Stroke

CLINICAL AND POPULATION SCIENCES

High Social Risk Influence Progression of White Matter Hyperintensities of Presumed Vascular Origin: A Prospective Study in Community-Dwelling Older Adults

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BACKGROUND: Information on cerebrovascular consequences of high social risk, as determined by the social determinants of health, is limited. We sought to evaluate the impact of high social risk on the progression of white matter hyperintensities (WMHs) of presumed vascular origin.

METHODS: Following a longitudinal prospective study design, participants of the Atahualpa Project Cohort received baseline social risk determinations by means of social determinants of health components included in the Gijon's Social-Familial Evaluation Scale together with clinical interviews and brain magnetic resonance imagings. Those who also received follow-up brain magnetic resonance imaging at the end of the study were included. We used Poisson regression models adjusted for demographics, education levels and traditional cardiovascular risk factors to assess the incidence rate ratio of WMH progression according to the Gijon's Social-Familial Evaluation Scale score.

RESULTS: The study included 263 individuals aged ≥60 years (mean age, 65.7±6.2 years; 57% women). The Gijon's Social-Familial Evaluation Scale mean score was 8.9±2.2 points. Follow-up magnetic resonance imagings revealed WMH progression in 103 (39%) individuals after a mean follow-up of 6.5 years (SD±1.4 years). Poisson regression models showed increased WMH progression rate among individuals in the third tertile of the Gijon's Social-Familial Evaluation Scale score compared with those in the first tertile (incidence rate ratio, 1.65 [95% CI, 1.05–2.61]; *P*=0.032). Separate Poisson regression models using individual social determinants of health components showed that poor social relationships (incidence rate ratio, 1.39 [95% CI, 1.10–1.77]; *P*=0.006) and deficient support networks (incidence rate ratio, 1.79 [95% CI, 1.19–2.69]; *P*=0.005) were independently associated with WMH progression, whereas family situation, economic status, and housing did not.

CONCLUSIONS: Poor social relationships and deficient support networks were significantly associated with WMH progression in community-dwelling older adults living in a rural setting. Our findings may help planning cost-effective preventive policies to reduce progression of cerebral small vessel disease among vulnerable populations.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebral small vessel disease ■ prospective cohort study ■ social isolation ■ social risk ■ white matter hyperintensities

Social risk, as determined by the social determinants of health (SDH), is increasingly used in geriatric and vascular research. SDH refer to situations in which individuals are born, grow up, live, work, and age and include factors such as living conditions, economic stability, education quality, social relationships, support networks,

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Nonstandard Abbreviations and Acronyms

CVH	cardiovascular health
IRR	incidence rate ratio
MRI	magnetic resonance imaging
SDH	social determinants of health
SFES	Social-Familial Evaluation Scale

and access to health care.[1] SDH have a substantial impact on health status (particularly in vulnerable populations) and may result in the occurrence or progression of chronic conditions and diseases.[2,3] Moreover, SDH have been associated to increased stroke incidence and worse outcomes after a stroke.[4–8] However, specific cerebrovascular consequences of SDH have not been well evaluated to date. This knowledge is of interest since tailored interventions targeting the diverse SDH may prove cost-effective to reduce stroke burden in different populations beyond the control of traditional vascular risk factors.[9]

White matter hyperintensities (WMHs) of presumed vascular origin is a common imaging biomarker of cerebral small vessel disease tightly linked with stroke risk and cognitive decline.[10] WMH prevalence increases with age, as well as in the presence of vascular risk factors such as hypertension, diabetes, smoking and many other as yet undetermined risk factors.[10] Information about the relationship between SDH and WMH is limited and results are inconsistent.[11–13] One study using a data-driven machine-learning approach demonstrated that the social environment significantly contributed to WMH burden.[11] A systematic review suggested a possible but inconclusive association between early life factors (including low socioeconomic status and poor education) and WMH burden later in life.[12] Conversely, another study did not find an association between the socioeconomic index (composed by education, income, occupation and minority status) and WMH burden.[13] Taking the opportunity of the population-based Atahualpa Project Cohort, this longitudinal prospective study aims to assess the impact of high social risk determined by SDH factors (family situation, economic status, housing, social relationships, and support networks) on WMH progression in community-dwelling older adults living in an underserved community in rural Ecuador.

METHODS

Data Availability Statement

Aggregated data from this study are available from the corresponding author upon reasonable request.

Study Population

The study was conducted in community-dwellers aged ≥60 years living in Atahualpa, an isolated rural village of coastal Ecuador. As detailed elsewhere, the population is homogeneous about ethnicity (Amerindian ancestry), low levels of education, socioeconomic status (most men work as artisan carpenters or farmers and most women are homemakers), living conditions, and dietary habits.[14] The diet is ancestrally rich in oily fish, fruits and carbohydrates, but limited in other types of meat, dairy products, and highly processed foods. Overall, physical activity is adequate, since inhabitants mobilize within the village mainly by walking or bicycle riding, as very few people own a motor vehicle. The village has only one health center of the Minister of Health staffed by 2 general physicians, 2 nurses, an odontologist, and an obstetrician.

Following a longitudinal prospective design, individuals aged ≥60 years who had baseline brain magnetic resonance imaging (MRI), evaluation of cardiovascular risk factors, SDH determinations between 2012 and 2019, and were actively participating in the Atahualpa Project Cohort as of May 2021, were invited to undergo a follow-up brain MRI. Disabled individuals and those with contraindications for MRI were excluded. As detailed elsewhere, study participants have been identified by means of door-to-door surveys and have signed a comprehensive informed consent before enrollment.[13] Individuals signed a new informed consent before follow-up MRIs. The present study followed the STROBE checklist (The Strengthening the Reporting of Observational Studies in Epidemiology; see Supplemental Material)[15] and was approved by the Ethics Committee of Hospital-Clínica Kennedy, Guayaquil (FWA 00030727).

Social Risk Assessment

Social risk was determined using SDH included in the Gijon's Social-Familial Evaluation Scale (SFES).[16] This validated field instrument (originally constructed in the Spanish language) rates 5 components of social risk situations including family situation, economic status, housing, social relationships, and support networks.[16] Each of these components has 5 questions weighted on a 1 to 5 scale, for a maximal score of 25, with increased scores indicating higher social risk (Table 1). The Gijon's SFES scale was selected because of its appropriateness to the living conditions of the study population (where race/ethnicity and access to health care are similar for most individuals). In addition, this scale has been officially endorsed by the Ecuadorian Minister of Health for the assessment of social risk.[17]

Neuroimaging Studies

Both baseline and follow-up MRIs were performed with the same equipment (Philips Intera 1.5T; Philips Medical Systems, Eindhoven, the Netherlands) following previously described research standards.[18] Interest focused on the presence and severity of WMH, which were defined as lesions appearing hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and graded according to the modified Fazekas scale.[19] This widely used visual scale recognize 3 degrees of WMH severity: mild, moderate, and severe. Mild WMH refers to the presence of periventricular caps or thin lesions and punctate hyperintensities in subcortical white matter. In moderate WMH, there is a smooth periventricular halo and subcortical foci begin to merge. Severe WMH is characterized by extension of periventricular lesions into the subcortical white matter and large confluent subcortical foci. Both, baseline

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Table 1. Components and Scores of the Gijon's Social-Familial Evaluation Scale (English Translation From Original Spanish Version)

Family situation	
Do you live with your family with no physical or psychological dependence?	1
Do you live with your spouse of a similar age?	2
Do you live with your spouse and/or other family members but present some degree of dependence?	3
Do you live alone but have adult children living in your neighborhood?	4
Do you live alone and do not have children or they live away from where you live?	5
Economic status (monthly income)	
More than 1.5× the minimum wage (≥$700)	1
Between 1.5× and the minimum wage ($450–$700)	2
Less than the minimum wage ($200–$450)	3
Nonsignificant retirement pension (≤$200)	4
No income or receive a government bonus (≤$100)	5
Housing	
Adapted to needs	1
Architectural barriers, steps, narrow doors, small bathrooms	2
Humidity, poor hygiene, no full bathroom, or no drinking water	3
No telephone	4
Inadequate housing with absence of minimum equipment	5
Social relationships	
Full social relationships	1
Only with family members and neighbors	2
Only with family members or neighbors	3
Individual does not leave the home, but receive visitors	4
Individual does not leave home and does not receive visitors	5
Support networks	
Support from family members and neighbors	1
Receives social volunteering or has domestic help	2
No support	3
About to enter a geriatric center	4
Needs permanent help	5

and follow-up MRIs were independently read by one neuroradiologist and one neurologist blinded to clinical information. WMH progression was defined as the increase in at least one grade of the Fazekas scale in the follow-up MRI (Figure 1). Kappa coefficients for interrater agreement of WMH severity were 0.91 at baseline and 0.93 at follow-up, and discrepancies were resolved by consensus.

Covariates Investigated

Demographics, level of education (primary school education or higher), and cardiovascular health (CVH) metrics were recorded at baseline. Interviews and procedures for determining CVH metrics followed the recommendations proposed by the American Heart Association (AHA), which stratifies each of the following metrics in the poor range according to well-defined cutoffs, including (1) poor smoking status if the subject is a current smoker or quit <1 year prior; (2) poor body mass index if ≥30 kg/m^2; (3) poor physical activity if there is no moderate and vigorous activity; (4) poor diet if there is none or only 1 of 5 AHA healthy dietary components; (5) poor blood pressure if ≥140/90 mm Hg; (6) poor fasting glucose if ≥126 mg/dL; and (7) poor total cholesterol blood levels if ≥240 mg/dL.[20]

Statistical Analysis

In unadjusted analyses, continuous variables were compared by linear models and categorical variables by the χ^2 or Fisher exact test as appropriate. To compute person-years of follow-up, we considered the time from baseline to follow-up MRIs (last censoring date). Multivariate Poisson regression models were fitted to estimate the incidence rate ratio (IRR) of WMH progression according to the social risk based on the Gijon's SFES score at baseline stratified in tertiles. Separate multivariate Poisson regression models were used to assess the independent association between WMH progression and the individual scores of family situation, economic status, housing, social relationships, and support networks. Multivariate models were adjusted for demographics, levels of education, and CVH metrics. WMH progression (dependent variable) was assessed according to baseline social risk determined by the total Gijon's SFES score, as well as the individual score of its components (independent variables). We used the goodness of fit chi-squared test for Poisson regression, which corroborated the fit of the Poisson model to the data. Smoking was not included as a covariate in any of these models due to collinearity with other predictors. All data analyses were carried out by using STATA version 17 (College Station, TX).

RESULTS

A total of 403 (84%) out of 478 individuals aged ≥60 years enrolled in the Atahualpa Project cohort had a baseline brain MRI, clinical interviews, and SDH assessment. Among the 75 excluded individuals, 36 died or emigrated before the MRI, 19 declined consent, 17 were severely disabled or had contraindications for MRI, and 3 had missing clinical information. Of 403 eligible candidates, 263 (65%) had a follow-up brain MRI and were included in the study. Ninety of the 140 nonincluded participants died, and the remaining 50 either declined further consent, became disabled over the study years, or emigrated between baseline and follow-up MRI. Figure 2 shows the reasons for exclusion of participants at each stage of the enrollment process. Follow-up time between baseline and follow-up brain MRIs was 1711 person-years (95% CI, 1665–1757 years). The mean person years of follow-up was 6.5 years with a SD of ±1.4 (range, 2.2–9.1 years).

The mean (±SD) age of 263 study participants at baseline was 65.7±6.2 years (median age, 63.9 years; age range, 60–91 years), 149 (57%) were women, and 192 (73%) had primary school education only. Individual CVH metrics in the poor range included: smoking status: 11 (4%); body mass index: 63 (24%); physical activity: 12 (5%); diet: 11 (4%); blood pressure: 104 (40%); fasting glucose: 72 (27%); and total cholesterol

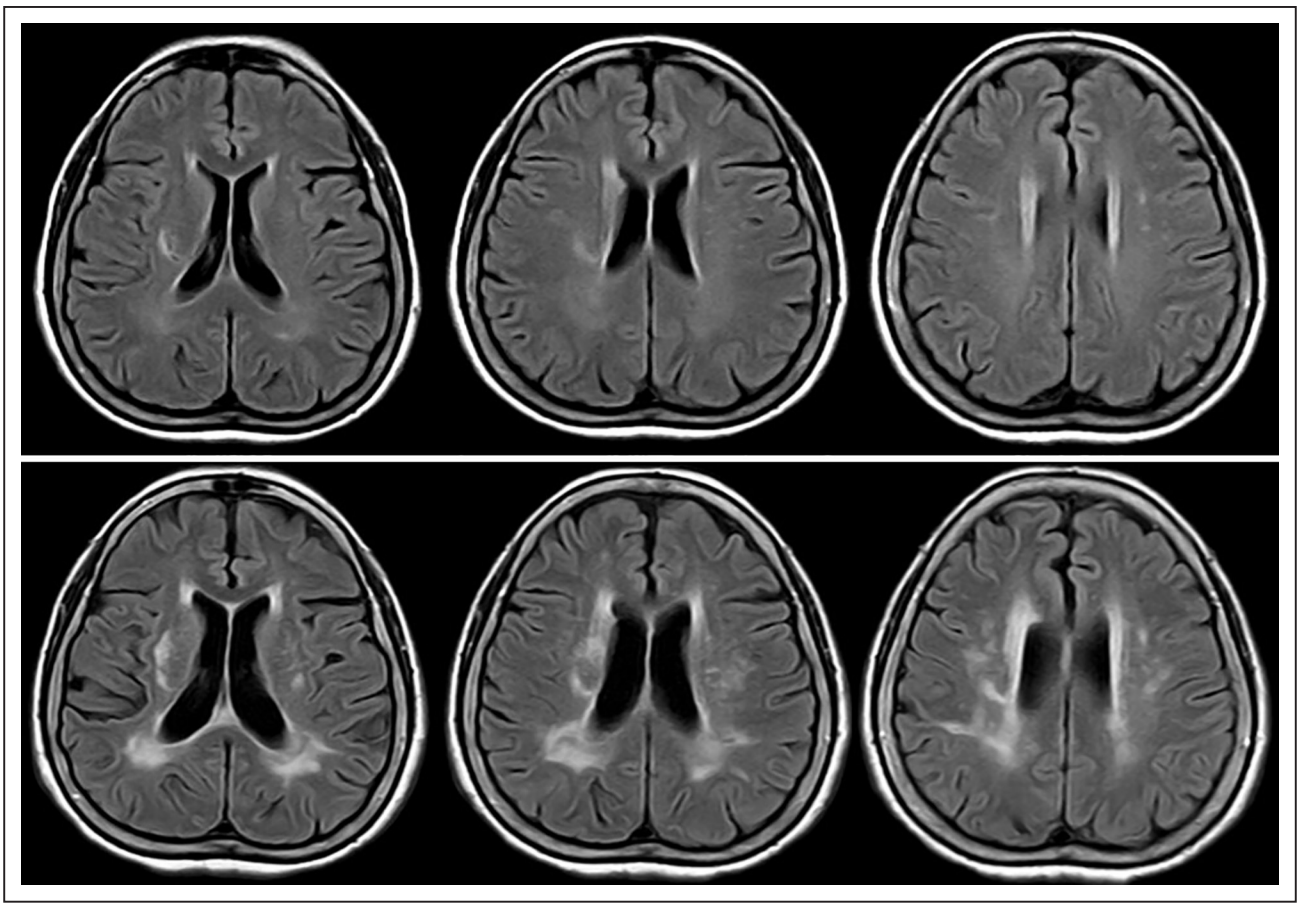

Figure 1. Fluid-attenuated inversion recovery magnetic resonance imaging (MRI; TR 9000, TE 120, TI 2500).
A 62-y-old man with a high social risk showing progression of white matter hyperintensities from baseline MRI (**upper row**) performed in February 2014, to follow-up MRI (**lower row**) performed in May 2021.

blood levels: 41 (16%). The mean Gijon's SFES score was 8.9±2.2 points (out of a possible 25 points) with a median of 9, and with the first and the third tertiles having means of 7.1 and 11.3 points, respectively. Mean scores of individual components were as follows: family situation: 1.6±1.1 points; economic status: 3.1±1 points; housing: 1.7±0.8 points; social relationships: 1.3±0.7 points; and support networks: 1.1±0.3 points. On baseline MRI, 90 (34%) participants did not have WMH, 131 (50%) had mild, 33 (13%) had moderate, and 9 (3%) had severe WMH.

There were several differences in clinical characteristics, Gijon's SFES scores and WMH severity at baseline across the 140 individuals who were excluded because lack of follow-up MRI and the 263 who completed the study (Table 2). Such differences were expected since most individuals who did not complete the study died or became disabled during follow-up.

At follow-up, 52 (20%) individuals did not have WMH, 112 (43%) had mild, 67 (25%) had moderate, and 32 (12%) had severe WMH. Overall, 103 (39%) individuals had MRI evidence of WMH progression. Progression from none-to-mild WMH was noticed in 33 cases, from none-to-moderate in 5, from mild-to-moderate in 42, from mild-to-severe in 10, and from moderate-to-severe in 13. Study participants who had WMH progression were older (67.9±6 versus 64.3±5.8 years; $P<0.001$) and were less often obese (17% versus 29%; $P=0.023$) than those without WMH progression; otherwise, there were no significant differences in baseline clinical characteristics across groups. In unadjusted analysis, mean values of the continuous Gijon's SFES score, as well as 2 of its individual components (social relationships and support networks) were higher among individuals who had WMH progression (Table 3).

In a fully adjusted model, with the Gijon's SFES score stratified in tertiles (4–8, 9, and 10–17 points), we found a significant increase in the IRR of WMH progression when individuals with higher social risk were compared with those with lower social risk (Table 4). In addition, separate Poisson regression models using individual SDH components showed that poor social relationships (IRR, 1.39 [95% CI, 1.10–1.77]; $P=0.006$) and deficient support networks (IRR, 1.79 [95% CI, 1.19–2.69]; $P=0.005$) were significantly associated with WMH progression, whereas family situation ($P=0.760$), economic status ($P=0.963$), and housing ($P=0.674$) did not.

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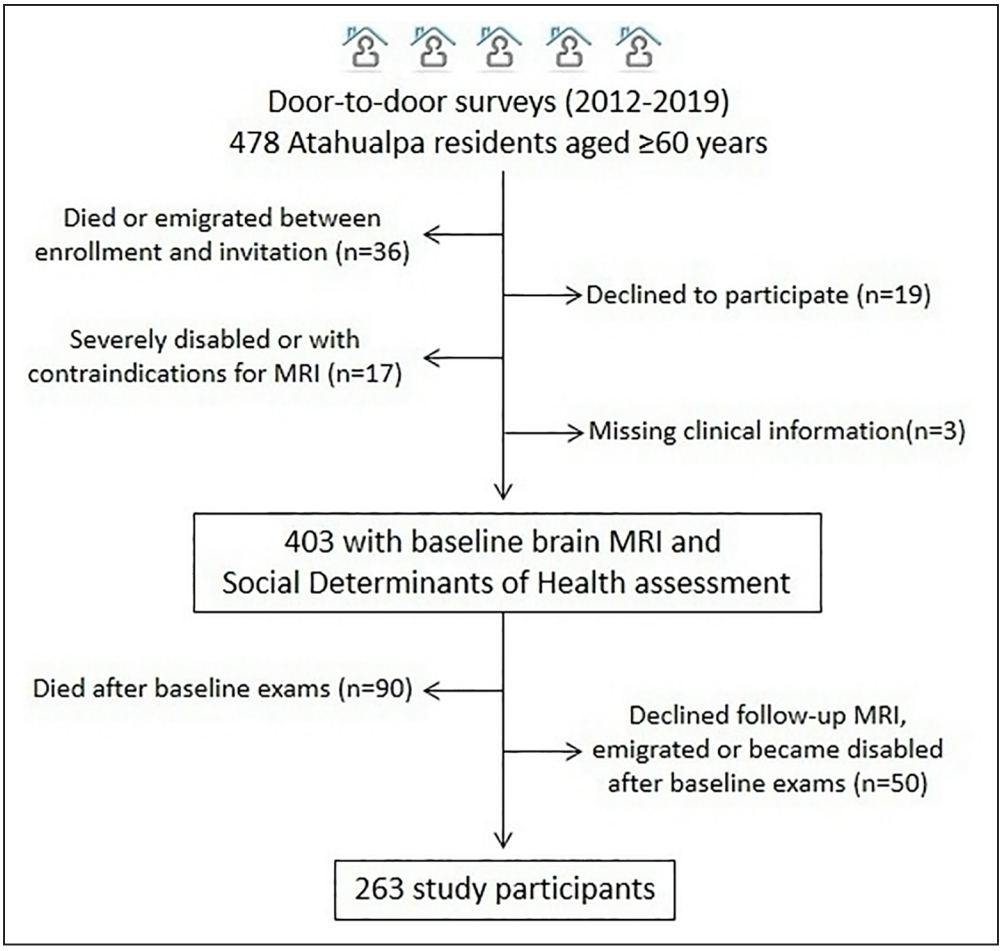

Figure 2. Flow chart depicting enrollment and the number of excluded individuals at each stage of this process.
MRI indicates magnetic resonance imaging.

DISCUSSION

This prospective population-based study, conducted in a cohort of community-dwelling older adults living in rural Ecuador, shows a significant relationship between high social risk (determined by SDH) and WMH progression. Two individual components of SDH, including social relationships and support networks, also showed independent relationships with WMH progression. Of interest, none of the investigated covariates tempered the significance of the aforementioned relationships, suggesting that the impact of high social risk on WMH progression exceeds that of increasing age, sex, level of education, and traditional cardiovascular risk factors.

Some individual components of SDH, namely, family situation, economic status, and housing, were not independently associated with WMH progression. This suggests that the effect of those components is surpassed by poor social relationships and deficient support networks. Our results align with previous studies disclosing that social isolation is associated with an increased risk of cardio- and cerebrovascular diseases among older adults.[21–23]

While race/ethnicity, low levels of education, poverty, food insecurity, and disparities in access to health care have been frequently signaled as important contributors to the social health and its detrimental consequences in individuals living in urban centers of developed countries,[4,9,23] these determinants seem to be less important in people from remote rural communities, where social relationships and support networks play a major role in the wellbeing of individuals, in particular, older adults. Findings of the present work, as well as those of other studies conducted in similar rural communities, underline the importance of selecting the proper field instrument to investigate SDH in underserved populations.[3,24] SDH assessment is not a matter of "one-size-fits-all", and must be tailored according to the specific characteristics of the study population. SDH vary according to the level of development of a given community and their assessment must be adapted consequently.[25,26]

While mechanisms explaining the link between social risk and WMH progression are still elusive, data extracted from the literature provide important pieces of evidence supporting the role of social risk on structural brain damage, including the cerebral cortex and

Table 2. Differences at Baseline Across Individuals Excluded Because Follow-Up MRI Could Not Be Performed and Those Who Completed the Study (Unadjusted Analysis)

	Excluded from cohort (n=140)	Finished the study (n=263)	*P* value
Clinical characteristics			
Age at baseline, mean±SD	73.5±9.3	65.7±6.2	<0.001*
Women, n (%)	77 (55)	149 (57)	0.750
Primary school education, n (%)	118 (84)	192 (73)	0.010*
Current smoker, n (%)	3 (2)	11 (4)	0.396
Body mass index ≥30 kg/m²	34 (24)	63 (24)	0.941
Poor physical activity	29 (21)	12 (5)	<0.001*
Poor diet	6 (4)	11 (4)	…
Blood pressure ≥140/90 mm Hg	77 (55)	104 (40)	0.003*
Fasting glucose ≥126 mg/dL	59 (42)	72 (27)	0.003*
Total cholesterol ≥240 mg/dL	9 (6)	41 (16)	0.008*
Gijon's Social Familial Evaluation Scale score			
Total score, mean±SD	9.5±2.9	8.9±2.2	0.020*
Family situation, mean±SD	1.9±1.1	1.6±1.1	0.009*
Economic status, mean±SD	3.1±0.9	3.1±1	0.323
Housing, mean±SD	1.6±0.7	1.7±0.8	0.213
Social relationships, mean±SD	1.8±1.2	1.3±0.7	<0.001*
Support networks, mean±SD	1.3±0.8	1.1±0.3	<0.001*
White matter hyperintensities			
None, n (%)	23 (16)	90 (34)	<0.001*
Mild, n (%)	59 (42)	131 (50)	0.142
Moderate, n (%)	33 (24)	33 (13)	0.004*
Severe, n (%)	25 (18)	9 (3)	<0.001*

*Statistically significant result.

the subcortical white matter.[27] A comprehensive review elaborates on several potential links between these conditions,[28] being the most relevant the role of immune-mediated inflammation. Poor social relationships and deficient support networks may compromise the neuroimmune system and may trigger immune-mediated inflammation by the release of cytokines and other pro-inflammatory molecules.[29] These mechanisms are in the path of WMH appearance and progression, namely, increased expression of inflammatory mechanisms leading to endothelial damage, blood-brain barrier dysfunction, and vessel stiffening.[29] In addition, social isolation has been associated with decrements in sleep quality,[30] a well-known contributor to the presence and severity of WMH.[31] Moreover, it has been suggested that social isolation may increase the presence of traditional cardiovascular risk factors (poor physical activity, dietary habits) and reduce the medication compliance aimed to the control of blood pressure, blood glucose levels, and other diseases that, in turn, favor WMH progression.[28] The latter seems not to be the case of our population, since the frequency of CVH metrics were evenly distributed across individuals with and without WMH progression. Much remains to be learned about theoretical pathways linking poor social health with WMH progression.

This study has limitations. First of all, the SARS-CoV-2 pandemic severely struck Atahualpa from the first trimester of 2020, resulting in a high mortality rate among older adults.[32] Also, several individuals left the village or declined consent for the practice of the follow-up MRI because of fears to the pandemic. These events could have contributed to selection bias. CVH metrics were measured at baseline, and they may have changed during follow-up, leading to over or underestimation of our findings. However, the population has been closely followed and almost all individuals had repeated CVH metrics determinations over the study years. Our records did not identify significant changes in CVH metrics with the exception of a transient decline in physical activity and dietary habits among older adults during the past year as a result of the SARS-CoV-2 pandemic.[33] In addition, the treatment gap (< 15% of the population with vascular risk factors received proper therapy during the study years) precluded assessment of the impact of medications on WMH progression. The present study included a homogeneous population of older adults of Amerindian ancestry and our results may not be generalizable to other races/ethnic groups. It is also possible that some unmeasured confounders may be responsible for at least part of the findings of the present study. In

Table 3. Social Determinants of Health, as Measured by the Gijon's Social-Familial Evaluation Scale, According to White Matter Hyperintensities Progression on Follow-Up MRIs (Unadjusted Analysis)

	Total series (n=263)	No progression of WMH (n=160)	Progression of WMH (n=103)	*P* value
Gijon's SFES score, mean±SD	8.9±2.2	8.5±2.1	9.4±2.2	<0.001*
Family situation, mean±SD	1.6±1.1	1.5±1.1	1.7±1.1	0.151
Economic status, mean±SD	3.1±1	3.1±1	3.2±0.9	0.411
Housing, mean±SD	1.7±0.8	1.7±0.8	1.7±0.8	…
Social relationships, mean±SD	1.3±0.7	1.1±0.5	1.6±0.9	<0.001*
Support networks, mean±SD	1.1±0.3	1.0±0.2	1.2±0.5	<0.001*

SDH indicates social determinants of health; SFES, Social-Familial Evaluation Scale; and WMH, white matter hyperintensity.
*Statistically significant result.

Table 4. Poisson Regression Model Disclosing That the IRR of White Matter Hyperintensities Progression Is Significantly Higher When Individuals in the Third Tertile of the Gijon's Social Familial-Evaluation Scale, Meaning High Social Risk, Are Compared With Those in the First Tertile (Low Social Risk)

WMH progression	IRR	95% CI	*P* value
First tertile of the Gijon's SFES score	Referent category		
Second tertile of the Gijon's SFES score	1.44	0.83–2.49	0.195
Third tertile of the Gijon's SFES score	1.65	1.05–2.61	0.032*
Age at baseline	1.03	1.00–1.06	0.042*
Being female	0.92	0.61–1.40	0.711
Primary school education	0.98	0.59–1.60	0.928
Body mass index ≥30 kg/m^2	0.80	0.46–1.40	0.433
Poor physical activity	0.61	0.18–1.99	0.411
Poor diet	0.79	0.28–2.21	0.658
Blood pressure ≥140/90 mm Hg	1.02	0.67–1.55	0.940
Fasting glucose ≥126 mg/dL	0.92	0.56–1.45	0.707
Total cholesterol ≥240 mg/dL	1.02	0.57–1.80	0.958

IRR indicates incidence rate ratio; SFES, Social-Familial Evaluation Scale; and WMH, white matter hyperintensity.
*Statistically significant result.

addition, cause of death and disability were not taken into account and this may weakens the overall study interpretation.

The possibility of a reverse causation phenomenon, that is, WMH progression causing increased Gijon's SFES scores, is unlikely since all individuals received baseline MRIs at the time of SDH determinations, and WMH progression was objectively assessed at the end of the study by means of repeated MRIs. We visually rated WMH, and this may be perceived as another limitation of this study, since the modified Fazekas scale may be less reliable than volumetry to assess slight changes in the follow-up.[34] This may explain why we did not identify WMH regression in any subject, which has been reported to occur in some individuals.[35]

Despite these limitations, the study has several strengths including its population-based design, the homogeneity of the study population about race/ethnicity, lifestyles, dietary habits and access to medical care, the systematic assessment of cardiovascular risk factors by means of uniform and standardized protocols, the determination of social risk by means of a field instrument that adjusts to the characteristics of the study population, and the practice of baseline and follow-up MRIs using the same equipment and protocols.

Knowledge on the burden of social risk is important for public health planning and the development of cost-effective preventive policies for controlling WMH progression among vulnerable populations. Intervention strategies may include periodical group activities and the reinforcement of social networks among older adults living in rural settings. These activities must be tailored according to the social needs of a given population and can be accomplished by health care social workers or by community leaders trained on these tasks. It is unknown, however, the intensity and duration of interventions needed to positively influence adverse outcomes or if they may only be effective in a subset of the population at risk. Results of the present study open new avenues of research to better understand pathogenic mechanisms involved in the relationship between high social risk and progression of WMH of presumed vascular origin.

In conclusion, older adults living in a rural setting who had higher social risk at baseline, as determined by SDH, were more likely to have WMH progression independently of baseline clinical characteristics. Individual SDH related to social isolation, namely social relationships and support network, showed an independent association with progression of WMH. Our results add to the growing evidence on the impact of social health on structural brain damage, and identify potential interventional targets focused on encouraging social interactions which may prove to be cost-effective in promoting brain health and decreasing cerebrovascular disease burden in vulnerable populations.

ARTICLE INFORMATION

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Disclosures

None.

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