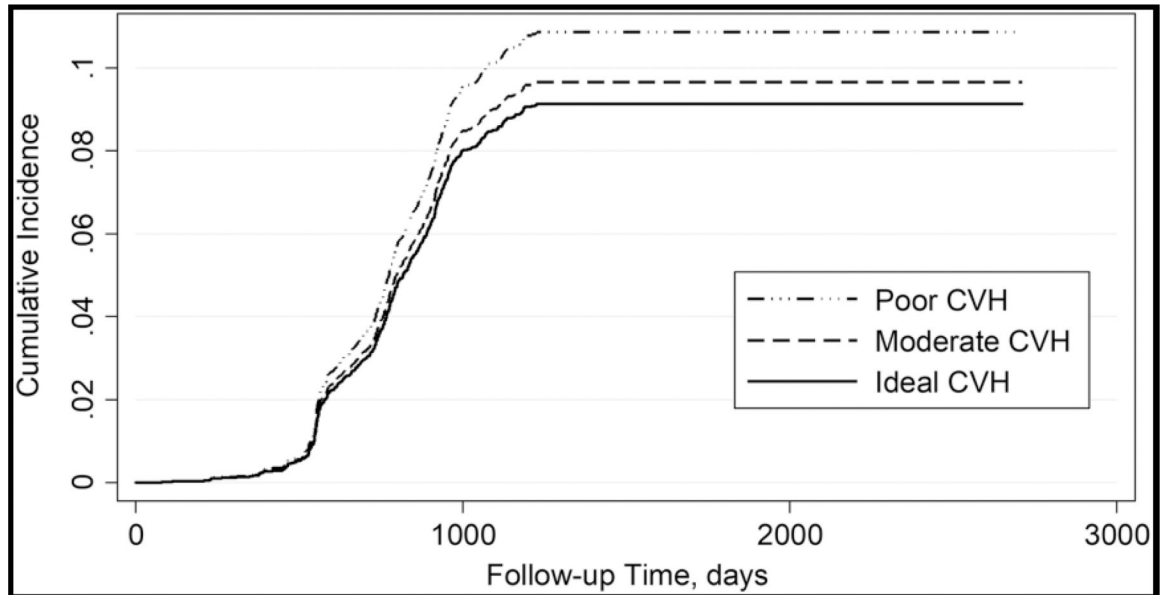- The association between cardiovascular health and dementia risk differs by wealth

Figure 1.
Cumulative incidence function for dementia by cardiovascular health (CVH) score categories.

Table 1:

Baseline characteristics of 10/66 participants by categories of cardiovascular health (CVH) and dementia status (N=6447)

	Cardiovascular Health (CVH) Status			Dementia Status		
	Poor CVH (0–5) n=400	Moderate CVH (6–10) n=5222	Ideal CVH (11–14) n=825	No Dementia n=4996	Dementia n=605	Deceased n=846
Age group						
65–69	123, 30.8%	1490, 25.6%	298, 36.1%	1712, 34.3%	65, 10.8%	134, 15.8%
70–74	101, 25.3%	1473, 28.2%	224, 27.2%	1481, 29.7%	137, 22.7%	180, 21.3%
75–79	84, 21.1%	1150, 22.0%	176, 21.3%	1067, 21.4%	157, 26.0%	186, 22.0%
80+	91, 22.8%	1105, 21.2%	127, 15.4%	733, 14.7%	244, 40.5%	346, 40.9%
Sex						
Female	204, 51.0%	3385, 64.8%	667, 80.9%	3362, 67.3%	420, 69.4%	474, 56.0%
Male	196, 49.0%	1837, 35.2%	158, 19.2%	1634, 32.7%	185, 30.6%	372, 44.0%
Education						
Incomplete Primary	159, 39.9%	2009, 38.5%	297, 36.0%	1774, 35.5%	279, 43.1%	412, 48.8%
Completed Primary	126, 31.6%	1440, 27.6%	205, 24.9%	1375, 27.6%	178, 29.4%	218, 25.8%
Completed Secondary	114, 28.6%	1767, 33.9%	322, 39.1%	1841, 36.9%	1448, 24.5%	214, 25.4%
Wealth						
Bottom 50%	180, 45.0%	2607, 49.9%	455, 55.1%	2456, 49.2%	312, 51.6%	474, 56.0%
Top 50%	220, 55.0%	2613, 50.1%	370, 44.9%	2538, 50.8%	293, 48.4%	372, 44.0%
Country						
Cuba	141, 35.3%	1476, 28.3%	194, 23.5%	1319, 26.4%	157, 25.9%	335, 39.6%
Dominican Republic	64, 16.0%	859, 16.5%	110, 13.3%	711, 14.2%	113, 18.7%	209, 24.7%
Peru	13, 3.3%	395, 7.6%	102, 12.4%	465, 9.3%	21, 3.5%	24, 2.8%
Venezuela	52, 13.0%	572, 10.9%	99, 12.0%	572, 11.5%	90, 14.9%	61, 7.2%
Mexico	57, 14.3%	1007, 19.3%	221, 26.8%	1056, 21.1%	108, 17.8%	121, 14.3%
Puerto Rico	73, 18.3%	913, 17.5%	99, 12.0%	873, 17.5%	116, 19.2%	96, 11.4%

Table 2:

Unadjusted and adjusted subhazard ratios of dementia by baseline categories of cardiovascular health (CVH), total and stratified by level of wealth

	Unadjusted SHR	p-value	Adjusted SHR[*]	p-value
Total (n=6447)				
Total CVH	0.96 (0.92, 0.997)	0.040	0.97 (0.93, 1.02)	0.189
CVH Category				
Poor	Reference		Reference	
Moderate	0.72 (0.54, 0.95)	0.022	0.73 (0.54, 0.97)	0.030
Ideal	0.59 (0.41, 0.85)	0.004	0.66 (0.46, 0.96)	0.031
Top 50% Wealth (n=3203)				
CVH Category				
Poor	Reference		Reference	
Moderate	0.88 (0.58, 1.33)	0.545	0.93 (0.61, 1.42)	0.725
Ideal	0.49 (0.27, 0.89)	0.019	0.60 (0.33, 1.1)	0.098
Bottom 50% Wealth (n=3242)				
CVH Category				
Poor	Reference		Reference	
Moderate	0.58 (0.39, 0.86)	0.006	0.57 (0.39, 0.85)	0.005
Ideal	0.61 (0.68, 0.97)	0.038	0.65 (0.40, 1.1)	0.082

[*] Adjusted for age (4 categories), sex, education (3 categories), wealth, country